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S3-Leitlinie

FETALE ALKOHOLSPEKTRUMSTÖRUNGEN

bei Kindern und Jugendlichen

Diagnose & Intervention

LEITLINIENBERICHT

AWMF-Registernr.: 022-025

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Hinweis: In der vorliegenden Leitlinie werden personenbezogene Bezeichnungen, die sich auf alle Geschlechter beziehen, vorwiegend mithilfe des Gendersternchens „*“ ausgedrückt. Sollte dies zur besseren Lesbarkeit jedoch nicht möglich sein, können personenbezogene Bezeichnungen auch nur in der männlichen oder weiblichen Form angeführt werden. Dies impliziert keinesfalls eine Benachteiligung anderer Geschlechter. Alle Geschlechter sind gleichermaßen angesprochen.

Inhaltsverzeichnis

Abkürzungen und Übersetzungen

ADHS	Attention Deficit Hyperactivity Syndrome – Aufmerksamkeitsdefizit-Hyperaktivitäts-Syndrom
ARBD	Alcohol Related Birth Defects – alkoholbedingte angeborene Malformationen
ARND	Alcohol Related Neurodevelopmental Disorder – alkoholbedingte entwicklungsneurologische Störung
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
Binge Drinking	Exzessiver Alkoholkonsum zu einer Gelegenheit
BMI	Body Mass Index
BMG	Bundesministerium für Gesundheit
FAS	Fetal Alcohol Syndrome – Fetales Alkoholsyndrom
FASD	Fetal Alcohol Spectrum Disorders – Fetale Alkohol-Spektrum-Störungen
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
IFEM	Institut für Evidenz in der Medizin
IOM	Institute of Medicine, USA
iSPZ	integriertes Sozialpädiatrisches Zentrum
LoE	Level of Evidence – Evidenzlevel
LMU München	Ludwig-Maximilians-Universität München
PAE	Prenatal Alcohol Exposure – pränatale Alkoholexposition
PFAS	partial Fetal Alcohol Syndrome – Partielles Fetales Alkoholsyndrom
PICO	Patient – Intervention – Comparator – Outcome
RoB	Risk of Bias
SPZ	Sozialpädiatrisches Zentrum
ZNS	Zentrales Nervensystem

1 Einleitung

1.1 Definition

Mütterlicher Alkoholkonsum während der Schwangerschaft führt häufig zu Schäden beim ungeborenen Kind. Pränatale Alkoholexposition (PAE) kann Auffälligkeiten des Wachstums, kranio-faziale, kardiale, renale, ossäre und okuläre Malformationen, Störungen der Entwicklung, der Kognition und des Verhaltens sowie Einschränkungen in Teilleistungen und somit globale Einschränkungen im Alltag bewirken.

Schädigungen, die durch PAE hervorgerufen werden, werden unter dem Oberbegriff Fetale Alkoholspektrumstörungen (FASD – fetal alcohol spectrum disorders) zusammengefasst. Zu den FASD gehören (auch wenn diese Einteilung umstritten ist und ein fließender Übergang im Spektrum diskutiert wird) vier Krankheitsbilder: das Fetale Alkoholsyndrom (FAS – fetal alcohol syndrome), das partielle Fetale Alkoholsyndrom (pFAS – partial fetal alcohol syndrome), die alkoholbedingte entwicklungsneurologische Störung (ARND – alcohol related neurodevelopmental disorder) und die alkoholbedingten angeborenen Malformationen (ARBD – alcohol related birth defects).

Die FASD entsprechen einem sogenannten hirnorganischen Psychosyndrom oder einer sogenannten statischen Enzephalopathie. Dabei ist jedoch zu beachten, dass die cerebrale Schädigung durch PAE zwar statisch ist, die Funktions- und Alltagsbeeinträchtigung der betroffenen Kinder jedoch durch frühe und individuelle Förderung deutlich positiv beeinflussbar sind und die FASD damit die klassischen Kriterien einer „developmental disorder“ aufweisen.

1.2 Geltungsbereich und Zweck

1.2.1 Begründung für die Auswahl des Leitlinienthemas

Durch die festgelegten diagnostischen Kriterien der FASD soll das Störungsbild früh erfasst und eine entsprechende Therapie und Förderung des Kindes/Jugendlichen initiiert werden. Dadurch kann das Auftreten von Folgeerkrankungen oder Komorbiditäten von Kindern mit FASD vermindert werden.

Die Gesundheitsdienste und die Bevölkerung in Deutschland sollen über die schwerwiegenden Folgen des Alkoholkonsums während der Schwangerschaft aufgeklärt werden. Langfristig soll die Prävalenz von Alkoholkonsum in der Schwangerschaft und die Inzidenz von FASD in Deutschland reduziert werden.

2010 initiierte das Bundesministerium für Gesundheit (BMG) ein Projekt (STOP-FAS) zur Erstellung einer diagnostischen Leitlinie des FAS für Deutschland, das von der Deutschen Gesellschaft für Kinder- und Jugendmedizin angenommen und dessen Federführung der Gesellschaft für Neuropädiatrie übertragen wurde. Im Rahmen dieses ersten Schritts wurde 2012 eine Leitlinie nur für das FAS erstellt. Als zweiter Schritt wurde ein Folgeprojekt für die Ergänzung der S3-Leitlinie um einen Expertenkonsensus für die Diagnostik der anderen FASD (pFAS, ARND und ARBD) vom BMG unterstützt. Die Veröffentlichung dieser erweiterten Leitlinie fand 2016 statt. Das im Rahmen eines Innovationsfonds vom G-BA unterstützte dritte Projekt beinhaltet einerseits eine Aktualisierung im Bereich der diagnostische Kriterien für FASD unter Einbezug neu erschienener Publikationen und andererseits erstmalig evidenz- und konsensbasierte Empfehlungen bezüglich Interventionen für Kindern und Jugendlichen mit FASD (0 bis 18 Jahre).

Diese Projekte wurden von Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf und Prof. Dr. med. Florian Heinen im Dr. von Haunerschen Kinderspital der Ludwig-Maximilians-Universität München (Abteilung für Pädiatrische Neurologie, Entwicklungsneurologie und Sozialpädiatrie (integriertes Sozialpädiatrisches Zentrum, iSPZ Hauner)) geleitet.

Die Leitlinie beschränkt sich aktuell auf Empfehlungen für Kinder und Jugendliche. Um alle Betroffenen abzudecken, ist eine Erweiterung auf Erwachsene mit FASD als nächster Schritt notwendig.

1.2.2 Zielorientierung der Leitlinie

Die vorliegende S3-Leitlinie definiert standardisierte und transdisziplinäre diagnostische Kriterien für FASD bei Kindern und Jugendlichen. Um diese Kriterien effektiv anwenden zu können, beinhaltet diese Leitlinie praxisnahe Empfehlungen, Diagnostik-Algorithmen sowie einen übersichtlichen Pocket Guide als Kurzzusammenfassung der Diagnosekriterien.

Zusätzlich gibt die Leitlinie evidenzbasierte Empfehlungen für Interventionsmöglichkeiten bei Kindern und Jugendlichen mit FASD. Angesichts der Vielzahl an Symptomen und ihren unterschiedlichen Ausprägungen, sollten Interventionen an die Stärken und Schwächen der erkrankten Kinder und Jugendlichen individuell angepasst werden. Die Wahl der Behandlung sollte dabei vom gewünschten, vorher festgelegten Interventionsziel ausgehen. Um dieses Vorgehen zu erleichtern, ist diese Leitlinie Outcome-orientiert aufgebaut.

1.2.3 Patientenzielgruppe

Die Patientenzielgruppe dieser Leitlinie umfasst sowohl Kinder/Jugendliche mit Verdacht auf eine FASD als auch Kinder/Jugendliche, die bereits mit einer FASD diagnostiziert wurden.

1.2.4 Anwenderzielgruppe/Adressaten

Die Anwenderzielgruppe der Leitlinie beinhaltet personell und strukturell:

- Niedergelassene sowie ambulant oder in der Klinik tätige Ärztinnen und Ärzte der folgenden Gebiete und Schwerpunkte: Gynäkologie und Geburtshilfe, Kinder- und Jugendmedizin, Neonatologie, Neuropädiatrie, Entwicklungsneurologie und Sozialpädiatrie, Kinder- und Jugendpsychiatrie, Psychotherapie und Psychosomatik,

Suchtmedizin und des öffentlichen Gesundheitsdienstes einschließlich des Schulärztlichen Dienstes.
- Niedergelassene und in der Klinik tätige Kinder- und Jugendlichen-Psychotherapeut*innen sowie Diplom- und Master-Psycholog*innen
- Hebammen
- Sozialpädagog*innen, Sozialarbeiter*innen, Sozialhelfer*innen
- Sozialpädiatrische Zentren
- FASD-Spezialambulanzen und FASD-Spezialist*innen

Ebenfalls zur Information von:

- Physio-, Ergo- und Sprachtherapeut*innen
- Niedergelassene sowie ambulant oder in der Klinik tätige Ärztinnen und Ärzte der Allgemeinmedizin

1.3 Zusammensetzung der Leitliniengruppe: Beteiligung von Interessensgruppen

1.3.1 Erste beiden Teile des Leitlinienprojektes (2011 und 2015/2016)

Die Organisation des ersten Teils der Leitlinienentwicklung, beschränkt auf das Vollbild FAS, übernahmen:

- Dr. med. Dipl.-Psych. Mirjam N. Landgraf (Leitlinienkoordination, Literaturrecherche, Moderation und Leitlinien-Sekretariat)
- Prof. Dr. med. Florian Heinen (Leitlinienkoordination und Moderation)
- Dr. med. Monika Nothacker, MPH (Literaturrecherche und Evidenzbewertung)
- Prof. Dr. med. Ina Kopp (Methodische Führung und Moderation)
- Dr. Sandra Dybowski (Organisatorische Unterstützung und Ansprechpartnerin im BMG)
- Dr. Tilmann Holzer (Ansprechpartner in der Geschäftsstelle der Drogenbeauftragten)

Die Konsensusgruppe der vorliegenden Leitlinie besteht aus Mandatsträger*innen der sich mit dem Krankheitsbild FASD auseinandersetzenden deutschen Fachgesellschaften und Berufsverbänden sowie aus Expert*innen und Patientenvertreterinnen (siehe Abbildung 1). Die Mandatsträger*innen repräsentieren die jeweilige Fachgesellschaft in mündlichen und schriftlichen Beratschlagungen und Beschlüssen hinsichtlich des Leitlinienprojektes.

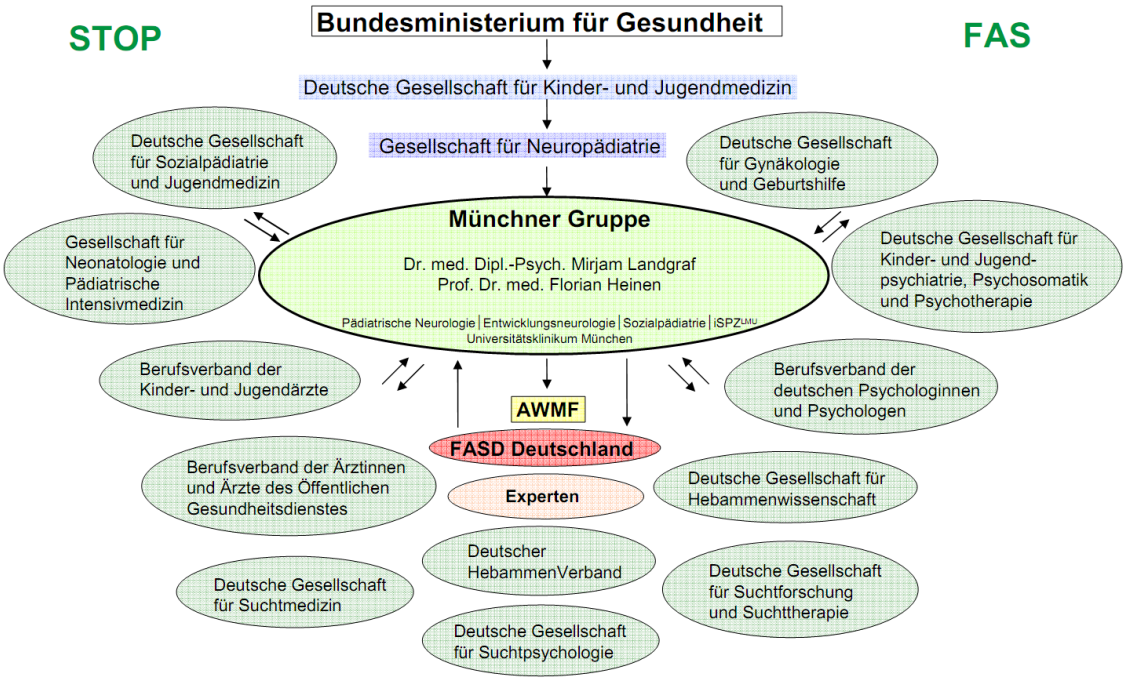


Abbildung 1: Schaubild über die Teilnehmer*innen an den ersten beiden Teilen des Leitlinienprojektes (2011 und 2015/2016).

Die Organisation des zweiten Teils des Leitlinienprojektes FASD (Ergänzung der S3-Leitlinie um die Diagnose pFAS, ARND, ARBD) übernahmen:

- Dr. med. Dipl.-Psych. Mirjam N. Landgraf (Leitlinienkoordination und –verfassung, systematische Literaturrecherche, Moderation und Leitlinien-Sekretariat)
- Prof. Dr. med. Florian Heinen (Leitlinienkoordination und Moderation)
- Prof. Dr. med. Ina Kopp (Methodische Führung und Moderation)
- Albert Kern (Organisatorische Unterstützung und Ansprechpartner im BMG)
- Dr. Kirsten Reinhard (Ansprechpartnerin in der Geschäftsstelle der Drogenbeauftragten)

An der Ergänzung der Leitlinie waren die gleichen Fachgesellschaften und Berufsverbände beteiligt, die Ihre Mandatsträger*innen durch den Vorstand bestätigten bzw. neu ernannten, sowie nationale FASD-Expert*innen.

1.3.1.1 Repräsentativität der Leitliniengruppe: Beteiligte Berufsgruppen

In den folgenden Tabellen werden alle Personen aufgeführt, die an den ersten beiden Teilen des Leitlinienprojektes FASD beteiligt waren, inklusive ihrer zugehörigen Fachgesellschaft/Organisation.

Erster Teil des Leitlinienprojektes (2011)

Tabelle 1: Am ersten Teil des Leitlinienprojektes FASD (beschränkt auf FAS) beteiligte Mandatstragende und Fachgesellschaften/Organisationen (2011).

Mandatstragende	Fachgesellschaft/Organisation
Prof. Dr. med. Florian Heinen	Deutsche Gesellschaft für Kinder- und Jugendmedizin
PD Dr. med. Dipl.-Psych. Mirjam N. Landgraf	Gesellschaft für Neuropädiatrie
Dr. med. Juliane Spiegler	Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin
Prof. Dr. med. Franz Kainer	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
Prof. Dr. med. Rolf F. Maier	Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin
Prof. Dr. med. Frank Häßler	Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie
Dr. med. Regina Rasenack	Deutsche Gesellschaft für Suchtforschung und Suchttherapie
Prof. Dr. Dipl.-Psych. Tanja Hoff	Deutsche Gesellschaft für Suchtpsychologie
PD Dr. med. Gerhard Reymann	Deutsche Gesellschaft für Suchtmedizin
Prof. Dr. rer. medic. Rainhild Schäfers	Deutsche Gesellschaft für Hebammenwissenschaft
Lisa Fehrenbach → ab 01.01.2012 Regine Gresens	Deutscher Hebammenverband
Dipl.-Psych. Laszlo A. Pota	Berufsverband der deutschen Psychologinnen und Psychologen
Dr. Dr. med. Nikolaus Weissenrieder	Berufsverband der Kinder- und Jugendärzte
Dr. med. Gabriele Trost-Brinkhues	Bundesverband der Ärztinnen und Ärzte des Öffentlichen Gesundheitsdienstes

Tabelle 2: Am ersten Teil des Leitlinienprojektes FASD (beschränkt auf FAS) beteiligte Expert*innen (2011).

Expert*innen	Funktion
Dipl.-Psych. Gela Becker	Fachliche Leiterin Evangelisches Kinderheim Sonnenhof
Dr. med. Beate Erbas	Bayerische Akademie für Sucht- und Gesundheitsfragen
Dr. rer.med. Reinhold Feldmann, Dipl.-Psych.	Klinik für Kinder- und Jugendmedizin) (Allgemeine Pädiatrie des Universitätsklinikums Münster und FASD-Ambulanz Walstedde
PD Dr. med. Anne Hilgendorff	Neonatologie und Neuropädiatrie, Universität München (LMU)
Dr. med. Heike Hoff-Emden	Chefärztin KMG Rehabilitationszentrum Sülzhayn
Dr. med. Ulrike Horacek	Vorstandsmitglied der DGSPJ, Gesundheitsamt Recklinghausen
Prof. Dr. med. Ina Kopp	Leiterin AWMF-IMWi (nicht stimmberechtigt)
Dr. med. Dipl.-Psych. Mirjam N. Landgraf	Abteilung für Neuropädiatrie, FASD-Ambulanz, iSPZ, Dr. von Haunersches Kinderspital, Universität München (LMU)
Dr. med. Monika Nothacker	ÄZQ (nicht stimmberechtigt)
Carla Pertl	Stadtjugendamt München
Dr. Eva Rehfueß	IBE, Universität München (LMU))
Dr. med. Monika Reincke	Referat für Gesundheit und Umwelt der Landeshauptstadt München, Gesundheitsvorsorge für Kinder und Jugendliche
Andreas Rösslein	Neonatologie, Universität München (LMU)
Gila Schindler	Rechtsanwältin für Kinder- und Jugendhilferecht
Prof. Dr. med. Andreas Schulze	Leiter der Neonatologie, Universität München (LMU)
Dr. med. Martin Sobanski	Kinder- und Jugendpsychiatrie, FASD-Ambulanz, Heckscher Klinikum, München
Prof. Dr. med. Hans-Ludwig Spohr	FASD-Zentrum, Charité Berlin
Dipl.-Psych. Penelope Thomas	Kinder- und Jugendpsychiatrie, FASD-Ambulanz, Heckscher Klinikum, München
Dipl.-Psych. Jessica Wagner	FASD-Zentrum, Charité Berlin

Zweiter Teil des Leitlinienprojektes (2015/2016)

Tabelle 3: Am zweiten Teil des Leitlinienprojektes FASD (Ergänzung um pFAS, ARND und ARBD) beteiligte Mandatstragende und Fachgesellschaften/Organisationen (2015/2016).

Mandatstragende	Fachgesellschaft/Organisation
Prof. Dr. med. Florian Heinen	Deutsche Gesellschaft für Kinder- und Jugendmedizin
PD Dr. med. Dipl.-Psych. Mirjam N. Landgraf	Gesellschaft für Neuropädiatrie
Dr. med. Juliane Spiegler	Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin
Prof. Dr. med. Tamme Goecke	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
Prof. Dr. med. Rolf F. Maier	Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin
Prof. Dr. med. Frank Häßler	Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie
Dr. med. Anette Stiegler	Deutsche Gesellschaft für Suchtforschung und Suchttherapie
Prof. Dr. Dipl.-Psych. Tanja Hoff	Deutsche Gesellschaft für Suchtpsychologie
PD Dr. med. Gerhard Reymann	Deutsche Gesellschaft für Suchtmedizin
Prof. Dr. rer. medic. Rainhild Schäfers	Deutsche Gesellschaft für Hebammenwissenschaft
Jule Friedrich	Deutscher Hebammenverband
Dipl.-Psych. Laszlo A. Pota	Berufsverband der deutschen Psychologinnen und Psychologen
Dr. Dr. med. Nikolaus Weissenrieder → ab 08.01.2016: Dr. med. Matthias Brockstedt	Berufsverband der Kinder- und Jugendärzte
Dr. med. Gabriele Trost-Brinkhues	Bundesverband der Ärztinnen und Ärzte des Öffentlichen Gesundheitsdienstes

Tabelle 4: Am zweiten Teil des Leitlinienprojektes FASD (Ergänzung um pFAS, ARND und ARBD) beteiligte Expert*innen (2015/2016).

Expert*innen	Funktion
Dipl.-Psych. Gela Becker	Fachliche Leiterin Evangelischer Verein Sonnenhof e. V. – FASD-Fachzentrum, Berlin
Dr. med. Antje Erencin	Elisabeth Krankenhaus, SPZ Essen
Dr. rer.med. Reinhold Feldmann, Dipl.-Psych.	Klinik für Kinder- und Jugendmedizin) (Allgemeine Pädiatrie des Universitätsklinikums Münster und FASD-Ambulanz Walstedde
Dr. med. Heike Hoff-Emden	Leitende Ärztin SPZ Leipzig, FHLE e. V.
Prof. Dr. med. Ina Kopp	Leiterin AWMF-IMWi (nicht stimmberechtigt)
Dr. med. Dipl.-Psych. Mirjam N. Landgraf	Leiterin der Ambulanz für Toxinexposition in der Schwangerschaft, iSPZ Hauner, Dr. von Haunersches Kinderspital, Klinikum der Universität München (LMU)
Gila Schindler	Rechtsanwältin für Kinder- und Jugendhilferecht
Dr. med. Martin Sobanski	Leiter der Abteilung für Entwicklungsstörungen, kbo-Heckscher Klinikum für Kinder- und Jugendpsychiatrie, München
Dipl.-Psych. Jessica Wagner	Evangelisches Krankenhaus Königin Elisabeth Herzberge, Berlin-Lichtenberg und Universität Flensburg
Heike Wolter	FASD-Zentrum, Charité Berlin

1.3.1.2 Repräsentativität der Leitliniengruppe: Beteiligte Patientengruppen

In Deutschland existiert eine bundesweite Patientenvertretung und Selbsthilfegruppe FASD Deutschland e. V.. Diese wurde einbezogen und befand sich seit Beginn der Leitlinienentwicklung in regem Austausch mit den Leitlinienkoordinator*innen.

Tabelle 5: An den ersten beiden Teilen des Leitlinienprojektes beteiligte Patientenvertreterinnen (2011 und 2015/2016).

Teilnehmende	Funktion
Dipl.-Soz.-Päd. Gisela Michalowski	Vorsitzende von FASD Deutschland e. V.
Veerle Moubax	Vorstand von FASD Deutschland e. V.
Dr. med. Wendelina Wendenburg	Vorstand von FASD Deutschland e. V.

1.3.2 Dritter Teil des Leitlinienprojektes (2022/2023)

Die Koordination der aktuell vorliegenden Leitlinie zu Diagnostik und Intervention bei Kindern und Jugendlichen mit FASD übernahmen:

- Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf (Leitlinienkoordination, Formulierung von Schlüsselfragen und Outcomes, klinischer Input für die methodische Aufarbeitung der Diagnostik, Vorbereitung der Leitlinienkonferenzen und Präsentation, Empfehlungsformulierung, Leitlinien-Sekretariat und Leitlinienautorin)
- Prof. Dr. med. Florian Heinen (Leitlinienkoordination)
- Sonja Strieker, M.Sc. (Leitlinienkoordination, Evaluation der bisherigen Leitlinie und Präsentation der Ergebnisse und Schlussfolgerungen, Formulierung von Schlüsselfragen und Outcomes, Literaturrecherche und Evidenzbewertung – Intervention, Interessenkonfliktbeauftragte, Vorbereitung der Leitlinienkonferenzen und Präsentation, Leitliniensekretariat)
- PD Dr. sc. hum. Christine Schmucker (Leitlinienkoordination, Literaturrecherche und Evidenzbewertung – Diagnostik)
- Annika Ziegler (Leitlinienkoordination, Literaturrecherche und Evidenzbewertung – Diagnostik)
- Prof. Dr. med. Ina Kopp (methodische Beratung der Leitlinienkoordinator*innen und Moderation der Leitlinienkonferenzen)

Die systematische Literaturrecherche und Evidenzbewertung im Bereich Diagnostik wurde im Institut für Evidenz in der Medizin (IFEM) am Universitätsklinikum Freiburg durchgeführt. Die daraus resultierenden zu konsentierenden Handlungsempfehlungen wurden anschließend in Kooperation mit den Münchner Leitlinienkoordinatorinnen formuliert.

Die systematische Literaturrecherche und Evidenzbewertung im Bereich Intervention wurde durch Leitlinienkoordinatorinnen der LMU München durchgeführt und entsprechende Empfehlungen zur Konsentierung formuliert.

Die Leitliniengruppe wurde von den Koordinator*innen einberufen. Gemäß den AWMF-Vorgaben wurde sie multidisziplinär und für den Adressatenkreis repräsentativ zusammengesetzt. Die Vorstände der Fachgesellschaften und Berufsverbände nominierten Mandatsträger*innen zur inhaltlichen Arbeit an der Leitlinie und bestätigten deren Stimmrecht für die Konsentierung der Leitlinieninhalte (Mandat).

Die Leitliniengruppe beinhaltete zusätzlich zu den Mandatsträger*innen der sich mit dem Krankheitsbild FASD auseinandersetzenden deutschen Fachgesellschaften und

Berufsverbänden auch FASD-Expert*innen und Patientenvertreter*innen (siehe nachfolgende Abbildung 2 und Tabelle 6).

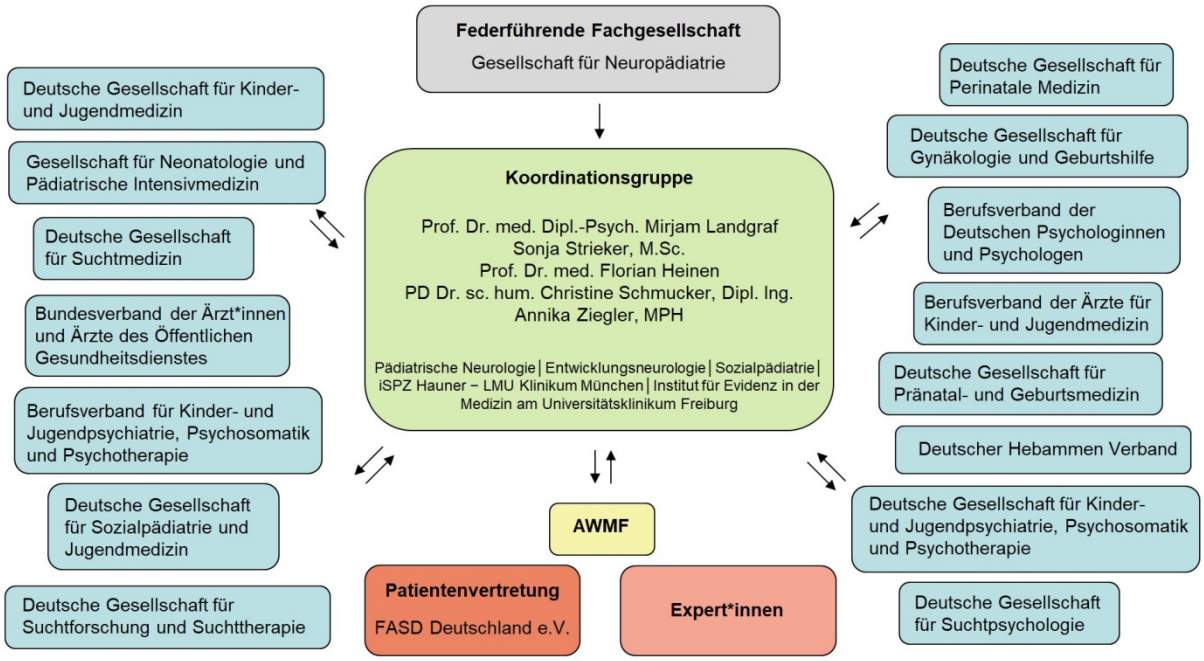


Abbildung 2: Schaubild über die Teilnehmer*innen am dritten Teil des Leitlinienprojektes (2022/2023).

Tabelle 6: Koordinationsgruppe des dritten Teils des Leitlinienprojektes (2022/2023).

Leitlinienkoordinator*innen/-sekretariat	Fachgesellschaft/Organisation
Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf	FASD-Expertin, Gesellschaft für Neuropädiatrie (GNP), LMU Klinikum München
Sonja Strieker, M.Sc.	iSPZ Hauner, Dr. von Haunersches Kinderspital, LMU Klinikum München
Veronika Raum	iSPZ Hauner, Dr. von Haunersches Kinderspital, LMU Klinikum München
Iris Zillinger	iSPZ Hauner, Dr. von Haunersches Kinderspital, LMU Klinikum München
Prof. Dr. med. Prof. h.c. Florian Heinen	Gesellschaft für Neuropädiatrie (GNP), Deutsche Gesellschaft für Kinder- und Jugendmedizin e. V. (DGKJ), LMU Klinikum München
PD Dr. sc. hum. Christine Schmucker, Dipl. Ing.	Institut für Evidenz in der Medizin am Universitätsklinikum Freiburg
Annika Ziegler, MPH	Institut für Evidenz in der Medizin am Universitätsklinikum Freiburg

1.3.2.1 Repräsentativität der Leitliniengruppe: Beteiligte Berufsgruppen

In den folgenden Tabellen werden alle Personen aufgeführt, die am dritten Teil des Leitlinienprojektes FASD beteiligt waren, inklusive ihrer zugehörigen Fachgesellschaft/Organisation.

Tabelle 7: Am dritten Teil des Leitlinienprojektes FASD (Aktualisierung der Leitlinie Diagnostik FASD und Ergänzung um Interventionen bei FASD) beteiligte Mandatstragende und Fachgesellschaften/Organisationen (2022/2023).

Mandatstragende	Fachgesellschaft/Organisation
Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf	Gesellschaft für Neuropädiatrie (GNP)
Prof. Dr. med. Prof. h.c. Florian Heinen	Deutsche Gesellschaft für Kinder- und Jugendmedizin e. V. (DGKJ)
Prof. Dr. med. Juliane Spiegler	Deutsche Gesellschaft für Sozialpädiatrie und Jugendmedizin e. V. (DGSPJ)
Prof. Dr. med. Rolf Maier	Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin e. V. (GNPI)
Prof. Dr. med. Silvia Lobmaier	Deutsche Gesellschaft für Perinatale Medizin (DGPM)
Prof. Dr. med. Christine Freitag Stellvertr.: Prof. Dr. med. Frank Häßler	Deutsche Gesellschaft für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie e. V. (DGKJP)
PD. Dr. med. Dietmar Schlembach	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe e. V. (DGGG) Deutsche Gesellschaft für Pränatal- und Geburtsmedizin e.V. (DGPGM)
Prof. Dr. med. Bernd Lenz	Deutsche Gesellschaft für Suchtforschung und Suchttherapie e. V. (DG-Sucht)
Prof. Dr. med. Ulrich Preuß Stellvertr.: Prof. Dr. med. Markus Backmund	Deutsche Gesellschaft für Suchtmedizin e. V. (DGS)
Prof. Dr. Phil. Dipl.-Psych. Tanja Hoff	Deutsche Gesellschaft für Suchtpsychologie e. V. (dg sps)
Andrea Ramsell	Deutscher Hebammenverband (DHV)
Dr. med. Matthias Brockstedt	Berufsverband der Ärzte für Kinder- und Jugendmedizin e. V. (bvkj e. V.)
Dr. med. Annegret Brauer	Berufsverband für Kinder- und Jugendpsychiatrie, Psychosomatik und

	Psychotherapie (bkjpp)
Dr. med. Gabriele Trost-Brinkhues	Bundesverband der Ärztinnen und Ärzte des Öffentlichen Gesundheitsdienstes e. V. (BVÖGD)
Dipl.-Psych. Ralph Schliewenz Stellvertr.: Dr. rer. nat. Johanna Thünker	Berufsverband Deutscher Psychologinnen und Psychologen (BDP)

Tabelle 8: Am dritten Teil des Leitlinienprojektes FASD (Aktualisierung der Leitlinie Diagnostik FASD und Ergänzung um Interventionen bei FASD) beteiligte Berater*innen, Expert*innen und Beobachter*innen (2022/2023).

Teilnehmende	Funktion
Prof. Dr. med. Ina Kopp	AWMF-Beratung
Prof. Dr. med. Hans-Ludwig Spohr	Experte
Heike Wolter	Expertin
Dipl.-Psych. Gela Becker Stellvertr.: Lina Schwerg MSc	Expertin
Dr. med. Heike Hoff-Emden	Expertin
Dr. Dipl.-Psych. Reinhold Feldmann	Experte
Dr. med. Dorothee Veer	Expertin
Dr. med. Kristina Kölzsch	Expertin
Dipl.-Psych. Jessica Wagner & Dr. med. Björn Kruse	Expert*in
Gila Schindler	Expertin
Dr. med. Anna Hutzelmeyer-Nickels	Expertin
Manuela Schumann	Beobachterin BMG
Dr. Kirsten Reinhard	Beobachterin BMG

1.3.3 Repräsentativität der Leitliniengruppe: Beteiligte Patientengruppen

FASD Deutschland e. V. wurde einbezogen und befand sich auch im dritten Teil des Leitlinienprojektes in regem Austausch mit den Leitlinienkoordinator*innen.

Tabelle 9: Am dritten Teil des Leitlinienprojektes beteiligte Patientenvertreterinnen (2022/2023).

Teilnehmende	Funktion
Dipl.-Soz.-Päd. Gisela Michalowski Stellvertr: Katrin Lepke	Patientenvertretung FASD Deutschland e. V.
Sandra Kramme	Patientenvertretung FASD Deutschland e. V.

2 Methodik

2.1 Erster und zweiter Teil des Leitlinienprojektes (2011 und 2015/2016)

2.1.1 Fokussierte Literaturrecherche

Eine fokussierte Literaturrecherche wurde 2011 zu folgenden Teilbereichen durchgeführt:

1. Epidemiologie: Prävalenz von mütterlichem Alkoholkonsum in der Schwangerschaft und Prävalenz des FAS: Peer Voss und Dr. Eva Rehfueß, Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, LMU München
2. Risikofaktoren für mütterlichen Alkoholkonsum während der Schwangerschaft: Dr. med. Dipl.-Psych. Mirjam N. Landgraf, Leitlinienkoordinatorin, Abteilung für Pädiatrische Neurologie, Entwicklungsneurologie und Sozialpädiatrie, LMU München
3. Risikofaktoren für die Entwicklung eines FAS: PD Dr. med. Anne Hilgendorff, Abteilung für Pädiatrische Neurologie, Entwicklungsneurologie und Sozialpädiatrie sowie Abteilung für Neonatologie, LMU München

In allen drei Teilbereichen fand eine Vor-Recherche durch das Ärztliche Zentrum für Qualität in der Medizin (ÄZQ) mit Auswahl der Abstracts anhand von Suchkriterien und Ausschlusskriterien statt (siehe Anhang A. 1).

Die fokussierte Literatursuche musste aus Kapazitätsgründen auf einige Länder begrenzt werden. Aufgrund der ähnlichen gesellschaftlichen und kulturellen Zusammensetzung wurde die Literaturrecherche auf die Länder Europas sowie USA und Kanada beschränkt.

Die Suche umfasste den Zeitraum vom 01. Januar 2001 bis zum 12. Oktober 2011 und Dokumente in deutscher und englischer Sprache.

Die Suche wurde in folgenden Recherchequellen durchgeführt:

- Literaturdatenbank Medline über http://www.pubmed.org
- The Cochrane Library (Datenbank systematischer Reviews) über http://www.thecochranelibrary.com

Die gemäß den Suchkriterien gefundenen Abstracts wurden den zuständigen Mitarbeiter*innen geschickt, die alle Abstracts sichteten. Dabei wurden anhand der vorher definierten Ausschlusskriterien weitere Publikationen durch Sichtung der Abstracts ausgeschlossen oder an die Bearbeiter*innen anderer Teilbereiche weitergeleitet.

Die relevanten Publikationen wurden durchgearbeitet, zusammengefasst und deren Ergebnisse zu finalen Aussagen zusammengeführt.

2.1.2 Diagnostik

2.1.2.1 Formulierung von Schlüsselfragen, Outcome-Kriterien und Confoundern der Literaturrecherche

Die Schlüsselfrage wurde in der 1. Konsensuskonferenz am 14.09.2011 im Bundesministerium für Gesundheit in Bonn folgendermaßen konsentiert:

Welche Kriterien ermöglichen entwicklungsbezogen die Diagnose eines Fetalen Alkoholsyndroms (FAS) im Kindes- und Jugendalter (0 bis 18 Jahre)?

Ergänzung einer Schlüsselfrage zu pFAS, ARND und ARBD 2015/2016

Die Schlüsselfrage für die Ergänzung der Leitlinie um die FASD (außer FAS) wurde in der Konsensuskonferenz am 25.01.2016 folgendermaßen konsentiert:

Welche Kriterien ermöglichen entwicklungsbezogen die Diagnose eines partiellen Fetalen Alkoholsyndroms (pFAS), einer alkoholbedingten entwicklungsneurologischen Störung (ARND) und alkoholbedingter angeborener Malformationen (ARBD) aus dem Formenkreis der Fetalen Alkoholspektrumstörungen (FASD) im Kindes- und Jugendalter (0 bis 18 Jahre)?

Als weitere wichtige Frage an die Literaturrecherche wurde konsentiert:

Ist die Diagnose eines FAS oder einer anderen FASD beim Kind oder Jugendlichen mit positiven Outcome-Kriterien assoziiert?

Als Outcome-Kriterien sowohl für das FAS als auch für die anderen FASD wurden konsentiert:

1. Konzeptualisierung der Betreuungsaufgabe durch die richtige Diagnose zum frühestmöglichen Zeitpunkt
2. Vermeidung von Fehlbehandlung
3. Verbesserung des Funktionsniveaus/der Teilhabe
4. Reduktion von:
    - psychiatrischen Erkrankungen
    - Schulversagen und -abbruch (bzw. höhere Rate an Schulabschlüssen und Berufsausbildungen)
    - Delinquenz
    - Misshandlung
    - Krankenhaus- oder sonstigen stationären Aufenthalten
5. Entlastung der Eltern (biologische, Pflege- und Adoptiv-Eltern) und Verbesserung der Lebensqualität der gesamten betroffenen Familie
6. Verbesserung der sozialen Kompetenz, Ausbau des Freundeskreises, Stabilisierung des Umfeldes
7. Stärkung der Rolle der Väter als hilfreiche Unterstützer einer alkoholfreien Schwangerschaft
8. Reduktion von mütterlichem Alkoholkonsum in den Folge-Schwangerschaften
9. Aufklärung der Gesellschaft über die lebenslangen negativen Folgen von intrauteriner Alkoholexposition
10. Langfristig Reduktion der Inzidenz von FAS durch Aufklärung

Als Störfaktoren in der Literaturbewertung zum FAS wurden konsentiert:

- Fraglich unterschiedliche Normwerte der Fazialen Auffälligkeiten in den verschiedenen Altersgruppen
- Intelligenz

Ergänzung der Störfaktoren zu pFAS, ARND und ARBD 2015/2016
Als Störfaktoren für die Ergänzung der Leitlinie um pFAS, ARND und ARBD wurden *zusätzlich* bestimmt und konsentiert:

- Bias soziale Erwünschtheit in Richtung Verneinung von pränataler Alkoholexposition
- Recall Bias
- Incorporation Bias
- Patienten wurden mit unterschiedlichen diagnostischen Kriterien klassifiziert (IOM, Canadian, 4-Digit, Majewski Skala, Dysmorphologie-Beurteilung, Interviews mütterlicher Alkoholkonsum)
- Studien beinhalten häufig keine Unterscheidung der verschiedenen FASD
- Häufig pränatale Alkoholexposition (PAE) zusammen mit FASD oder sogar alleiniges Kriterium zur Patientenklassifikation

2.1.2.2 Verwendung existierender Leitlinien zum Thema

Am 11. Dezember 2011 wurde eine Leitlinienrecherche in Pubmed, Leitliniendatenbanken und bei bekannten Leitlinienanbietern durchgeführt.

Als Recherchevokabular wurden folgende Begriffe verwendet:

- fetal alcohol syndrome; fetal alcohol related deficit; fetal alcohol spectrum disorders; FASD; alcohol embryopathy; fetal alcohol effects
- guideline; practice guideline; clinical guideline; consensus development conference

Die Suche wurde in folgenden Recherchequellen durchgeführt:

- Literaturdatenbank Medline über http://www.pubmed.org
- Leitlinien-Datenbanken:
    - Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF) (D) (http://www.leitlinien.net),
    - Guidelines International Network (GIN) (International) (http://www.g-i-n.net)
    - National Guideline Clearinghouse (NGC) (USA) (http://www.guidelines.gov)
    - NHS Evidence (GB) (http://www.evidence.nhs.uk/)

Leitlinien-Seiten einzelner fachübergreifender und fachspezifischer Anbieterorganisationen:

- Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) (D) (http://www.akdae.de),
- National Health and Medical Research Council (NHMRC) (AUS) (http://www.nhmrc.gov.au),
- National Institute for Health and Clinical Excellence (NICE) (GB) (http://www.nice.org.uk/),
- New Zealand Guidelines Group (NZGG) (NZ) (http://www.nzgg.org.nz)
- Scottish Intercollegiate Guidelines Network (SIGN) (GB) (http://www.sign.ac.uk).

Im Rahmen der Recherche wurden folgende Leitlinien zur Diagnostik des Fetalen Alkoholsyndroms identifiziert:

1. Astley, S. 2004. Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. University of Washington Publication Services.
2. Chudley A et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Can Med Assoc J 2005; 172(Suppl): Mar05-S21 sowie deren Aktualisierung 2008, (Goh et al., 2008 [6]).
3. National Centre on Birth Defects and Developmental Disabilities. Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. 2004. Centre for Disease Control.
4. Stratton K et al., 1996. Fetal alcohol syndrome: diagnosis, epidemiology, prevention, and treatment. Washington: Institute of Medicine and National Academy Press.
5. Hoyme HE et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 Institute of Medicine Criteria. Paediatrics 2005; 115(39):47.

Die Leitlinien wurden nicht extrahiert, der Fokus lag auf Primärevidenz. Die Ergebnisse wurden an die Leitliniengruppe weitergegeben.

Ergänzung von Leitlinien zur Diagnose der FASD 2015/2016

Bei der Ergänzung der Leitlinie um die Diagnose der FASD wurde eine weitere Leitlinie gefunden: Watkins et al. Recommendations from a consensus development workshop on the diagnosis of fetal alcohol spectrum disorders in Australia. BMC Pediatrics 2013, 13:156. Diese trug jedoch aufgrund der mangelnden Methodik und des Fehlens neuer Evidenz nicht zur Leitlinienergänzung der deutschen S3-Leitlinie bei.

2.1.2.3 Systematische Literaturrecherche

Die Aspekte zu FASD wurden 2015/2016 ergänzt und in die folgenden Informationen integriert.

Die diagnostischen Kriterien für die FASD wurden durch die Leitliniengruppe wie folgt in vier diagnostische Säulen unterteilt:

1. Wachstumsauffälligkeiten
2. Faziale Auffälligkeiten
3. ZNS-Auffälligkeiten: funktionell und strukturell
4. Alkoholkonsum der Mutter während der Schwangerschaft

Zu den vier Diagnose-Säulen wurden, sowohl im 1. Schritt für die Diagnose des FAS, als auch im 2. Schritt für die Diagnose der anderen FASD, folgende Fragen an die systematische Literaturrecherche gestellt und konsentiert:

1. **Prä- und/oder postnatale Wachstumsstörung**

   Welche Art der Wachstumsstörung im Hinblick auf Gewichts-, Längen- und Kopfumfangsmaße im Alter von 0 bis 18 Jahren ist mit der Diagnose FASD assoziiert?

2. **Faziale Auffälligkeiten**

   Welche Fazialen Auffälligkeiten oder Kombinationen davon treten bei den FASD im Alter von 0 bis 18 Jahren auf (basierend auf vorliegenden internationalen Leitlinien: 1. kurze Lidachsen, 2. schmales Oberlippenrot, 3. verstrichenes Philtrum)?

3. **Anomalien des ZNS**

   Welche cerebralen Störungen (funktionell und/oder strukturell) sind im Alter zwischen 0 und 18 Jahren mit der Diagnose FASD assoziiert und welche Teilbereiche funktioneller Störungen sind bei Kindern mit FASD typischerweise betroffen?

4. **Intrauterine Alkohol-Exposition**

   Welche Gewichtung hat die Bestätigung des mütterlichen Alkoholkonsums in der Schwangerschaft für die Diagnose einer FASD bei Kindern und Jugendlichen (0-18 Jahre)?

Systematische Literaturrecherche zum FAS 2011

Für die Sichtung der Abstracts im Rahmen der systematischen Literaturrecherche wurden prospektiv Ein- und Ausschlusskriterien festgelegt (siehe Anhang A. 2). Bezüglich der einzuschließenden Studientypen wurde zunächst nach randomisierten kontrollierten Studien und systematischen Übersichtsarbeiten gesucht. Da vermutet wurde, dass zum

Themenkomplex Diagnostik des FAS wenig randomisierte Studien existieren, wurde die Suche im zweiten Schritt bezüglich des Einschlusskriteriums Studienmethodik erweitert.

Folgende Datenbanken wurden für die systematische Suche genutzt:

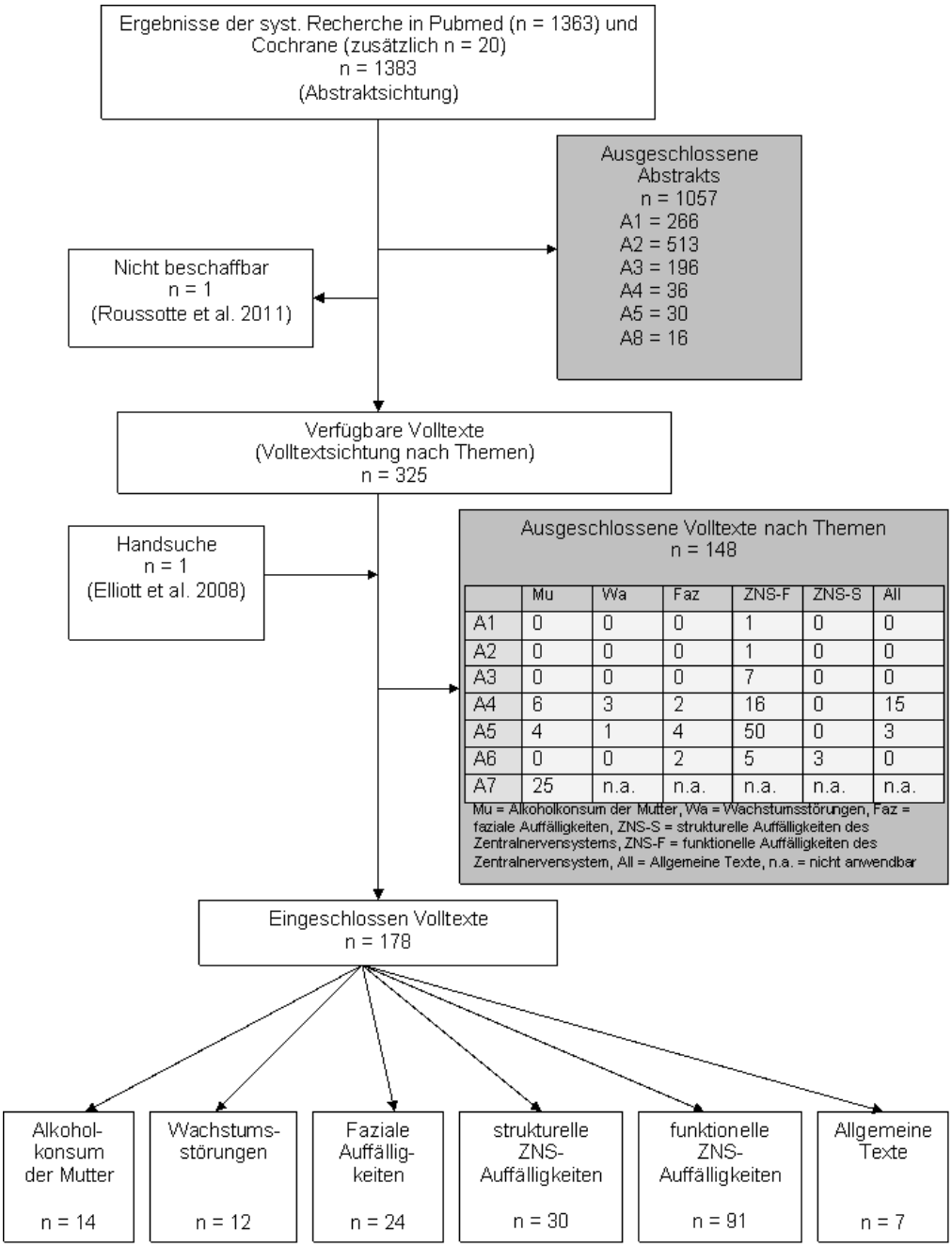
- PubMed (Internetportal der National Library of Medicine) (http://www.pubmed.org)
- Datenbanken der Cochrane Library (http://www.thecochranelibrary.com)

Nach Rücksprache mit der Leitlinienkoordinatorin Frau Dr. med. Mirjam N. Landgraf bezüglich der Suchstrategie wurde vom ÄZQ die erste Recherche zur Diagnostik vom 10.10.2011 am 31.10.2011 mit angepassten Suchbegriffen wiederholt.

Die Recherchestrategie mit den angepassten Suchbegriffen und die Ergebnisse der Recherchen sind dem Anhang A. 2 zu entnehmen.

Die Recherche umfasste den Zeitraum von 01.01.2001 bis 31.10.2011.
Es gab im Verlauf der Berichterstellung ein besonderes Interesse der Leitliniengruppe an Publikationen vor dem genannten Recherchezeitraum zu Fazialen Kriterien. Zur Identifizierung dieser Publikationen wurde in Absprache mit den Leitlinienkoordinator*innen in den Referenzen der identifizierten Publikationen sowie in Pubmed-Referenzen gesucht.

Die systematische Recherche in Pubmed ergab insgesamt 1363 Treffer. Die Suche in den Datenbanken der Cochrane Library ergab 20 Treffer. Nach Sichtung von Titel und Abstract der identifizierten Publikationen wurden insgesamt 326 Publikationen eingeschlossen und zur Volltextsichtung bestellt. Die Volltexte wurden sechs verschiedenen Themenbereichen (allgemeine Texte, Wachstumsauffälligkeiten, Faziale Auffälligkeiten, strukturelle ZNS-Auffälligkeiten, funktionelle ZNS-Auffälligkeiten, Alkoholkonsum der Mutter) zugeordnet und dann nach den festgelegten Ausschlusskriterien (siehe Anhang A. 2) gesichtet. Die Sichtung der Volltexte führte zum Ausschluss von 148 weiteren Publikationen, sodass insgesamt 178 Publikationen zur Evidenzbewertung eingeschlossen wurden. Der Ablauf der Literaturauswahl ist in der folgenden Abbildung 3 zusammenfassend dargestellt.



	Mu	Wa	Faz	ZNS-F	ZNS-S	All
A1	0	0	0	1	0	0
A2	0	0	0	1	0	0
A3	0	0	0	7	0	0
A4	6	3	2	16	0	15
A5	4	1	4	50	0	3
A6	0	0	2	5	3	0
A7	25	n.a.	n.a.	n.a.	n.a.	n.a.

Abbildung 3: Ablauf der systematischen Literaturrecherche zum FAS (2011).

Die vom ÄZQ während der systematischen Literaturrecherche nicht beschaffbare Publikation (siehe Abbildung 3) konnte von den Leitlinienkoordinator*innen nach Abschluss des Evidenzberichtes beschafft werden. Aus der Publikation Roussotte et al. Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: The

effects of methamphetamine, alcohol, and polydrug exposure. NeuroImage 54: 3067–3075 (2011) resultierte keine inhaltliche Änderung der Leitlinie.

Von den Volltextpublikationen wurden im ersten Schritt alle Reviews mit Angabe einer systematischen Suchstrategie extrahiert (n = 10). Zwei dieser Reviews enthielten Angaben zu allen Kriterien des FAS [1, 2] die anderen zu Teilaspekten.

Im Weiteren wurden Einzelstudien zu den Themen Wachstumsstörungen (n = 3), Faziale Auffälligkeiten (n = 5), funktionelle (n = 20) und strukturelle (n = 5) ZNS-Störungen (n = 19) sowie Gewichtung des Alkoholkonsums der Mutter (1) bewertet, an denen die aktuelle Evidenzlage zu dem jeweiligen Thema verdeutlicht werden kann. Es wurden überwiegend Studien berücksichtigt, die nach dem Rechercheschlussdatum der Reviews mit Angabe systematischer Recherchestrategie publiziert wurden.

Im ersten Schritt wurden Studien mit Angabe von Testgüteparametern (z. B. Sensitivität, Spezifität) berücksichtigt (n = 1 zum Kriterium „Wachstumsauffälligkeiten“, n = 4 zum Kriterium „Faziale Auffälligkeiten“, n = 4 zum Kriterium „Funktionelle ZNS-Auffälligkeiten“ und n = 1 zur Gewichtung des Alkoholkonsums der Mutter während der Schwangerschaft). Im zweiten Schritt wurden weitere Studien eingeschlossen, die zusätzliche Aspekte der diagnostischen Kriterien abbildeten, aber nur Korrelationen oder signifikante Unterschiede von FAS-Betroffenen im Vergleich zu Kontrollen auswiesen (n = 2 zu „Wachstumsauffälligkeiten“, n = 5 zu „Faziale Auffälligkeiten“, n = 16 zu „Funktionelle ZNS-Auffälligkeiten“, n = 5 zu „Strukturelle ZNS-Auffälligkeiten“). Zu „Funktionelle ZNS-Auffälligkeiten“ wurden dabei die 2010 und 2011 publizierten Studien bewertet und extrahiert, zu “Faziale Auffälligkeiten“ wurden drei Studien berücksichtigt, die vor 2001 publiziert wurden, um den Prozess der Bestimmung und später auch Messung der für FAS typischen Fazialen Auffälligkeiten zu verdeutlichen. Aus Ressourcengründen konnten nicht alle identifizierten Studien berücksichtigt werden (Literaturliste siehe Anhang A. 5).

Systematische Literaturrecherche zum pFAS, zu den ARND und ARBD 2015/2016

Für die Ergänzung der Leitlinie um pFAS, ARND und ARBD wurde von Frau Dr. med. Dipl.-Psych. Mirjam N. Landgraf eine systematische Literaturrecherche für den Zeitraum vom 01.11.2011 bis 31.06.2015 (anschließend an den Zeitraum für die Literaturrecherche zur Diagnose des FAS) durchgeführt.

Für die Sichtung der Abstracts im Rahmen der systematischen Literaturrecherche wurden prospektiv Ein- und Ausschlusskriterien festgelegt (siehe Anhang A. 6).

Nach Sichtung von Titel und Abstract der identifizierten Publikationen wurden insgesamt 107 Publikationen eingeschlossen und zur Volltextsichtung bestellt. Die Volltexte wurden nach den festgelegten Ausschlusskriterien (siehe Anhang A. 6) gesichtet und in fünf verschiedene Themenbereiche (Wachstumsauffälligkeiten, Faziale Auffälligkeiten, strukturelle ZNS-Auffälligkeiten, funktionelle ZNS-Auffälligkeiten, Alkoholkonsum der Mutter) eingeordnet. Die Sichtung der Volltexte führte zum Ausschluss von 49 weiteren Publikationen, sodass insgesamt 58 Publikationen zur Bewertung eingeschlossen wurden (Literaturliste siehe Anhang A. 7).

Der Ablauf der Literaturauswahl ist in der folgenden Abbildung 4 zusammenfassend dargestellt.

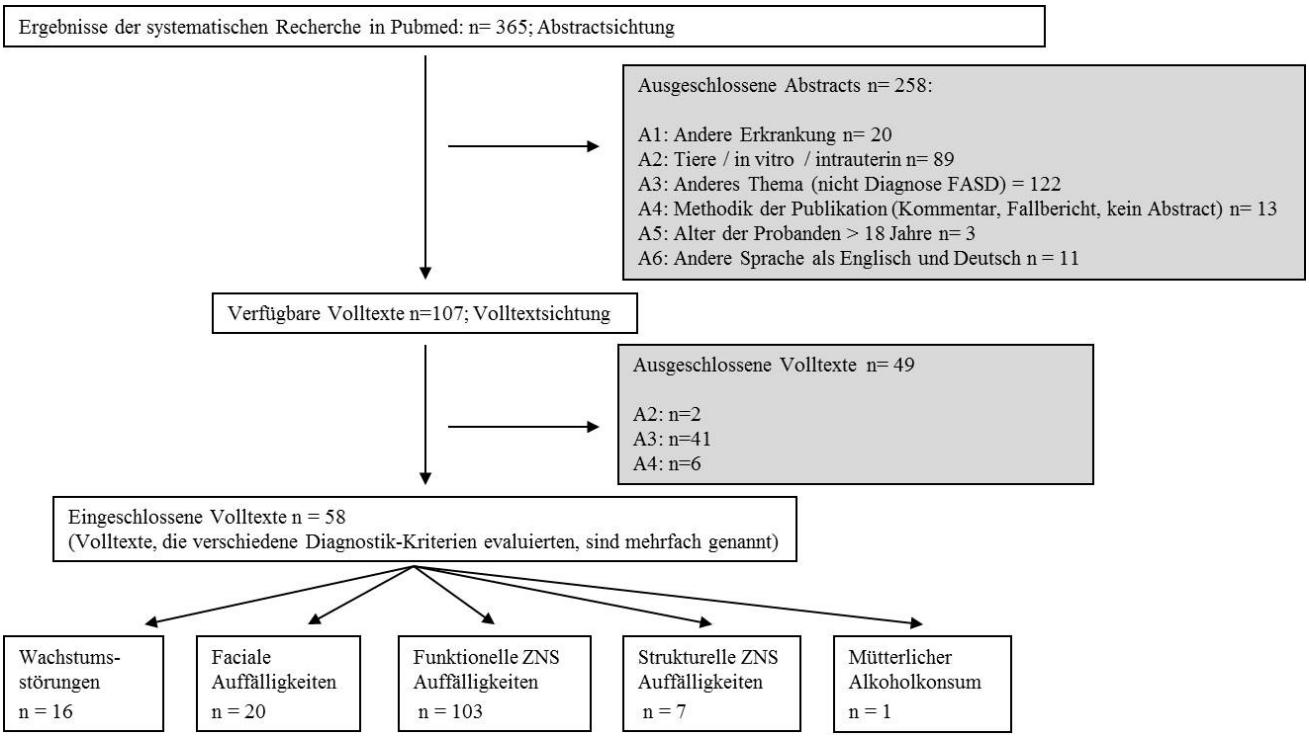


Abbildung 4: Ablauf der systematischen Literaturrecherche zum pFAS, zu den ARND und ARBD (2015/2016).

2.1.2.4 Bewertung der Evidenz 2011

Die vorliegenden Studien über diagnostische Kriterien des FAS (erster Teil des Leitlinienprojektes) wurden bei der systematischen Literaturrecherche mit dem Evidenzgraduierungs-System nach Oxford 2009 für diagnostische Studien bewertet (siehe Anhang A. 3).

Kohortenstudien wurden entsprechend der Oxford-Evidenzklassifikation für diagnostische Studie in explorative Kohortenstudien (LoE 2b) und Validierungskohortenstudien (LoE 1b) unterteilt. Bei einer Validierungskohortenstudie wird ein, in einer explorativen Studie identifiziertes, diagnostisches Merkmal an einem unabhängigen Kollektiv überprüft. Nicht-konsekutive Kohortenstudien oder solche mit sehr kleiner Teilnehmerzahl wurden mit einem LoE von 3b, Fall-Kontroll-Studien mit einem LoE von 4 bewertet.

Ergänzung 2015/2016

Die Studien bei der 2. systematischen Literaturrecherche zur Diagnose des pFAS ARND und ARBD (2. Teil des Leitlinienprojektes) wurden zur methodischen Bewertung in folgende Gruppen eingeteilt:

Einzelstudien:

- prospektiv
- retrospektiv
- explorativ
- validierend

Reviews:

- narrativ
- systematisch

Eine weitere Evidenzklassifikation fand nicht statt, da offensichtlich war, dass die meisten Studien einen geringen LoE aufwiesen.

2.1.2.5 Erstellung von Evidenztabellen

Die vom Ärztlichen Zentrum für Qualität in der Medizin erstellten Evidenztabellen zur Literatur über diagnostische Kriterien des Vollbildes FAS sind in Anhang A. 4 dargestellt. Bei der Ergänzung 2015 wurden zu FASD keine zusätzlichen Evidenztabellen erstellt.

2.2 Dritter Teil des Leitlinienprojektes (2022/2023)

2.2.1 Fragebogen an Fachpersonal zur Evaluation der bisherigen Leitlinie zur Diagnostik der FASD

Um die bisherige S3-Leitlinie zu Diagnostik der FASD bei Kindern und Jugendlichen zu evaluieren und die neue S3-Leitlinie FASD noch stärker an die Bedürfnisse der Zielgruppe anpassen zu können, wurden Fragebogendaten zu diesem Thema erhoben. Dazu wurde ein online Fragebogen auf der online Plattform LimeSurvey erstellt. Ein Link zum Fragebogen

wurde ab dem 16.08.2022 über das Netzwerk der Leitliniengruppe an Vertreter*innen der Zielgruppe dieser Leitlinie gesendet. Die Datenerhebung fand anonymisiert und unter Einhaltung aller Datenschutzbestimmungen statt. Um die Teilnahmebereitschaft zu erhöhen, wurden mehrfach Erinnerungsmails gesendet. Ausgewertet wurden alle Fragebögen, die bis zum 31.10.2022 ausgefüllt wurden und mindestens eine Antwort ab der fünften Frage (d. h. ab den inhaltlichen Fragen) beinhalteten. Die statistische Datenanalyse fand mittels der IBM® SPSS®-Softwareplattform (Version: 29.0.0.0 (241)) statt.

Das Ergebnis der ausgewerteten Fragebögen befindet sich in Anhang A. 8.

2.2.2 Gruppendiskussion

Um bei der Erstellung der Leitlinie die Sichtweise von Kindern und Jugendlichen mit FASD zu berücksichtigen, wurde am 19.05.2023 online eine Gruppendiskussion mit Kindern und Jugendlichen mit FASD geführt (Protokoll: siehe Anhang A. 9).

2.2.3 Fokussierte Literaturrecherche

Mithilfe einer fokussierten Literaturrecherche wurden 2022 bzw. 2023 folgende Bereiche aktualisiert:

1. Prävalenz von mütterlichem Alkoholkonsum in der Schwangerschaft: Frau Heike Wolters, Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Kindes- und Jugendalters, Charité – Universitätsmedizin Berlin
2. Prävalenz der FASD:
    a. Deutschland: PD Dr. sc. hum. Christine Schmucker, Institut für Evidenz in der Medizin am Universitätsklinikum Freiburg
    b. International: Frau Dr. Heike Hoff-Emden, Fachzentrum für FASD, Sozialpädiatrisches Zentrum Leipzig

Bei der fokussierten Literaturrecherche zu mütterlichem Alkoholkonsum wurden 2023 unter Verwendung der in Anhang A. 10 aufgeführten Suchstrategie folgende Datenbanken nach relevanten Publikationen (ab 2011) durchsucht:

- Pubmed

- Google Scholar
- Web of Science
- EBSCO-Datenbanken

Publikationen zur Prävalenz der FASD in Deutschland wurden 2022 mithilfe der in Anhang A. 10 aufgeführten Suchstrategie in PubMed gesucht.

Die Recherche nach Publikationen (ab 2011) zu internationalen Prävalenzangaben der FASD fand 2023 in folgenden Datenbanken statt (Suchstrategie: siehe Anhang A. 10):

- Pubmed
- Cochrane Bibliothek-Deutsch

Die fokussierten Literaturrecherchen wurden von Frau Prof. Dr. med. Dipl.-Psych. Landgraf und Frau Strieker koordiniert und deren Ergebnisse zusammengefasst.

Da es sich bei den Ergebnissen der fokussierten Literaturrecherche nicht um die Haupt-Fragestellung der Leitlinie (Diagnostik des FAS) sondern um Hintergrundinformationen für die Leitlinie handelt, wurden keine Evidenzbewertungen der Literatur durchgeführt und keine evidenzbasierten Empfehlungen abgeleitet.

2.2.4 Diagnostik

2.2.4.1 Formulierung von Schlüsselfragen, Outcome-Kriterien und Confoundern der Literaturrecherche

Bei der ersten Leitlinienkonferenz am 01.06.2022 wurde folgende PICO-Fragestellung an die systematische Literaturrecherche zur Diagnostik der FASD konsentiert:

Welche Kriterien (I) im Kindes- und Jugendalter (0 bis 18 Jahre) (P) ermöglichen entwicklungsbezogen:

> die Diagnose eines Fetalen Alkoholsyndroms (FAS), eines partiellen Fetalen Alkoholsyndroms (pFAS), einer alkoholbedingten entwicklungsneurologischen Störung (ARND) und alkoholbedingter angeborener Malformationen (ARBD) aus dem Formenkreis der Fetalen Alkoholspektrumstörungen (FASD) (O)

und/oder

sind mit positiven Outcomes beim FAS, pFAS, ARND und ARBD aus dem Formenkreis der FASD assoziiert (O)?

Als Confounder (zufällige Störfaktoren) in der Literaturbewertung zur Diagnostik FASD wurden konsentiert:

Im Hinblick auf die Eltern

- Körpermaße der Eltern (Körpergröße, Körpergewicht, BMI)
- Herkunft der Eltern
- anderer Drogenkonsum der Mutter während der Schwangerschaft
- Vorerkrankung, Begleiterkrankung der Eltern
- Alter der Mutter bei der Schwangerschaft

Im Hinblick auf die Kinder/Jugendlichen

- Intelligenzminderung bzw. andere kognitive Beeinträchtigungen
- Medikamentöse und nicht-medikamentöse Behandlung
- Soziales Umfeld
- FASD Unterform
- Geschlecht
- Vorerkrankungen, Begleiterkrankung
- Anzahl von Geschwistern

Als Bias (systematische Störfaktoren) in der Literaturbewertung zur Diagnostik FASD wurden konsentiert**:**

- Incorporation Bias
- Information Bias
- Recall Bias

2.2.4.2 Verwendung existierender Leitlinien zum Thema

Die Recherche nach internationalen Leitlinien fand im Juli 2022 in zwei bibliographischen Datenbanken (Medline, Trip Datenbank) statt. Bei der Leitlinienrecherche wurden folgende diagnostische Leitlinien zu FASD gefunden:

1. Landgraf MN, Heinen F: AWMF S3-Leitlinie: Fetale Alkoholspektrumstörungen, FASD - Diagnostik. https://register.awmf.org/de/leitlinien/detail/022-025. 2016.
2. Broccia M, Vikre-Jørgensen J, Rausgaard NLK: A Danish fetal alcohol spectrum disorders definition. Ugeskr Laeger 2017; 179: V03170202.
3. Okulicz-Kozaryn K, Maryniak A, Borkowska M, Śmigiel R, Dylag KA: Diagnosis of Fetal Alcohol Spectrum Disorders (FASDs): Guidelines of Interdisciplinary Group of Polish Professionals. Int J Environ Res Public Health 2021; 18: 7526.

4. Cook JL, Green CR, Lilley CM, et al.: Fetal alcohol spectrum disorder: A guideline for diagnosis across the lifespan. CMAJ 2016; 188: 191-7.
5. Hoyme HE, Kalberg WO, Elliott AJ, et al.: Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders. Pediatrics 2016; 138: e20154256.
6. SIGN: Children and young people exposed prenatally to alcohol. https://www.sign.ac.uk/media/1092/sign156.pdf. Edinburgh: SIGN; 2019.
7. Bower C, Elliott EJ 2016, on behalf of the Steering Group. Report to the Australian Government Department of Health: "Australian Guide to the diagnosis of Fetal Alcohol Spectrum Disorder (FASD)" (ISBN. 978-0-6481297-4-5).
   &
   Bower C, Elliott EJ, Zimmet M, et al.: Australian guide to the diagnosis of foetal alcohol spectrum disorder: A summary. J Paediatr Child Health 2017; 53: 1021-3.
8. Astley SJ (2004) Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. Third Edition. University of Washington, Seattle, Washington
9. Bertrand J, Floyd R, Weber M, et al.: Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. https://www.cdc.gov/ncbddd/fasd/documents/fas_guidelines_accessible.pdf. Atlanta, GA: Centers for Disease Control (CDC) and Prevention; 2004.
10. Hagan JF, Jr., Balachova T, Bertrand J, et al.: Neurobehavioral Disorder Associated With Prenatal Alcohol Exposure. Pediatrics 2016; 138.
    &
    Kable JA, Mukherjee RA: Neurodevelopmental disorder associated with prenatal exposure to alcohol (ND-PAE): A proposed diagnostic method of capturing the neurocognitive phenotype of FASD. Eur J Med Genet 2017; 60: 49-54.

Abgesehen von der S3-Leitlinie Fetale Alkoholspektrumstörungen, FASD – Diagnostik (Landgraf & Heinen, 2016), die im Zuge dieser Leitlinie aktualisiert wird, konnte keine der internationalen Leitlinien nach den AWMF-Vorgaben die methodischen Kriterien einer S3-Leitlinie erfüllen.

Hoyme et al. veröffentlichten 2016 ein Update ihrer 2005 erschienen Leitlinie zur Diagnostik einer FASD. Außerdem wurde eine schottische Publikation (SIGN: Children and young people exposed prenatally to alcohol. https://www.sign.ac.uk/media/1092/sign156.pdf. Edinburgh: SIGN; 2019.) gefunden, die jedoch keine eigenstätige Leitlinie darstellte und ihre Evidenz aus der kanadischen bzw. aus der australischen Leitlinie bezog. Auch eine 2016 erschienene Publikation (Bower C, Elliott EJ 2016, on behalf of the Steering Group. Report to the Australian Government Department of Health: "Australian Guide to the diagnosis of Fetal Alcohol Spectrum Disorder (FASD)" (ISBN. 978-0-6481297-4-5) (Zusammenfassung: Bower C, Elliott EJ, Zimmet M, et al.: Australian guide to the diagnosis of foetal alcohol spectrum disorder: A summary. J Paediatr Child Health 2017; 53: 1021-3.)) aus Australien wurde nicht als eigenständige Leitlinie eingestuft, da ihre Empfehlungen identisch zur kanadischen Leitlinie sind.

2.2.4.3 Systematische Literaturrecherche

Die Recherchen fanden in insgesamt sieben bibliographischen Datenbanken (Medline, Cochrane Library, PsycInfo, PsycArticles, Psyndex, Trip Datenbank, Epistemonikos) statt. Aufgrund des Leitlinien Updates wurde die Recherche zu Primärliteratur auf den Zeitraum von 01.07.2015 (letzte Suche) bis 06.07.2022 (Zeitraum der Update-Suche zwischen dem 28.06. und 06.07.2022, abhängig von Datenbank) eingegrenzt, während bei der zusätzlichen Suche nach internationalen Leitlinien keine zeitliche Eingrenzung erfolgte. Darüber hinaus wurden die Referenzlisten gefundener Übersichtsarbeiten und Leitlinien nach weiteren potentiell relevanten Studien gesichtet. Eine genaue Auflistung der Datenbanken und Trefferzahlen findet sich in Tabelle 10, Tabelle 11 und Tabelle 12. Die Suchstrategien befinden sich in Anhang A. 11.

In Abbildung 5 ist die bibliographische Literatursuche, einschließlich der Ausschlussgründe und des final relevanten Studienpools dargestellt. Der komplette Auswahlprozess wurde von insgesamt vier Reviewer*innen des IFEM Freiburg durchgeführt (Christine Schmucker, Annika Ziegler, Lena Mertink, Eberhard Thörel).

Tabelle 10: Informationsbeschaffung Primärstudien.

Literaturdatenbank	Anzahl der Treffer
Medline, Suchoberfläche: PubMed	1.081
Cochrane Library, Suchoberfläche: Wiley	52
PsycInfo, Suchoberfläche EBSCO	481
PsycArticles, Suchoberfläche: EBSCO	18
Psyndex, Suchoberfläche: EBSCO	34
Trefferzahl	**1.666**

Tabelle 1: Informationsbeschaffung Leitlinien.

Literaturdatenbank	Anzahl der Treffer
Medline, Suchoberfläche: PubMed	71

Trip Datenbank (https://www.tripdatabase.com/)	27
Trefferzahl	**98**

Tabelle 2: Informationsbeschaffung Systematische Übersichtsarbeiten.

Literaturdatenbank	Anzahl der Treffer
Medline, Suchoberfläche: PubMed	38
Epistemonikos (www.epistemonikos.org)	45
Trefferzahl	**83**

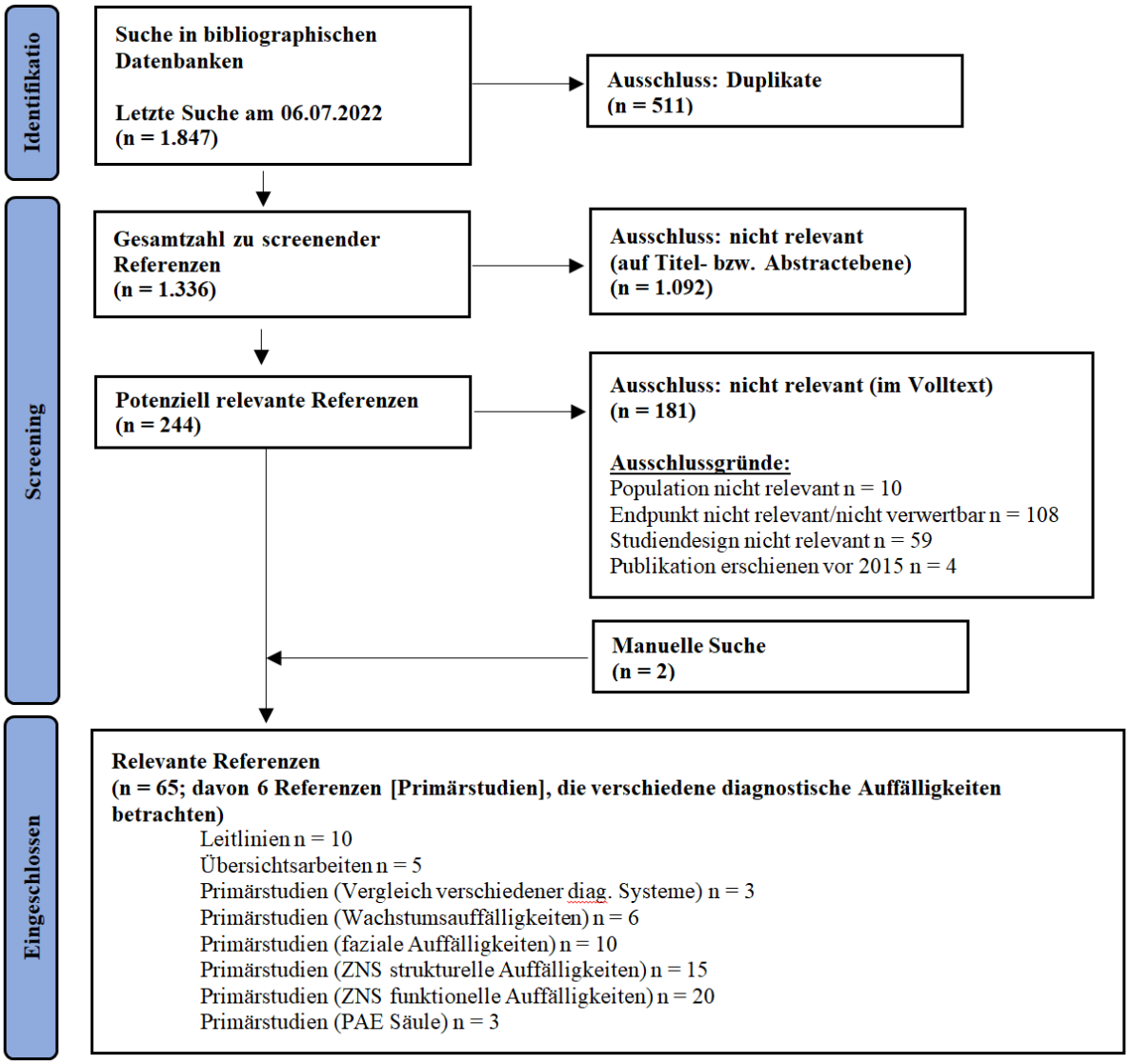


Abbildung 5: Ergebnis der umfassenden Informationsbeschaffung aus den bibliografischen Datenbanken und

2.2.4.4 Bewertung der Evidenz

Bei der aktuellsten Literaturrecherche erfolgte die Biasbewertung der eingeschlossenen Primärstudien (Kohortenstudien und Querschnittsstudien, die keine Angaben zur diagnostischen Genauigkeit machten, sondern den Anteil von Auffälligkeiten oder Assoziationen berichteten) in Anlehnung an das Manual zur Bewertung von klinischen Studien von Cochrane Deutschland [3] bzw. an das „Tool for assessing risk of bias in non-randomised studies of interventions“ ROBINS-I [4]. Darüber hinaus wurden die Studien, die ausschließlich die diagnostische Genauigkeit der verschiedenen diagnostischen Systeme untersuchten in Anlehnung an QUADAS-2 bewertet [5]. Systematische Reviews wurden im Bereich „Diagnostik“ mithilfe einer modifizierten Form des AMSTAR-Tools (A MeaSurement Tool to Assess systematic Reviews) bewertet [6].

2.2.4.5 Erstellung von Evidenztabellen

Die vom Institut für Evidenz in der Medizin erstellten Evidenztabellen zur jetzigen Aktualisierung der gesamten diagnostischen Kriterien sind in Anhang A. 12 zu finden.

2.2.5 Intervention

2.2.5.1 Formulierung von Schlüsselfragen, Outcome-Kriterien und Confoundern der Literaturrecherche

In der ersten online Konsensuskonferenz am 01.07.2022 wurden folgende Schlüsselfragen konsentiert:

1. Welche *nicht-medikamentösen* Interventionen (I) sind im Vergleich zu keiner Intervention, Placebo, zu einem Kontexteffekt, zu einer alternativen Intervention oder im Vorher-Nachher-Vergleich (C) bei Kindern und

Jugendlichen (0 bis 18 Jahre) mit FASD (P) mit positiven Outcome-Kriterien (O) assoziiert?

2. Welche medikamentösen Interventionen (I) sind im Vergleich zu keiner Intervention, Placebo, zu einem Kontexteffekt, zu einer alternativen Intervention oder im Vorher-Nachher-Vergleich (C) bei Kindern und Jugendlichen (0 bis 18 Jahre) mit FASD (P) mit positiven Outcome-Kriterien (O) assoziiert?
3. Welche *kombiniert medikamentös-nicht-medikamentösen* Interventionen (I) sind im Vergleich zu keiner Intervention, Placebo, zu einem Kontexteffekt, einer alternativen Intervention oder im Vorher-Nachher-Vergleich (C) bei Kindern und Jugendlichen (0 bis 18 Jahre) mit FASD (P) mit positiven Outcome-Kriterien (O) assoziiert?

Aufgrund der geringen Anzahl an Ergebnissen in der Literaturrecherche im Bereich der medikamentösen und kombiniert medikamentös-nicht-medikamentösen Interventionen wurden die drei Schlüsselfragen in Absprache mit der Leitliniengruppe zu folgender Schlüsselfrage zusammengefasst:

Welche Interventionen (I) sind im Vergleich zu keiner Intervention, Placebo, zu einem Kontexteffekt, zu einer alternativen Intervention oder im Vorher-Nachher-Vergleich (C) bei Kindern und Jugendlichen (0 bis 18 Jahre) mit FASD (P) mit positiven Outcome-Kriterien (O) assoziiert?

P	Kinder und Jugendliche mit Fetalen Alkoholspektrumstörungen FASD (0-18 Jahre)

I	- Medikamentöse Therapien des Kindes/Jugendlichen: • Stimulanzien • Neuroleptika • Nahrungsergänzungsmittel • Medikamente zur Regulierung des Schlafrhythmus - Nicht-medikamentöse Therapien: • Psychoedukation des Kindes/Jugendlichen • Psychoedukation der Eltern/Sorgeberechtigten/Bezugspersonen • Funktionelle, nicht-medikamentöse Intervention beim Kind/Jugendlichen: ○ Ergotherapie ○ Physiotherapie ○ Sprachtherapie ○ Psychotherapie ○ Training spezifischer schulischer Fertigkeiten (z. B. Mathematik) - Kombiniert medikamentös-nicht-medikamentöse Interventionen - Andere funktionelle Therapien
C	- Keine Intervention - Placebo - Kontexteffekt - Alternative Intervention - Vorher-Nachher-Vergleich

O	- Verbesserung des neuropsychologischen Funktionsniveaus/ Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD z. B. (Relevanz 8): • Kognitive Leistung/Intelligenz • Entwicklung • Epilepsie • Sprache • Fein-/Graphomotorik oder grobmotorische Koordination • Räumlich-visuelle Wahrnehmung oder räumlich-konstruktive Fähigkeiten • Exekutivfunktionen • Rechenfertigkeiten • Lern- und Merkfähigkeit • Aufmerksamkeit • Soziale Fertigkeiten und Verhalten - Vermeidung von Nebenwirkungen der Interventionen (Relevanz 9) - Reduktion von Komplikationen/Sekundärerkrankungen z. B. (Relevanz 8): • Somatische Erkrankungen • Psychiatrischen Erkrankungen inkl. Suchterkrankungen • Risikoverhalten (riskanter Alkohol-/Drogenkonsum, Eigen-/Fremdgefährdung, suizidale Handlungen) • Schulversagen und -abbruch (bzw. höhere Rate an Schulabschlüssen und Berufsausbildungen) • Delinquenz • Misshandlung • Krankenhaus- oder sonstigen stationären Aufenthalten - Verbesserung der Partizipation der Kinder/Jugendlichen mit FASD (Relevanz 9) • Lernen und Wissensanwendung • Allgemeine Aufgaben und Anforderungen • Kommunikation • Mobilität • Selbstversorgung • Häusliches Leben • Interpersonelle Interaktion und Beziehungen • Bedeutende Lebensbereiche • Gemeinschafts-, soziales- und staatsbürgerliches Leben - Verbesserung der Lebensqualität der Kinder/Jugendlichen mit FASD (Relevanz 9) - Entlastung der Bezugspersonen (biologische, Pflege- und Adoptiv-Eltern, Bezugsbetreuer*innen) und Verbesserung der Lebensqualität der gesamten betroffenen Familie/Einrichtung (Relevanz 8) - Verbesserung des Wissens um den abweichenden Gesundheitszustand/die Erkrankung/Störung/Behinderung und Verbesserung der Krankheitseinsicht (Relevanz 8) - Verbesserung der Krankheitsbewältigung/Coping und Selbstwirksamkeit (Relevanz 8)

P: Patient*innen, I: Intervention (hier Indextest), C: Comparator (hier Vergleichstest), O: Outcomes

Als Confounder (zufällige Störfaktoren) wurden in der Literaturbewertung konsentiert:

- Intelligenzminderung des Kindes
- Exekutivfunktionsstörung des Kindes
- Beeinträchtigung anderer, verschiedener ZNS-Auffälligkeit als Ziel-Gehirnfunktion der Intervention
- Medikation des Kindes
- Andere psychiatrische Erkrankungen des Kindes
- Therapieerfolg durch andere, parallel laufende Therapie
- Verschiedene, parallel laufende Zusatztherapien
- Soziales Umfeld als Gegeneffekt zum Interventionserfolg
- Fähigkeiten der Betreuungsperson (fehlerhafte Ausführung der Intervention, fehlerhafte Berichterstattung des Therapieerfolgs, z. B. durch Lese-/Schreibschwächen, Sprachbarrieren, Intelligenzminderung)
- Patienten wurden mit unterschiedlichen diagnostischen Kriterien klassifiziert, Effekt der Untergruppe der FASD auf Therapieerfolg (IOM, Canadian, 4-Digit, Majewski Skala, Dysmorphologie-Beurteilung, Interviews mütterlicher Alkoholkonsum)
- Studien beinhalten häufig keine Unterscheidung der verschiedenen FASD
- Häufig pränatale Alkoholexposition PAE zusammen mit FASD oder sogar alleiniges Kriterium zur Patientenklassifikation

Als Bias (systematische Störfaktoren) wurden in der Literaturbewertung konsentiert:

- Bias soziale Erwünschtheit (Kind und/oder Eltern)
- Selektionsbias
- Reporting Bias
- Incorporation Bias
- Fehlende Verblindung der Teilnehmer*innen bzw. der Studienleiter*innen

2.2.5.2 Verwendung existierender Leitlinien zum Thema

Die systematische Suche nach internationalen Leitlinien und evidenzbasierten Handlungsempfehlungen für Therapiemöglichkeiten bei Kindern und Jugendlichen mit FASD wurde im Juni 2022 in der Datenbanken Medline (über http://www.pubmed.org) durchgeführt. Außerdem wurden weitere Seiten für Evidenz-basierte Empfehlungen händisch durchsucht (z. B. NICE National Institute for Health and Care Excellence, SIGN Healthcare Improvement Scottland). Diese Suchen ergaben keine Treffer, sodass alle

evidenzbasierten Empfehlungen dieser Leitlinie bezüglich Interventionen auf systematischen Reviews und Primärliteratur beruhen.

2.2.5.3 Systematische Literaturrecherche

Die systematische Literaturrecherche zu Interventionen für Kinder und Jugendliche mit FASD erfolgte gemäß der im Leitlinienbericht und in Anhang A. 14 dargestellten Strategie. Die Recherche umfasste sowohl englisch- als auch deutschsprachige Literatur im Zeitraum von 01.01.2012 bis 09.08.2022. Nach Sichtung der Titel und Abstracts und der Begutachtung der daraus ausgewählten Volltexte wurden insgesamt 32 Publikationen zur Evidenzbewertung eingeschlossen (siehe Abbildung 6). Bei vier der gefundenen Publikationen handelt es sich um systematische Reviews. Um weitere relevante Literatur zu finden, wurde anschließend eine Handrecherche bis 31.10.2022 durchgeführt. Diese Suche ergab keine weiteren Publikationen, die alle Suchkriterien erfüllten.

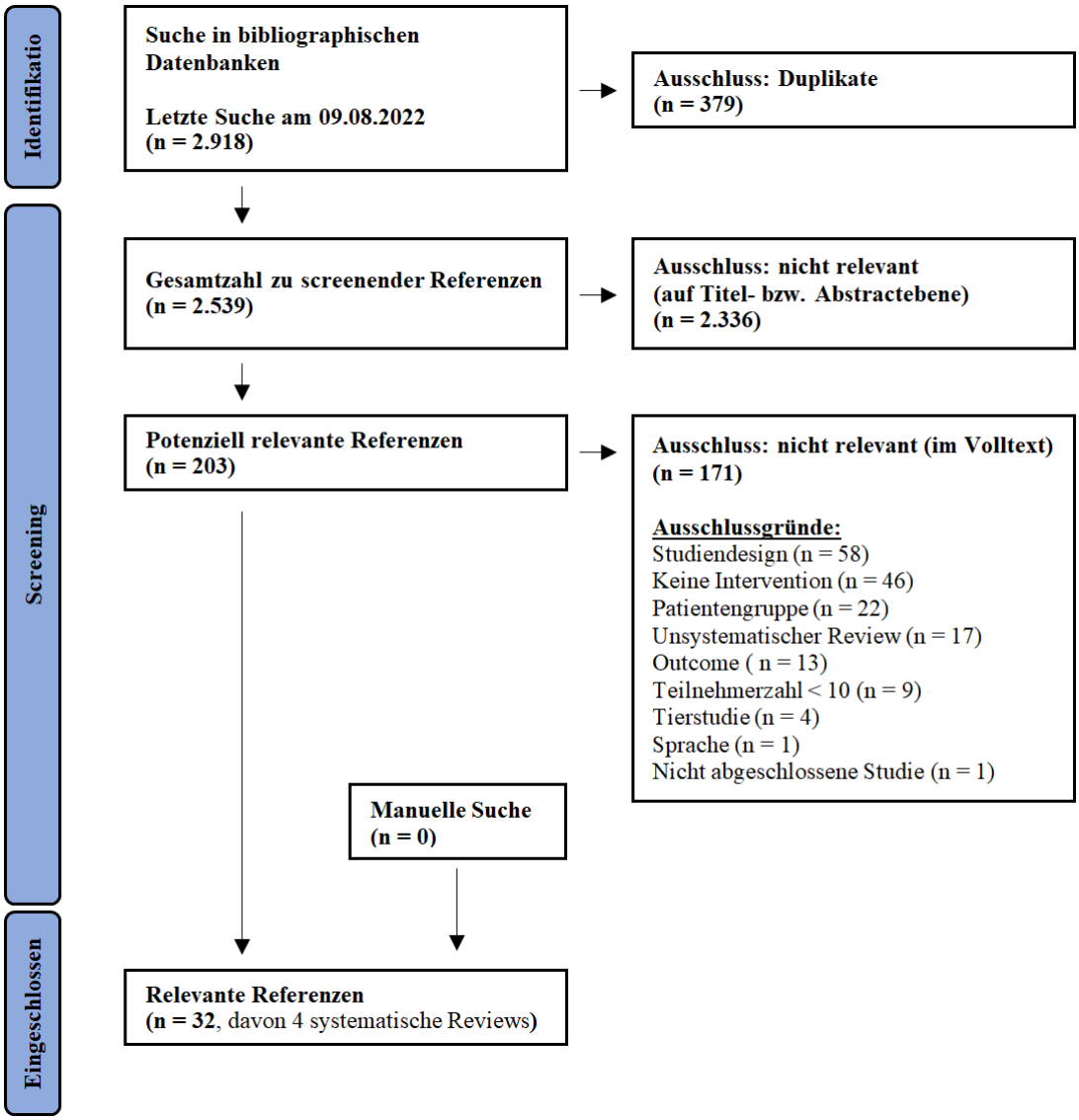


Abbildung 6: Ergebnis der umfassenden Informationsbeschaffung zu Interventionen bei Kindern und Jugendlichen mit FASD aus den bibliografischen Datenbanken und Ergebnis der Studienselektion gemäß den Kriterien zum Studieneinschluss (2022/2023).

2.2.5.4 Bewertung der Evidenz

Wie von der AWMF empfohlen, wurde die Qualität der Evidenz der Outcomes mithilfe der GRADE-Methode bewertet. Dazu wurde zunächst der Risk of Bias (RoB) der einzelnen Publikationen ermittelt. Für randomisiert kontrollierte Studien (n = 16) wurde hierfür RoB 2 (Cochrane risk-of-bias tool – 2nd Version) verwendet [7]. Nicht-randomisiert kontrollierte Studien (n = 7) wurden mit ROBINS-I bewertet [4]. Die RoB Bewertung nicht-kontrollierter

Studien (n = 5) basierte auf einer angepassten Version des ROBINS-I-Instruments. Der RoB der systematischen Reviews (n = 4) wurde mithilfe des AMSTAR-2-Instruments beurteilt [6]. Anschließend wurde mithilfe der GRADE-Kriterien (Risk of Bias/Studienlimitationen, Indirektheit, Inkonsistenz der Ergebnisse, mangelnde Präzision, Publikations-Bias, Effektstärke, Dosis-Wirkungs-Beziehung und der Einfluss der residuellen und plausiblen Störgrößen (Confounder)) die Qualität der Evidenz für jedes der betrachteten Outcomes bewertet und in vier Kategorien eingeteilt: sehr niedrig, niedrig, moderat, hoch. Die Summary of Findings Tabellen (GRADE-Tabellen) befinden sich in Anhang A. 15.

2.2.5.5 Erstellung von Evidenztabellen

Die vom iSPZ Hauner erstellten Evidenztabellen zur Literatur über Interventionen bei FASD sind in Anhang A. 16 dargestellt.

3 Kriterien für die Diagnose Fetale Alkoholspektrumstörungen und Empfehlungen für Interventionen bei Kindern/Jugendlichen mit FASD

3.1 Ergebnisse der systematischen Literaturrecherche

3.1.1 Erster und zweiter Teil des Leitlinienrojektes (2011 und 2015/2016)

3.1.1.1 Ergebnisse zur Diagnostik des FAS 2011

Die systematische Literaturrecherche und die Evidenzbewertung der Studien zum FAS wurden durch Frau Dr. med. Monika Nothacker MPH vom ÄZQ und (in intensiver dialogischer Rücksprache und Korrektur) durch die Leitlinienkoordinatorin Frau Dr. med. Dipl.-Psych. Mirjam N. Landgraf durchgeführt.

Lediglich ein Review der systematischen Literaturrecherche kann als systematischer Review von guter methodischer Qualität über einen Zeitraum bis Juli 2008 bezeichnet werden (mit Evidenzklassifikation des NHMRC): Fetal Alcohol Spectrum Disorders (FASD): systematic reviews of prevention, diagnosis and management. [8].

Bei den übrigen Reviews mit Angabe einer systematischen Recherche fehlen meist Suchfragen, Angaben zu Treffern, Ein- und Ausschlusskriterien sowie eine Beschreibung bzw. Bewertung der methodischen Güte der eingeschlossenen Studien. Die Studienqualität für diese Reviews ist als mäßig bis schlecht zu bezeichnen. Aus diesen Reviews kann ein inhaltlicher Überblick der beschriebenen Ergebnisse gegeben werden, eine Beurteilung der Qualität der zugrundeliegenden Studien ist nicht durchgehend möglich.

Die Literaturliste der eingeschlossenen Studien bei der systematischen Literaturrecherche befindet sich in Anhang A. 5.

3.1.1.2 Ergebnisse zur Diagnostik des pFAS, den ARND und ARBD 2015/2016

Es wurden 37 prospektiv-explorative, 1 prospektiv validierende, 8 retrospektiv explorative und 0 retrospektiv validierende Studien sowie 5 narrative und 7 systematische Reviews eingeschlossen (Bewertung der Studien siehe Anhang A. 7).

3.1.2 Dritter Teil des Leitlinienprojektes (2022/2023)

3.1.2.1 Diagnostik

Die Literaturrecherchen wurden durch die Recherchespezialistin Kathrin Grummich durchgeführt. Insgesamt wurden 5 Übersichtsarbeiten und 50 Primärstudien gefunden. Die Zusammensetzung der Primärliteratur war wie folgt (Mehrfachnennung möglich):

- Vergleich verschiedener diagnostischer Systeme: n = 3
- Wachstumsauffälligkeiten: n = 6
- faziale Auffälligkeiten: n = 10
- ZNS strukturelle Auffälligkeiten: n = 15
- ZNS funktionelle Auffälligkeiten: n = 20
- Pränatale Alkoholexposition Säule: n = 3

Die Literaturliste der eingeschlossenen Studien bei der systematischen Literaturrecherche befindet sich in Anhang A. 13.

3.1.2.2 Interventionen

Für Interventionsmöglichkeiten bei Kindern und Jugendlichen mit FASD – dem zweiten Themenbereich dieser S3-Leitlinie – wurde eine systematische Literaturrecherche von Frau Strieker, Leitlinienkoordinatorin und wissenschaftliche Mitarbeiterin des iSPZ des Dr. von Haunerschen Kinderspital, in intensiver dialogischer Rücksprache und Korrektur durch die Leitlinienkoordinatorin Frau Prof. Dr. med. Dipl.-Psych. Landgraf durchgeführt. Methodisch wurde die Literaturrecherche und Evidenzbewertung durch das IFEM Freiburg und durch Frau Prof. Kopp der AWMF geprüft. Insgesamt wurden 4 systematische Reviews sowie 28 Primärstudien gefunden.

Die Literaturliste der eingeschlossenen Studien bei der systematischen Literaturrecherche befindet sich in Anhang A. 17.

3.2 Generelle methodische Anmerkung zu den FASD-Studien

Die Zuverlässigkeit der Aussagen, die auf Studien mit bekannten Fällen (Kinder mit der Diagnose FASD) und Kontrollen (gesunde Kinder) basieren, ist begrenzt, da die Diagnosen bereits feststehen. Häufig fällt auch eine hohe Prävalenzrate an Kindern mit FASD in den Studienpopulationen auf, die die Übertragung der Studienergebnisse auf eine Normalpopulation problematisch macht.

Diagnostische Studien zu den Fetalen Alkoholspektrumstörungen stellen bezüglich eines optimalen Studiendesigns eine besondere Herausforderung dar. Für gute diagnostische Studien ist allgemein ein unabhängiger verlässlicher Referenzstandard erforderlich. Die Validierung von diagnostischen FASD-Kriterien wurde jedoch an bereits mit FASD diagnostizierten Kindern und Jugendlichen überprüft. Dafür wurden unterschiedliche Instrumente angewendet (vor allem IOM Kriterien und 4-Digit Diagnostic Code), die aufgrund der differenten diagnostischen Kriterien oder Cut-off-Werte (Perzentile von Kopfumfangskurven, Anzahl Fazialer Auffälligkeiten, Berücksichtigung funktioneller ZNS-Auffälligkeiten) in ihrer diagnostischen Diskrimination nicht übereinstimmen. Insbesondere die Fazialen Kriterien unterliegen einem sogenannten Incorporation Bias, bei dem das Testkriterium grundsätzlich auch Teil des Referenzstandards ist. In den meisten Studien wurden als Vergleichsgruppen Kinder und Jugendliche gewählt, deren Mütter keinen Alkoholkonsum während der Schwangerschaft angaben. Dabei sollte allerdings berücksichtigt werden, dass die Aussagen zum mütterlichen Alkoholkonsum in der Schwangerschaft wahrscheinlich häufig aufgrund sozialer Erwünschtheit ungenau und retrospektiv nicht objektivierbar sind. Daher könnten sich auch in den gesunden Kontrollgruppen Kinder mit intrauteriner Alkoholexposition befinden und den Vergleich mit Kindern mit FASD beeinträchtigen.

3.3 Formale Konsensfindung: Verfahren und Durchführung

3.3.1 Formale Konsensfindung: Verfahren und Durchführung in den ersten beiden Teilen des Leitlinienprojektes (2011 und 2015/2016)

Anhand der evidenzbewerteten Studien wurden von den Leitlinienkoordinatoren Empfehlungsvorschläge für die Diagnostik des FAS (erster Teil des Leitlinienprojektes, 2011) erarbeitet. Diese Empfehlungen wurden in der zweiten (17.02.12) und dritten (25.05.12) Konsensuskonferenz zum FAS von der Leitliniengruppe diskutiert, je nach klinischer Relevanz modifiziert und graduiert. Die daraus resultierenden handlungsleitenden Empfehlungen für die Diagnostik des FAS bei Kindern und Jugendlichen in Deutschland wurden in den gleichen Konsensussitzungen mittels einer formalen Konsensfindung in Form eines nominalen Gruppenprozesses konsentiert.

Der nominale Gruppenprozess wurde in den folgenden Schritten unter Moderation von Fr. Prof. Ina Kopp (AWMF) durchgeführt:

1. Präsentation der Ergebnisse der Literaturrecherche und der darauf basierenden, zu konsentierenden Leitlinien-Empfehlungen

2. Verfassen von Änderungsvorschlägen und Anmerkungen zu den vorgeschlagenen diagnostischen Kriterien und Empfehlungen durch alle Teilnehmer*innen der Konsensuskonferenz

3. Die Änderungsvorschläge wurden der Reihe nach von Fr. Prof. Kopp als unabhängiger und nicht stimmberechtigter Moderatorin abgefragt, schriftlich festgehalten und per Beamer für alle sichtbar projiziert.

4. Vorherabstimmung aller diagnostischen Kriterien, Empfehlungen und Empfehlungsgrade sowie der Änderungsvorschläge

5. Diskussion der Punkte, für die kein Konsensus erzielt werden konnte

6. Endgültige Abstimmung und Protokollierung der Konsensstärke.

In der 2. und 3. Konsensuskonferenz zum FAS wurden die Ergebnisse der Literatur mit den jeweils bestimmten Evidenzklassen präsentiert und die von den Leitlinienkoordinatoren vorgeschlagenen diagnostischen Kriterien und Empfehlungen inklusive der Empfehlungsgrade durch die Leitliniengruppe diskutiert. Bei der Festlegung der endgültigen Empfehlungsgrade im formalen Konsensusverfahren durch die Leitliniengruppe wurden neben der zugrundeliegenden Evidenzstärke auch die methodische Qualität der gesamten bisherigen Literatur zum Thema FAS, die klinische Relevanz der Studien, die Umsetzbarkeit in die Praxis und ethische Verpflichtungen berücksichtigt.

Die Ergebnisse der systematischen Literaturrecherche zur Ergänzung der S3-Leitlinie um die Diagnostik des pFAS, der ARND und der ARBD (zweiter Teil des Leitlinienprojektes, 2015/2016) wurden von der Leitlinienkoordinatorin zusammengefasst und der Leitliniengruppe vor der 1. Konsensussitzung per Mail zur Verfügung gestellt. Aus den Literaturergebnissen wurden von den Leitlinienkoordinatoren Empfehlungsvorschläge für die Diagnostik der FASD (pFAS, ARND, ARBD) erarbeitet. Diese Empfehlungen wurden in der ersten (07.09.2015) und zweiten (25.01.2016) Konsensuskonferenz von der Leitliniengruppe diskutiert, je nach klinischer Relevanz modifiziert und graduiert. Die daraus resultierenden handlungsleitenden Empfehlungen für die Diagnostik des pFAS, der ARND und ARBD bei Kindern und Jugendlichen in Deutschland wurden in den gleichen Konsensussitzungen mittels einer formalen Konsensfindung in Form eines nominalen Gruppenprozesses konsentiert.

Der nominale Gruppenprozess wurde in den gleichen Schritten wie bei der Konsentierung der Empfehlungen zur Diagnostik des Vollbildes FAS (siehe oben) unter Moderation von Fr. Prof. Ina Kopp (AWMF) in der 1. Konsensussitzung und unter Moderation von Fr. Dr. Mirjam N. Landgraf in der 2. Konsensussitzung durchgeführt. Bei der 2. Konsensuskonferenz wurden, ergänzend zu den bereits abgestimmten diagnostischen Kriterien, nur Hintergrundtexte verabschiedet. Die Unabhängigkeit der Moderatorin (Fr. Dr. Landgraf) war gewährleistet, da keine thematisch relevanten Interessenkonflikte vorlagen.

Alle Empfehlungen zu diagnostischen Kriterien der FASD (bis auf die Cut-off-Perzentilenkurve des Kopfumfanges beim FAS) wurden im "starken Konsensus" (Zustimmung von > 95 % der Teilnehmer*innen) oder im „Konsensus“ (Zustimmung von > 75 % der Teilnehmer*innen) verabschiedet.

Die Abstimmungs- und Ergebnisprotokolle der Sitzungen können über die Leitlinienkoordinatorin Frau Prof. Dr. med. Dipl.-Psych. Landgraf angefordert und eingesehen werden.

Bei den Empfehlungen wurde zwischen drei Empfehlungsgraden unterschieden, deren unterschiedliche Qualität durch die Formulierung ("soll", "sollte", "kann") ausgedrückt wird. In der Regel bestimmt die Evidenzstärke den Empfehlungsgrad (siehe nachfolgende Abbildung 7 der AWMF):

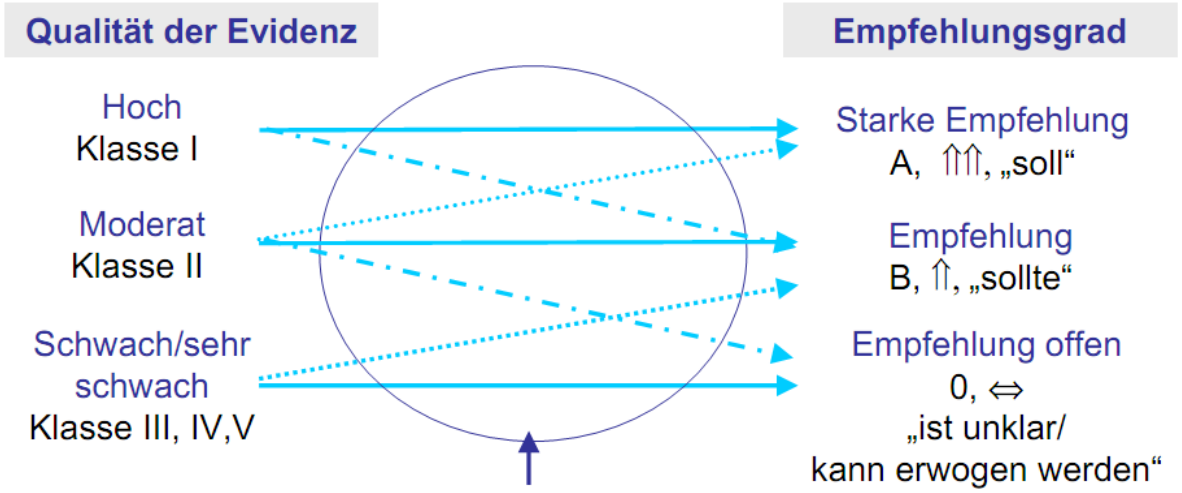


Abbildung 7: Bestimmung von Empfehlungsgraden anhand der Evidenzbewertung der Literatur gemäß AWMF (mit freundlicher Genehmigung der AWMF).

3.3.2 Formale Konsensfindung: Verfahren und Durchführung im dritten Teil des Leitlinienprojektes (2022/2023)

Anhand der evidenzbewerteten Literatur wurde von den Leitlinienkoordinatorinnen des LMU Klinikums München Frau Prof. Dr. med. Dipl.-Psych. Landgraf und Frau Strieker in

Rücksprache mit Frau Dr. Schmucker und Frau Ziegler vom IFEM Freiburg die diagnostischen Handlungsempfehlungen überarbeitet. Empfehlungsvorschläge für Interventionsmöglichkeiten bei Kindern und Jugendlichen mit FASD wurden von Frau Prof. Dr. med. Dipl.-Psych. Landgraf und Frau Strieker formuliert. Deren Empfehlungsgrad orientierte sich an der Qualität der Evidenz und berücksichtigte Kriterien wie unter anderen eine Nutzen-Schadens-Abwägung, die Umsetzbarkeit im Alltag und die Anzahl der vorhandenen Publikationen. Wie bei den Empfehlungen der ersten beiden Teile des Leitlinienprojektes wurde zwischen drei Empfehlungsgraden unterschieden, deren unterschiedliche Qualität durch die Formulierung ("soll", "sollte", "kann") ausgedrückt wird (siehe Abbildung 7 in Kapitel 3.3.1).

War für eine Fragestellung keine direkte Evidenz verfügbar, so wurden Vorschläge für Expertenkonsensus von den Leitlinienkoordinatorinnen erarbeitet. Dabei stützen sich deren Inhalte vor allem auf die klinische Erfahrung von Frau Prof. Dr. med. Dipl.-Psych. Landgraf sowie die Auswertung der Gruppendiskussion von Kindern und Jugendlichen mit FASD. Der Grad des Konsensuspunktes wurde analog zu den evidenzbasierten Leitlinienempfehlungen als „soll“, „sollte“ oder „kann“ formuliert.

Die Empfehlungen und Expertenkonsensus für die Diagnostik und Intervention bei Kindern und Jugendlichen mit FASD wurden in der zweiten (16.12.2022), dritten (31.03.2023) und vierten (07.06.2023) online Konsensuskonferenz von der Leitliniengruppe hinsichtlich Evidenz, klinischer Relevanz, praktischer Anwendbarkeit und Nutzen-Schaden-Abwägungen diskutiert, modifiziert und graduiert. Die daraus resultierenden handlungsleitenden Empfehlungen und Expertenkonsensus für die Diagnostik und Intervention bei Kindern und Jugendlichen mit FASD in Deutschland wurden in den gleichen Konsensussitzungen mittels einer formalen Konsensfindung in Form eines nominalen Gruppenprozesses konsentiert.

Der nominale Gruppenprozess wurde im Bereich Diagnostik sowie in der ersten Konsensuskonferenz zu Interventionsmöglichkeiten von Frau Prof. Ina Kopp (AWMF) als unabhängige und nicht stimmberechtigte Moderatorin geleitet. In der dritten Konsensuskonferenz wurde Frau Prof. Kopp von Frau Dr. med. Monika Nothacker vertreten, die ebenfalls unabhängig und nicht stimmberechtigt war. Folgende Schritte wurden bei der

Konsentierung jeder einzelnen Empfehlung und jedes einzelnen Expertenkonsensus eingehalten:

1. Präsentation der Ergebnisse der Literaturrecherche und der darauf basierenden, zu konsentierenden Leitlinienempfehlung/Expertenkonsensus
2. Klärung von Fragen bezüglich der gefundenen Literatur
3. Abstimmung über die vorab formulierten, vorgeschlagenen Leitlinienempfehlungen/Expertenkonsensus durch die stimmberechtigten Teilnehmer*innen der Konsensuskonferenz
4. Diskussion der Punkte, für die kein Konsensus erzielt werden konnte
5. Verfassen von Änderungsvorschlägen und Empfehlungen/Expertenkonsensus durch die Teilnehmer*innen der Konsensuskonferenz
6. Abstimmung über die neu formulierten Leitlinienempfehlungen/Expertenkonsensus durch die stimmberechtigten Teilnehmer*innen der Konsensuskonferenz
7. Protokollierung der Konsensstärke der konsentierten Leitlinienempfehlung/Expertenkonsensus

Für die Verabschiedung einer konsentierten Empfehlung oder eines konsentierten Expertenkonsensus wurde entweder ein "starker Konsensus" (Zustimmung von > 95 % der Teilnehmer*innen) bzw. ein „Konsensus“ (Zustimmung von ≥ 75 % der Teilnehmer) benötigt. Die Ergebnisprotokolle der einzelnen Konferenzen wurden für die Transparenz und zur Kontrolle im Nachgang an alle Mitglieder der Leitliniengruppe per E-Mail gesendet. Diese können bei den Leitlinienkoordinator*innen angefordert und eingesehen werden.

4 Verbreitung und Implementierung

4.1 Konzept zur Verbreitung und Implementierung und unterstützende Materialien für die Anwendung der Leitlinie

Zur Implementierung der empfohlenen diagnostischen Kriterien und Interventionen wurde ein Pocket Guide FASD für alle Beteiligten des Gesundheits- und Hilfesystems entworfen. Dieser Pocket Guide beinhaltet den Algorithmus für die Abklärung des FAS, des pFAS und der ARND bei Kindern und Jugendlichen sowie die konsentierten diagnostischen Kriterien in Gegenüberstellung zu möglichen Differentialdiagnosen der FASD in der jeweiligen diagnostischen Säule. Außerdem sind im Pocket Guide alle Empfehlungen sowie Expertenkonsensus zu Interventionsmöglichkeiten für Kinder und Jugendliche mit FASD nach Outcomes sortiert aufgeführt. Der Pocket Guide FASD und zusätzliche Informationen über die Diagnostik der FASD bei Kindern und Jugendlichen werden auf der wissenschaftlichen FASD-Homepage des iSPZ Hauner (www.ispz-hauner.de) und des Deutschen FASD KOMPETENZZENTRUMS Bayern (www.deutsches-fasd-kompetenzzentrum-bayern.de) frei verfügbar sein.

Die Kurz- und Langfassung der Leitlinie, der Leitlinienbericht und der Pocket Guide FASD sind auf der Homepage der AWMF (http://www.awmf.org/leitlinien/detail/ll/022-025.html) veröffentlicht, um deren Inhalte allen Interessierten frei zugänglich zu machen.

Bei Formulierung eines Verdachtes auf FASD oder bei Unsicherheit hinsichtlich der Diagnose FASD soll der/die betreuende professionelle Helfer*in, einschließlich Pflegepersonal, Hebammen, Psycholog*innen, Psychotherapeut*innen, Sozialpädagog*innen, Sozialarbeiter*innen, medizinische Therapeut*innen, klinisch oder institutionell tätige oder niedergelassene Ärztinnen und Ärzte der Gynäkologie, der Kinder- und Jugendmedizin einschließlich der Schwerpunktgebiete Neonatologie, Intensivmedizin, Neuropädiatrie, der Kinder- und Jugendpsychiatrie, Psychotherapie und Psychosomatik, der Allgemeinmedizin und des öffentlichen Gesundheitsdienstes, das Kind zur weiterführenden Diagnostik an einen

FASD-erfahrenen Leistungserbringer überweisen. Der Algorithmus veranschaulicht die für diese Leitlinie konsentierten Kriterien, anhand derer die Diagnose FAS, pFAS oder ARND in Deutschland gestellt werden soll.

4.2 Diskussion möglicher organisatorischer und/oder finanzieller Barrieren gegenüber der Anwendung der Leitlinienempfehlungen

Ein Ziel der Leitliniengruppe ist die Sensibilisierung des Hilfe- und Gesundheitssystems gegenüber Alkoholkonsum in der Schwangerschaft mit seinen schwerwiegenden und lebenslangen Folgen und gegenüber dem Krankheitsbild FASD mithilfe der vorliegenden Leitlinie. In den Konsensuskonferenzen wurde diskutiert, dass der Verdacht auf eine FASD vermehrt gestellt werden soll und die betroffenen Kinder baldmöglichst zu Expert*innen geschickt werden sollen, die sich intensiv mit dem Krankheitsbild FASD auseinandersetzen und entsprechende Kompetenzen personell und institutionell vorhalten. Schätzungen zufolge liegt in Deutschland die Inzidenz der FASD bei etwa 1,77 % der Lebendgeburten [9] und die Prävalenz von FAS bei etwa 3,83 % in der Allgemeinbevölkerung. Deutschen Krankenkassendaten (BARMER) zufolge lag die FASD-Prävalenz bei Kindern (0–18 Jahre) 2015 bei nur 0,07 % (unpublizierte Daten), sodass davon auszugehen ist, dass viel zu wenige Kinder mit FASD in Deutschland tatsächlich auch die Diagnose FASD bekommen. Das Erhalten der Diagnose FASD ist jedoch unabdingbar für eine adäquate Förderung, Beschulung, Ausbildung und Unterbringung des Kindes/Jugendlichen mit FASD sowie zur Reduktion von Sekundärerkrankungen. Außerdem kann erst durch die richtige Diagnose eine individuelle Unterstützung und Entlastung der betroffenen Familie erreicht werden.

Da aktuell noch zu wenige auf FASD spezialisierte Anlaufstellen in Deutschland existieren, ist es dringend notwendig, Fortbildungen für die verschiedenen involvierten Berufsgruppen zu halten. Die Leitliniengruppe legt sich dabei nicht nur auf die Ärzteschaft oder die Psycholog*innen als Expert*innen fest, sondern hofft, auch bei anderen Berufsgruppen für das Thema FASD Interesse und Aufmerksamkeit zu wecken. Die Diagnose FASD sollte bei

Kindern und Jugendlichen interdisziplinär gestellt werden, wobei die abschließende ärztliche und psychologische Beurteilung einen besonders hohen Stellenwert hat.

Die Mandatsträger*innen der beteiligten Fachgesellschaften werden versuchen, in ihrem Fachbereich das Krankheitsbild FASD intensiv zu kommunizieren und über dessen Symptome und Komplikationen im Rahmen von Kongressen oder Fortbildungen aufzuklären.

Die Gesellschaft für Neuropädiatrie als federführende Gesellschaft der vorliegenden Leitlinie hat als ihre Verantwortliche für FASD die Leitlinienkoordinatorin Frau Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf bestimmt.

Aufklärungskampagnen über die langfristige Schädigung des Kindes durch Alkoholkonsum der Schwangeren, nicht alleine für die betroffenen Berufsgruppen, sondern für die gesamte Bevölkerung sind erforderlich, jedoch aufgrund beschränkter finanzieller Ressourcen bisher noch nicht ausreichend durchgeführt worden.

FASD wird bisher in der International Classification of Diseases (ICD-10) als „Alkoholembryopathie (mit Dysmorphien)“ mit Q86.0 unter Kapitel XVII „Angeborene Fehlbildungen, Deformitäten und Chromosomenanomalien“ klassifiziert. Dabei werden die Beeinträchtigungen der Patienten mit FASD in funktionellen ZNS-Bereichen, z. B. in der Entwicklung, in den Exekutivfunktionen und im Verhalten, nicht berücksichtigt. Die Diagnostik von Kindern und Jugendlichen mit FASD ist jedoch besonders hinsichtlich dieser Beeinträchtigungen sehr komplex. Da die medizinischen Leistungen nach ICD-10 abgerechnet werden, wird diese notwendige, aber aufwendige Diagnostik bei Kindern mit FASD nur teilweise entlohnt. Eine adäquate Anpassung der Klassifikation von FASD wäre für das ICD-11 wünschenswert.

5 Öffentliche Konsultation und Verabschiedung durch die Vorstände aller beteiligten Fachgesellschaften und Organisationen

Die Mandatsträger*innen aller beteiligten Fachgesellschaften und Berufsverbände sowie die Expert*innen der Konsensusgruppe hatten die Möglichkeit, Anmerkungen oder Korrekturen zum Leitlinienbericht und zur Leitlinie zu machen. Anhand dieser Anregungen wurde die Leitlinie von den Leitlinienkoordinatorinnen modifiziert.

Daraufhin erfolgte am 06. Februar 2024 eine öffentliche Konsultation über die Website der AWMF über 3 Wochen. Daraus ergaben sich weder Kommentare noch Änderungswünsche an der Langfassung der Leitlinie und am Leitlinienbericht.

Die Mandatsträger*innen mit der vollen Prokura ihrer Fachgesellschaft stimmten den Inhalten der finalen Version der Leitlinie eigenständig zu. Andere Mandatsträger*innen präsentierten die Leitlinie den Vorständen oder Leitliniengremien ihrer Fachgesellschaften oder Berufsverbände. Die Vorstände aller beteiligten Fachgesellschaften stimmten der finalen Version der Leitlinie zu und erreichten damit die Verabschiedung der Leitlinie.

6 Redaktionelle Unabhängigkeit

6.1 Finanzierung der Leitlinie

Die Entwicklung der Leitlinie zum FAS (erster Teil des Leitlinienprojektes, 2011) wurde durch die Drogenbeauftragte der Bundesregierung, Frau Dr. Dyckmans, initiiert und im Wesentlichen durch das Bundesministerium für Gesundheit (BMG) finanziert. Auch die Ergänzung der Leitlinie um die FASD (zweiter Teil des Leitlinienprojektes, 2015/2016) wurde finanziell vom BMG und der nachfolgenden Drogenbeauftragten der Bundesregierung Frau Mortler unterstützt.

Das Update des Diagnostik-Teils und die Ergänzung des Interventions-Teils der Leitlinie zu den FASD sowie die Änderung der Leitlinie in eine „living guideline“ (dritter Teil des Leitlinienprojektes, 2022/2023) wurden aus Mitteln des Innovationsfonds zur Förderung von Versorgungsforschung (§ 92a Absatz 2 Satz 4 zweite Alternative SGB V) des Innovationsausschusses beim Gemeinsamen Bundesausschuss (G-BA – Förderkennzeichen 01VSF21012, Förderzeitraum 01.04.2022 bis 31.03.2025) finanziert.

Die Finanzierung der Leitlinie hat zu keinem Zeitpunkt zu inhaltlichen Interferenzen oder Anpassungen der Leitlinie geführt. Die Gesellschaft für Neuropädiatrie und der Landesverband Bayern für körper- und mehrfachbehinderte Menschen e. V. als Träger des iSPZ Hauner haben die Projekte zusätzlich unterstützt. Weitere Kosten wurden durch die Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital der Universität München (LMU) getragen.

6.2 Darlegung von Interessen und Umgang mit Interessenkonflikten

Alle Mitglieder der Koordinations- und der deutschlandweiten Konsensusgruppe legten vor Beginn der Leitlinienarbeit erklärten ihre Interessen sowohl für die Leitlinie zum FAS (2011/2012) als auch für die Ergänzung der Leitlinie um die anderen FASD (2015/2016) und

die Aktualisierung der Diagnostik-Leitlinie und Erweiterung der Leitlinie auf Intervention für FASD (2022/2023) schriftlich offen. Die Angaben zu den Interessen wurden mit dem AWMF-Formblatt von 2018 erhoben. Die Interessenserklärungen beim dritten Teil des Leitlinienprojektes (2022/2023) wurden bei der Leitlinienkoordinatorin Frau Prof. Dr. med. Dipl.-Psych. Landgraf gesammelt und anschließend von der Interessenkonfliktbeauftragten Frau Strieker auf vorhandene Konflikte geprüft, deren Interessenserklärung vorher von Frau Prof. Dr. med. Dipl.-Psych. Landgraf geprüft wurde. Lagen materielle/finanzielle oder immaterielle/akademische Interessenkonflikte mit Themenbezug zur Leitlinie vor, wurde deren Relevanz durch die Auspägung der Sekundärinteressen (Art und Höhe der Zuwendung, Empfänger) sowie dem Ausmaß des Konflikts (Art und Zeitraum der Beziehung/Tätigkeit, Kooperationspartner) bewertet. Als geringer Interessenkonflikt wurden einzelne Vorträge gewertet, die von der Industrie finanziert wurden. Als moderater Interessenkonflikt wurden bezahlte Tätigkeiten in einem industriefinanzierten Advisory Board/Wiss. Beirat/als Gutachter gewertet. Auch Managementverantwortung in industriefinanzierten Studien, Federführung bei Fort-/Weiterbildungen mit direkter Industriefinanzierung, regelmäßige Vortragstätigkeiten für bestimmte Firmen und Aktionenbesitz einzelner Firmen war ein moderater Interessenkonflikt. Ein hoher Interessenkonflikt lag bei Eigentumsinteresse (z. B. Patente), einem Arbeitsverhältnis bei der Industrie und bei einem hohen Aktienbesitz einzelner Formen vor.

Geringe Interessenkonflikte führen zu einer Limitierung von Leitungsfunktionen insgesamt (Koordination, ggf. Peer; AGs waren nicht vorhanden). Als Konsequenz für moderate Interessenkonflikte ergibt sich ein Abstimmungsverbot für thematisch relevante Empfehlungen oder eine Doppelabstimmung. Personen mit hohen Interessenkonflikten dürfen weder an thematisch relevanten Beratungen teilnehmen noch abstimmen.

Da bei zwei Leitlinienkoordinator*innen geringe Interessenkonflikte vorlagen, wurden ihnen gemäß den AWMF-Regularien zwei Leitlinienkoordinatorinnen ohne Interessenkonflikte zur Seite gestellt. Dies ermöglichte allen Leitlinienkoordinator*innen, als solche tätig zu werden. Bei keinem Mitglied der Konsensusgruppe lagen Interessenkonflikte vor, welche einen Ausschluss im Abstimmungsprozess oder in Teilen davon verlangten. Personen, die bei den

Konsensuskonferenzen eine reine Beobachterfunktion hatten (Vertreterinnen des BMG) und den Abstimmungprozess daher nicht beeinflussen konnten, gaben keine Interessenserklärungen ab. Die Interessenserklärungen wurden in einer Liste (siehe Anhang A. 18) zusammengefasst und allen Konsensusmitgliedern zur Verfügung gestellt, um deren Vollständigkeit und Korrektheit zu bestätigen. Kein Mitglied erhob Einspruch gegen die Bewertung eventueller Interessenkonflikte.

7 Gültigkeitsdauer und Aktualisierungsverfahren

Die Gültigkeit der ersten Leitlinie zum FAS 2011 war auf fünf Jahre festgelegt. Ein Addendum wurde im September 2013 hinzugefügt. Die Leitlinie wurde 2015/2016 um die FASD ergänzt und deren Gültigkeit erneut auf fünf Jahre festgelegt. Die hier vorliegende, aktualisierte, um die Intervention erweiterte und bis zum 06. Mai 2024 inhaltlich überarbeitete Leitlinie ist eine living guideline. Das bedeutet, dass die Leitlinie eine Gültigkeitsdauer von einem Jahr aufweist und daher mindestens jährlich aktualisiert wird (aktuell gültig bis 06. Mai 2025). Dazu wird die neue Literatur durchsucht und in einer Umfrage durch die Leitlinienkoordinator*innen unter den Mandatsträger*innen, Expert*innen und Patientenvertreter*innen geklärt, welche Neuigkeiten im Bereich der Diagnostik und Intervention bei Kindern und Jugendlichen vorliegen und ob diese in die Aktualisierung der Leitlinie integriert werden müssen. Frau Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf fungiert als verantwortliche Ansprechpartnerin für die Aktualisierung der Leitlinie (Kontaktdaten: mirjam.landgraf@med.uni-muenchen.de, Tel.: 089 44005 2811).

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3. Cochrane. Deutschland, Institut für Medizinische Biometrie und Statistik, Freiburg, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften- Institut für Medizinisches Wissensmanagement, Ärztliches Zentrum für Qualität in der Medizin. „Manual zur Bewertung des Biasrisikos in Interventionsstudien“. 2. Auflage, 2021. Verfügbar bei: Cochrane Deutschland: https://www.cochrane.de/de/literaturbewertung; ; AWMF: https://www.awmf.org/leitlinien/awmf-regelwerk/ll-entwicklung.html; ÄZQ: https://www.leitlinien.de/methodik. DOI: 10.6094/UNIFR/194900, https://freidok.uni-freiburg.de/data/194900.
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6. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017:j4008.
7. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019:l4898.
8. Elliott L, Coleman K, Suebwongpat A, Norris S. Fetal Alcohol Spectrum Disorders (FASD): systematic reviews of prevention, diagnosis and management. HSAC Report. 2008;1(9).
9. Kraus L, Seitz N-N, Shield KD, Gmel G, Rehm J. Quantifying harms to others due to alcohol consumption in Germany: a register-based study. BMC Medicine. 2019;17(1).
10. Brown JM, Bland R, Jonsson E, Greenshaw AJ. The standardization of diagnostic criteria for Fetal Alcohol Spectrum Disorder (FASD): Implications for research, clinical practice and population health. Can J Psych 2019;64(3):169-76.
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A. 1 Hintergrundinformationen – Fokussierte Literaturrecherche im Rahmen des ersten Teils des Leitlinienprojektes 2011

Die Suche umfasste den Zeitraum vom 01. Januar 2001 bis zum 12. Oktober 2011 und Dokumente in deutscher und englischer Sprache. Die fokussierte Literatursuche musste aus Kapazitätsgründen auf einige Länder begrenzt werden. Aufgrund der ähnlichen gesellschaftlichen und kulturellen Zusammensetzung wurde die Literaturrecherche auf die Länder Europas sowie USA und Canada beschränkt.

Die Suche wurde in folgenden Recherchequellen durchgeführt:

- Literaturdatenbank Medline über http://www.pubmed.org
- The Cochrane Library über http://www.thecochranelibrary.com

Die gemäß den Suchkriterien gefundenen Abstracts wurden den zuständigen Mitarbeitern geschickt, die alle Abstracts sichteten. Dabei wurden anhand der vorher definierten Ausschlußkriterien weitere Artikel durch Sichtung der Abstracts ausgeschlossen oder an die Bearbeiter anderer Teilbereiche weitergeleitet. Die relevanten Artikel wurden durchgearbeitet, zusammengefasst und deren Ergebnisse zu finalen Aussagen zusammengeführt.

Da es sich bei den Ergebnissen der fokussierten Literaturrecherche nicht um die Haupt-Fragestellung der Leitlinie (Diagnostik der FASD) sondern um Hintergrundinformationen für die Leitlinie handelt, wurde keine formale Bewertung der Studien bezüglich Studiendurchführung, Anzahl der Teilnehmer*innen und Berücksichtigung möglicher Fehlerquellen sowie keine Evidenzbewertung der Literatur durchgeführt und keine evidenzbasierten Empfehlungen abgeleitet.

Teilbereich 1: Epidemiologie

Als Recherchevokabular wurden folgende Begriffe verwendet:

- fetal alcohol syndrome, fetal alcohol related deficit, fetal alcohol spectrum disorders, FAS, FASD, embryopathy, fetal alcohol effects
- epidemiology, incidence, frequency, prevalence, occurrence, statistics

Ausschlusskriterien für die Relevanzsichtung:

- A1: andere Erkrankung
- A2: Tiere/in vitro
- A3: anderes Thema
- A4: keine echten Studien z. B. Leserbriefe etc.
- A5: anderes Land als Länder Europas, USA und Canada

PubMed (12. Oktober 2011)

Nr.	Suchfrage	Anzahl
#4	#1 AND #2 Limits: English, German, Publication Date from 2001	1914
#3	#1 AND #2	3123
#2	epidemiology OR incidence OR frequency OR prevalence OR occurrence OR statistics (Details: ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "epidemiology"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "incidence"[All Fields] OR "incidence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "frequency"[All Fields] OR "epidemiology"[MeSH Terms] OR "frequency"[All Fields]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]) OR ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "occurrence"[All Fields] OR "epidemiology"[MeSH Terms] OR "occurrence"[All Fields]) OR ("Statistics (Ber)"[Journal] OR "statistics"[All Fields]))	2701325
#1	fetal alcohol syndrome OR fetal alcohol related deficit OR fetal alcohol spectrum disorders OR FAS OR FASD OR (alcohol AND embryopathy) OR fetal alcohol effects (Details: ("foetal alcohol syndrome"[All Fields] OR "fetal alcohol syndrome"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "syndrome"[All Fields]) OR "fetal alcohol syndrome"[All Fields]) OR (("fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND related[All Fields] AND ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR "deficit"[All Fields])) OR (("fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND ("Spectrum"[Journal] OR "spectrum"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "disorders"[All Fields])) OR ("fas"[All Fields]) OR FASD[All Fields] OR (("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND ("fetal diseases"[MeSH Terms] OR ("fetal"[All Fields] AND "diseases"[All Fields]) OR "fetal diseases"[All Fields] OR "embryopathy"[All Fields])) OR ("fetal alcohol syndrome"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "syndrome"[All Fields]) OR "fetal alcohol syndrome"[All Fields] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "effects"[All Fields]) OR "fetal alcohol effects"[All Fields]))	27344

Anzahl der Treffer: 1914

Davon relevant: 450

Die Recherche ergab für die erste Fragestellung zur Prävalenz von mütterlichem Alkoholkonsum in der Schwangerschaft und von FAS in den entsprechenden Ländern 450 als potentiell relevant eingestufte Abstracts, die entsprechend der formulierten Ausschlusskriterien gescreent wurden.

Nach dem Screening der Abstracts verblieben 50 Studien; weitere 10 Studien wurden über die separate Recherche zum Teilbereich Risikofaktoren für mütterlichen Alkoholkonsum identifiziert. Nach dem Screening des Volltextes dieser 60 Studien wurden 27 Primärstudien eingeschlossen.

Aus diesen Studien wurden folgende Informationen extrahiert:

- Autor*innen
- Journal
- Land
- Population
- Dauer der Studie
- Anzahl der Teilnehmer*innen
- FAS Prävalenz oder Inzidenz und Konfidenzintervalle
- Definition von binge drinking (Sturz-Trinken, Komasaufen)
- Prävalenz von mütterlichem Alkoholkonsum während der Schwangerschaft (Konfidenzintervalle wurden in den eingeschlossenen Studien nicht berichtet)
- Notizen (z. B. genauere Beschreibung der Studie, Abkürzungen)

Eingeschlossene Literatur zur Prävalenz von mütterlichem Alkoholkonsum während der Schwangerschaft und zur Prävalenz des FAS (2011)

1. May et al. Prevalence of children with severe fetal alcohol spectrum disorders in communities near Rome, Italy: new estimated rates are higher than previous estimates. Int J Environ Res Public Health. 2011;8(6):2331-51.
2. Morleo et al. Under-reporting of foetal alcohol spectrum disorders: an analysis of hospital episode statistics. BMC Pediatr 2011;11:14.
3. Thanh et al. Drinking alcohol during pregnancy: evidence from Canadian Community Health Survey 2007/2008. J Popul Ther Clin Pharmacol. 2010;17(2):e302-e307
4. Centres for Disease Control and Prevention. Alcohol use among pregnant and nonpregnant women of childbearing age - United States, 1991-2005. MMWR Morb Mortal Wkly Rep. 2009;58(19):529-32.
5. Aliyu et al. Prenatal alcohol consumption and fetal growth restriction: potentiation effect by concomitant smoking. Nicotine Tob Res 2009;11(1):36-43.

6. de Chazeron et al. Is pregnancy the time to change alcohol consumption habits in France? Alcohol Clin Exp Res 2008;32(5):868-73.
7. Druschel et al. Issues in estimating the prevalence of fetal alcohol syndrome: examination of 2 counties in New York State. Pediatrics 2007;119(2):e384-e390.
8. Elgen et al. Lack of recognition and complexity of foetal alcohol neuroimpairments. Acta Paediatr 2007;96(2):237-41.
9. Tsai et al. Patterns and average volume of alcohol use among women of childbearing age Matern Child Health J 2007;11(5):437-45.
10. May et al. Epidemiology of FASD in a province in Italy: Prevalence and characteristics of children in a random sample of schools. Alcohol Clin Exp Res 2006;30(9):1562-75.
11. Chambers et al. Alcohol consumption among low-income pregnant Latinas Alcohol Clin Exp Res 2005;29(11):2022-8.
12. Astley. Fetal alcohol syndrome prevention in Washington State: evidence of success. Paediatr Perinat Epidemiol. 2004;18(5):344-51.
13. Weiss et al. The Wisconsin Fetal Alcohol Syndrome Screening Project WMJ 2004;103(5):53-60.
14. Drews et al. Prevalence of prenatal drinking assessed at an urban public hospital and a suburban private hospital J Matern Fetal Neonatal Med 2003;13(2):85-93.
15. Fox et al. Estimating prevalence of fetal alcohol syndrome (FAS): effectiveness of a passive birth defects registry system. Birth Defects Res A Clin Mol Teratol 2003;67(9):604-8.
16. Goransson et al. Fetus at risk: prevalence of alcohol consumption during pregnancy estimated with a simple screening method in Swedish antenatal clinics. Addiction 2003;98(11):1513-20.
17. O'Connor et al. Alcohol use in pregnant low-income women J Stud Alcohol 2003;64(6):773-83.
18. Poitra et al. A school-based screening program for fetal alcohol syndrome Neurotoxicol Teratol 2003;25(6):725-9.
19. Centers for Disease Control and Prevention. Fetal alcohol syndrome--Alaska, Arizona, Colorado, and New York, 1995-1997. JAMA 2002;288(1):38-40.
20. Astley et al. Application of the fetal alcohol syndrome facial photographic screening tool in a foster care population. J Pediatr 2002;141(5):712-7.
21. Ethen et al. Alcohol consumption by women before and during pregnancy. Matern Child Health J 2009; 13(2):274-285.
22. Grant et al. Alcohol use before and during pregnancy in western Washington, 1989-2004: implications for the prevention of fetal alcohol spectrum disorders. Am J Obstet Gynecol 2009; 200(3):278.
23. Donnelly et al. Illegal drug use, smoking and alcohol consumption in a low-risk Irish primigravid population. J Perinat Med 2008; 36(1):70-72.
24. Strandberg-Larsen et al. Characteristics of women who binge drink before and after they become aware of their pregnancy. Eur J Epidemiol 2008; 23(8):565-572.
25. Bergmann et al. Perinatal risk factors for long-term health. Results of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2007; 50(5-6):670-676.
26. Alvik et al. Alcohol use before and during pregnancy: a population-based study. Acta Obstet Gynecol Scand 2006; 85(11):1292-1298.
27. U.S. Government. Birth defects surveillance data from selected states, 1996-2000 Birth Defects Res A Clin Mol Teratol 2003;67(9):729-818.
28. GEDA - Studie zur Gesundheit in Deutschland des Robert Koch Instituts. (2012). Retrieved June 22, 2016, from http://dip21.bundestag.de/dip21/btd/18/033/1803378.pdf

Teilbereich 2: Risikofaktoren für mütterlichen Alkoholkonsum während der Schwangerschaft

Als Recherchevokabular wurden folgende Begriffe verwendet:

- risk
- alcohol
- pregnancy

Ausschlusskriterien für Relevanzsichtung:

- A1: anderes Thema/andere Erkrankung
- A2: Tiere/in vitro
- A3: keine echten Studien z. B. Leserbriefe etc.
- A4: anderes Land als Länder Europas, USA und Canada
- A5: Erwachsene

PubMed (19. Oktober 2011)

Nr.	Suchfrage	Anzahl
#2	#1 Limits: English, German, Publication Date from 2001	1864
#1	risk AND alcohol AND pregnancy (Details: ("risk"[MeSH Terms] OR "risk"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]))	3796

Anzahl der Treffer: 1864

Davon relevant: 298

Cochrane (19. Oktober 2011)

Nr.	Suchfrage	Anzahl
#1	(risk AND alcohol and pregnancy):ti,ab,kw from 2001 to 2011	43

- Cochrane Database of Systematic Reviews (9)
- Database of Abstracts of Reviews of Effects (0)
- Cochrane Central Register of Controlled Trials (31)
- Cochrane Methodology Register (1)
- Health Technology Assessment Database (1)
- NHS Economic Evaluation Database (1)

Anzahl der Treffer: 43

Davon neu: 8

Davon relevant: 1

Insgesamt wurden bei der ersten Recherche mittels Recherchemaske 399 Abstracts gefunden, denen aus anderen Bereichen der fokussierten Literaturrecherche drei Abstracts folgten. Nach Sichtung der Abstracts wurden 60 Publikationen in die Volltextrecherche eingeschlossen.

In der Volltextrecherche wurden 38 Artikel aus USA, drei Artikel aus Kanada und neun Artikel aus Europa (1-mal Dänemark, 2-mal Deutschland, 1-mal Großbritannien, 1-mal Irland, 1-mal Italien, 1-mal Norwegen, 2-mal Schweden) gefunden, die Risikofaktoren für Alkoholkonsum in der Schwangerschaft bestimmt haben.

Eingeschlossene Literatur zu Risikofaktoren für mütterlichen Alkoholkonsum während der Schwangerschaft

1. Mullally et al. Prevalence, predictors and perinatal outcomes of peri-conceptional alcohol exposure-retrospective cohort study in an urban obstetric population in Ireland.
BMC Pregnancy and Childbirth. 2011; 11:27
2. De Santis et al. Smoking, alcohol consumption and illicit drug use in an Italian population of pregnant women. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2011; 159:106–110
3. Jones. The Effects of Alcohol on Fetal Development. Birth Defects Research (Part C). 2011; 93:3–11
4. Kiely et al. Patterns of alcohol consumption among pregnant African-American women in Washington, DC, USA. Paediatric and Perinatal Epidemiology. 2011; 25: 328–339
5. Muckle et al. Alcohol, Smoking, and Drug Use Among Inuit Women of Childbearing Age During Pregnancy and the Risk to Children. Alcohol Clin Exp Res. 2011; 35:1081–1091
6. Elo & Culhane. Variations in Health and Health Behaviors by Nativity Among Pregnant Black Women in Philadelphia. Am J Public Health. 2010; 100: 2185–2192.
7. Thanh & Jonsson. Drinking alcohol during pregnany: evidence from Canadian Community Health Survey 2007/2008. J Popul Ther Clin Pharmacol. 2010; 17
8. Page et al. Does Religiosity Affect Health Risk Behaviors in Pregnant and Postpartum Women? Matern Child Health J. 2009; 13:621–632
9. Ethen et al. Alcohol Consumption by Women Before and During Pregnancy
National Birth Defects Prevention Study. Matern Child Health J. 2009; 13:274–285
10. Harrison & Sidebottom. Alcohol and Drug Use Before and During Pregnancy:
An Examination of Use Patterns and Predictors of Cessation. Matern Child Health J. 2009; 13:386–394
11. Tenkku et al. Racial Disparities in Pregnancy-Related Drinking Reduction. Matern Child Health J. 2009; 13:604–613
12. Alvanzo & Svikis. History of Physical Abuse and Periconceptional Drinking in PregnantWomen. Substance Use & Misuse. 2008; 43:1098–1109
13. Meschke et al. Correlates of Prenatal Alcohol Use. Matern Child Health J. 2008; 12:442–451

14. McGartland Rubio et al. Factors Associated with Alcohol Use, Depression, and Their Cooccurrence during Pregnancy. Alcohol Clin Exp Res. 2008; 32(9): 1543–1551.
15. Strandberg-Larsen et al. Characteristics of women who binge drink before and after they become aware of their pregnancy. Eur J Epidemiol. 2008; 23:565–572
16. Bergmann et al. Perinatale Einflussfaktoren auf die spätere Gesundheit - Ergebnisse des Kinder- und Jugendgesundheitssurveys (KiGGS). Bundesgesundheitsblatt - Gesundheitsforschung – Gesundheitsschutz. 2007; 50:670–676
17. Flynn et al. Brief detection and co-occurrence of violence, depression and alcohol risk in prenatal care settings. Arch Womens Ment Health. 2007; 10: 155–161
18. Tsai et al. Patterns and Average Volume of Alcohol Use Among Women of Childbearing Age. Matern Child Health J. 2007; 11:437–445
19. Alvik et al. Alcohol use before and during pregnancy: a population-based study. Acta Obstetricia et Gynecologica. 2006; 85: 1292-1298
20. Perreira & Cortes. Race/Ethnicity and Nativity Differences in Alcohol and Tobacco Use During Pregnancy. Am J Public Health. 2006; 96:1629–1636.
21. Chambers et al. Alcohol Consumption among Low-Income Pregnant Latinas. Alcohol Clin Exp Res. 2005; 29:2022–2028
22. Knight & Plugge. Risk factors for adverse perinatal outcomes in imprisoned pregnant women: a systematic review. BMC Public Health. 2005; 5:111
23. Phares et al. Surveillance for Disparities in Maternal Health-Related Behaviors -Selected States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2000-2001. MMWR Surveill Summ. 2004; 53(4):1-13
24. Flynn et al. Rates and Correlates of Alcohol Use Among Pregnant Women in Obstetrics Clinics. Alcohol Clin Exp Res. 2003; 27 :81–87
25. Göransson et al. Fetus at risk: prevalence of alcohol consumption during pregnancy estimated with a simple screening method in Swedish antenatal clinics. Addiction. 2003; 98:1513–1520
26. Kvigne et al. Characteristics of Mothers Who Have Children with Fetal Alcohol Syndrome or Some Characteristics of Fetal Alcohol Syndrome. J Am Board Fam Pract 2003; 16:296 –303
27. May & Gossage. Estimating the Prevalence of Fetal Alcohol Syndrome: A Summary. Alcohol Res Health. 2001; 25:159-67
28. Rebhan et al. Rauchen, Alkoholkonsum und koffeinhaltige Getränke vor, während und nach der Schwangerschaft – Ergebnisse aus der Studie „Stillverhalten in Bayern“. Gesundheitswesen. 2009; 71:391-8
29. Cheng et al. Alcohol Consumption During Pregnancy Prevalence and Provider Assessment. Obstet Gynecol. 2011; 117:212–7
30. Karjane et al. Alcohol Abuse Risk Factors and Psychiatric Disorders in Pregnant Women with a History of Infertility. Journal of Women's health. 2008; 17
31. Meshberg-Cohen & Svikis. Panic disorder, trait anxiety, and alcohol use in pregnant und nonpregnant women. Comprehensive Psychiatry. 2007; 48:504-510.
32. Lucas et al. Alcohol use among pregnant African American women: Ecological Considerations. Health & Social Work. 2003; 28
33. Pevalin et al. Beyond biology: the social context of prenatal behaviour and birth outcomes. Soz Praventivmed. 2001; 46:233-239
34. Sharpe & Velasquez. Risk of Alcohol-Exposed Pregnancies among Low-Income, Illicit Drug-Using Women. Journal of Women's health. 2008; 17
35. Harelick et al. Preconception Health of Low Socioeconomic Status Women: Assessing Knowledge and Behaviors. Women's Health Issues. 2011; 21:272-276.
36. Bobo et al. Identifying social drinkers likely to consume alcohol during pregnancy: Findings from a prospective cohort study. Psychological Reports. 2007; 101:857-870.
37. O'Connor & Whaley. Health Care Provider Advice and Risk Factors Associated With Alcohol Consumption Following Pregnancy Recognition. J Stud Alcohol. 2006; 67:22-31
38. Bakhireva et al. Periconceptional binge drinking and acculturation among pregnant Latinas in New Mexico. Alcohol. 2009; 43:475-481

39. Havens et al. Factors associated with substance use during pregnancy: Results from a national sample. Drug and Alcohol Dependence. 2009; 99:89–95
40. Orr et al. Unintended Pregnancy and Prenatal Behaviors Among Urban, Black Women in Baltimore, Maryland: The Baltimore Preterm Birth Study. Ann Epidemiol. 2008; 18:545–551.
41. Magnusson et al. Hazardous alcohol users during pregnancy: Psychiatric health and personality traits. Drug and Alcohol Dependence. 2007; 89:275–281.
42. Haynes et al. Determinants of alcohol use in pregnant women at risk for alcohol consumption. Neurotoxicology and Teratology. 2003; 25:659–666
43. Leonardson & Loudenburg. Risk factors for alcohol use during pregnancy in a multistate area. Neurotoxicology and Teratology. 2003; 25:651–658
44. Meschke et al. Assessing the risk of fetal alcohol syndrome: understanding substance use among pregnant women. Neurotoxicology and Teratology. 2003; 25:667–674
45. Floyd et al. Alcohol-Exposed Pregnancy. Characteristics Associated with Risk. Project CHOICES Research Group. Am J Prev Med. 2002; 23:166–173
46. Flynn & Chermack. Prenatal Alcohol Use: The Role of Lifetime Problems With Alcohol, Drugs, Depression, and Violence. J. Stud. Alcohol Drugs. 2008; 69:500-509,
47. Ahluwalia et al. Mental and Physical Distress and High-Risk Behaviors Among Reproductive-Age Women. Obstet Gynecol. 2004;104:477–83.
48. Stotts et al. Tobacco, alcohol and caffeine use in a low-income, pregnant population. Journal of Obstetrics and Gynaecology. 2003; 23:247–251
49. Martin et al. Substance Use Before and During Pregnancy: Links to Intimate Partner Violence. Am J Drug Alcohol Abuse. 2003; 29:599-617.
50. Hayes et al. Prenatal Alcohol Intake in a Rural, Caucasian Clinic. Fam Med 2002; 34:120-5.

Teilbereich 3: Risikofaktoren für die Entwicklung einer FASD

Als Recherchevokabular wurden folgende Begriffe verwendet:

- risk
- alcohol
- pregnancy

Am 09. Dezember 2011 erfolgte eine erneute Recherche mit folgendem Vokabular, mit dem Ziel, zusätzliche Dokumente zu identifizieren:

- early pregnancy, late pregnancy
- fetal alcohol syndrome, fetal alcohol related deficit, fetal alcohol spectrum disorders, FASD, FAS, alcohol embryopathy, fetal alcohol effects

Ausschlusskriterien für Relevanzsichtung:

- A1: anderes Thema / andere Erkrankung
- A2: Tiere / in vitro
- A3: keine echten Studien z. B. Leserbriefe etc.
- A4: anderes Land als Länder Europas, USA und Canada

PubMed (09. Dezember 2011)

Nr.	Suchfrage	Anzahl
#4	#3 Limits: English, German, Publication Date from 2001	303
#3	#2 NOT #1	580
#2	(late Or early) And pregnancy AND (fetal alcohol syndrome OR fetal alcohol related deficit OR fetal alcohol spectrum disorders OR FASD OR FAS OR (alcohol AND embryopathy) OR fetal alcohol effects)	785
#1	risk AND alcohol AND pregnancy (Details: ("risk"[MeSH Terms] OR "risk"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields]))	3818

Anzahl der Treffer: 303

Davon relevant: 71

Cochrane (09. Dezember 2011)

Nr.	Suchfrage	Anzahl
#4	#3 from 2001 to 2011	2
#3	#2 NOT #1	4
#2	(late pregnancy OR early pregnancy):ti,ab,kw and (fetal alcohol syndrome OR fetal alcohol related deficit OR fetal alcohol spectrum disorders OR FASD OR FAS OR (alcohol AND embryopathy) OR fetal alcohol effects):ti,ab,kw	7
#1	(risk):ti,ab,kw and (alcohol):ti,ab,kw and (pregnancy):ti,ab,kw	65

- Cochrane Database of Systematic Reviews (0)
- Database of Abstracts of Reviews of Effects (0)
- Cochrane Central Register of Controlled Trials (2)
- Cochrane Methodology Register (0)
- Health Technology Assessment Database (0)
- NHS Economic Evaluation Database (0)

Anzahl der Treffer: 2

Davon neu: 1

Davon relevant: 0

Eingeschlossene Literatur zu Risikofaktoren für die Entstehung einer FASD

1. Aros S, Mills JL, Iniguez G, Avila A, Conley MR, Troendle J et al. Effects of prenatal ethanol exposure on postnatal growth and the insulin-like growth factor axis. Horm Res Paediatr 2011; 75(3):166-173.
2. Bakker R, Pluimgraaff LE, Steegers EA, Raat H, Tiemeier H, Hofman A et al. Associations of light and moderate maternal alcohol consumption with fetal growth characteristics in different periods of pregnancy: the Generation R Study. Int J Epidemiol 2010; 39(3):777-789.

3. Burden MJ, Westerlund A, Muckle G, Dodge N, Dewailly E, Nelson CA et al. The effects of maternal binge drinking during pregnancy on neural correlates of response inhibition and memory in childhood. Alcohol Clin Exp Res 2011; 35(1):69-82.
4. Chudley AE. Fetal alcohol spectrum disorder: counting the invisible - mission impossible? Arch Dis Child 2008; 93(9):721-722.
5. Clarren SK, Randels SP, Sanderson M, Fineman RM. Screening for fetal alcohol syndrome in primary schools: a feasibility study. Teratology 2001; 63(1):3-10.
6. Cone-Wesson B. Prenatal alcohol and cocaine exposure: influences on cognition, speech, language, and hearing. J Commun Disord 2005; 38(4):279-302.
7. Cook JD. Biochemical markers of alcohol use in pregnant women. Clin Biochem 2003; 36(1):9-19.
8. Day NL, Leech SL, Richardson GA, Cornelius MD, Robles N, Larkby C. Prenatal alcohol exposure predicts continued deficits in offspring size at 14 years of age. Alcohol Clin Exp Res 2002; 26(10):1584-1591.
9. Drabble LA, Poole N, Magri R, Tumwesigye NM, Li Q, Plant M. Conceiving risk, divergent responses: perspectives on the construction of risk of FASD in six countries. Subst Use Misuse 2011; 46(8):943-958.
10. Fetal alcohol syndrome. Paediatr Child Health 2002; 7(3):161-195.
11. Gallot D, de C, I, Boussiron D, Ughetto S, Vendittelli F, Legros FJ et al. Limits of usual biochemical alcohol markers in cord blood at term: a fetal/maternal population-based study. Clin Chem Lab Med 2007; 45(4):546-548.
12. Gmel G, Kuntsche E, Rehm J. Risky single-occasion drinking: bingeing is not bingeing. Addiction 2011; 106(6):1037-1045.
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A. 2 Methodik systematische Literaturrecherche – Diagnostische Kriterien des FAS (erster Teil des Leitlinienprojektes 2011)

a) Einschlusskriterien

Population	**Kinder und Jugendliche (< 18 Jahre) mit FAS**
Intervention	Diagnostische Tests zu den folgenden Kriterien ▪ Wachstumsstörungen ▪ Faziale Auffälligkeiten ▪ ZNS-Anomalien ▪ Alkoholkonsum der Mutter.
Kontrolle	Gesunde Kinder/Jugendliche Kinder/Jugendliche mit einer diagnostizierten anderen neuropsychologischen Störung (ADHS) Kinder/Jugendliche mit nicht Vollbild-FAS
Endpunkte	Haupt-Zielgröße war die Sicherheit der diagnostischen Diskriminierung der eingesetzten Testverfahren im Hinblick auf die Diagnose Fetales Alkoholsyndrom. Weitere Zielgrößen wurden nicht festgelegt
Studientypen	Einschluss von randomisierten kontrollierten Studien, nachrangig Einschluss von Kohortenstudien oder Fall-Kontrollstudien bzw. Fallserien (> 10 Patienten) bzw. systematische Reviews bzw. Metaanalysen dieser Studien Anmerkung: Bei der 2. Sichtung der Volltexte wurden Fallserien ausgeschlossen
Sprachen	Englisch, Deutsch

b) Ausschlusskriterien auf Abstrakt- und Volltextebene

A1	andere Erkrankung
A2	Studien an Tieren/in vitro
A3	anderes Thema (nicht Diagnose oder Screening des FAS)
A4	Methodik der Publikation, anderer Publikationstyp
A5	unsystematischer Review
A6	Alter der Probanden überwiegend > 18 Jahre (mehr als 80 %)
A7	Zum Thema Alkoholkonsum der Mutter: Publikation vor 2008 (da systematischer Review von Elliot et al [3] mit Literaturrecherche bis Juli 2008)
A8	Doppelpublikationen (Dubletten)

Recherchestrategie in Pubmed am 31. Oktober 2011

Nr.	Suchfrage	Anzahl
#6	#1 AND #4 Limits: English, German, Publication Date from 2001	1363
#5	#1 AND #4	3480
#4	#2 OR #3	7693746
#3	(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR deficits OR growth deficiency OR facial phenotype OR **("central nervous system"** AND (**damage OR dysfunction)**) OR ((**cognitive OR communication OR behavioral)** AND (**difficulties OR disabilities)**) OR adverse life outcomes OR mental health concerns OR ((**fluency OR articulation**) AND abilities) (Details: (developmental[All Fields] AND (defect[All Fields] OR ("abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "defects"[All Fields]) OR abnormality[All Fields] OR ("abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "congenital abnormalities"[MeSH Terms] OR ("congenital"[All Fields] AND "abnormalities"[All Fields]) OR "congenital abnormalities"[All Fields]) OR anomaly[All Fields] OR ("abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "anomalies"[All Fields]))) OR deficits[All Fields] OR (("growth and development"[Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms]) AND ("deficiency"[Subheading] OR "deficiency"[All Fields])) OR (("face"[MeSH Terms] OR "face"[All Fields] OR "facial"[All Fields]) AND ("phenotype"[MeSH Terms] OR "phenotype"[All Fields])) OR ("central nervous system"[All Fields] AND (damage[All Fields] OR ("physiopathology"[Subheading] OR "physiopathology"[All Fields] OR "dysfunction"[All Fields])))) OR ((cognitive[All Fields] OR ("communication"[MeSH Terms] OR "communication"[All Fields]) OR ("behavior"[MeSH Terms] OR "behavior"[All Fields] OR "behavioral"[All Fields])) AND (difficulties[All Fields] OR disabilities[All Fields])) OR (adverse[All Fields] AND ("life"[MeSH Terms] OR "life"[All Fields]) AND outcomes[All Fields]) OR (("mental health"[MeSH Terms] OR ("mental"[All Fields] AND "health"[All Fields]) OR "mental health"[All Fields]) AND concerns[All Fields]) OR ((fluency[All Fields] OR ("joints"[MeSH Terms] OR "joints"[All Fields] OR "articulation"[All Fields])) AND ("aptitude"[MeSH Terms] OR "aptitude"[All Fields] OR "abilities"[All Fields])))	234689
#2	diagnostic OR diagnosis OR diagnoses OR screening ("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields]) OR ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]) OR ("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnoses"[All Fields]) OR ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "screening"[All Fields] OR "mass screening"[MeSH Terms] OR ("mass"[All Fields] AND "screening"[All Fields]) OR "mass screening"[All Fields] OR "screening"[All Fields])	7587987

#1	fetal alcohol syndrome OR fetal alcohol related deficit OR fetal alcohol spectrum disorders OR FASD OR (alcohol AND embryopathy) OR fetal alcohol effects (Details: ("foetal alcohol syndrome"[All Fields] OR "fetal alcohol syndrome"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "syndrome"[All Fields]) OR "fetal alcohol syndrome"[All Fields]) OR (("fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND related[All Fields] AND ("malnutrition"[MeSH Terms] OR "malnutrition"[All Fields] OR "deficit"[All Fields])) OR (("fetus"[MeSH Terms] OR "fetus"[All Fields] OR "fetal"[All Fields]) AND ("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND ("Spectrum"[Journal] OR "spectrum"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "disorders"[All Fields])) OR FASD[All Fields] OR (("ethanol"[MeSH Terms] OR "ethanol"[All Fields] OR "alcohol"[All Fields] OR "alcohols"[MeSH Terms] OR "alcohols"[All Fields]) AND ("fetal diseases"[MeSH Terms] OR ("fetal"[All Fields] AND "diseases"[All Fields]) OR "fetal diseases"[All Fields] OR "embryopathy"[All Fields])) OR ("fetal alcohol syndrome"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "syndrome"[All Fields]) OR "fetal alcohol syndrome"[All Fields] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "effects"[All Fields]) OR "fetal alcohol effects"[All Fields])	5953

Recherchestrategie in Cochrane Library am 31. Oktober 2011

Nr.	Suchfrage	Anzahl
#3	#1 AND #2 from 2001 to 2011	20
#2	(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR deficits OR growth deficiency OR facial phenotype OR ("central nervous system" AND (damage OR dysfunction)) OR ((cognitive OR communication OR behavioral) AND (difficulties OR disabilities)) OR adverse life outcomes OR mental health concerns OR ((fluency OR articulation) AND abilities) in Title, Abstract or Keywords or diagnostic OR diagnosis OR diagnoses OR screening in Title, Abstract or Keywords	85863
#1	fetal alcohol syndrome OR fetal alcohol related deficit OR fetal alcohol spectrum disorders OR FASD OR (alcohol AND embryopathy) OR fetal alcohol effects in Title, Abstract or Keywords	46

- Cochrane Database of Systematic Reviews (3)
- Database of Abstracts of Reviews of Effects (1)
- Cochrane Central Register of Controlled Trials (14)
- Cochrane Methodology Register (0)
- Health Technology Assessment Database (1)
- NHS Economic Evaluation Database (1)

Anzahl der Treffer insgesamt: 20

A. 3 Evidenzklassifikationssystem nach Oxford (March 2009)

Level **1A**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	1a SR (with homogeneity*) of RCTs SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres SR (with homogeneity*) of prospective cohort studies SR (with homogeneity*) of Level 1 economic studies
Level **1b**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual RCT (with narrow Confidence Interval‡) Individual inception cohort study with > 80 % follow-up; CDR† validated in asingle population Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre Prospective cohort study with good follow-up**** Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level **1c**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	All or none§ All or none case series Absolute SpPins and SnNouts†† All or none case-series Absolute better-value or worse-value analyses ††††
Level **2a**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of cohort studies SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs SR (with homogeneity*) of Level >2 diagnostic studies SR (with homogeneity*) of 2b and better studies SR (withhomogeneity*) of Level >2 economic studies
Level **2b**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual cohort study (including low quality RCT; e.g., <80% followup) Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split sample §§§ only Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases Retrospective cohort study, or poor follow-up Analysis based on clinically sensible costs or alternatives;

		limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
Level **2c**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	"Outcomes" Research; Ecological studies "Outcomes" Research Ecological studies Audit or outcomes research
Level **3a**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of case-control studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b And better studies
Level **3b**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual Case-Control Study Non-consecutive study; or without consistently applied reference standards Non-consecutive cohort study, or very limited population Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
Level **4**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Case-series (and poor quality cohort and case-control studies§§) Case-series (and poor quality prognostic cohort studies***) Case-control study, poor or nonindependent reference standard Case-series or superseded reference standards Analysis with no sensitivity analysis
Level **5**	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

NOTES
Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:
EITHER a single result with a wide Confidence Interval
OR a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and nonexposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e. g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in < 80 % of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1–6 months acute, 1–5 years chronic).

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009) (for definitions of terms used see glossary at http://www.cebm.net/?o=1116)
Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998. Updated by Jeremy Howick March 2009.

A. 4 Evidenztabellen zur eingeschlossenen Literatur über die diagnostischen Kriterien des FAS (erster Teil des Leitlinienprojektes 2011)

5.1 Evidenztabelle der eingeschlossenen systematischen Übersichtsarbeiten und HTA-Berichte

Tabelle 7: Evidenztabelle systematische Reviews und HTA-Berichte (themenübergreifend)

Studien-typ/ Autoren, Jahr	Suchstrategie Ein- und Ausschlusskriterien,	Welche Behandlungen wurden geprüft	Charakteristik eingeschlossener Studien/ Befunde in Bezug auf Diagnostik	Methodische Besonderheiten/ Bemerkungen	Evidenzgraduierung nach CEBM 2009 (University of Oxford)	Literaturbelege
FAS all aspects, focus on prevention						
Systematic review/ Elliott L. et al., 2008 [3]	Systematic search in Medline, EMBASE, Scopus and PsychInfo databases. Review databases: Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessment database, NHS Economic Evaluation database. HTA databases. Clinical Practice Guideline: National Guideline Clearing House database; Agency for Healthcare Research and Quality; US Preventative Services Task Force,	Aim of the whole review: evaluation of the main strategies of prevention, screening, diagnosis and management of FAS. 1. Prenatal screening : **Reseach questions:** Are screening tools able to identify women at increased risk of having a child with FASD? **Intervention:** 1. Any strategy that aims to reduce the incidence of FASD 2. Any alcohol screening tool that has been: a) designed for use in pregnant women or designed to evaluate a woman's risk of having a child with FASD or b) designed for use in the general population but has	1. Prenatal screening/ screening tools: **Biomarkers**: The literature search identified five publications which evaluated the ability of biomarkers to detect alcohol consumption in pregnant women (see Table 42). AST, ALT, MCV, GGT, CDT Combination of all biomarkers PAUI ACOG antepartum record WBAA, Urine Analysis There is no evidence that biomarkers are appropriate either as a screening tool in a clinical setting or as a comparator. **Questionnaires,** which aim to identify pregnant women with alcohol problems : The pregnancy specific screening tools TWEAK and T-ACE were evaluated in seven publications: the most appropriate screening tool for use in the prenatal setting is the	Only facts with regard to diagnostics were extracted for the evidence report "Diagnostik des FAS": Evidence assessment with NHMRC. Studies on fatty acid ethyl esters are not completely taken into account. Assessment of study eligibility by one reviewer. Data extraction by two reviewers Evidence for screening tools with questionairs limited:	1. Prenatal screening/ screening tools: LoE 3-4 for this part of the review 2. Post-natal screening and diagnosis: LoE 5 (in this part of the review the authors do not report any evaluation with NHMRC. Quality / methodology of the single papers were not described) Methodik dieser Publikationen werden ebenfalls kaum bis gar nicht beschrieben.	1. Prenatal screening/ screening tools: Biomarkers: Magnusson A et al. J Stud Alcohol 2005; 66(2):157-164. Budd KW et al., (2000). J Obstet Gynecol Neonatal Nurs. 29(2):129-136. Stoler JM et al. (1998). J Pediatr. 133(3):346-352. Christmas JT et al., (1992). Obstet Gynecol. 80(5):750-754. Larsson G et al., (1983). Am J Obstet Gynecol. 147(6):654-657. Questionaire: Sokol RJ et al., , (1989).

Studien-typ/ Autoren, Jahr	Suchstrategie Ein- und Ausschlusskriterien,	Welche Behandlungen wurden geprüft	Charakteristik eingeschlossener Studien/ Befunde in Bezug auf Diagnostik	Methodische Besonderheiten/ Bemerkungen	Evidenzgraduierung nach CEBM 2009 (University of Oxford)	Literaturbelege
	Scottish Intercollegiate Guidelines Network Library + hand searching of relevant journals. **Zeit:** <1966 until Juli 2008 1: Prenatal screening **Inclusion criterias:** English language. All levels of evidence including existing systematic reviews and clinical practice guidelines, as well as different types of original studies will be eligible for inclusion (controlled and uncontrolled). **Exclusion:** not a clinical study, wrong intervention, wrong outcome, not in English **Patient population** Women at high risk of having a child with FASD (to identify tertiary prevention strategies) 2. Post-natal screening and	been evaluated in pregnant women or used to determine if women are at increased risk of having a child with FASD **Comparator** Any comparator **Outcomes** 1. Reduction in the incidence of FASD 2. Reduction in alcohol use during pregnancy or in women of childbearing age 3. Sensitivity and specificity of the screening tool 2. Post-natal screening and diagnosis: **Reseach questions:** - Are postnatal screening tools (aimed at an individual suspected of having FASD and/or their mother) effective at identifying individuals who should undergo a full diagnostic FASD evaluation? - Do diagnostic tools increase the accuracy of FASD identification? **Intervention:** Any strategy that aims to identify an individual who may have FAS or diagnose an individual who may have FAS **Comparator:**	TWEAK or T-ACE (Level III-2) All publications which compared the TWEAK and T-ACE with other screening tools reported that these two screening tools had the highest sensitivity and specificity. The standard cut-point for „risk drinking" is a score of ≥2 using either test, however a score of ≥1 or ≥3 may be appropriate in a clinic with an unusually high or low-risk population.(S.130) 2. Post-natal screening and diagnosis The literature search did not identify any systematic reviews of screening or diagnostic criteria. The literature search identified three articles describing FASD or FAS postnatal diagnostic criteria: Institute of Medicine, 4-Digit Diagnostic Code and Hoyme Updated Institute of Medicine Criteria. Two guidelines addressing screening (Canadian FASD Referral Guidelines and Centre for Disease Control FASerral Guidelines) and three guidelines addressing Diagnostics (Canadian Guidelines, Centre for Disease Control Guidelines and British Medical Association Guidelines) were identified. There was very little high level evidence available for these strategies. A review by Peadon 2008 found that the 4-Digit Diagnostic code was the most commonly used diagnostic criteria	small number of published studies and low-level of evidence available (Level III-2). For the assessment of postnatal screening and diagnosis literature only systematic reviews and published guidelines eligible for inclusion. Post-natal screening and diagnosis : According to the authors of the review were the studies identified in the literature search generally of limited quality (methodology and appraisal for these references not reported) This "top level" review of the postnatal screening and diagnostic literature did not identify any publications that evaluated the accuracy of the	(da für die betrachteten verschiedenen Abschnitte des Reviews unterschiedliche Einschluss-Kriterien der Studientypen angewendet wurden und sehr unterschiedliche Studien betrachtet wurden, ist eine Gesamtbewertung nicht möglich).	Am J Obstet Gynecol. 160(4):863-870. Russell M et al., (1994). Clin Exp Res. 18(5):1156-1161. Russell M et al., (1996). Am J Public Health. 86(10):1435-1439. Chang G et al., ,. (1998). Obstet Gynecol. 91(6):892-898. Chang G et al., J Stud Alcohol 1999; 60(3):306-309. Chang G et al. Am J Addict 1999; 8(2):87-93. Dawson DA et al. Alcohol Clin Exp Res 2001; 25(9):1342-1349. 2. Post-natal screening and diagnosis: 4-Digit Diagnostic Code Astley, S. 2004. Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. University of Washington Publication Services.

Studien-typ/ Autoren, Jahr	Suchstrategie Ein- und Ausschlusskriterien,	Welche Behandlungen wurden geprüft	Charakteristik eingeschlossener Studien/ Befunde in Bezug auf Diagnostik	Methodische Besonderheiten/ Bemerkungen	Evidenzgraduierung nach CEBM 2009 (University of Oxford)	Literaturbelege
	diagnosis: **Inclusion criterias:** English language. Assessment of literature was conducted as a top level review. Therefore, only systematic reviews and published guidelines were eligible for inclusion. **Population:** Individuals who may have FAS or mothers of individuals who may have FAS	any Comparator **Outcome:** Sensitivity und specificity of FAS diagnostics	worldwide. Results: Two **guidelines** addressing **screening:** Recommendation that screening should occur based on identification of facial features, known exposure to alcohol or learning and/or behavioural difficulties. The CDC guidelines state that the screening should provide assistance in making the referral decision, rather than be used as a definitive screening tool. **Guidelines und articles addressing Diagnostics :** The five diagnostic approaches were broadly similar, evaluating maternal prenatal alcohol exposure, characteristic facial abnormalities, growth retardation and CNS abnormalities. All publications discussed the significant problems associated with diagnosing the less severe forms of FASD (i.e. children who did not meet the definition of FAS but had significant disabilities as a result of prenatal alcohol exposure). The diagnostic criteria and guidelines are widely used internationally, however there is no consensus on which criteria are most appropriate in the clinical setting.	diagnostic criteria. Conclusion of the authors is that no evidence exists for any criterion as the most appropriate.		Canadian Guidelines Chudley A et al. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Can Med Assoc J 2005; 172(Suppl):Mar05-S21. CDC - National Centre on Birth Defects and Developmental Disabilities. Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. 2004. Centre for Disease Control. Institute of Medicine - Stratton K et al., 1996. Fetal alcohol syndrome: diagnosis, epidemiology, prevention, and treatment. Washington: Institute of Medicine and National Academy Press. Hoyme Updated Institute of Medicine - Hoyme HE et al. A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 Institute of Medicine Criteria. Paediatrics 2005; 115(39):47.

Studien-typ/ Autoren, Jahr	Suchstrategie Ein- und Ausschlusskriterien,	Welche Behandlungen wurden geprüft	Charakteristik eingeschlossener Studien/ Befunde in Bezug auf Diagnostik	Methodische Besonderheiten/ Bemerkungen	Evidenzgraduierung nach CEBM 2009 (University of Oxford)	Literaturbelege
						BMA Board of Science. Fetal alcohol spectrum disorders: A guide for healthcare professionals. 2007. Peadon E et al., (2008). BMC Paed; 8:12-20. FASD referral guidelines (Public Health Agency of Canada, 2005).
Anmerkung: Goh et al. 2008 wird unter den jeweiligen Themen extrahiert, da sehr ausführlich.						

Studien-typ/ Autoren, Jahr	Suchstrategie Ein- und Ausschlusskriterien,	Welche Behandlungen wurden geprüft	Charakteristik eingeschlossener Studien/ Befunde in Bezug auf Diagnostik	Methodische Besonderheiten/ Bemerkungen	Evidenzgraduierung nach CEBM 2009 (University of Oxford)	Literaturbelege
Mukherjee RA et al., 2006 review with systematic search [10]	Search in all major electronic databases incl. Medline, Embase, Psychlit, Ovid from 1966-2006. Using mesh headings: Fetal alcohol syndrome, Fetal alcohol effects, Fetal alcohol spectrum disorder and Prenatal alcohol. Databases were combined to give an overall single category with no exclusions from which further searches were combined. These included knowledge of fetal alcohol syndrome, pathology, psychology and management. References cited in published articles were also reviewed. Inclusion/ Exclusion: Detailed criteria are not described Patient population: Not described	Overview of following points: **1)Definition and clinical criteria of FASD** and its subgroups **2) Knowledge levels of fetal alcohol spectrum disorders** by the general public and health professionals **3) Pathology** **4) Neurocognitive Deficits** and secondary disabilities **5) Management**	*Only data with regard to diagnostics are referred, i.e. to point 1) and 4) and a part of 5):* **1) Definition and clinical criteria** 1. Fetal alcohol syndrome: confirmed alcohol exposure criteria a alcohol exposure b facial pattern of short palpebral fissures <10 percentile, thin upper lip vermillion, smooth philtrum c evidence of pre/postnatal growth retardation d evidence of neurocognitive deficits 2 Fetal alcohol syndrome: no confirmed alcohol exposure a as above but no alcohol exposure found **3 Partial fetal alcohol syndrome:** confirmed alcohol exposure a not all of the above features are present but neurocognitive and some facial features needed **4 Alcohol related birth defect** a confirmed maternal alcohol consumption as well as some but not all of the facial features are present, however, the behavioural features or structural abnormalities are more pronounced **5 Alcohol related neurodevelopmental disorder** a confirmed maternal alcohol consumption with the absence of growth retardation or facial features	Cited "systematic reviews" such as Rasmussen et al. had not systematically searched literature (in this review methodology is not described) Quality/methodology of single studies is not described There is no description of efforts to identify publication bias. How many reviewers the studies assessed is not mentioned. Heterogenity is not discussed. P values, confidence intervals or other statistical measures are not reported.	2a-5 The review comprises studies of different kinds of quality (guideline, reviews, expert opinions (4digitcode) and primary studies – as far as assessable	**1)** - Chudley AE et al., Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis. Can Med Assoc J 2005;172:S1–21 - Hoyme HE et al. A practical clinical approach to the diagnosis of fetal alcohol spectrum disorder: clarification of the 1996 institute of medicine criteria. Paediatrics 2005;115:39–47 **4)** - Jacobson JL et al. Alcohol Res Health 2002;26:282–6 - Rasmussen C. Alcohol Clin Expl Res 2005;29: 1359–67 - Streithguth AP et al.. Sem Clin Neuropsychiatry 2000;5:177–90 5) - Russel M. Alcohol Res Health 1994;18:55–61 - Chan D. J FAS Int 2003;1:e9

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			and with the neurocognitive features being prominent. **Methods of diagnosis of facial abnormalities:** note all of these require careful history taking and evidence of growth retardation to make the diagnosis: **1 Gestalt:** facial pattern recognition requires experience and clear history. Issues of accuracy and inconsistency often found **2 D score method:** computational method for facial pattern based on careful measurements of abnormalities: requires a high degree of training and skill restricting practice to a few **3 4-digit scoring method and facial photographic recognition software:** applies areas of history and facial recognition to four 4-point Likert scales to establish diagnosis. Requires minimal training and can be used easily by all in clinical settings **4) Neurocognitive Deficits** -.Core areas of psychological deficits (Jacobson JL et al. 2002) . Hyperactivity . Attention deficits . Sustained attention . Focused attention . Cognitive flexibility . Planning difficulties . Learning/memory problems . New memories not consolidated . Lower IQ			

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			. Arithmetic difficulties . Receptive language difficulties . Verbal processing problems . Social understanding difficulties - Common secondary difficulties seen (Streithguth AP et al.) . Psychiatric problem (95% have some form of diagnosable mental disorder: ADHD (attention deficit hyperacitivity disorder), social and communicatory impairments, personality disorder, schizophrenia, addiction and depression. . Disrupted school experience . Trouble with the law . Confinement . Inappropriate sexual behaviour (50%) . Alcohol/drug problems Much of this can be related to their inability to control and maintain their behaviour attributable to damage caused to their executive function abilities combined with difficulties in receptive language and inability to consolidate memories because of temporal/ hippocampal damage. **5)Methods of detection alcohol consumption of mothers:** Emerging methods such as the use of routine screening tools such as **TWEAK, hair sampling, or meconium testing** have been suggested. However, the ethical debate around their use is in its infancy thus clarification is required before they can			

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Biomarker			be recommended routinely.			

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Systematic review, Burd L et al., 2008 [8]	Literature search was conducted in Pubmed using the terms meconium, fatty acid ethyl esters, biomarkers and prenatal alcohol exposure. + hand searching Inclusion criteria: only peer reviewed studies utilizing analysis of meconium for the presence of FAEE in humans up through the year 2007 and all languages. Exclusion: not peer reviewed or without data on humans Population: data on 2221 subjects; 455 (20.5%) met their respective study's criteria for alcohol exposure. 502 (22,6%) FAEE levels above the study's cut-off.	Measurement of fatty acid ethyl esters (FAEE) in meconium as biomarkers for prenatal alcohol exposure (PAE). 1)laboratory techniques 2)individual FAEE or combined FAEE 3) Cut-offs 4)Sensitivity and Specificity 5) exposure assessement for prenatal alcohol use Reported alcohol exposure serves as reference (s. remark in column of special features).	10 article were found with 6 different assessment strategies and 4 different analytical techniques. 1)Multiple laboratory techniques for detection of FAEE in meconium were used (s. table 1): - Gas chromatography/ Flame Ionization Detection (GC-FID) - Gas chromatograph/ Mass Spectroscopy (GC-MS) - Selected ion monitoring (SIM with GC-MS) - GC-MS/MS (tandem MS) According to the authors , tandem mass Spectroscopy is one of the most selective detection techniques. 2) A variable range of individual FAEE (9 FAEEs) or combinations for PAE as a positive marker were used (table 2): Ethyl laureate, ethyl palmitate etc. 3) There was also variance in the methods used to determine the cutoffs (table 3) 4) Sensitivity and Specifity (table 4) also vary. Best values were found for ethyl oleate with sensitivity of 84.2% and specifity of 83.3%, cut-off 0.032 µg/g (Bearer et al. 2003). Thus, developing a summary estimate of the accurancy of detection of PAE of combined estimates of sensitivity or specifity was not possible.	Beginning of time period for literature search is not indicated. Quality and study design (control groups?) of single studies are not described. Assessment of history of alcohol exposure is highly variable, most were not assessing the time period of alcohol consumption in pregnancy (most relevant 3rd trimester when meconium is formed, only 4 studies). Thus, consumption earlier in pregnancy is not detectable by meconium assay. Limitation of the review is the troublesome heterogeneity of measurements of the single studies. Thus, outcome measures are not comparable.	3b - (as without reference standard and troublesome heterogeneity)	Bearer CF et al., 2003. J Pediatr 143: 463-469. Bearer CF et al., 1999. Alcohol Clin Exp Res 23: 487-492. Bearer CF et al., 2005. J Pediatr 146: 824-830. Chan D et al., 2003. Ther Drug Monit 25: 271-278. Chan D et al., 2004. Ther Drug Monit 26: 474-481. Derauf C et al., 2003. Am J of Epedimiol 158: 705-709. Klein J et al., 1999. Ther Drug Monit 21: 644-646. Moore C et al., 2003. Clin Chem 49:133-136 Moore C et al., 2001. Clin Chem Acta 312:235-238. Ostrea EM et al., 2006. Alcohol Clin Exp Res 30: 1152-1159

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			5) Strategies for exposure assessment for prenatal alcohol use were also variable (table 5): Maternal self-reporting; medical record review, clinician suspicion; screening questionnaire or interview, timeline follow-back approach. 9 articles found a correlation between FAEE levels and maternal alcohol consumption, one article found not (Derauf et al.).	Due to incompleteness of data pooling of the variables were not possible. Except for data to sensitivity and specifity other statistical measures were not reported. There is no description of efforts to identify publication bias.		
Goh I.Y. et al. 2008 Systematic Review Here extracted: underlying evidence report of the sited publication given in a link **Biomarker**	Search Methods: Search in Medline and Pubmed 1966 up to 12/2007 No language restriction Search terms: screening, fetal alcohol spectrum disorder, fetal alcohol syndrome Inclusion criteria: methodologies of screening for FASD in children up to 18 years, Studies of adults	Different Screening methods for FAS Evaluation of Test accuracy: Sensitivity Specificity Positive predictive Value Negative predictive Value	**Biomarker** **1. Meconium** Fatty acid ethyl esters (FAEE) – true correlate, only 2.+3. trimester Quantified as linoleic, palmitic, oleic, steric, palmitoleic esters. 1. Study in Hawaii prevalence 16,7% positive 2. Study anonymous population study: 2,5% positive 3. Study in Montevideo 44% positive 4. Study anonymous population: 26% positive The disadvantage of meconium screening is that there is a limited window to collect meconium. Meconium is only able to detect prenatal ethanol exposure in the second and third	No description of the underlying study quality	LOE not possible	**Biomarker** **1. Meconium** **Koren G,** et al.Ther Drug Monit 2002; 24(1):23-25. **Moore C,** et al. Clin Chem 2003; 49(1):133-136. **Gareri J** et al. Ther Drug Monit 2008; 30(2):239-245. **Hutson J. R.** et al. Can J Clin Pharm 2007; 14(2):e169. **Goh, Y. I.**,et al. Clin Pharm Ther 2008; 83(S1):S75. **2. Hair** **Caprara DL** et al. Ther

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	excluded		trimester of pregnancy. **Moreover, there has not yet been a correlation of how much FAEE correspond to the development of FASD.** **2. Hair** FAEE have been demonstrated to concentrate in the hair matrix in adults. Studies in neonates have demonstrated that babies exposed to alcohol have been able to quantify FAEE in infants exposed to excessive quantities of alcohol **This test is in its developmental stages and its clinical sensitivity and specificity have not yet been determined.** **3. Cord blood** Gallot et al. measured AST, ALT, GGT, CDT in fetal cord blood to exposed neonates immediately after birth over a 1-year period.Of 870 samples, only 2 cases of FASD were identified and there were no significant correlations between maternal and cord blood biomarkers. **Thus, using these parameters is not an effective means of screening for prenatal alcohol exposure.**			Drug Monit 2005; 27(6):811-815. **Klein J et al.** Ther Drug Monit 1999; 21(6):644-646. **3. Cord blood** **Gallot D** et al. Clin Chem Lab Med 2007; 45(4):546-548.
FAS –faziale Auffälligkeiten						

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Abdelrahman A et al., 2009 [9] Review with systematic search	Search was conducted in Medline from its inception to March 2009 for original research and review articles relating to prenatal alcohol exposure, using combinations of the terms 'fetal alcohol', 'eye', 'ophthalmic' and 'alcohol teratogenesis'. No language restrictions were applied. Reference lists of identified articles were also searched Inclusion/ Exclusion: detailed criteria not described Patient population: children with FAS	Objective of the review was to describe the effects of prenatal alcohol exposure on the eye, quantify their incidence and comment on their importance in diagnosis of children with FAS.	**1) Short palpebral fissures:** A shortened distance between the inner and outer corners of each eye , defined as a length two or more standard deviations below the mean. The presence of short palpebral fissures is of particular discriminant value in FAS. **2) Epicanthus**: This is a lateral extension of the skin of the bridge of the nose over the endocanthion. A study found 80% of children prenatally exposed to ethanol had epicanthus; **3) Ocular hypertelorism:** Defined as an increased interorbital distance, and may be measured as the distance from right endocanthion to left endocanthion. It is a commonly reported finding in FAS, although not pathognomonic of the condition **4) Coloboma:** Normally the choroid fissure closes during the seventh week of development - failure of closure results in the formation of a distinctive cleft in the iris known as coloboma iridis. This is one of the key extensive malformations that may be found in children with FAS (no reference indicated) **5) Strabismus:** An abnormal alignment of the two eyes. While it is a non-specific finding, it is common in FAS and may be diagnostically useful in conjunction with other features;	References are partially not indicated. Quality/methodology of single studies is not described There is no description of efforts to identify publication bias. How many reviewers the studies assessed is not mentioned. Heterogenity is not discussed. P values, confidence intervals or other statistical measures are not reported.	As quality and design of studies are not indicated a level of evidence (LoE) cannot be assigned or is Expertopinion	1) Clarren SK, Smith DW. New Engl J Med 1978;298(19):1063-7. 2) Manning MA, Hoyme HH. Neurosci Biobehav Rev 2007;31(2): 230-8. 3) Astley SJ, Clarren SK. Alcohol Alcohol 2001;36(2):147-59. 5) +6) Strömland K. Surv Ophthalmol 1987;31(4):277. 8) Ribeiro IM et al.. Eur J Ophthalmol 2007;17(1):104-9. Flanigan EY et al.. J Pediatr 2008;153(3):391-5. Hug TE et al..J Appos 2000;4(4):200-4.

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			Strömland et al. found that of thirty children with FAS, 13 had strabismus, 12 of which had a horizontal convergent form (esotropia) **6) Blepharoptosis:** (or ptosis), is drooping of the upper eyelid. Although it is a non-specific sign, Strömland found that 20% of children with FAS had blepharoptosis. **7) Microphthalmia:** An abnormally small eye – is a frequent finding in FAS and was included in the Fetal Alcohol Study Group diagnostic criteria. However, the diagnostic usefulness of this condition is limited by difficulty in detection, particularly in the presence of confounding factors such as microcephaly and short palpebral fissures (no reference indicated) **8) Abnormalities** of the fundus: The fundus may be affected by various abnormalities - the most common findings are hypoplasia of the optic nerve and increased tortuosity of the retinal vessels. In a cohort of Swedish children with FAS, Strömland found optic nerve hypoplasia in 48% and increased tortuosity in 49%2. More recently, Hug et al suggested that prenatal alcohol exposure leads to disturbed retinal function on the basis of abnormal electroretinograms in ten children with FAS. On the whole, the authors recommend full ophthalmic examination with • Inspection for periocular features,			

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			possibly supplemented by morphometric analysis • Measurement of visual acuity (using visual evoked potentials), visual fields and eye movements • Slit lamp examination of anterior segment and media • Ophthalmoscopic examination with particular attention paid to the optic disc			
Goh I.Y. et al. 2008 Systematic Review Here extracted: underlying evidence report of the sited publication given in a link [6] **Facial**	Search Methods: Search in Medline and Pubmed 1966 up to 12/2007 No language restriction Search terms: screening, fetal alcohol spectrum disorder, fetal alcohol syndrome Inclusion criteria: methodologies of screening for FASD in children up to 18 years, Studies of adults excluded	Different Screening methods for FAS Evaluation of Test accuracy: Sensitivity Specificity Positive predictive Value Negative predictive Value	**1. Physical Screening Tools** **1a. Facial Phenotype** ***Astley + Clarren 1995*: quantitative case definition of FAS facial phenotype** evaluating children 0-10y, 1993-95 Best discriminating between FAS and No-Fas: **Hypoplastic midface, smooth philtrum, thin upper lip** **D-scores :** **100% sensitive,** **87.2% specific** (3-point Likert scale). ***Astley+Clarren 1996*** **Development of a photographic screening tool for the FAS facial phenotype** (4-digit diagnostic code: growth deficiency, FAS face phenotype, CNS damage/dysfunction, and gestational alcohol exposure and D-score to measure the magnitude of expression of FAS facial phenotype. **Evaluation** **1.** 42 subjects with FAS /84 controls. Photographs were obtained aligned to the frontal plane and phenotypic expressions were recorded on a 5-point	No consistent information about underlying study quality. Case-Control-Studies Cohortstudies No information about control groups resp. how the diagnosis was validated	Keine Angabe der Studienqualität – LOE nicht möglich	**1. Physical Screening tools** **1a. Facial Phenotype** **Astley SJ**, Clarren SK. Alcohol Clin Exp Res 1995; 19(6):1565-1571. **Astley SJ,** Clarren SK. J Pediatr 1996; 129(1):33-41. **Astley SJ**, Clarren SK. Alcohol Alcohol 2000; 35(4):400-410. **Astley SJ** et al. J Pediatr 2002; 141(5):712-717. **Avner M,** et al. J FAS Int 2006; 4(e20):1-7. **Douglas TS,** Viljoen DL Ann Hum Biol 2006; 33(2):241-254. **Moore ES** et al. Alcohol Clin Exp Res 2007; 31(10):1707-1713. **Mutsvangwa T,** Douglas TS. J Anat 2007; 210(2):209-220. **1b. Screning Checklist**

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			Likert scale . **99% sensitivity,** **95% specificity, and** **98% accuracy.** Sensitivity and specificity were not affected by race, gender, and age. **2. Astley et al. 2002** Screening of children in a Foster program, age 0–12 years (1999-2001). Facial features were ranked using the Lip-Philtrum Guide in their **Fetal Alcohol Syndrome Facial Photographic Analysis Software (Version 1.0.0.).** Prevalence of FAS 10/1.000. screening tool: **100% sensitivity,** **99.8% specificity,** 85.7% predictive value positive, 100% predictive value negative **3.** Validation in 40 children resulted in 4 false positive and no false negative **100% Sensitivity** **64% Specificity** Problem computer-assisted measurement tended to underestimate true length of palpebral fissure e. <4y children. **4.** Studies with different ethnies revealed that ethnical differences exist (f.e.eye distance measurement different in southafrican children) Reduces size of eye orbit consistent discriminating feature **Checklist FAS-Screen (32.items)** **1. Checklist** focuses physical parameters but addresses also			**Burd L** et al. **The FAS Screen**, Addict Biol 1999; 4:329-336. **Poitra BA** et al. Neurotoxicol Teratol 2003; 25(6):725-729.

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			developmental changes 100% sensitivity, 94%specificity, PPV 92%, Accuracy 94% **2. Validation** in kindergarden children Staff received 4hours of training on the screening tool, 10-minute screening by the school after informed consent "normal sample", **1.384 children were screened over 9 years, during which 69 (5%) were positive. After referral 7 (10%) were found to have FAS or partial FAS.** Diagnose was given in a center, interdisciplinary experts. **100% sensitivity** **95,43% specific** **95% accurate**			
FAS – ZNS-strukturelle Auffälligkeiten						
Geuze E, 2005;10(2): 160-84. [7]	Literature search Medline Indexed with keywords Hippocampus, volume and MRI English-language, human subject, 423 relevant hits 1988 up to 12/2003	data-driven papers on hippocampal volumetry	Disease related changes of hippocampus volume	Only results for FAS, Autism, Low birth weight, ADHD stated 1. FAS : 1 study volume not changed compared to controls Archibald SL et al. 2001 14 FAS, 12 AE + 41 healthy controls 2. ADHD: 1 study volume not changed in comparison to controls Castellanos FX et al.	1. Archibald SL et al. 2001 2. Castellanos FX et al. 1996	

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				1996 57 boys with ADHD and 55 healthy matched controls		
Goh I.Y. et al. 2008 Systematic Review Here extracted: underlying evidence report of the sited publication given in a link **Neuroimaging**	Search Methods: Search in Medline and Pubmed 1966 up to 12/2007 No language restriction Search terms: screening, fetal alcohol spectrum disorder, fetal alcohol syndrome Inclusion criteria: methodologies of screening for FASD in children up to 18 years, Studies of adults excluded	Different Screening methods for FAS Evaluation of Test accuracy: Sensitivity Specificity Positive predictive Value Negative predictive Value	**Neuroimaging** **1. Ultrasound** ultrasound screening for small for gestational age has 80-90% sensitivity, but low specificity – many causing conditions 1 study with small number assessing 18 children 5-6weeks after birth: 50 freeze-frame midsaggital sections. Midline corpus callosum in PAE children with abnormal splenium. Results limited by number **2. EEG** see Review D-Angiulli et al. 2006! **3. Magnetic Resonance Imaging** **a. MRI** MRI studies: persons with FASD: . reduction in size of the cranial vault, - reduced brain size - alteration in size and shape of corpus callosum - displacement of corpus callosum - reduction of basal ganglia size - reduction of cerebellum size - reduction in white matter in cerebrum, - altered corpus callosum, frontal and parietal lobe anomalies, - reduced surface area and volume of cerebellum, - altered frontal-striatal response, - abnormal cortical thickness - reduced volume of basal ganglia.			**MRI** **Mattson SN** et al. Alcohol Clin Exp Res 1996; 20(5):810-816. **Mattson SN** et al. Alcohol Clin Exp Res 1992; 16(5):1001-1003. **Mattson SN,** et al. Neurotoxicol Teratol 1994; 16(3):283-289. **Archibald SL et al. ,** Dev Med Child Neurol 2001; 43(3):148-154. **Riikonen RS et al.** Biol Psychiatry 2005; 57(12):1565-1572. **Sowell ER et al.** Cereb Cortex 2002; 12(8):856-865. **Riley EP** et al. Alcohol Clin Exp Res 1995; 19(5):1198-1202. **Hynd GW** et al. J Learn Disabil 1991; 24(3):141-146. **Bhatara VS,** et al. S D J Med 2002; 55(2):59-62. **Bookstein FL**,et al. Neuroimage 2002; 15(1):233-251. **Bookstein FL** et al. , Teratology 2001;

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			- Greater inferior-middle frontal lobe activity was observed in FASD in children and adults. **b.Magnetic Resonance Spectroskopy** - MRS studies demonstrated altered N-acetylaspartate/choline metabolite ratios in persons affected with FASD compared to controls. **MRI has neither been validated as a screening tool nor has specificity and sensitivity been determined.** **Perhaps MRI may be more effective in the diagnostic process to confirm neurological irregularities.** **Diffusion tensor imaging (DTI)** Microstructural abnormalities have been observed in patients with FAS. 1.Study: DTI to examine corpus callosum in adults with FASD – lower fractional anisotrophy, higher MD in splenium and genu of corpus callosum vs. controls. No associations between DTI and dysmorphia score, IQ or processing speed. 2. Study: 14 children (10-13) trend toward smaller total cerebral vomue p=0,057 vs. controls. Greater mean diffusivity in the isthmus of corpus callosum (p=0,013). **The disadvantages are the same as MRI**			64(1):4-32. **Riley EP et al.** Am J Med Genet C Semin Med Genet 2004; 127(1):35-41. **Mattson SN,** et al.Alcohol Clin Exp Res 1996; 20(6):1088-1093. **Jones KL, Smith DW.**. Lancet 1973; 2(7836):999-1001. **Clarren SK et al.** J Pediatr 1978; 92(1):64-67. **Swayze VW,**et al. Pediatrics 1997; 99(2):232-240. **Riikonen R, et al.** Dev Med Child Neurol 1999; 41(10):652-659. **Clark CM,** et al. Pediatrics 2000; 105(5):1096-1099. **Bookstein FL**, et al. Anat Rec 2002; 269(3):162-174. **Johnson VP** et al. Am J Med Genet 1996; 61(4):329-339. **Sowell ER**, et al. Neuroreport 2001; 12(3):515-523. **Fryer SL**,et al. Alcohol Clin Exp Res 2007; 31(8):1415-1424. **Sowell ER,** et al. Cereb Cortex 2008; 18(1):136-

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						144. **Malisza KL,** et al. Pediatr Res 2005; 58(6):1150-1157. **MRS** **Fagerlund A** et al. Alcohol Clin Exp Res 2006; 30(12):2097-2104. **Cortese BM,** et al. Neurotoxicol Teratol 2006; 28(5):597-606. **DTI** **Wozniak JR, Lim KO.** Neurosci Biobehav Rev 2006; 30(6):762-774. **Ma X et al.** Alcohol Clin Exp Res 2005; 29(7):1214-1222.
Systematic review/ D'Angiulli et al. 2006 [12]	**Databases:** Systematic search in Medline, reference check **Period** 1966 to June 2006 **Inclusion criterias:** Publication in peer-refeered journal. at least summaries of EEG or evoked	**Reseach questions:** 1.) Is EEG a useful neuroimaging technique for investigating the brain correlates of PEA (prental alcohol exposure) in infants and children? 2. Are there indeed consistent EEG correlates of PEA in literature?	17 publications (16 studies) were included. Information on study designs and methodological quality are not given by the authors. The studies were evaluated according to three types of processes that were measured (Sleep and wakefulness, sensory processes, attention). **1. Sleep and wakefulness** 7 Studies (n = 491), 6 analyzed infants, in 1 study participants were 4-19 years. All children were classified as PEA positive. No study used a FAS diagnosis as	Review searched only in Medline Methodological quality of studies was not systematically assessed and considered. Publication bias not considered. There is no specific	4	**Literatur according to the types of processes** **Sleep and wakefulness** **Chernick**, V., Childiaeva, R., & Ioffe, S. (1983). Am J Obstet Gynecol 146, 41–47. **Havlicek et al.** (1977). Neuropadiatrie 8, 360–373. **Ioffe, S., & Chernick**, V. (1988). Dev Med Child Neurol 30, 797–807.

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	potential (EP) data, English publications **Patient population** infants and children with known prenatal exposure to alcohol (PEA), including Fetal Alcohol Syndrome (FAS) and more subtle but adverse neuroanatomical and neurobehavioral problems, described as fetal alcohol effects (FAE)	3.) On the basis of EEG correlates, are there emerging implications for the study of PEA and its effects in infants and children.	inclusion criteria. Summary of findings: EEG studies on the effects of PEA in infants and children specifically focusing on sleep and wakefulness show that different patterns and timing of alcohol consumption by mothers have a differential impact on infants' brain. Patterns of neonatal EEG hypersynchrony and increased spectral power during REM and quiet sleep are consistent correlates of PEA, which are not confounded by the use of other substances. Some evidence also suggests that abnormal EEG activity during sleep in infants is associated with later developmental outcomes. **2. Sensory processes** 5 Studies (n = 127), in 3 studies infants were analyzed, 1 study analyzed participants from 0,2 to 17 years, in 1 study age was unknown. 3 studies focused on auditory evoked potential (EP) and 2 studies on visual and somatosensory EP. 2 studies used a FAS diagnosis as inclusion criteria. **Summary of findings:** all studies focusing on sensory processes in infants and children with	question which structured the review. This is more an overview of available studies. Most serious limitations of the evidence according to the authors: 1.) Difficulty in comparing studies that used different measures (such as threshold for hearing loss), 2.) insufficient details of methodology (i.e., specific type of EEG anomaly, detailed description of subjects), 3.) highly questionable reliability of assessing alcohol consumption solely by self-reporting methods, often long after the actual		**Ioffe, S., & Chernick,** V. (1990). Neuropediatrics 21, 11–17. **Ioffe et al.** (1984). Pediatrics 74, 330–335. **Scher** et al. (1988). Pediatr Res 24, 101–105. **O'Malley**, K., & Barr, H. (1998). Can J Psychol 43, 1051. **Sensory processes** **Church**, M., & Gerkin, K. (1988). Pediatrics 82, 147–154. **Pettigrew, A., & Hutchinson**, I. (1984). Ciba Found Symp 105, 26–46. **Rossig** et al. (1994). Neuropediatrics 25, 245–249. **Scher** et al. (1988). Pediatr Res 24, 101–105. **Olegard** et al. (1979). Acta Paediatr Scand Suppl 275, 112–121.

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			PEA have found evidence of sensory impairment suggestive of atypical brain maturation. From these studies, it seems that the cluster of conditions associated with PEA may include impaired hearing, vision, and somatosensory functions that presumably persist through the entire development and life span. **3. Attention and cognition** 4 Studies (n = 75), participants age ranged from 4 to 15 years, all studies used FAS diagnosis as inclusion criteria. Summary of findings: EEG and EP studies focusing on attention and cognitive functions have indicated that these techniques can be valuable in providing functional assessment of the brain of children with PEA. Although there is no clear marker of specific effects of PEA, the available data suggest that older children may suffer impairments in attention and/ or related cognitive functions that are associated. **Concrete Findings:** **Kaneko (n = 18 FAS 4-15y)** 1. Atypical EP (P300) – significant longer wave latencies in FAS vs. Down or Control Children 2. in 50% of FAS children borderline or	event, 4.) lack of control for several factors that influence the exposure of the fetus to alcohol (e.g., critical developmental periods, patterns of exposure, and maternal metabolism).		**Attention and cognition** **Buffington** et al. (1981). Neurobehav Toxicol Teratol 3, 183–185. **Kaneko et al.** (1996a). Alcohol Clin Exp Res 20, 35–42. **Kaneko et al.** (1996b). Clin Neurophysiol 98, 20–28. **Mattson et al.** (1992). Alcohol Clin Exp Res 16, 1001–1003.

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			abnormal EEG: immature, low amplitude, parietal lobe more affected **Buffington (n= 10FAS 6-14y, controls)** Reduced or absent contingent negative variation not statistically significant low sample size) **Mattson (n=2 FAS 13+14y)** Moderately abnormal EEGs; theta activity dominant **Spohr and Steinhausen** (n=45 FSA, 4-8J, Follow up 3-4)Fewer abnormal EEGs at follow up ! First EEG 51% normal acticity, Follow up after 3 years 71% normal Severe Sleep disturbances 22% follow up 15%. "Although these children also improved with regard to neurologic performance, psychiatric status, and cognitive function, they continued to show hyperactivity and distractibility at school, and a persisting handicap, particularly reflected in low levels of educational achievement, was evident."			
FAS – dysfunctional behaviour/mental health						
Goh I.Y. et al. 2008 Systematic Review	Search Methods: Search in Medline and Pubmed 1966 up to 12/2007 No language	Different Screening methods for FAS Evaluation of Test accuracy: Sensitivity	**Psychological/Neurobehavioural/Neurophysiological** **There is limited literature regarding using psychological evaluations to screen for FASD. The majority of**	Case-control studies,	LoE 3-4	**1. Streissguth AP,** Bookstein FL, Barr HM, Press S, Sampson PD. A fetal alcohol behavior scale. Alcohol Clin Exp

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Here extracted: underlying evidence report of the sited publication given in a link **Neuropsych.**	restriction Search terms: screening, fetal alcohol spectrum disorder, fetal alcohol syndrome Inclusion criteria: methodologies of screening for FASD in children up to 18 years, Studies of adults excluded	Specificity Positive predictive Value Negative predictive Value	**literature reports on psychological testing as a process used in of FASD diagnoses.** Testing methods include the use of Bayley Scales, Wechsler Intelligence Scale for Children (WISC-III), Griffiths Mental Developmental Scales, Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R), Fagan Test of Infant Intelligence, Children's Memory Scale (CMS), Behavioral Rating Inventory of Executive Function (BRIEF), Parent and Teachers Conners' Ratings Scales-Revised (CRS-R), and Child Behavioral Checklist (CBCL). **1. 36-item scale : the Fetal Alcohol Behavior Scale (FABS), Streissguth et al.** Development and Evaluation 5 minute questionnaire. 186 caregivers completed for their children. Cronbach's coefficient: 0.89, indicating high reliability. FABS scores appear to be correlated with maternal alcohol problems and reflect the behavioral phenotype of fetal alcohol fairly specifically rather than being raised in an alcoholic environment. Further studies are needed to clarify its utility in a diagnosis or screening context. Instruments like the FABS should not be used clinically for diagnosis without			Res 1998; 22(2):325-333. **2. Nash K, et al.** Arch Womens Ment Health 2006; 9(4):181-186. **Greenbaum R,** et al. Can J Clin Pharmacol 2002; 9(4): 215-225. **3. Green CR, et al.** Alcohol Clin Exp Res 2007; 31(3):500-511. 4a. **Green JH**. J Sch Health 2007; 77(3):103-108. **4b. Kodituwakku PW** et al, Alcohol Clin Exp Res 1995; 19(6):1558-1564. **Mattson SN**, Riley EP. J Int Neuropsychol Soc 1999; 5(5):462-471. **Schonfeld AM** et al, J Stud Alcohol 2001; 62(2):239-246. **4c. Olson HC,** et al, Semin Clin Neuropsychiatry 1998; 3(4):262-284. **Burd L,** et al, Neurotoxicol Teratol 2003; 25(6):697-705. **Steinhausen HC**, Spohr HL.. Alcohol Clin Exp Res 1998; 22(2):334-338.82 **4d. Kodituwakku PW** et al, Alcohol Clin Exp Res

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			additional evidence of prenatal alcohol exposure. **2. CBCL** The CBCL has open-ended questions and a rating scale of 113 behavioural descriptors Greenbaum et al: CBCL in a sample of 35 children affected with ARND. Significant differences in 62 items when compared to a control group of 35 matched for age, gender, and socioeconomic status. **Twelve items were significantly different p<0.00196.** These were 'acts too young for age', 'argues', 'can't concentrate=poor attention', 'can't sit still=restless=hyperactive', 'cruelty, bullying or meanness to others', 'disobedient at home', 'no guilt after misbehaving', 'impulsive=acts without thinking', 'lying or cheating', 'showing off=clowning', 'steals from home', and 'steals outside' **Nash et al. : E**valuation with a sample of children diagnosed with FASD and ADHD. Parents of 54 children (11 FAS, 43 ARND) completed the CBCL. In this study the 12 items were scored. **Seven of the 12 items strongly differentiated FASD children from ADHD and normal controls (p<0.001)**. They were "no guilt", "lying or cheating", "can't concentrate", "restless", "impulsive", "disobedient", and "acts young".			1995; 19(6):1558-1564. **Mattson SN,** Riley EP. Alcohol Clin Exp Res 2000; 24(2):226-231. **Coles CD,** et al, Alcohol Clin Exp Res 1997; 21(1):150-161. **4e. Streissguth AP,** et al, Psychol Sci 1999; 10(3):186-190. **Mattson SN,** Riley EP. Alcohol Clin Exp Res 1998; 22(2):279-294. **Olson HC,** et al, J Am Acad Child Adolesc Psychiatry 1997; 36(9):1187-1194.

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			Six items differentiated the FAS/ ARND from ADHD group (P<0.001). They were "no guilt", "cruelty", "acts young", "steals from home", "steals outside", and "lying or cheating". **86% sensitivity and 82% specificity were observed with 6 of the 7 items when comparing FASD, ADHD, and controls.** **81% sensitivity and 72% specificity were observed with 3 of 6 items when comparing FASD vs. ADHD group ("no guilt", "cruelty", "acts young").** From these observations Nash et al. proposed that a FASD screening tool should be considered involving a 2-step approach: first identify behaviours suggesting FASD and then discriminate FASD from ADHD. The limitation is that these are primary results which have not been replicated in a large sample size. In addition it has not been validated in different ethnicities or languages. **3. Ocular motor testing.** Ocular motor tasks are sensitive tools for assessing executive function. Green et al. measured saccadic reaction times in FASD and control children 8–12 years 97. Children with FASD were observed to have elongated reaction times, excessive direction error, and no express saccades compared to controls. This tool is very early in its			

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			development and further investigation is warranted to establish its validity and reproducibility. **4. Range of Studies on neuropsychological issues:** **a. Persons affected with FASD** have **deficits in cognitive and academic functioning, psychological disorders behavioural problems**, and **difficulties with independent living**. **b. Neuropsychological sequelae including executive functioning difficulties** have been observed. **c. Social skills deficits** including poor social judgment, failure to learn from experience, difficulty understanding consequences of actions, aggression, inappropriate sexual behaviour, delinquency, lack of understanding of social cues, and communicating in social contexts have also been observed. Individuals with FASD also often demonstrate impulsivity, poor judgment, and great difficulty learning from consequences. **d. Hyperactivity and attention problems** are some of the **most frequently reported** symptoms associated with prenatal alcohol exposure and reported in the research literature. **e.** Exposure to alcohol in the first and second trimesters has been associated with **lower overall academic achievement.** Lower reading scores,			

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			spatial and verbal memory and learning were associated with second trimester binge drinking as were problems in processing and arithmetic. Mattson et al.reviewed **IQ** in many studies with **children diagnosed with FAS and found a mean of 65.73 (20–120)**. The **mean IQ for FASD was 72.26 (47.4–98.2)** They concluded that high levels of prenatal alcohol exposure are related to increased eficits in intellectual functioning.			
Momino W. et al. 2008 Review with systematic search [13]	Literature search in Pubmed between 1968 and 2006 search terms ethanol, pregnancy, behaviour limits: human no information about number of hits or inclusion criteria	Focus on literature on FAS adressing maldaptive behaviour	Contents of included studies with children/youth: **1. + 2. Streissguth et al. 1996 and 1997** 415 patients with FAS or FASD a. experience of mental health problem >90% b. disrupted school 60% c. trouble with law 60%, 32% incarcerated for a crime criminal activity impulsive d. confinement 50%, e. inappropriate sexual behaviour 50% f. alcohol/drug problem 30% **protective factors (only the first 4)** a. longer period of living in a stable and nuturant home b. being diagnosed with FAS or FASD before the age of 6 years c. never experienced violence against oneself d. longer duration of resicende in each living **3. Boland et al. 1998**	no information about number of hits or inclusion criteria No characteristic of included studies, only communication of content.	4-5	**1. Streissguth AP et al,** (CDC). Seattle: University of Washington, Fetal Alcohol & Drug Unit; 1996. **2. Streissguth AP.** Seattle: University of Washington Press; 1997. p. 25-39. **3. Boland FJ.** Correctional Service of Canada; 1998. **4. Fast DK**, Conry J, Loock CA. 1999;20:370-2. **5. Conry J**, Fast DK. British Columbia Fetal Alcohol Syndrome Resource Society; 2000.

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			developmental pathway similar to similar to attention deficit disorder (ADD) with or without hyperactivity Predictors of conduct disorder similar: Impulsivity, low intellgence, poor school achievement, antisocial behaviour **4.+5. FAST et al. 1999, Conry et al. 2000** Prevalence of FASD in youth in the criminal systems 287 offenders 23,3% 67 with alcohol related diagnosis, 3 with FAS diagnosed before			
Pei J. et al. 2011 Systematic review [61]	Search in Medline, PsycINFO, Google Scholar, Academic Search Complete and Education Resources Information Centre Search terms FASD, ARND, FAS PAE paired with mental health, depression, oppositional defiant disorder (ODD), conduct disorder (CD) and anxiety disorder	Prevalence and scope of mental health issues 1. Mental health in childhood and adolescents 2. FASD and mood and anxiety disorders 3. FASD and Attention deficit hyperactivity disorder (ADHD) 4. FASD and CD (other outcomes not reported in this table)	**1. Mental health in childhood and adolescence** **Cohort study:** Steinhausen and Spohr 1998: 158 West German children followed from preschool til adolescence 1977-1991 – cognitive impairmants and psychiatric symptoms are generally persistent. 63% of sample with diagnose of at least 1 psychiatric disorder. High rates of psychopathology (hyperkinetic, emotional. conduct, sleep disorders, sterotypies, abnormal habilts) **Case-control Fryer 2007**: 39 American children (12,1J) matched to 30 nonalcohol-exposed children (11,2J) for age, gender, SES. Stand. Diagn. And Statistical Manual of Mental Disorders-IV with all caregivers 97,44% with at least one Axis I disorder vs. 40% of nonalcohol-exposed controls. Sign. Diff. (p<0,05) in ADHD!,	No flow chart of search given (hits, numbers of excluded studies) No inclusion criteria given		**Steinhausen HC** et al. (1998), Alcoholism: Clinical and experimental Research, 22,334-338 **Fryer S.** et al. (2007), Pediatrics,119, e733-741 **Walthall J.** et al 2008. Mental health Aspects of Developmental Disabilities, 11, 69-78 **Streissguth AP** et al., 1996, Seatle: University of Washington, Fetal Alcohol and Drug unit. Disney E et al 2008, Pediatrics, 122, 1225-1230. **Schonefeld AM** et al. 2005,Journal of studies onj alcohol, 66, 545-554 **Barr HM et al.,** 2006, American Journal of Psychiatry, 163,1061-1065

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			depressive disorder, oppositional defiant disorder, conduct disorder , anxiety disorder,. 71,5% vs 50% disruptive disorders **Case series O'Connor et al. 2006 :** 130 patients from an inpatient psychiatric setting in the US, 30% prenatal alcohol exposed (m. a. 8.64J, 7,7% met criteris for FAS **2. FAS and mood and anxiety disorders** **Case-Control Fryer 2007:** FAS-Children with more internalizing disorders then general population Case series O'Connor et al. 2002: 23 american in- and outpatient children (5-13J) 87% with psychiatric disorder, 61% of which were mood disorders **Walthall et al.** 2008 link between anxiety , mood disorders, and PAE **3. FAS and ADHD** **Mattson et al , 2006:** significant attention problems among children and adolescents with FAS. **Cohortstudy Streissguth et al. 1996** n=415 6-51J, mean 14J 60% attention related problems reported by caretakers **Case-Control Study Fryer 2007**: FAS with 95% ADHD, controls with 30% p<0,05 **Case-Control Study Coles et al. 1997** n=149 low-income 7-8.5J African American children (mean 7.63) 4 groups			**Clark et al. 2004,** Journal of Fetal Alcohol Syndrom International.2, 1-12 **Yates et al., 1998,** Alcoholism: Clinical and Experimental Research,22, 914-920 **O´Connor** MJ et al. 2006, Mental Health Aspects of Developmental Disabilities, 9, 105-109. **O´Connor MJ** et al. 2006, Journal of Pediatric Psychology, 31 (1), 50-64. **Mattson** SN et al., 2006. Neuropsychology, 20, 361-369. **Coles CD et al**., 1997. Alcoholism: Clinical and Experimental Research, 21, 150-161. **Burden MJ** et al., 2005 Alcoholism: Clinical and Experimental Research, 29 (3), 443-452. **O'Malley KD and Nanson J**., 2002. Canadian Journal of Psychiatry, 47, 349-354. **Disney et al. 2008**

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			Only ADHD = greatest difficulty with focused and sustained attention FAS = deficits in visual/spatial skills, encoding of the information they focused on, flexibility in problem solving. **Case serie Burden et al. 2005:** 337 African-American children 7,5J prospectively recuited to overrepresent PAE moderate to heavy level no evidence of sustained attention deficits Most affected: working memory ability to actively manipulate information in memory-related task execution Only ADHD specific problems in response inhibition. **Review O'Malley and Nanson (2002)**: children with FAS and ADHD comorbidities unique in the ADHD presentation **Bhatara et al. 2006:** A review of 2231 charts of children with PAE (mean age 8,7) found ADHD as most prevalent disorder **4. FAS and Conduct Disorder** Two cohort studies (not matched for IQ) showed that PAE (FU at 17 years) was significantly associated with CD (Disney et al 2008, Schonefeld et al 2005). Only Schoenefeld et al included children with FAS. The children with FAS did'nt show conduct disorder.			

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FAS - Birth defects Liver, Kidney, GI						
Hofer R, Burd L. Clin Mol Teratol 2009;85 (3):179-83. [11] Systematic Review	Search in Pubmed Terms: fetal alcohol syndrome and gastrointestinal tract, liver, kidney, congenital abnormalities "all years" no end of search stated, only English citations only studies with evidence of examination of subjects for FASD (FAS, fetalalcohol effect, alcohol embryopathy, partial FAS or FASD) and specifiying an association between FASD and abnormalities only humans + hand searching of reference lists	Studies of 1. liver 2. kidney 3. gastrointestinal birth defects in fetal alcohol spectrum disorders	**No distinctive abnormality associated with FASD for either of the three organ systems was found** **1**. n=12 publications of co-occurence of birth defects of the liver and FASD 19 case reports 14 newborns up to 1 year, 5 1y up to 8 years n= 7 hyperbilirubinemia, raised liverenzymes n=3 hepatomegaly with fibrosis (Birth, 4 Month, 17 Month) single cases with vascuolar degenerative changes (4y) , fatty degeneration (5y), Hepatoblastoma (27 Months) etc. 2. n=12 publications of co-occurrence of birth defects of the kidney and FASD 27 case report, 1 case serie (n=76) n=4 Hydronephrosis, n= 9 renal hypoplasy n=14 single other causes Case serie: "minimal renal findings" **3.** n= 2 publications of co-occurrence of gastrointestinal birth defects and FASD 7 case reports n=5 with chronic intestinal pseudoobstruction in children aged 20 months to 9 years n=2 (twins) with gastroschisis in both twins		case reports, 1 case serie	1. Co-occurence of liver birth defects Dunigan and Werlin 1981 Habbick et al. 1979 Moller et al. 1979 Newman et al. 1979 Peiffer et al. 1979 Christoffel and salafsky, 1975 Jones and Smith 1973 Khan et al. 1979 Mulvihil et al. 1976 Lefkowitch et al. 1983 Rosenlicht et al. 1979 Van Dyke et al. 1982 2. Co-occurence of kidney birth defects Tenbrinck et Buchin, 1975 Hanson et al. 1978 Goetzman et al. 1975 DeBeukelar and Rndall 1977 Dunigan and Werlin 1981 Havers et al. 1980 Qazi et al. 1979 Sokol et al. 1980 Smith et al. 1981 Mulvihill et al. 1976 Assadi 1990 Goldstein and Arulanantham 1978 3. Co-occurrence of gastrointestinal birth defects Uc A. et al. 1997 Sarda P., Barth H, 1984

Tabelle 1: Evidenztabelle zu funktionellen ZNS-Auffälligkeiten

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
Neuropsychological Profile/ Diagnostic Tools in general						
Astley S.J. et al. **2006 [36]** **USA, Washington**	n= 952 with Evaluation for FAS, 16 with confirmed absence of prenatal alcohol exposure	Comparison of the 4 diagnostic digit code and the Hoyme fetal alcohol spectrum disorders guidelines Hoyme: only 2 from 3 facial criteria in comparison to 4DDC, using 10th percentile, 4DDC using 3 criteria, and <3th percentile as cut-off for philtrum microcephaly and growth retardation measures	Prevalence of diagnosis FAS with eather test	1. 3,7% FAS with 4 Diagnostic Digit Code (n=35) 2. 4,1% FAS with Hoyme Guidelines (n=39) Only 17 Patients similar! 35% of patients with Hoyme facial criteria positive (n=330), low specificity! Only 39 met alle Hoyme FAS criteria 4/16 children without alcohol exposure were positive fo Hoyme Facial criteria Hoyme exclude functional and neurologic measures of CNS, only include structural, morphologic measures **Conclusion of the author:** Without a specific facial phenotype, a valid diagnosis of fetal alcohol syndrome cannot be rendered for patients with prenatal alcohol exposure, because a causal link between their outcomes and exposure cannot be established, and a valid diagnosis of fetal alcohol syndrome cannot be rendered	Hoyme does not seem to be adequate for diagnosing FAS 4DDC –good refererence standard?	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				for patients with unknown alcohol exposure, because the face cannot serve as a valid proxy measure for alcohol exposure. Diagnostic guidelines must confirm the specificity of their fetal alcohol syndrome facial criteria to validate their diagnostic criteria.		
Aragon AS et al. Alcohol Clin Exp Res **2008**;32(11):1909-19 [38] Case- Control-Study Italy	n= 80 children 6-7 years **n= 23 with FAS** (19 partial FAS) according to revised IOM criteria (Hoyme 2005) **n= 57 peer controls** actively randomly assigned from the same 1st grade cohort same classes informed consent of the parents all children of 25 schools randomly selected out of 68 elementary schools close to Rome, Laszio Region (spanning 60 km) Mothers did not differ significantly in age, education, income FAS-children age + gender well matched to controls Significantly differences in:	Tests done by Italian licensed psychologists affiliated with the University of Rome blinded to the membership of children 3h test battery Mothers+ Teachers: **Parent/Teacher Disruptive Behaviour Disorder Rating Scale (Pelham 1992)** Only items for assessing inattention and hyperactivity/impulsivity + Italian Questionaire to identify difficulties in Learning) Test used: **Wechlser Intelligence Scale for Children Revised** (WISC-R;Rubini&Padovani 1986) valided Italian Version	Differences (SD) In 1. Disruptive behaviour focussing on inattention and hyperactivity/ impulsivity 2. Verbal. performance and Fullscale IQ WISC-R profile analysis on 12 subtests information, similarities, arithmetic, vocabulary, comprehension, memory, picture completion, picture arrangement. Block design, object assembly, coding and mazes. (MANOVA) 3. Language comprehension	1. Teacher Disruptive Behaviour rating of attention sign. higher for FAS p=0,05. Hyperactivity/Impulsivity similar. Parent ratings not sign. 2. FAS with significant lower scores on Verbal IQ 0,015, Performance IQ p<0,01, Full Scale IQ p=0,01 WISCR-profile analysis sign. Deviated from parallelism for FAS. FAS scored sign. lower especially for Block design (p=0,02, object assembly p<0,01 and Mazes p=0,03. Similarity and Vocabulary similar. IQ Scores FAS fell within the average range 3.+4. Almost all Raven CPM (incl. percentile	Main limitations: IQ was not a covariate, - possible impact on findings. Limited generalzability due to small sample size.	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	Height, centile, weight, head circumference, total dysmorphology score	**Rustioni-Test** (1994, Italian specific normed linguistic understanding, modelled after Test for Reception of Grammar Bishop 1989 **IPDA questionnaire** (Terrini 2002) to measure academic achievement in language and math Italian normed **Raven Colored Progressive Matrices (CPM)** to assess nonverbal reasoning ability Alderton&Larson 1990. **Mothers:** collection of epidemiological data Demographic variables, **drinking patterns**. Nutrition, fertility, childbearing, behaviourial health issues Interview by employees of the University of Rome	4. Nonverbal Intelligence 5. Discriminative function of differences 6. Correlation with FAS features	score) p= 0,007 and 0,015 lower for FAS = nonverbal abstract reasoning, Rustioni (qualitative language understanding) p= 0,028 lower for FAS only similar for errors made IPDA p=0,05 lower for FAS = academic achievement 5. Teacher rating of attention and hyperactiviy = X^2 12,16 p=0,002, accounted for 15% of the between group variability and maximally separated FASD-Diagnosed children from controls 75% correct classified. Attentional problems 73,9% of children correct classified - Best discriminator according to loading matrix FAS more inattentivs symptoms 26% vs 5% controls P=0,08 similar rate of hyperactivity 6. Pearson product correlation coefficients between height, weight and head circumference centiles, Total Dysmorphology Raw Score , FullScale, Verbal and performance IQ Scores and Raven CPM percentile scores:		

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				Head circumference high correlated with WISC-R summary score as was dysmorphology raw score. Raven PM and Performance IQ also high correlated.		
Astley SJ et al. The Can J Clin Pharmacol **2009**;16:e178-e201. [39] Case-Control-Study	N=81 children, Age 8-15,9y 4 groups (16-24 per group) 1. FAS, pFAS 2. Static encephalopathy, alcohol exposed but no facial phenotype of FAS (SA/AE) 1+2 with severe cognitive dysfunction 3. Neuurobehavioural disorder, alcohol exposed - mild to moderate, no facial phenotype (ND/AE) 4. healthy controls, no alcohol exposure Identified according to the 4 diagnositc digit code	4 visits during 4-6 weeks Visit 1+2: neuropsychological and sociodemographic data collection a.Quick neurological screening test II b. Wechsler Intelligence test for children III c. Wechsler Individual achievement test reading subtest + Keymath revised d. Beery Buktenica Developmental Test of Visual-Motor Integration (VMI) + Rey Complex Figure Test (RCFT) e. Delis-Kaplan-Kaplan-Executive Function System (Trail making test, tower test, color-word-interference-test, verbal fluency test) + Wisconsin Card Sorting test 3.ed. f. California Verbal Learning Test-Children's Version (CVLT-C) g. Integrated Visual and Auditory Continuous	a. Soft neurological signs b. General intellectual function c. achademic achievement (reading and math) d. Visuospatial skills, visual memory and organization e. executive function f. verbal memory g.attention h.receptive and expressive language i. adaptive behaviour j. Behavior Problems and Social Competence k. Caregiver Report of Behaviors Related to Executive Function	4DDC produced 3 clinically and statistically groups Alcohol anamnese (amount)was not different! The three subgroups (ND/AE, SE/AE and FAS/PFAS) reflected a linear continuum of increasing neuropsychological impairment and physical abnormality, representing the full continuum of FASD. Behavioral and psychiatric disorders were comparably prevalent across the three FASD groups, and significantly more prevalent than among the controls. All three FASD subgroups had comparably high levels of prenatal alcohol exposure. Differences between FAS/PAS and Controls (% Scores < 2 SD below population mean) a. FAS/PFAS: 20% Controls:0%	Controls had higher IQ than population mean	4

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		Performance Test (IVA CPT) h. Test of Language Development-Intermediate: Third Edition (TOLD-I:3) Sentence Combining subtest (subjects aged 8 to 10 years). Test of Language Competence-Expanded Edition Level 1 .Oral Expression: R-ecreating Speech Arts subtest (subjects aged 8 to 9 years).Test of Language Competence-Expanded Edition Level 2.Oral Expression: Recreating Sentences subtest (subjects aged 10 to 15.9 years.Test of Word Knowledge (TOWK) Conjunctions and Tran-sition Words subtest (subjects aged 11 to 15.9 years i. Vineland Adaptive Behavior Scales (VABS) j. Child Behavior Checklist for Ages 6-18 (k. Behavior Rating Inventory of Executive Function (BRIEF), 3 criteria l. Computerized Diagnostic Interview Schedule for Children: Parent Form (C-		b. FAS/PFAS:15%-40% Controls:0% c. FAS/PFAS: 5% , 20% Controls:0% d. FAS/PFAS:VMI 33%, RCFT 50-85% Controls:VMI 0%, RCFT 12,5% e: FAS/PFAS: D-KFS: 0-50%, WCST: 20% Controls: 0% f: FAS/PFAS: 25%-50% Controls:0% g. FAS/PFAS:75% Controls:12,5% h. FAS/PFAS: TOWK 43%, TLC-2 28% Controls:0% i. FAS/PFAS: 75%, 65% Controls:6,3% , 6,3% j. FAS/PFAS:20%-65% Controls:0%, 6,3% k. . FAS/PFAS:80%, 85%, 90% Controls:0%, 6,3%, 0% MRT results not reported in that publication		

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		DISC **Visit 3+4: imaging** MR-imaging **Visit 5:** results communication with caregiver				
Burd L. et al. **2010** Cohortstudy [37] Dakota, USA Retrospective chart review	n= 385 patients seen in a North Dakota Medical Genetics Clinic no sociodemographic data given standardized Evaluation with Fetal Alcohol Syndrome Diagnostic Checklist (FASDC) Diagnosed as FAS or pFAS/FAE	Assigning an IOM Category out of chart information 1. FAS growth impairment brain dysfunction craniofacial features characteristic of FAS 2. Partial FAS IOM ARND or pFAS when patients did not meet IOM FAS criteria 3. NO FAS Reference Standard: IOM?!	Accuracy Groups according to IOM Sensitivity, Specificity, (False positives, False negatives, Likelihodd-Ratios Kappa = Measures not stated in this table) Accuracy of diagnosis without exposure (Multivariate logistic regression to estimate best-fit cutoff points for FASCD scales, Correlation between Diagnostic Instrument FASDC and IOM)	1. FAS = 152 pFAS = 151 no FAS = 87 FASDC Total Score with best accuracy 71% FASDC total FAS pFAS no FAS Sensitivity 84,9 54,3 77,0 Specificity 82,4 83,3 90,8 1a. FASDC no alcohol criteria FAS pFAS no FAS Sensitivity 89,3 **10,4** 88,5 Specificity 71,7 95,9 72,6 Classifiying subjects into FAS or NO FAS rate of agreement 58-89% pFAS only 10-54% agreement lowest without exposure information – data available not sufficient to produce distinctive profile ambigious classification		3b, 4?

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				FAs vs pFAS = 15,6% without alcohol 19,6% pFAs vs not FAS 9,7% without alcohol 45,9% FAS not FAS 1% Without alcohol 5,4%		
Chasnoff U. et al. **2010 [40]** Case Control Study	78 foster or adopted children - 3 groups with the 4DDC Maternal alcohol use in gestation confirmed, but not amount/dosage **a. n= 21 with FAS = 1. growth retardation** <3th percentile not 10th!), **2. facial dyspmorphology** (abnormal measurements of upper lip and philtrum Rank 4-5, and shortened palpabral fissures >2SD below the mean **3. neurodevelopmental deficits** (microcephaly <3th percentile and/or functional deficits <3th percentile of a test or >2SD below the mean for more than 3 components of cognitive, executive, memory, adaptive behaviour, attentional. social skills or sensory functions **b. n= 10 with partial FAS = only 2.+3.** **c. n= 47 with ARND = only 3.** FAS children with significant less height, pFAs and ARND not significantly different	**General Intelligence** 1. Wechsler Intelligence Test for Children III 12 subtests that combine to form a Verbal IQ Score, Performance IQ score, Ful Scale IQ Score, +4 other indices Verbal Comprehension, Perceptual Organization, Freedom fro Distractibility, Processing Speed **Executive Function** 2. Behaviour Rating Inventory of Executive Function (86 behaviours of dailiy functioning that are accessible to parents) 3. Childrens Colour Trails Test 4. Wisconsin Card Sorting Test **Achievement** 5. Wide Range Achievement Test 3. edition (word reading, spelling, arithmetic)	Differences in neuropsychological profile -intellectual. -executive - academic -memory, adaptive, behavioural (with X"-Test, ANOVA and MANOVA)	**1. General intelligence** Multivariate analysis for 4 index socre for variance stat. sign. F= 3,63, p= 0,01 Observed power of analysis 0,981 FAS group significant lower than, pFAS (F=3,18 p=0,019 and ARND (F=6,6 p<0,01) pFAS and ARND not sign. Different (F=1.16, p=0,34) **2. Memory** Overall MANOVA stat. sign. F=,38, p=0,019 Observed power 0,880 language based memory lo west in pFAS group statistically differente only FAS vs ARND: p=0,042 **3. executive functioning** sequencing and shiftign significant longer in the FAS grup than in pFAs and ARND Behaviour Rating without sign, diff. Power ok, Wisconsin Card Sortine without difference, power low.	Gruppengöße sehr stark unterschiedlich .Auswirkungen auf Effekte?! LImiation: small sample size, special group of children! Further studies with lager sample size needed	4

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	Groups similar for age, gender, racial/ethnic distribution, country of birth, adoption status, age of caregiver, rates of polydrug misuse, children welfare history	**Memory** Wide Range assessment of memory and learning screening (verbal. story, picture and design memory) **Adaptive Living Skills** Vineland adaptive behaviour scales, Interview with parents on communication, daily living and socialization **Behaviour** Child Behaviour Checklist		**4. academic function** No statistic difference, power 0,69 **5. adaptive functioning** differences in MANOVA p=0,012, power of analysis 0,876 "functional communication" FAS group sign. lower than pFAS, F= 4,48p= 0,06 ARND in between, no stat. diff. **6. Behaviour** No statistical sign. Diff., power 0,83. **Authors conclude** that FAS children are sign. Different, IQ has an impact on other tests, but can be misleading using as a covariate. High rate of attention deficit disorders in all groups **In Discussion;** Time of alcohol exposure and mean volume of the frontal lobes? (FAS throughput the pregnancy, pFAS only first trimester?)		
Mattson SN et al. **2010 [41]** Case-Control-Study USA /Finland (2 centers of the "Collaborative Initiative	Patients from the Center for Behavioural Teratology (San Diego USA) and Patients from a Research Center in Helsinki, Finland age 7-21 years (Mean age 13.0-13.7 per group n.s.)	Standardized neuropsychological test battery, age appropriate tests in the childrens native language, limiting emphasis on verbal	**1. Profile Group 1 vs Group2:** Overall accuracy of correct classification, Exposed FAS and Controls **2. Profile Group 3 vs**	**1. Test accuracy Group 1 vs Group 2:** Overall accuracy for Exposed/FAS and Controls/Not Fas: 92% Accuracy Exposed/FAS: 78,8%	No power calculation! Limitation Sample size, Measures chosen, no validation of	3b-4

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on Fetal Alcohol Spectrum Disorders = CIFASD USA, San Diego and Helsinki, Finland)	both with middle socioeconomic status levels and generally similar postnatal environments 1. Group of exposed children (>4drinks at least once a week or >13 drinks/week) Exposure history was confirmed via review of records or maternal report. 2. Group of nonexposed children recruited from same sites with no evidence of more than one drink per week and never more than 2 drinks on any occasion during pregnancy Diagnosis of FAS only by 2 of 3 dysmorphologic criteria (short palpebral fissures, smooth philtrum, thin vermillion) and microcephaly (<10th percentile) or growth deficiency (weight and/or height </= 10th percentile) **Categorization in 4 groups** 1. Exposed/FAS (n=41) 2. Exposed/Non-FAS or Deferred (n=38) 3. Control/Non-FAS (n=46) 4. Control/Deferred or Not FAS (n=60) Characteristics similar despite: 1. IQ Group 1 statistically lower than group 2	instructions/responses due to internationality. 547 variables from the following tests: - Edinburgh Handedness - Leiter-R - Cambridge Neuropsychological Test Automated Battery (CANTAB) - Grooved Pegboard - Virtual Water Maze, - Neurobehavioural Evaluation System 3 NES3- Continous Performance Test (Animals) - Visual Discrimination - Reversal Learning, - Progressive Planning Test, - Finger Localization, - Delis Kaplan Executive Function System (D-KEFS) Scored According to published test manuals, Data entered in cantralized database Converted to Standard Scores according to age norms	**Group 4** Overall Accuracy and accuracy per group **3. Comparison with IQ** **4. Misclassified Subjects** **0. First step:** Identification of the most discriminationg variables, Than person-centered statistical approach by Latent Profile Analysis (LPA) = Model Based Approach, 2 class solution for profiles group1 vs group 2 and 3 vs 4 using logistical regression to evaluate the association between the groups.	Accuracy controls: 95,7% **2. Test accuracy Group 3 vs Group 4:** Overall accuracy for Exposed Not-FAS and similar Controls: 84,7% Accuracy Exposed/Non-FAS: 68,4% Accuracy Controls: 95% **3. Comparison with IQ** FAS probands statistically sign. lower than controls (91,6 vs. 110,0 p<0,01)) **IQ** was not included in the initial analysis because of the goal to define a neurobehavioural profile more specific than decreased IQ. In both analyses profile significantly better than IQ alone for distinguishing Overall Accuracy IQ 75,9% 75,6% in the exposed group, 76,1% in the control group. **4. Misclassified Subjects** Group 1 vs 2 = 7 / 2 controls Group 3 vs 4 = 16 / 1 control In misclassified controls any alcohol consum was denied by the parents No statistical sign. diff. Between	findings in an other group, Controls recruited retrospectively! – recall about alcohol exposure impacted In some cases only report of the mother	

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				misclassified Group members. **0. LPA : 2 class-solution fitted best.** **22 most discriminating variables identified covering the following functions:** 1. Executive Functions (14/22) 2. Cognitive Flexibility (4/22) 3. Fine Motor (2/22) 4. Fluency (3/22) 5. Planning (1/22) 6. Sequencing (1/22) 7. Set Maintenance (1/22) 8. Spatial Learning (1/22) 9. Spatial Reasoning (4/22) 10. Sustained Attention (3/22) 11. Visual Memory (3/22) 12. Visual Motor (1/22) **a. 4 x tests of CANTAB** (recognition memory, spatial span length, spatial working memory strategy, spatial working memory total errors) **b. 9 x tests of D-KEFS** 4 Trail Making (Combined Number/Letter, Switch vs. Number, Switch vs. Visual. Switch Errors)		

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				5 Verbal Fluency (Total Correct Letter, Total Correct Category, Total Correct Switch, 2nd Interval Correct, Set Loss Errors) **c. 1 x Morris Virtual Water Maze Test** Time in Target Qudrant on Probe Trial (raw score) **d. 3x Neurobehavioural Evaluation System 3** Animals Following Subtest, Number Correct, Animals Repeating Subtest, Number Correct, Animals Single Subtest, Number Correct **e. 2xGrooved Pegboard Test** Dominant hand Completion Time, Non-Dominant Hand Completion time **f. 1x progressive planning test** maximally constrained total score **g. Visual Discrimination Reversal Learning Test (VDRL)** Number of Reversals (raw score) **h. Visual Motor Integration Test (VMI)** Visual Motor Integration Test Total (standard score)		

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Thorne J.C. et Coggins T, 2008 [55] Retrospective Case-Control-Study	n=32 school-aged children (8 years;5-11,5) 16 with FASD, 5 with FAS or partial FAS, 16 Controls, typically developed Age-mathced, 13 also gender-matched, Not matched for IQ	Tallying Nominal Reference Errors in oral narratives (ca. 300 words) of the same wordless picture book used as a visual prompt (f.e. introducing "the "frog instead of "a " frog)	Diagnostic accuracy for FASD/FAS	Intercoder Agreement (out of 25% of the material): (second coder: 10h face to face training and 40h coding practise): Kappa 0,90 [95%CI 0,87-0,93]. **1. FASD vs Controls : 88% overall accuracy'** **2. FAS vs all others: 97% overall accuracy** cut-off 3,7% Sensitivity 100% Specificity 92,6%	Exploratory, needs prospective confirmation IQ could be a confounder Controls were not neropsychologically tested Comparison with a former reference error test or other variables not stated	3b
Vaurio L. et al. **2011 [42]** Case-control-study USA, San Diego	n= 110 children aged 6 to 16 IQ matched pairs within 5 points of the Wechlser Intelligence Scale for children III as well as matched for age and SES as measured by Hollingshead a. Group 1 (n=55) Alcohol Exposed (with FAS full or partial dysmorphological criteria) recruited by professional and self referral at least 4 drinks per occasion at least once a week or 14 drinks a week throughout pregnancy, seldom reports of the mother, records, adoption papers etc. b= Group 2 (n=55) controls via	Application of the following tests : **1.Receptive Language** - Peabody Picture Vocabulary Test-(PPVT-III) **2.Expressive Language** - Boston Naming Test **3. Verbal Fluency** - Controlled oral word association test **4. Nonverbal Problem Solving** - Wisonsin Card Sorting Test **5. Visual Motor Ability** - Beery Visual Motor Integration **6. Fine Motor Ability** - Grooved Pegboard **7. Academic**	Differences in Neuropsychological profile 1. broad neuropsychological measures 2. (items see tests) adjusted for IQ using a doubly multivariate design (multivariate analog of a matched paired t-test – the matched pair as within subject variable to maximize power, the neuropsychological outcome as dependant variable). Holm-Bonferroni for multiple	**1. Analysis of broad neuropsychological measures –** **a.all matched pairs** 1.-7. : marginally significant effect of group F(10,43)=2.02, p=0,05. in univariate Follow-up Analysis sign. diff. in 4. Wisconsin Card Sorting p=0,03) 5. Visual Motor Ability, p=0,02 7.VRAT arithmetic p=0,009 Alc. Exposed with poorer performance **b. because of wide IQ range - repeated analysis with 38 matched pairs** significant effect of group	Exminers blinded to group membership Limitations: Sample size Group selection Test selection No screening for psychopathology	3b-4?

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	advertising and child-related venues, mostly reports of mothers concerning alcohol, inclusion of y 2 drinks on any occasion and up to 1 oz AA/day cave 11% with smoking of cigarettes, 4% Marihuana 13(23,6%) with IQ below the average range <85 with no systematic reason	**Achievement** - Wide Range Achievement Test (VRAT) n=3 **8.Verbal Lerning Memory** - California Verbal Learning Test- Childrens Version **9.Sustained visual attention** - Test of Variables of Attention,Visual Subtest, **10.Child Beaviour Checklist** (parent guardian reported) All Tests applied within 2-3 days in same order	comparisons was used..	p=0,029 **2. Verbal Learning and Recall** 8. CVLT overall effect of group, alcohol exposed with poorer performance, but retention of verbal material no significant difference **3. Visual Sustained Attention (9.)** no group differences **4. Behaviour Problems (CBCL)** (10.) Overall effect of group F(8,47) = 10,24 p<0,01 Alcohol exposed group had more behaviour problems than the controls on all CBCL scales Except for somatic complaint .		

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Epilepsy						
Bell SH et al., 2010, ecological study [43]	N= 425 subjects at two FASD clinics with confirmed diagnosis of FASD following the Canadian Guidelines for diagnosis No control group. Ages of 2-49 (mean age 15.2). Age group 2-14: 51% Age group 15+: 48.5% 20% FAS or partial FAS (pFAS), 80% Alcohol related Neurodevelopmental disorder (ARND)	Evaluation of prevalence of epilepsy or history of seizures in subjects with FASD and contribution of risk factors (as prenatal alcohol exposure)	1) Prevalence of epilepsy or /and seizures among individuals with FASD 2)a) Association of specific types of seizure disorders with FASD b) Association of epilepsy and /or seizures with specific subgroup of FASD (FAS , pFAS, ARND) 3) Association of history of prenatal alcohol exposure with epilepsy as an independent risk factor	1) 25 (5.9%) with FASD had a diagnosis of epilepsy, 50 (11.8%) had one or more seizure episodes 2) a)No difference between FASD diagnosis and risk of epilepsy or one or more seizures (p=0.73) b) FAS group: 3 (20%9) pFAS: 10 (14.1%) ARND: 62 (18.23%) The authors describe these results as "no difference of prevalence between the groups", no p-values or CI are shown 3) History of prenatal drug exposure showed no significant results (p=0.054) for epilepsy or seizures	Chi-square and multivariate multinominal logistic regression were used. No control group For the results of testing the association of epilepsy and/or seizures with specific subgroup of FASD (FAS , pFAS, ARND no p-values or KI were shown. The authors describe these results as "no difference of prevalence". No separated analysis for the different age groups. There is no description about getting information with concerning maternal drinking history (self-reporting?)	2c -

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Learning, Cognition different aspects						
Simmons et al. 2010 [44]	Children aged 7 -17 years **Group1:** n= 28 children with alcohol exposition (PAE) n=9 with FAS, n=19 without defined characteristics of FAS, **Group 2:** n= 23 non-alcohol exposed control children FSIQ and SES as variables	1. 24 trials Reaction Time: lifting forarm and Hand when stimulus light was activated 2. 48 Trials Reaction Time and Movement Task: Same as above +hitting the target keays in a designated sequence	-reaction time -reaction time and movement task (complexe movement) ANCOVA FSIQ and SES as variables Bonferroni T-Test post hoc analyses Alpha 0,05	1. Reaction time No significant differences 2. Reaction time + movement = response programming and movement time FAS significantly longer times and with more variables PAE and Controls comparable		4
Executive function /social and adaptive skills/behaviour						
Carr J et al., 2010 [45] Cohort study and ecological study,	Data were extracted from participants` clinics file of Ontario Fetal Alcohol Disorder clinic. FASD assessment was done according to Canadian guidelines, including an assessment for ADHD. Sample size n=46, age between 3-14 (mean age 8): PEA group n= 15 ARND n=16 pFAS n=15 (no significant differences in age and guardianship)	**Short sensory Profile (SSP)** measured sensory processing ability: 38-items standardized and norm-referenced questionnaire for children between 3-18 (lower scores show more impaired sensory processing). "Definite difference" indicates performance -2.0 standard deviations below the mean. In addition to the total score, there are 7 subsections: tactile sensitivity, taste/smell sensitivity, movement	Differences between the groups of pFAS, ARND, PEA in 1)sensory processing ability (measured by SSP) 2) adaptive behaviour capability (measured by ABAS II) 3)neurocognitive functioning (WPPSI-III and WISC-IV) 4)Korrelation between IQ scores and adaptive behaviour 5) Korrelation between	1) Children with ARND scored significantly lower than children with PEA on the total score (p= 0.010, taste/smell sensitivity (p=0.031) and low energy/weak (p=0.014) 2) Children with ARND scored significantly lower than children with PEA on GAC score (p=0.002). Children with pFAS did not score significantly different from the ARND or PEA group on the ABAS-II composites. 3) Children with pFAS scored significantly lower than the ARND or PEA group on	The 3 groups were compared using a multivariate analysis of variance (MANOVA). Power values of 0.628, 0.584 and 0.912 were found for SSP, ABAS-II and IQ MANOVA´s, respectively. Thus, implications of the the results of SSP and	3b (very limited population)

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		sensitivity, underresponsive/ seeks sensation, auditory filtering, low energy/weak, visual/auditory sensitivity. **Adaptive Behaviour System Second edition (ABAS II)** measured adaptive behaviour capability: 10 skill areas grouped into 3 broad domains: conceptional. social. practical. Additional there is General Adaptive Composite (GAC) that reflects overall adaptive behaviour. As a measure of neurocognitive functioning **Wechsler Preschool and Primary Scale of Intelligence – 3rd ed. (WPPSI-III)** with 3 subsections (Perceptual/Perfomance IQ, Full Scale and Verbal IQ) and **Wechsler Intelligence Scale for Children – 4rd ed. (WISC-IV)** was used.	sensory processing deficits and adaptive behaviour difficulties	Perceptual/Perfomance IQ (p= 0.034). There was no significant main effect of group on Full Scale and Verbal IQ. 4) No significant correlations between any index or full scale score on IQ and any ABAS-II domains across all the diagnostic categories. 5) There was a significant positive relationship between SSP Low energy subscale with the ABAS-II GAC score (p=0.014).	ABAS-II are very limited.	
Fagerlund A et al., 2011 [46] Case-control	All children born between 1984 and 1996 and diagnosed as	CBCL (Child Behavior Checklist) was used to	1)Comparison of scale scores on the CBCL	1) NC group differed significantly from FASD group	- NC was not matched on social	4

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study and ecological study,	FASD in Helsinki were screened. The final group consisted of 73 children, FAS n=41, PFAS=23, ARND n=9, 60% were girls, age range from 8-21, mean age 13 years. 44 (60.3%) was described with ADHD. Normal control group (NC) with N=40, recruited through random sampling from the Finnish national population registry and were matched on age, sex, and geographical region. Maternal alcohol consumption was confirmed by review of patient records. Diagnosis of FASD was according to the revised IOM diagnostic criteria. Children were assigned a dysmorphology score (not described in more detail)	provide a syndrome profile with three broad dimensions: 1) internalizing problems such as anxiety, depressive symptoms, social withdrawl. 2) externalizing problems with inappropriate behaviour such as rule breaking and aggressive behaviour. 3) total behaviour problems, i.e. problems with thought and attention.	between FASD group and control group 2) Association of diagnostic factors as dysmorphology score with behaviour (measured by CBCL) was explored by a regression analyses (no control group)	on all three dimensions of the CBCL. - total problems in clinical range: 22,5 % FASD, 0 % NC (p< 0.0001) - internalizing problems in clinical range: 18,3 % FASD, 2,5 % NC (p< 0.0001) - externalizing problems in clinical range: 14,1 % FASD, 0 % NC (p< 0.0001) 2) dysmorphology score after controlling for IQ, sex and age was negatively associated with internalizing problems (r_p -0.357, β -0.289, p<0.05) and total problems (r_p -0.229, β -0.267, p<0.05).	and environmental background - There was no control group assessing association of diagnostic factors as dysmorphology score with behaviour. Majority of FASD group was described with ADHD. Assessment of dysmorphology score is not described in more detail	
Nash K et al., 2011, retrospective cohort study [47]	Participants: The sample included 220 children aged 6 to 18 years, 56 with an FASD (Fetal Alcohol Spectrum Disorder, 4 with FAS), 50 with ADHD (Attention Deficit Hyperactivity Disorder), 60 with	10-item screening tool based on items from a standardized behavior problems questionnaire known as the Child Behavior Checklist (CBCL).	Difference of items between 3 groups using the chi-square test. 1)FASD vs. NC, 2)FASD vs. ADHD,	1) Significant higher values in all items used Acts too young, argues a lot, can't concentrate/pay attention for long, can't sit still/resteless hyperactive, cruelty/bullying/meanness to	Since data were collected retrospectively, certain background information was not available,	3b

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	ODD/CD (Oppositionla Defiant/ Conduct Disorder) and 53 typically developing normal control (NC) children. The FASD group was recruited from the Motherisk Follow-up Clinic, in Toronto. Inclusion: To be included in the FASD group, children had to have a documented history of prenatal exposure to alcohol and a diagnosis of ARND. Exclusion: -Children were excluded if their exposure history was unconfirmed, their primary exposure was to a substance other than alcohol (e.g. marijuana). -Any child of the comparison groups with a history of prenatal drug or alcohol exposure, defined as more than 2 drinks during pregnancy, was excluded. The NC group consisted of 53 previous control participants in other studies in our laboratory. The 4 groups were significant different with regard to SES, age,	Comparison of children with FASD to children with 3 comparing groups: 1)FASD vs. NC, 2)FASD vs. ADHD, 3)FASD vs. ODD/CD FAS or ARND diagnosis is based on the Canadian diagnostic guidelines. ADHD and ODD/CD diagnosis was based on using DSM-IV-TR criteria.	3)FASD vs. ODD/CD 4)Receiver Operating Characteristic (ROC) curve analyses were then performed for different group pairs using the sum of items most strongly differentiating each pair. Area-under-the-curve (AUC) values were used to classify cases as being FASD or NC, FASD or ADHD, and FASD or ODD/CD based on the number of endorsed items and critical cutoff values. ROC analyses provide 'sensitivity and 'specificity'	others disobedient at home Doesn't seem to feel guilty after misbehaviour Impulsive acts without thinkung Lying/cheating Showing off clowning Steals at home Steals outside home 2) FASD also had significantly higher endorsement rates than ADHD for the following five items: - "acts young" [χ2 (1) = 5.0, p < .03], - "cruelty bullying, meanness to others" [χ2 (1) = 8.7, p < .00], - "doesn't seem to feel guilty after misbehaving" [χ2 (1) = 17.7, p < .00], - "steals at home" [χ2 (1) = 17.0, p < .00], and - "steals outside the home" [χ2 (1) = 9.7, p < .00]. 3) Children in the FASD group received a higher score than ODD/CD on only one item, namely "acts young" [χ2 (1) = 7.2, p < .01]. However, children in the ODD/CD group had higher rates for being "disobedient at	particularly for the ADHD group. Finally, because the proposed screening tool is intended to be used as a screening instrument, variables important at the stage of diagnosis, such as age, family histories, and SES were not controlled for in the analyses (see demographic differences between groups). Quality of CBCL tool is not described or discussed. IQ was not assessed. Control groups were not matched for IQ For all groups, information was obtained via	

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	medication			home" [χ2 (1) = 4.1, p < .05]. 4) - Comparison of FASD and NC groups indicating the largest Area Under the Curve (AUC) was achieved with 0.970 (p < .001); using a cutoff of 3 of 10 items, achieving sensitivity of 98% and specificity of 42%. - Compared with ADHD, the largest AUC was achieved with 0.78 (p < .001); using a cutoff of 2 out of 5 items, attaining sensitivity of 89% and specificity of 54%. - Comparable ROC analysis could not be conducted between FASD and ODD/CD groups because only one item differentiated them; <u>Demographic Information:</u> There was a significant effect of age, [F (3, 210) = 27.0, p <.01] with children in the ODD/CD being significantly older than children in the FASD, ADHD and NC groups. There was also a significant effect of SES, [F (3, 199) = 23.8, p <.00]	retrospective chart review (socioeconomic status (SES)). From each child's chart, relevant CBCL data were extracted for each case using the items from previous screener.	

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				reflected in children in the NC and ADHD having significantly higher SES than children in the FASD and ODD/CD groups.		
Case-control study, Pei J et al. 2011 [48]	N= 70 (35 FASD, 35 control), aged 6-12 years, mean age 8.29 years (no significant difference between groups). Living situations were significant different (foster care, adopted, without birth parents etc. in the FASD group) FASD diagnosis was made according to the Canadian guidelines for FASD using the 4-digit diagnostic code. Control participants were recruited form a local elementary school, matched concerning gender and age	Rey-Osterrieth Complex Figure (ROCF): a neuropsychological assessment tool that requires 1) to copy a complex geometric design with multiple details 2) then recreate the figure from memory after 3 and after 30 minutes. This test includes the Rey Complex Figure Test (RCFT) and the Developmental Scoring System for the ROCF (DSS-ROCF) as a scoring system to provide information about the degree and type of differences. RCFT involved reproducing the figure three times: Copy trial (at once), after a 3-minute Immediate Recall (IR) trial. after a 30-minute Delayed Recall (DR) trial. DSS-ROCF measures 4 parameters of performance: organization, style, accuracy, and error	Difference in: 1) "Organization" score quantifies the appreciation for the organizational goodness of complex, visually represented materials. 2) "Style" categorized the approach to information processing 3) "Accuracy" score quantifies the elements are accurately reproduced. 4) "Error" score quantifies the extent of which elements are distorted (i.e. misplaced, conflated etc.)	1) Chi-square analyses: significant differences for the Copy trial ($p< 0.001$), but not for IR or DR, with FASD group showing less favourable results. 2) Chi-square analyses: no significant differences for Copy ($p>0.126$), IR ($p>0.633$) nor DR ($p>0.943$), with FASD group showing less favourable results. 3) Chi-square analyses: significant differences on structural an incidental accuracy ($p<0.001$) for the Copy trial. but not for IR or DR, with FASD group showing less favourable results. 4) Chi-square analyses: significant differences for each of the trials. Copy trial ($p< 0.001$), IR ($p< 0.05$) or DR ($p< 0.05$), with FASD group showing less favourable results.	Groups were only matched concerning gender and age, not in relation to IQ or family variables. Living situations were significant different (more children in the FASD group were in foster care, adopted, without birth parents)	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		within a developmental context of age appropriateness. Evaluations of reliability and validity for the RCFT have proved excellent.				
Memory						
Rasmussen et al. 2011 [49]	**Group 1:** 24 children with prenatal alcohol exposure (PAE, retrospective data), 12with FASD (2pFAS, 7 static encephalopathy, 3 neurobehavioural disorder 12 without diagnosis (deferred) Diagnostic with 4DDC (Astley) **Group 2:** 26 controls from a local school Children 6-17 years, no sign. Difference between groups	8 Subtests from the CANTAB (Cambridge Neuropsychological Test Automated Battery) 1. Visual (Pattern Recognition)and Spatial Memory Tasks 2. Executive Function and Working memory Spatial Span, Stockings of Cambridge (planning and motor skilss), Intra-Extra-Dimensional Set Shift (IED), Spatial Working Memory 3. Attention Reaction Time, Rapid Visual Information Processing	Statistical differences in Subtests from the CANTAB , Alpha set 0,01 because of numerous testing, Ancova	Children with PAE in comparison to controls stat. sign lower in RTI (reaction time) and Spatial working memory and Rapid Visual Information Processing Group differences approached significance in SPAN length (executive function/working memory). Only the SPAN length differentiated between FASD and PAE only.		4
Attention						
Coles CD, 2001, prospective cohort	Study sample was recruited from a longitudinal cohort of	**1)Focus :** Selective attention to	Difference in 4 attention factors:	Children with ADHD performed	-There is no definition or	3b

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
study [28]	149 children (with an average age of 7.63 years) - who were of low socioeconomic status (SES) and predominantly African-American – as their caregivers. Participants were from a hospital clinic for prenatal care. 4 groups: 1) 25 alcohol-exposed children who were physically affected (i. e., had either FAS or fetal alcohol effects (FAE)) 2) 62 alcohol-exposed children who were not affected 3) control group, consisting of 35 children who had not been exposed to alcohol during pregnancy but who were selected from the same low-SES population. 4) 27 ADHD-diagnosed children from the child psychiatry clinic at the same hospital where the other children were born. ADHD children were matched to the children in the study according to age, SES, and ethnic identification.	appropriate stimuli. WISC-R Coding: The child must rapidly identify and write in symbols associated with numbers **2) Shift:** Appropriate flexibility in response to new information; allocation of attentional resources. Wisconsin Card Sorting Test (WCST): The child must sort cards based on one of three underlying principles: color, shape, or number of items on card. When the sorting category is guessed, it is changed. Few ategories and perseverance on the wrong indicate lack of flexibility **3) Sustain:** Ability to maintain alert state and attention to task. **- Continuous Performance** Test (CPT) (also called Vigilance [VIG] Test):	1)Focus 2) Shift 3) Sustain 4) Encode	less well on measures of focused and sustained attention. In contrast, children in the FAS-FAE group performed less well on measures of encoding and shifting attention.	description concerning alcohol history. - Assessment of dysmorphia is not described more detailed (a checklist is mentionend, but no details are given) -No test statistics are shown, only a figure with z-scores	

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		From letters rapidly displayed on a computer screen, the child must identify a predesignated signal without missing letters or responding impulsively to wrong letters (i. e. , false alarms) . Reaction time is also measured. **4) Encode:** Ability to learn new material and manipulate material in working memory while processing into long-term memory. - Paired Associate(PA) Task (also called Zoo Task): Cards with animals are repeatedly paired with zoo homes of different colors. The child must recall the correct zoo when presented with the animal card - Number Recall subtest from the Kaufman Assessment Battery for				

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		Children (K- ABC) The child read a series of numbers and must repeat them accurately. - Arithmetic subtest from the K-ABC: The child must display basic math skills				
Coles CD, 2002, prospective cohort study, single blinded [50]	N=265, range 13-17 years (mean age15,1). 181 were recruited between 1980-85 from a preclinic serving a predominantly African-American, low socioeconomic population and were observed longitudinally, when their mother reported drinking during pregnancy (at least two drinks per week). Children of nondrinkers with the same SES were recruited as control group. 84 were additional recruited as control group with adolescents from special education programm. Diagnostic groups: 1)adolescents exposed/dysmorphic (DYSM)(n=46) 2)alcohol- exposed, but not dysmorphic (EtOH) (n=82)	Measures: Visual and auditory sustained attention measured with "AK" subtests from a commerciably available Continous Performance Task program. This test requires to identify a target letter "K" (either seeing or hearing)	Difference in total responses (corrects and incorrect), total correct responses (hits) and total errors (omissions, commissions preseverations), false alarm rate, reaction time, and response sensitivity to signals 1)visual or 2) auditory presentation of stimuli between the 4 groups	Dysmorphic adolescents had significantly more responses compared with the means for the contrast and special education group (DYSM mean 37, SD 0.68; control mean 35.04, SD 0.64; EtOH mean 35.37, SD 0.51; special education mean 34.36, SD0.51 – no p-values reported, results not in tables). With the exception of total responses (Fig.1), performance of DYSM group on the visual task was significantly different ($p<0.05$) from that of other groups, whereas except of the total responses performance on the auditory task was not different (p value n.s.) Visual performance: Total correct responses:	Cognitive ability evaluated with the Wechsler Intelligence test for children differed between the dysmorphic group and the other groups. Therefore, full-scale IQ was used as a covariate in analysis of attention measures. No drop outs after 15 years? Validity of the test battery is not described Testers were	3b

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	3) Control group: non-exposed (n=53) 4) additional control group with adolescents from special education programm (n=84) Cognitive ability was evaluated with the Wechsler Intelligence test for children, 3rd edition. IQ scores did not differ across the groups, except those in the dysmorphic group had significant lower cognictive scores (no discrepancy in verbal and performance IQ scores). Dysmorphia was checked on the basis of a physical examination with a "dysmorphia checklist" (Coles et al., 1985) Inclusion: adolescents exposed to alcohol/dysmorphic or alcohol-exposed, but not dysmorphic or non-exposed or adolescents from special education program. Exclusion: individuals with impaired physical mobility, hearing or vision or IQ <50.			p<0.003, F (3,257)=4.67 DSYM group: mean 28.96, SD 5.78 Control: mean30.9, SD 4.39 EtOH: mean 32.16, SD 4.11 Spec. education: mean 29.68, SD 6.54 Total errors: p<0.007, F (3,257)=4.07 DSYM group: mean 15.21, SD 13.37 Control: mean 9.57, SD 8.98 EtOH: mean 8.51 SD 9.33 Spec. education: mean 12.25, SD 12.39	blinded to maternal drinking history Assessment of dysmorphia is not described more detailed (a checklist is mentionend, but no details are given)	
Differential diagnosis						
Crocker et al. 2011[51]	n=66 children, 22 per group	California Verbal Learning	1. First: matching	1. Demographic Information		4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
Case-Control-Study San Diego	7-14y 1. children with heavy prenatal alcohol exposure and ADHD = ALC (meeting DSMV-IV criteria), Mothers with at least 4 drinks per occasion/week, or 14 drinks per week during pregnancy 36,4% with stimulant medicaments 2. Children with ADHD but without alcohol exposure 31,8% with stimulant medicaments (ADHD) 3. control group without alcohol exposure and ADHD matched on age (within 6 months), sex and race/ethnicity All recruited as part of a longer study, via several mechanisms (CON)	Test Childrens Version (good content, criterion and construct-related evidence of validity Results Controls as Reference Standard, Multivariate analysis	demographic data analyzed by Chi-Square or Standard Analysis of Variance (ANOVA) age, FSIQ, Freedom from Distractibility index Scores measured by Wechsler III and SES 2. Statistical Differences in Test Criteria Alcohol exposed vs Controls in Verbal Learning and Memory Raw Scores, Age included as variable 5	matched pairs similar on sex, handedness, race, ethnicity No significant diff. n age p=0,09 and SES p=0,08 FSIQ was significantly higher in the CON and ADHD group than in the ALC group p<0,001. 2. Differences in test results stat. sign: **Group interaction significant** (p=0,004) and also main effect of group p<0,001. **Overall differences were apparent on all trials**, pairwise comparison indicated the following diff. P<0,05: CON in all trials despite 1 better as ALC ADHD sign. worse than CON on 2+3 and sign. better than ALC on 4+5 **Free Recall** after 20 min delay-CON sign better **Retention** group differences p=0,065 ADHD worse than CON p=0,023 ALC no sign diff to the other groups **Recognition** main effect of group significant p=0,015 ALC more poorly than ADHD and CON p<0,05		

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
Kooistra L, et al. 2011 [52]	Almost the same patients as in the following study 47 ADHD, 30 ADHD-C, 16 ADHD-PI, 30 FASD with 29 ADHD-C 39 Controls,	Continous performance tasks button press responses to target stimuli (249 trials) Go/No-Go-task button press responses to frequent stimuli and not to infrequent (210 trials)	Measures of attention Response latency errors Decline in performance over time	Response latency significant effect of group F3,1=5,97 p=0,001 ADHD-C and FASD slower and with more variables than controls Errors significant effect of group F3,105=6,14, p=0,001 ADHD-C and FAS sign. More errors, but only ADHD-C significant more errors of commission 3. Performance of ADHD-C, ADHD-PI and FAS declined sign. More than that of controls over time (Go/No results not stated)		4
Kooistra et al. 2011 [53]	113 children aged 7-10 years **Group 1** 47 ADHD (31 –C =combined, 16 -PI primariliy inattentive) diagnosed between 5-7J 91% on stimulants 51% confirmed learning disability (LD) ADHD Confirmed with 3 Tests (all had to be positive): a. Summary ADHD Checklist Kaplan et al. 1997, Score 2+3 b.Conners Parents Rating Scale Revised (1997) cut-off Score >64	Wechsler Intelligence Scale III for IQ: (15min) than Attention Network Test: (25 minutes) 14 practice +144 experimental trials Computer based with children making left and right responses about target stimuli with 2 fingers , congruent and incongruent flankers	1.Demographical differences (ANCOVA) 2.Median reaction time (RT) 3.Response accuracy (MANCOVA) 4. alerting, orienting and conflict effects	Assessors blinded to groups 1. No difference for age and sex, statistically significant differences for FSIQ and SES FASD sign. lower 2.median RT ADHD-C and FAS most impaired by incongruent flankers compared to controls (F(1,55=7,39,p=0,02 and F(1,5=14,55 p<0,01) ADHD-C and FAS did not differ	ADH-PI with profile not distinguishable from controls – Number ? Discriminative power limited	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	on DSMV-IV Totale Scale c. Diagnostic interview for children and adolescents Reich 1997/2000 also subtype assignment IQ >/= 80 **Group 2** From a FASD clinic 28 FASD Diagnosed with Fetal Alcohol Syndrome Diagnostic And Prevention Network Diagnostic Guide(DPN) 4 digit code Astley+Clarren 1999 Category G+H (H= without facial signs) Alcohol exposure 3+4 27 met criteria for ADHD and hat stimulants 13% confirmed LD IQ >/= 80 **Group 3** 38 controls From 2 elementary school All tests negative No confirmed data for alcohol consum for group 2+3	Tests after 24h washout period for ADHD stimulants		3. Response accuracy Significant effect of group not dependant from flanker type (F3,7=5,16 p=0,02) ADHD-C had significantly lower accuracy compared to every of the other groups 4. no significant correlation in alerting, orientino or conflict effects Post hoc contrasts showed ADHD-C and FASD with higher conflicting scorse than controls		
Rasmussen et al. 2010 [54] Retrospective Case-Control Study	N= 52, 4-17 Y, with FASD (one child with FAS, 6 with partial FAS, 13 with Neurobehavioral Disorder, and 32 with Static Encephalopathy according to the 4-Digit Diagnostic Code) 39 with comorbidity of ADHD	The Sensory Profile Adolescent/Adult Sensory Profile Short Sensory Profile Bruininks-Oseretsky Test of Motor Proficiency – 2nd edition Movement Assessment Battery for Children –	sensory/motor, cognition, communication, academic achievement, memory, executive functioning, attention, adaptive behavior	Children with FASD and ADHD performed significantly worse than those without ADHD on attention but better on academic achievement. No other group differences were significant.	Retrospective, Number of patients very limited	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		Second Edition (Movement ABC-2) Clinical Evaluation of Language Fundamentals – Fourth Edition (CELF-4) Clinical Evaluation of Language Fundamentals – Preschool, Second Edition (CELF-P:2) Coggins Mental State Reasoning Tasks Comprehensive Assessment of Spoken Language (CASL) Expressive Language Test (ELT) Expressive Vocabulary Test – Second Edition (EVT-2) Mercer Mayer Wordless Story Books (Retell, Generate, Comprehension) Oral and Written Language Scales (OWLS) Peabody Picture Vocabulary Test – Fourth Edition (PPVT-4) Preschool Language Assessment Instrument – Second Edition (PLAI-2) Renfrew Bus Story – American Edition Test of Language Competence – Expanded Edition (TLC-E)				

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		Test of Language Development – Primary, Third Edition (TOLD-P:3) Test of Narrative Language (TNL) Test of Problem Solving 2 – Adolescent (TOPS-2 A) Test of Problem Solving – Third Edition (TOPS-3) Test of Word Knowledge (TOWK) Behavior Assessment System for Children – Second Edition (BASC-2) Conners Rating Scales – Revised (CRS-R) Continuous Performance Test (CPT) Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) Test of Nonverbal Intelligence – Third Edition (TONI-3) Wechsler Individual Achievement Test – Second Edition (WIAT-II) or Wide Range Achievement Test – Fourth Edition (WRAT-4) Children's Auditory Verbal Learning Test (CAVLT) Rey Complex Figure Test (also in EF) Memory subtests from the				

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		NEPSY-II NEPSY – Second Edition (NEPSY-II) Behavior Rating Inventory of Executive Function				

Tabelle 2: Evidenztabelle zu strukturellen ZNS-Auffälligkeiten

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
Archibald S.L. et al. 2001 [56] Case-control-study	n=14 patients with FAS (mean age 11,4y) n=12 p. with prenatal exposure of alcohol (mean 14,8y.): only few facial signs, no growth retardation FAs and PEA IQ similar n=41 age-matched controls	MRT whole brain image 3 series 1. gradient-echo weighted T1 with cont. 1,2mm section, 2. +3. fast spin-echos acquisitions 4mm (2 diff. image sets)	Neuroanatomical region of interest analysis brain volume white matter, gray matter and cerebrospinal fluid was measured for each cerebral lobe and the cerebellum as well as gray matter volume of subcortical stuctures	1. Analysis done by 2 anatomists for each MRT. Interoperator reliability of total tissue volumes for independent tissue classification by 2 anatomists (using 11 brain data sets) were 0,92 for white matter, 0,95 for gray matter, 0,99 for Cerebrospinal fluid **2. Significant group differences** **FAS versus Controls** Cerebral and Cerebellar cranial vault, gray matter and white matter. (p<0,05 each) Mediated through significant hypoplasia in the FAS group. **3. Detailed analysis:** Parietal lobe significant reduced in FAS (p<0,05) Proportional reduction of white matter in the cerebrum p<0,05 Parietal lobe gray and white matter reduced in FAS (p<0,05), more than Disproportionate reduction of cadatur nucleus volume in FAS,	Analysis done by trained anatomists, blinded to participants data Diff. between PEA and Controls almost all non significant	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				disproportionalte sparing of hippocampal volume (relatively preserved)		
Astley et al. 2009 [57]	Group 1: N=20 with FAS/partial FAS Group 2: N= 24 with static encephalopathy alcoholexposed Group3 : N= 21 with neurobehavioural disorders, alcohol exposed Group 4: N=16 controls with reported absence of prenatal alcohol exposure Diagnosed with 4-Digit Code Matched for age, gender, race	MRI imaging 1,5 Tesla (MR spectroscopy and functional MRI (fMRI)) and psychological and neuropsychological tests	1. size of brain/brain regions 2.correlation of FAs phenotype with brain size 3. correlation to CNS dysfunction 4. correlation with prenatal alcohol abuse	**1. size of brain/brain regions** (Only Results of FAS/partial FAS vs controls reported) Total brain volume and various regions significantly smaller in FAS/PFAS as in Controls Not significantly different in relative measures! ***Mean Total brain volume*** (cm^3 - all measures) FAS/PFAS: 1217,8 Controls: 1370,5 p=0,03 ***Frontal lobe volume*** FAS/PFAS: 346,1 Controls: 419,8 p=0,001 ***Total caudate volume*** FAS/PFAS: 7,4 Controls: 9,6 ***Total putamen volume*** FAS/PFAS: 6,6 Controls: 7,6 p=0,04 ***Total hippocampus volume*** FAS/PFAS: 5,7 Controls: 6,8 p=0,003 **2. correlation with facial phenotype** Difference between group 1 and 2 : sign smaller frontal lobe volume, mitsagittal area of	Controls with higher IQ than mean population	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				cerebellar vermis, caudate volume (p<0,05 each) **3. correlation to CNS dysfunction** Significant increase of 1 or more brain regions with 2 or more SD below the Mean of the control group from Group 3 to Group 1 **4. correlation with prenatal alcohol abuse** size of various brain regions decreased significantly and incrementally among FASD subjects with increasing frequency, quantitiy and/or duration of reported alcohol exposure		
Bjorkqvist et al. 2010 [58]	Thirty-one youth (ages 8–16) with histories of heavy prenatal alcohol exposure (n = 21, 10 FAS) , evaluated by 1 dysmorphologist (K.L:Jones, San Diego) and demographically-matched comparison subjects (n = 10)	MRT; structural magnetic resonance imaging, 1,5 T, T-1 weighted	Volume of gyrus cinguli, correlation to behaviour	1. Alcohol-exposed individuals had significantly smaller raw cingulate grey matter, white matter and total tissue volumes (grey and white matter together), compared to controls. 2. After adjusting for respective cranial tissue constituents, only white matter volumes remained significantly reduced, and this held regardless of whether or not the child qualified for a diagnosis of FAS. 3. A correlation between posterior cingulate grey matter volume and the WISC-III	Interrater correlation 0,90+0,92	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				Freedom from Distractibility Index was also observed in alcohol-exposed children. These data suggest that cingulate white matter is compromised beyond global white matter hypoplasia in alcohol-exposed individuals, regardless of FAS diagnosis. The observed volumetric reductions in the cingulate gyrus may contribute to the disruptive and emotionally dysregulated behavioral profile commonly observed in this population.		
Sowell et al. 2001 + 2008 [59]	21 children, adolescents and young adults with prenatal alcohol exposure (8-22y, mean 13y). All history of heavy alcohol exposure 14/21 with FAS (mean 12,6y) 7 no facial criteria but prenatal alcohol exposure 21 controls (8-23, mean 13,3y)	MRI 1,5T, T1-weighted series	1. Differerence in volumes (other results of statistical parametic maps not reported) 2. Difference in cortical thickness	1. Significant group differences were observed for: Total intracranial volume p<0,001 total gray matter volume p<0,01 Total white matter volume p<0,001 Total CSF volume p<0,01 Children with prenatal alcohol exposure had in all parameters lower volumes than the controls 2. Significant group by test score interactions were found in right dorsal frontal regions for the verbal recall measure and in left occipital regions for the	2001 and 2008 = same population	4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				visuospatial measure. These results are consistent with earlier analyses from our own and other research groups, but for the first time, we show that cortical thickness is also increased in right lateral frontal regions in children with prenatal alcohol exposure. Further, the significant interactions show for the first time that brain-behavior relationships are altered as a function of heavy prenatal alcohol exposure.		
Yang et al. 2011 [60]	N= 69 with FASD (21 with FAS) N=58 nonexposed controls IQ in FAS sign lower Matched fo Age (mean 13,2y) Gender, ethnicity Subjects coming from 3 sites (Cape Town, Los Angeles, San Diego)	MRI, 15,T T1-weighted series using „FreeSurfer"	1. Brain volume 2. Cortical thickness in differend brain regions (controlled for brain size)	1. Significantly smaller brain volume in FASD p<0,05 2. Across and within sites FASD patients showed am overall pattern of increased cortical thickness compared with nonexposed controls (left hemisphere p=0,028, right hemisphere p=0,019) Cortical thickness increases were observed in the left and right inferior frontal. right middle temporal. right superior temporal in FASD (all p<0,005).	IQ as covariate did not alter results	4

Tabelle 3: Evidenztabelle zu fazialen Auffälligkeiten

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
Faziale Auffälligkeiten						
Jones K.L , Smith D.W., Hanson J.W. 1976 [1]	N= 48 case reports of FAS up to the date of the publication whose **mothers all satsfied the criteria for alcoholism** as published 1972 by the Criteria Committee, National Council on Alcoholism	Description of principal features shared by the initial 11 children ascertained	Characteristic features of FAS	**1. prenatal and postnatal growth deficiency** prenatal growth deficiency more severe for birth length than for birth weight Postnatal Follow up up to 1 year: Average linear growth rate 65% of normal, avreage rate of weight gain only 38% Microcephaly: head circumference below 3th percentile for gestational age at birth in 10 of 11 children and after 1 year. **2. Craniofacial Signs** 11/11 Short palpebral fissures initially thought to be secondary to decreased growth of the eyes Other features commonly seen: 4/11Epicanthal fold, 7/11 maxillary hypoplasia, 1/11cleft palate, 3/11 micrognathia. **3. Neuropsychological Characteristics** IQ from 50-83, average 63 Developmental Delay or mental deficiency 11/11		4

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				Fine motor dysfunction 9/11 **Other:** a.o. Cardiac anomalies in 8/11 patients		
Clarren et al, 1987 Case-control-Study [32]	Group 1:N=21 7year old children with heavy prenatal alcohol exposure vs N= 21 7year old children with negligible gestational alcohol exposure (not more than 3 drinks per occasion) Groups matched for race and sex and maternal age and use of cigarettes, marijuana, valium and phenoparbital No mother used medical teratogens	Full Face and Lateral Face Photographs given to a panel of 7 expert clinicians to judge about FAS-related appearance. Morphometric analyses to identify facial differences between highly exposed and non exposed children	1.Percentage of correct Diagnosis by photos 2.Identified Differences between FAS and Non-FAS	**1.** 6 of 7 clinicians correctly identified the highly exposed children by photographs. **2.** Morphometric analysis confirmed special facial changes: short palpebral fissures relatively long and flat midface, retrusive mandibule Method to delineate more accurately the facial phenotype		4
Astley et Clarren, 1995 [23]	N=194 children 2-10 years, all patients of a FAS Clinic Service in Washington, Prevalence of FAS 20%, all evaluated in the clinic between 1/93-1/95. Randomization in 2 groups matched for age at examination, gender, race, diagnosis and date of examination	Diagnosis and evaluation of facial dysmorphology by a single dysmporphologist **Group 1 =** identification of patterns that discriminate best FAS – non FAS **Group 2 =** validation **Facial Measures collected:** **Eye and eyebrows** Palpebral fissure length Inner canthal distance Clown eyebrows Ptosis	Patterns that diagnose best FAS	**0. methods:** Discriminant analysis with step-wise variable selection (Wilks Lambda F to enter = 3,84 m F to remove = 2,71). Unstandardized canonical discriminant function coefficients were computed to derive the formula of calculation of each patients discriminant score. D-Score was ued to classify whether or not a patient was at risk for FAS. **1. Results** a. step-wise discriminant analysis selected hypoplastic midface, smooth philtrum and thin upper lip	Reference standard cannot be independent from pattern examined, therefore not 1b.	1b-

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		Epicanthal Folds Nose length **Midface** Nose Length Midface height Flat nasal bridge Hypoplastic Midface **Mouth** Smooth philtrum Thin upper lip Abnormal palate **Diagnosis of FAS:** complrehensive evaluation by a team including pediatrician/dysmorphologist, developmental pediatrician, genetist, clinical psychologist, educational psychologist, educational liaison, communication specialist, occupational therapist, social worker, public health nurse.		as best differentiating characteristics Sens. 100% Spec. 89,4% Palpebral Fissure Length and hypoplastic midface = correlation (spearman rank corr. -0,37 p<0,000). Because accurately to measure and less influencable by race, palpebral fissure length (% predicted for age) was substituted without loss of power. **D-Scores in Group 1 were plotted to identify cut-off for highest sensitivity and specificity. Cut-off was found ≥ 1,5.= screen positive.** **Group1:** Sensitivity: 100% (20/20 correct classified FAS) Specifity: 90,9% (70/77 correct non FAS) **Group 2 (validation)** Sensitivity 100% (19/19) [95%Ki97-100%] Specificity 87,2% (67/77) [95%KI Group1+2: 85-93%] **Group1+2:** **False positive: 17/194** (12/17 with PFAE=in utero alcohol		

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
				exposure, CNS dysfunction, absence of FAS facial phenotype, with or without growth retardation, 3 had other syndroms)		
Astley SJ et Clarren S. 2001 [33]	N=952 (84% of all patients of the clinic in Washington) with prenatal alcohol consum, mean age 6,7Y, 49% caucasian N= 462 with Gestalt method prior to 4DDC 9,8% FAS	Comparison of Gestalt diagnosis and 4 DDC diagnosis	% FAS diagnosed, Correlation with brain dysfunction	With 4 DDC Code 10 FAS, with Gestalt 34 ! Correlation to brain dysfunction and growth retardation only with 4 DDC		2b ?
Astley SJ et al., 2002, [25], validating cohort study	Inclusion criteria: - 0 to 12 years of age at the time of enrollment, - in out-of-home placement (foster care) or in the care of their relatives. - when a child screened positive for either FAS (with the features of the photograph) or structural/neurologic evidence of brain damage with confirmed prenatal alcohol exposure, the child was subsequently scheduled for a diagnostic evaluation at the FAS DPN clinic where he/she received a comprehensive diagnostic evaluation and treatment plan by the multidisciplinary team	Two University of Washington students were trained to take three standardized facial photographs (frontal. ¾ view and lateral) by using a handheld, 3-megapixel, digital camera. The photographers also measured the child's head circumference (occipital frontal circumference (OFC). All passports were reviewed by S. J. A. The passport was used to screen for structural or neurologic	1) A child was screened positive for FAS if all three of the following features were present in their facial photograph: (1) palpebral fissure lengths were >2 SD below the mean, (2) the philtrum was smooth (Likert rank 4 or 5 on the 5-point Lip-Philtrum	1) Of the first 600 children screened to date, 10 **screened positive for FAS**. They were 5.5 ± 3.1 years of age (range, 1.1-11.4 years), 30% female, 40% white, 20% black, and 10% native American. They all had confirmed prenatal alcohol exposure. Four of the 10 children who screened positive for FAS had microcephaly and only one was significantly growth deficient (height and weight <3rd percentile). Six had documented prenatal exposure to illicit drugs. **Diagnostic evaluations have been conducted on 7 of the 10 children** to date in this ongoing screening. **Six of the seven received a diagnosis of FAS.**	20% of the childrens´ families were sent a disposable camera with a one-page pictorial instruction sheet for how to take the three standardized photographs. to take the picture by themselves and return it by mail. For diagnostic evaluation the 4-Digit Diagnostic	1b – (minus because a "good" reference standard according to CEBM is not available. Thus the authors used their own developed tool

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	using the 4- Digit Diagnostic Code (Astley SJ, Clarren SK et al.) Between March of 1999 and September of 2001 screening was done. The study population comprised 600 children. They were on average 5.8 ± 4.1 SD years of age at the time they were screened, 48% were female, 48% were white, 32% were black, 12% were Native American, 15% had documented prenatal alcohol exposure, and 32% had documented prenatal drug exposure. The FAS screening was incorporated into an already established state program, in the Foster Care Passport Program (FCPP). Public health nurse (PHN) and a health program assistant work as a team to seek out and gather all available health history information (from birth to present) for each child	evidence of brain damage (seizures, microcephaly, abnormal brain magnetic resonance imaging/computed tomography/ positron emission tomography scans, neurologic disorders) and documentation of prenatal alcohol exposure, and to generate a clinical profile. Image analysis software (Astley SJ et al.) for facial photographic assessment was used to measure the magnitude of expression of the FAS facial phenotype (short palpebral fissure lengths, smooth philtrum, and thin upper lip) from the digital images. A diagnostic evaluation at the FAS DPN clinic was done using the 4-Digit Diagnostic Code	Guide), and (3) the vermilion border of the upper lip was thin (Likert rank 4 or 5 on the 5-point Lip-Philtrum Guide. 2) If prenatal alcohol exposure and structural or neurologic evidence of brain damage (microcephaly, seizures of unknown origin, abnormal brain image) were present, the child was screened positive for structural or neurologic evidence of	2) Fifteen (2.5%) of the 600 children **screened positive for structural or neurologic evidence of brain damage with prenatal alcohol exposure**, but did not have the FAS facial phenotype. 3) The **prevalence of FAS in this foster care population** will be 6 of 600 or 10 of 1000 (95% CI, 5-22 per 1000). This FAS prevalence estimates is statistically significantly greater (binomial test: P values < .001) than the FAS prevalence estimate of 1 to 3 per 1000 live births in the general population reported by the National Institute of Alcohol Abuse and Alcoholism. 4) Based on the seven screen-positive children with completed diagnostic evaluations and the 590 screen-negative children, the **positive predictive value** for the FAS photographic screening tool is 6 of 7 or 85.7%. The **sensitivity** of the screening tool in this populationbased sample is 6 of 6 or 100%. The **specificity** of the screening tool in	Code was used, published by the same authors (Astley SJ, Clarren SK et al.); no test accuracy or other details of the 4-digit code are described. Image analysis software for facial photographic assessment of the FAS facial phenotype was also released by Astley SJ et al., no test acuuracy or further details provided.	as referenc e standar d

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	enrolled in the program. A shortened summary (a Health and Education "passport") is provided with health recommendations to the social worker and the foster parent to share with the child's health care provider(s). Each child's passport is updated every 6 months.	(Astley SJ, Clarren SK et al.)	brain damage with prenatal alcohol exposure. 3) Estimated prevalence of FAS in foster care population 4) Positive and negative predictive value, sensitivity, specificity, accuracy for the FAS photographic screening tool	this population-based sample is 590 of 591 or 99.8%. The accuracy of the tool is 596 of 597 or 99.8%.		
Clarren et al. 2010 [62]	Normative sample of school age children (n= 1064 of 17 schools in Vancouver, British Columbia and n= 1033 of 31 schools in Winnipeg, Manitoba) to reflect the diversity of racial and national groups in Canada. The sample included students in grades 2, 4, 6, 8, and 10. Schools were selected based	students were photographed in a standardized way. Photographs were analyzed using a computerized method. The palpebral fissure lengths were measured from the digital facial photographs using the FAS Facial	To analyze palpebral fissure (PF) length values and to define Canadian standard measures according to age	Analysis demonstrated that PFs do grow with age and there is a slight but meaningful difference between boys and girls in each age group. It was possible to define Canadian standards without reference to racial or ethnic origin from age 6 to age 18 with 1 and 2 standard deviations seperately for boys and girls		2b

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	on racial diversity obtained from data from the 2001 Statistics Canada census. 43,1% Male 51% caucasian 30,3% Asian 18,7% other (racial/ethnical status only measured by appearance)	Photographic Analysis Software.17		1. Interrater correlation reliability according to quality of photos Group A : 0,73 Group B : 0,68 Differencens in PF acording to race/ethnie not significantly different (asian shorter <1mm)		
Astley SJ et al., 2011, [27], case-control study	Study Populations Short palpebral fissure lengths (PFL) from four existing U.S. (Washington State) study populations were used in this study. The populations were restricted to those individuals from 6.0 to 16.9 years of age to match the age range portrayed in the Canadian PFL charts. 1. Healthy School Population (1999): 90 healthy children (6.0-16.0 years of age) from a Washington State elementary school for gifted children. (47% female, 89% Caucasian, 1% African American). 2. Healthy MRI Control Study Population (2003): 16 healthy children (8.3-15.8 years of age) enrolled as controls in a University of Washington	All PFLs were measured by one individual (Astley SJ) from digital facial photographs taken by one photographer (SJA) using the FAS Facial Photographic Analysis Software. The software computes the subject's age in years, computes the right and left PFLs in mm, and computes the PFL z-score based on which normal PFL growth charts the User selected (Caucasian5, or African American). Objectives: To assess the goodness of fit of four populations (2 groups of healthy children, children with prenatal alcohol	1) Graphic comparison of Canadian and Hall PFL normal growth charts 2) Goodness of fit of the healthy U.S. groups on the Canadian and Hall PFL normal growth charts. 3) Goodness of fit of the U.S. group with FASD on the Canadian and Hall PFL normal	1) When the Canadian PFL charts are overlaid on the Hall PFL chart, the mean PFL growth curves for Canadian males and females fall 1.5 and 2.0 SDs below the mean, respectively on the Hall PFL growth chart. 2) The mean PFL z-scores for the school and MRI study groups were +0.17 and +0.19 respectively. Both the scatter plots and mean z-scores are reflective of a very good fit with the Canadian PFL charts. In contrast, these same children scatter, on average, 1.6 SDs below the mean PFL growth curve on the Hall PFL chart demonstrating a poor fit. (The Canadian PFL charts identify these children as having normal PFLs. The Hall PFL charts identify these children as having PFLs that	Measurement and data analysis were done by a single person (Astley SJ) using the FAS Facial Photographic Analysis Software released by Astley SJ. Only one reviewer.	2b (although the study is a case-control study we do not evaluate it as level 4 according to CEBM because it is a validating study

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	FASD magnetic resonance study. (50% female, 81% Caucasian, 6% African American). Prenatal alcohol exposure was confirmed absent. 3. FAS Clinical Population (1993-2005): 22 individuals (6.2-13.8 years of age) with a 4-Digit Diagnosis of FAS (Diagnostic categories A and B) from the WA State FAS DPN clinical database (50% female, 73% Caucasian, 5% African American). 4. Alcohol-Exposed Clinical Population (1993-2005): All 822 individuals (6.0-16.9 yrs of age) receiving a FASD diagnostic evaluation at the WA State FAS DPN (39% female, 49% Caucasian, 7% African American, 10% FAS/Partial FAS, 33% Static cephalopathy/Alcohol Exposed, 52% eurodevelopmental Disorder/Alcohol Exposed). All had confirmed prenatal alcohol exposures.	exposure and with FAS) when plotted on the Canadian, Hall and other published PFL normal growth charts. (The Hall chart (Hall et al) is a composite of four previously published charts to measure PFL. The Canadian chart was published by Clarren et al 2010. It is a PFL chart for a racial/ethnic cross section of Canadian girls (n=1,194) and boys (n=903), 6-16 years of age.))	growth charts. 4) Graphic comparison of the mean PFL growth curves across published PFL normal growth charts. 5) Assess the impact of race (specifically Caucasian versus African American) on PFL.	are, on average, 1.6 standard deviations below normal.) 3) The mean PFL z-score for the 22 children diagnosed with full FAS from the WA FAS DPN clinics was 2.4 SDs below the mean on the Canadian PFL charts and 3.9 SDs below the mean on the Hall PFL charts. These outcomes document the PFL for a child with FAS continues to fall 2 or more SDs below the mean when the Canadian PFL charts are used. The mean PFL z-score for the larger population of children with prenatal alcohol exposure was 1.1 SDs below the mean on the Canadian PFL charts and 2.6 SDs below the mean on the Hall PFL charts. Twenty-five percent of the children with prenatal alcohol exposure had PFLs two or more SDs below the mean on the Canadian PFL charts. Sixty-eight percent of these children had PFLs two or more SDs below the mean on the Hall PFL chart. 4) The mean PFL growth curves for the FAS Clinical Population (all FASD and the subset with FAS) was 1 and 2		

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				SDs below the mean Canadian PFL growth curve. 5) Of the 822 patients with prenatal alcohol exposure from the FAS DPN clinic between 6.0-16.9 years of age, 400 were Caucasian and 54 were African American. These two groups did not differ significantly in mean age, gender, or FASD diagnostic classification. The mean PFL for the African Americans (26.5 mm, 2.0 SD) was 1.5 mm longer than the mean PFL of the Caucasians (25.0 mm, 2.1 SD) (t = 5.0, p <0.001). A 1.5 mm difference is equivalent to 1 SD on the Canadian PFL chart. In other words, if these two racial groups were plotted on the Canadian male and female PFL charts, the mean PFL z-score for the African American group (-0.1, 1.3 SD) would be 1 SD larger than the mean PFL z-score for the Caucasian group (-1.2, 1.4 SD) (t = 6.0, p < 0.001).		
Fang et al., 2008, [35], exploratory cohort study	149 participants from two sites: Cape Town/ South Africa and Helsinki/Finland with 86 FAS and 63 controls. Data were collected as part of	Goal of study : To test a computational model that can automatically compute facial features from 3D	1) FC sample: Sensitivity, specifity, overall accuracy	1) FC - Sensitivity: 88.2% - Specifity: 100% - overall accuracy: 92.6 % Criteria: 15 features, 6 curvatures,	A classification system consistent with the **revised** Institute of	2b – (a "good" referenc e

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	an ongoing collaborative Initiative on Fetal Alcohol Spectrum Disorders. Subjects were examined independently by two dysmorphologists. Exclusion: patients with recognizable craniofacial syndrome other than FAS. Inclusion: Individuals with FAS and prenatal alcohol exposure. 55% were Finnish Caucasian (FC) and 45% were Cape-coloured (CC), 54.4% was female; age ranged from 2.8 to 21 years, mean age (SD) was FC 13.12 (3.5) and CC 5.09 (1.9). FC n=82; CC n= 67	scans and use this data to identify children with FAS. Face regions were coded with 4 features: 1. curvatures 2. flatness 3. aspect ratio 4. areas A classification system consistent with the revised Institute of Medicine was used to determine FAS diagnosis in combination with alcohol exposure (data collected through a standard questionnaire). Minolta Vivid 910 lase scanner and a novel automated facial feature analysis technique were used that compared mathematically defined surface features within selected regions of FAS and control faces. To validate the diagnostic function	2) CC sample: Sensitivity, specifity, overall accuracy 3) Combined CC and FC	4 flatness, 3 aspect ratios, 2 areas 2) CC - Sensitivity: 91.7% - Specifity: 90% - overall accuracy: 90.9 % Criteria: 19 features, 7 curvatures, 6 flatness, 3 aspect ratios, 3 areas 3) Combined: - Sensitivity: 82.75% - Specifity: 76.2% - overall accuracy: 80.0% The features for FC and CC are not specified	Medicine (Hoyme et al. 2005) was used. In this revision of IOM the CNS neurodevelopm ental abnormalities were replaced by "evidence of deficient brain growth or abnormal morphogenesis, including one of following 1. Structural brain abnormalities 2. Head circumference <10th percentile". Only limited information about this point is given (what kind of measurement was taken etc.). Thus, no neuropsychologi cal testing was	standar d accordin g to CEBM is not availabl e.) The authors used the **revised** diagnost ic criteria of the Institute of Medicin e (one of the authors (Hoyme HE) of this study is also author of the IOM paper)

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		generated from the analysis one third of the images were randomly selected and put aside.			done.	
Moore ES et al., 2007, [34], exploratory cohort study	4 Populations + control groups based on their ancestry: 1) Cape Coloured (CC), n=103 2) Finnish Caucasian (FC), n=99 3) African American (AA), n=24 4) North American Caucasian (NCA), n=50 Data were collected as part of an ongoing collaborative Initiative on Fetal Alcohol Spectrum Disorders or were recruited previously in another study. Subjects were examined by one or two dysmorphologists. Exclusion: patients with recognizable craniofacial syndrome other than FAS. Inclusion: Individuals with FAS and prenatal alcohol exposure. A total of 276 participants: 54% was female; age ranged	Goal of the study: To test whether computerized anthropometry can distinguish patients with FAS from controls across a wide age range and ethnically disparate study populations. Minolta Vivid 910fw laser scanner with a software package was used for merging the scans into single 3 D model of the participant´s face. Identification of 16 facial criteria: **Width 7** (Minimal Frontal. bizygomatic, bitragal. bigonial. innercanthal. outercanthal. palpebral fissure) **Depth 3** (upper, mid and lower facial)	1) FC sample: Sensitivity, specifity, overall accuracy 2) CC sample: Sensitivity, specifity, overall accuracy 3) AA sample 4) NAC sample	Sensitivity and Specificity as well as overall accuracy is given for the finnish caucasian population and the cape coloured population for using the 16 facial criteria (see "diagnostische Intervention") and defining maximal best distinguishing criteria for each group **1) FC** - Sensitivity:96% - Specifity: 91% - overall accuracy: 93% **8 definite criteria:** (all shorter) Bitragal width Inner canthal width Outer canthal width Palpebral fissure length Midfacial depth Nasal Length Nasal Bridge Length Ear Length **2) CC** - Sensitivity: 94% - Specifity: 91% - overall accuracy: 92 %	A classification system solely on the basis of structural features and growth deficiency consistent with the **revised** Institute of Medicine (Hoyme et al. 2005) was used. In this revision of IOM the CNS neurodevelopmental abnormalities were replaced by "evidence of deficient brain growth or abnormal morphogenesis, including one of following 1. Structural brain	2b – (minus because a "good" reference standard according to CEBM is not available. The authors used the **revised** diagnostic criteria of the Institute of Medicine (one of the authors

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
	from 2.75 to 21.17 years. Only the age of the AA sample differed significantly between FAS and control group. Therefore age-adjusted regression residuals were computed.	**Length 6** (Nasal. nasal bridge, philtrum, lower facial. total facial. ear) A classification system solely on the basis of structural features and growth deficiency consistent with the revised Institute of Medicine was used to dermine FAS diagnosis in combination with alcohol exposure (data collected through a standard questionnaire).		**5 definite criteria:** (all shorter) minimal frontal width Bizygomatic width Inner canthal width Philtrum length Ear Length **3) AA:** - Sensitivity:73 % - Specifity: 85% - overall accuracy: 79% **2 definite criteria:** Palpebral fissure length (shorter) Philtrum length (longer) **4) NAC:** - Sensitivity:74 % - Specifity: 81% - overall accuracy: 77% **2 definite criteria:** (both shorter) Inner Canthal Width Outer Canthal Width	abnormalities 2. Head circumference <10th percentile". Only limited information about this point is given (what kind of measurement was taken etc.). Thus, no neuro-psychological testing was done	(Hoyme HE) of this study is also author of the IOM paper)

Tabelle 4: Evidenztabelle zu Wachsstumsauffälligkeiten

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
Wachstumsauffälligkeiten						
Day N.L. et al. 2011 Cohort Study ID [30]	N= 580 Mother/Child pairs Women from an outpatient clinic May 1983 – July 1985 First interview 4th month of pregnancy >18y, healthy, lower socioeconomic status Everage 0,6drinks per day in 1. trimester (0-20) Assessment of 14 year old offsprings July 1998- June 2001	Interview of pregnant women a.o. use of alcohol at each trimester Assessment of children e.a. measurement of size, head circumference	Head circumference difference between children of drinking and non drinking mothers 2. Correlation between Alcohol exposure and head circumference (Controlling for Covariates: environmental variables, maternal variables, child variables, prenatal substance us other than alcohol 3. Significant predictors of head	1. Difference head circumference 6,6mm between children of abstinent mothers or drinking 1 or more drink 2. Alcohol exposure and head circumference after controlling for significant covariates **in the first trimester** non drinkers: 562,74 Light drinkers (0 up to 0,2 drinks per day) : 558,12 Moderate drinkers (>0,2 and <0,89 drinks/day): 556,95 heavy drinkers(>0,89 drinks per day): 556,12 Average head circumference: 559 mm (503-610) No dose-related correlation in 2. and 3. trimester 3. Significant predictors of head circumference (p<0,05) -number of siblings - height - Gender - Race - tobacco use in first trimester		2b

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
			circumference (stepwise linear regression analysis)			
Handmaker N. et al. 2006 [31] Cohort study	N=209 pregnant women of n= 4460 pregnant women screened with the TWEAK and AUDIT test for alcohol use. All with risk of steady drinking (>/=1drink per day) or binge drinking (3 or more drinks per episode) at first interview (max 28 weeks of gestation) And Motivational intervention (randomly assigned to 3 different interventions) against drinking And Interview on daily drinking after pregnancy Divided in early abstainers and continuing drinkers, subgroup heavy drinkers N= 56 non-drinking pregnant women	Comparison of intrauterine fetal growth and head circumference measured per ultrasound at 18 weeks or more up to 41,7 weeks (mean 27,1 weeks) With a Philips-ATL 3,5 or 5 Mhz by certified sonographers In 3 groups of women 1. heavy drinkers not abstaining after intervention (5 or more drinks a day n=51) 2. early abstainers after intervention Grouppt 1+2 were similar for other drug use (70% tobacco) 3. non drinkers	Difference in fetal growth and head circumference (Biparietal diameter, frontooccipital diameter, BPD/OPD, Head circumference (HC) calculation from BPD/OPD, femur length, abdominal circumference (AC), indices of brain structure: transcerebellar diameter, lateral ventricular atrial diameter, diameter of cisterna magnum) measured intrauterine per ultrasound Comparison with normative Data by Hadlock (1984)	1. Comparisons between Early Abstinence and Continued Alcohol exposure no significant differencen in head circumference, abdominal circumference or femure length oder BPD. Larger HC/AC Ratio with amphetamine use p=0,009 **2. Comparison between early abstinence and heavy drinkers: ANOVA: sign. lower HC/AC-Ratio p=0,02** No sign. diff. in BPD or HC alone. No alcohol effects for the measures of brain anatomy Lateral ventricle and cisterna magna. But significant effect for transcerebellar diameter (p= 0,008) – lower for heavy drinkers., significant decrease over time. **3. Comparison of heavy drinkers and non drinkers** HC/AC ratio significant lower p=0,06 TDC also smaller for heavy drinkers p=0,02 for slope ? Women who abstained after the first trimester had measures not distinguishable from non drinkers **Conclusion:** singular measures do not discirminate,		2b

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
			and By Hill (1990) ANCOVA Control of other substance use	but ratios.		
Klug et. al., 2003. [29], retrospective cohort study	The first group were subjects with a diagnosis of FAS, the second group was diagnosed with partial FAS/ARND and the third group was subjects with no FAS (who were referred for an FAS evaluation but did not receive a diagnosis of either FAS or partial FAS/ARND). They compared the growth of subjects by age, gender, and by diagnostic group. There were 1) 315 children in the sample that had weight measurements at birth and diagnosis and 2) 314 children with paired height measurements. 3) 322 children with calculated BMIs at diagnosis.	A chart review was done to assign a score or category for the criteria from the Institute of Medicine Report (IOM). During the chart review every 10th chart was independently reviewed. Where disagreement was present, the case was discussed and the categories were assigned by consensus. Each subject in the cohort was evaluated by a medical geneticist with extensive experience with FAS. A standardized examination using the Fetal Alcohol Syndrome Diagnostic Checklist (FASDC) was completed on each subject. Cases have	1) Weight measurements at birth and diagnosis 2) height measurements at birth and diagnosis. 3) calculated BMIs at diagnosis. 4) proportion of children who were below the 3rd, 5th, and 10th percentiles for growth measurements at birth and at diagnosis. Comparison between 3 groups - subjects with	Weight and height percentiles showed significant differences between IOM criteria ($P < 0.001$), but not gender and age. Children without FAS had higher height and weight percentiles on average, though children with partial FAS had higher BMIs on average (see below). 1) Weight percentiles showed significant differences between IOM criteria (mean birth weight percentile FAS: 18.212; Partial FAS: 28.268; no FAS: 39.666; mean weight percentile at diagnosis FAS: 31.547 ; Partial FAS: 45.348; no FAS: 56.547; $P < 0.001$), no difference in gender and age. 2) Height percentiles showed significant differences between IOM criteria (mean birth height percentile FAS: 33.505; Partial	In the section of discussion results for sensitivity and specifity, PPV, NPV and LR+/- are shown (see Anhang 7.3): Sensitivity using growth percentiles as a diagnosis of FAS. ranged from 4 to 46, specificities ranged from 71 to 100. The highest sensitivity is 46% for birth weight 10th percentile; the highest specifity is 100% for BMI 3rd percentile. The best PPV is 100% for 3rd	2b

Publikation (Autor, Jahr) Studientyp	Anzahl der Patienten Patienten-merkmale (incl. Alter)	Diagnostische Intervention/ Referenzstandard	Outcomes	Ergebnisse	Bemerkungen	Evidenz klassifikation nach Oxford
		been added to the FAS Registry continuously since 1980 (North Dakota). Paired weight and height percentiles (3rd, 5th, and 10th) from birth and diagnosis as well as BMIs at diagnosis for subjects 2 years and older were calculated.	a diagnosis of 1)FAS, 2) partial FAS/ARND and 3) no FAS	FAS: 52.088; No FAS: 58.677; mean height percentile at diagnosis FAS: 30.451; Partial FAS: 36.291; No FAS: 51.196P < 0.001) 3) Mean BMI differed between partial FAS (P= 0.014) with higher BMI (18.315 mean percentile rank at diagnosis) than group with no FAS or FAS (mean 17.072). 4) There were significantly ($p<0.05$) more children with FAS below the 5th and 10th percentiles in birth and current weight and heigth. Males were also more likely to be in lower birth weight percentiles. Children with FAS consistently have greater proportions in the lower percentiles for BMI (<3rd %tile 22 % with FAS vs. 3 % without FAS – no level of significance shown).	and 5th percentile for BMI. Limitation of the study: All subjects were only diagnosed by a single clinician. No inclusion or exclusion criteria, are described. No potential confounders are discussed. Test accuracy (validity, reliability) for the used Fetal Alcohol Syndrome Diagnostic Checklist (FASDC) is not described. No details regarding content of this test.	

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A. 6 Methodik systematische Literaturrecherche – Diagnostische Kriterien des pFAS, der ARND und der ARBD (zweiter Teil des Leitlinienprojektes 2015)

a) Einschlusskriterien

Population	**Kinder und Jugendliche (< 18 Jahre) mit FASD**
Intervention	Diagnostische Tests zu den folgenden Kriterien: - Wachstumsauffälligkeiten - Faziale Auffälligkeiten - ZNS-Auffälligkeiten - Alkoholkonsum der Mutter während der Schwangerschaft
Kontrolle	Gesunde Kinder/Jugendliche Kinder/Jugendliche mit einer diagnostizierten anderen neuropsychologischen Störung (z. B. ADHS)
Endpunkte	Einzelne Zielgrößen wurden nicht festgelegt. Allgemeine Zielgröße war die Sicherheit der diagnostischen Diskriminierung der eingesetzten Testverfahren im Hinblick auf die Diagnose Fetale Alkoholspektrumstörung FASD.
Studientypen	Einschluss von randomisierten kontrollierten Studien, Kohortenstudien, Fall-Kontrollstudien bzw. Fallserien (> 10 Patienten) bzw. systematische Reviews/Metaanalysen dieser Studien sowie narrativen Reviews
Sprachen	Englisch, Deutsch

b) Ausschlusskriterien auf Abstrakt- und Volltextebene

A1	andere Erkrankung
A2	Studien an Tieren/in vitro/intrauterin
A3	anderes Thema (nicht Diagnose FASD)
A4	Methodik der Publikation (z. B. Kommentar, Fallbericht, kein Abstract)
A5	Alter der Probanden überwiegend > 18 Jahre (mehr als 80 %)
A6	Andere Sprache als Englisch und Deutsch

Suchkriterien in Pubmed

(("foetal alcohol syndrome"[All Fields] OR "fetal alcohol spectrum disorders"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "spectrum"[All Fields] AND "disorders"[All Fields]) OR "fetal alcohol spectrum disorders"[All Fields] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "syndrome"[All Fields]) OR "fetal alcohol syndrome"[All Fields]) OR ("fetal alcohol spectrum disorders"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "spectrum"[All Fields] AND "disorders"[All Fields]) OR "fetal alcohol spectrum disorders"[All Fields] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "spectrum"[All Fields] AND "disorder"[All Fields]) OR "fetal alcohol spectrum disorder"[All Fields])) AND (("diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields]) OR ("diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms])) AND ("2011/11/01"[PDAT] : "3000"[PDAT])

Result	**365**	
Translations	fetal alcohol syndrome	"foetal alcohol syndrome"[All Fields] OR "fetal alcohol spectrum disorders"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "spectrum"[All Fields] AND "disorders"[All Fields]) OR "fetal alcohol spectrum disorders"[All Fields] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "syndrome"[All Fields]) OR "fetal alcohol syndrome"[All Fields]
	fetal alcohol spectrum disorder	"fetal alcohol spectrum disorders"[MeSH Terms] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "spectrum"[All Fields] AND "disorders"[All Fields]) OR "fetal alcohol spectrum disorders"[All Fields] OR ("fetal"[All Fields] AND "alcohol"[All Fields] AND "spectrum"[All Fields] AND "disorder"[All Fields]) OR "fetal alcohol spectrum disorder"[All Fields]
	diagnostic	"diagnosis"[MeSH Terms] OR "diagnosis"[All Fields] OR "diagnostic"[All Fields]
	diagnosis	"diagnosis"[Subheading] OR "diagnosis"[All Fields] OR "diagnosis"[MeSH Terms]
Database	PubMed	
User query	((fetal alcohol syndrome) OR fetal alcohol spectrum disorder) AND ((diagnostic) OR diagnosis) AND ("2011/11/01"[Date - Publication] : "3000"[Date - Publication])	

- Recherchezeitraum zur Diagnostik FASD: 01.11.2011 bis 01.07.2016.
- Zeitraum von 01.01.2001 bis 31.10.2011 in systematischer Literaturrecherche zum FAS.
- Treffer gesamt: 365 Treffer.

A. 7 Eingeschlossene Studien der systematischen Literaturrecherche zur Diagnostik des pFAS, der ARND und der ARBD (zweiter Teil des Leitlinienprojektes 2015)

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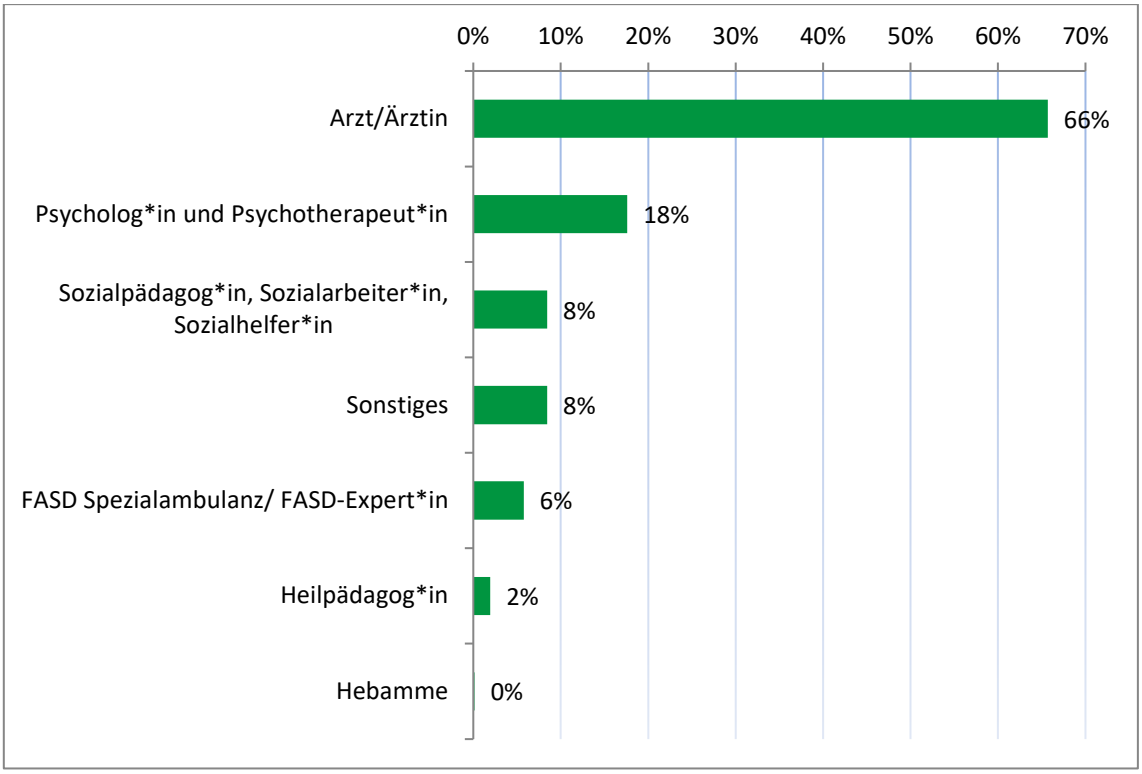
A. 8 Auswertung des Evaluationsfragebogens zur S3-Leitlinie FASD von 2016 (im Rahmen des dritten Teils des Leitlinienprojektes (2022))

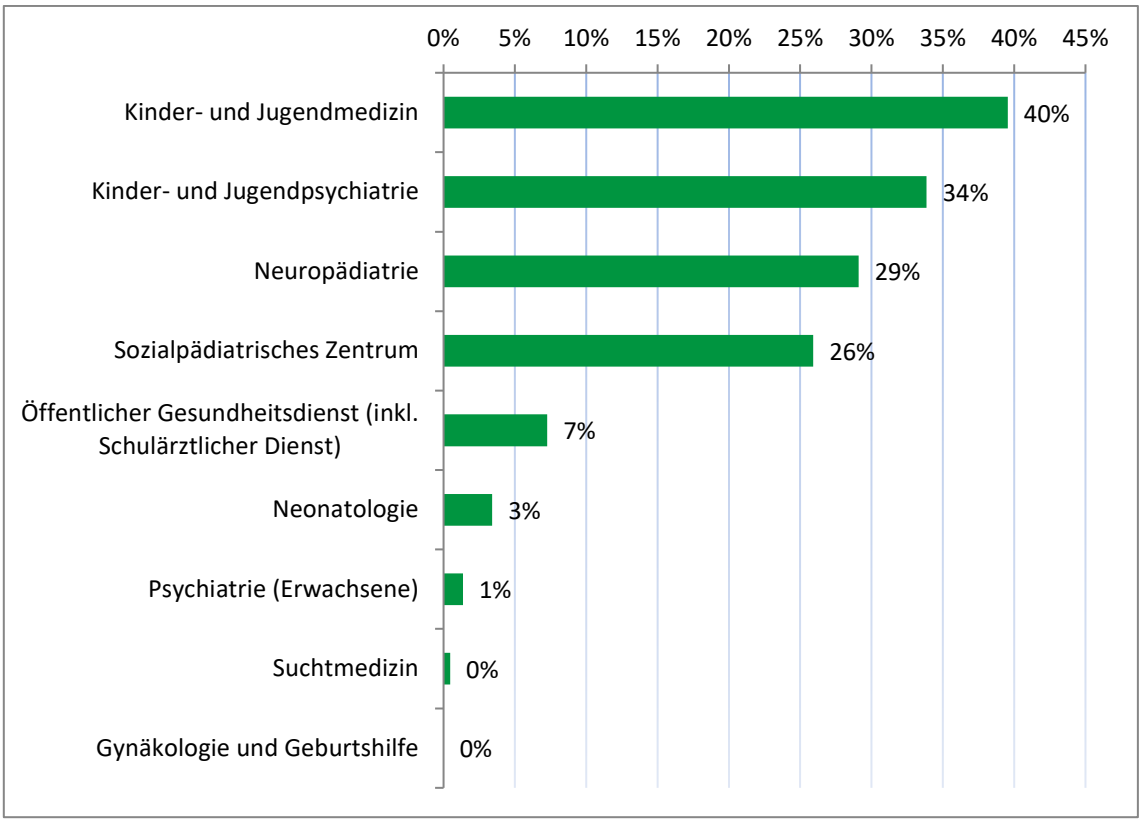
Ausgewertet wurden alle Fragebögen, die mindestens eine Antwort ab Frage 5 beinhalten. (n = 683)

1. Was sind Sie? (n = 676)

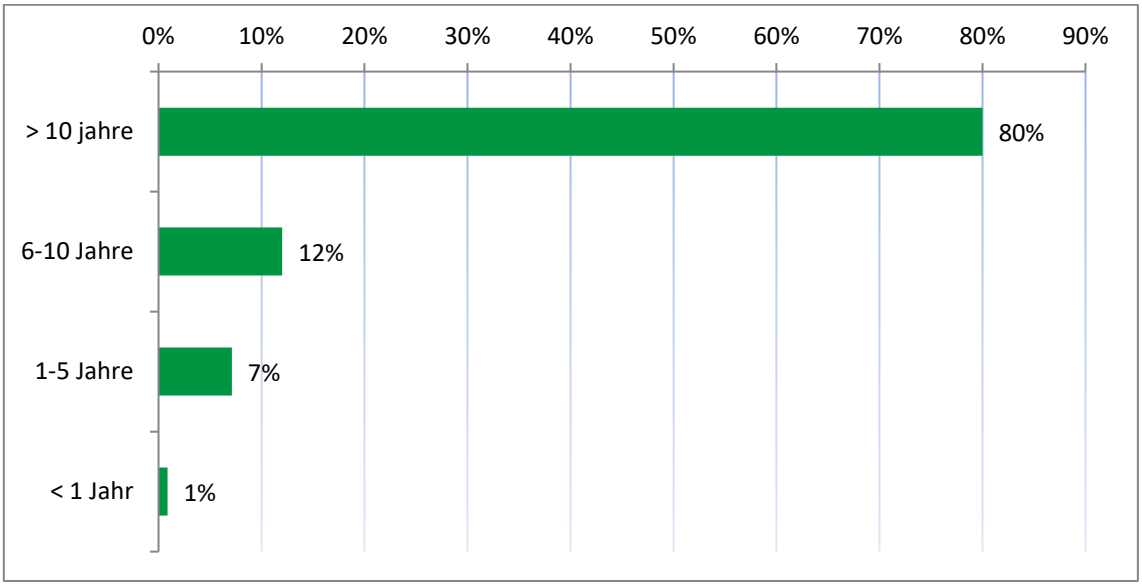


⇨ Sonstiges:
Vor allem Pflegeeltern (n = 11); Erzieher*innen/Erziehungsstellen (n = 11); Ergotherapeut*innen (n = 6)

2. In welchen Bereichen sind Sie als Arzt/Ärztin tätig? (n = 440)



3. Wie viele Jahre Berufserfahrung haben Sie? (n = 675)



4. **Betreuen Sie Menschen mit FASD? (Ja/Nein) (n = 681)**

⇨ Ja: 83 %

<u>Auswertung der Wissensfragen:</u>

5. **Gibt es eine wissenschaftlich belegte Menge an Alkohol, die während der Schwangerschaft für das ungeborene Kind ungefährlich ist? (Ja/Nein) (n = 680)**

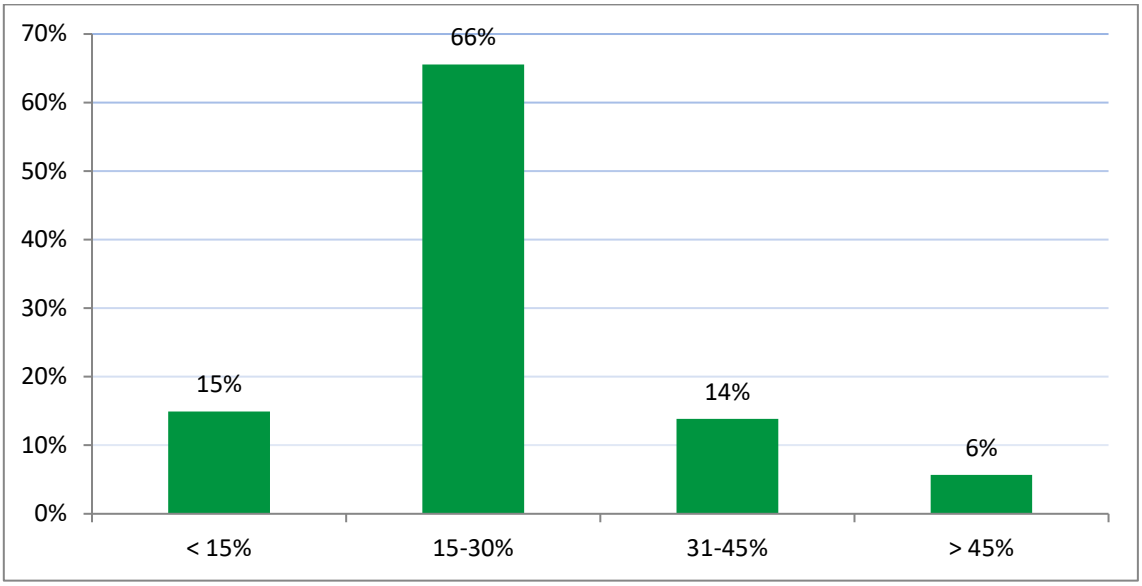
⇨ Richtige Antwort (Nein): 96 %

6. **Gibt es einen Zeitpunkt in der Schwangerschaft, zu dem der Konsum von Alkohol für das ungeborene Kind sicher ungefährlich ist? (Ja/Nein) (n = 680)**

⇨ Richtige Antwort (Nein): 97 %

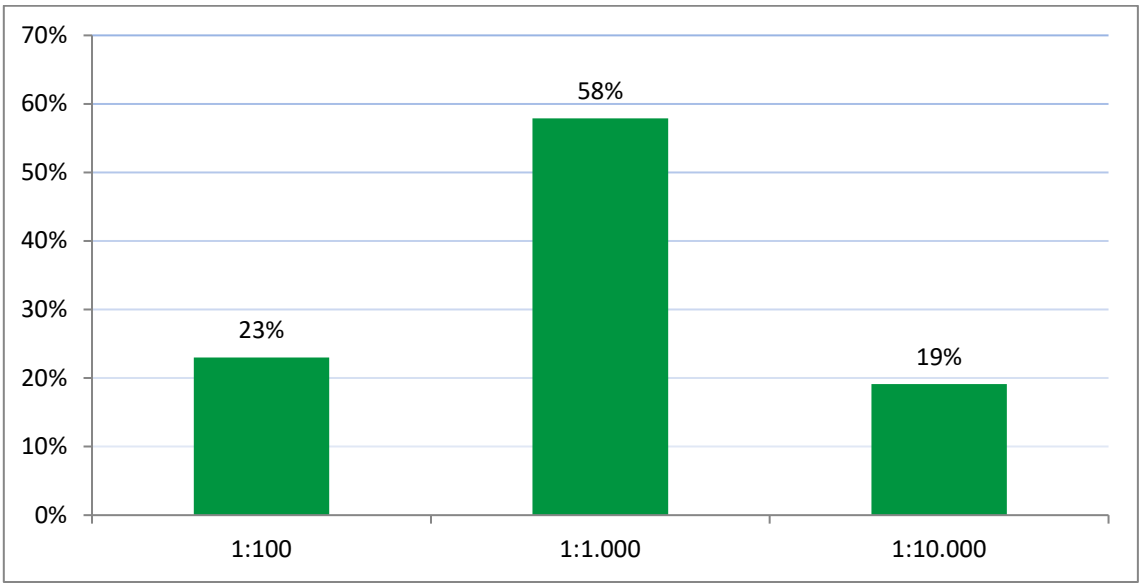
7. **Wie viele Frauen (ca.) trinken in der Schwangerschaft Alkohol? (n = 671)**

⇨ Richtige Antwort (15–30 %): 66 %



8. **Wie hoch wird die Prävalenz der Fetalen Alkoholspektrumstörung (FASD) als Folge einer Alkohol-Exposition im Mutterleib geschätzt? (n = 670)**

⇨ Richtige Antwort (1:100): 23 %



9. **FASD – Welche Erkrankungen gehören zu den Fetalen Alkoholspektrumstörungen? (n = 676)**

- **a. Alkoholbedingte entwicklungsneurologische Störung (ARND)**
- **b. Alkoholbedingte Schizophrenie (ARS)**
- **c. Fetales Alkoholsyndrom (FAS)**
- **d. Alkoholbedingte Persönlichkeitsstörung (ARP)**
- **e. Partielles Fetales Alkoholsyndrom (pFAS)**

⇨ Richtige Antworten (a, c, e): 74 %

10. **FAS – Welche Auffälligkeiten weisen Kinder/Jugendliche mit Fetalen Alkoholsyndrom *immer* auf? (n = 582)**

- **a. Wachstumsstörungen**
- **b. Beeinträchtigung in den Funktionen des zentralen Nervensystems**
- **c. Fehlbildungen der inneren Organe**
- **d. Schwerhörigkeit oder Sehstörungen**
- **e. Auffälligkeiten des Gesichts**
- **f. Wahrscheinlicher oder bestätigter Alkoholkonsum der Mutter in der Schwangerschaft**

⇨ Richtige Antworten (a, b, e, f): 40 %

11. **pFAS – Welche Auffälligkeiten weisen Kinder/Jugendliche mit partiellem Alkoholsyndrom *immer* auf? (n = 572)**

a. **Wachstumsstörungen**
b. **Beeinträchtigung in den Funktionen des zentralen Nervensystems**
c. **Fehlbildungen der inneren Organe**
d. **Schwerhörigkeit oder Sehstörungen**
e. **Auffälligkeiten des Gesichts**
f. **Wahrscheinlicher oder bestätigter Alkoholkonsum der Mutter in der Schwangerschaft**

⇨ Richtige Antworten (b, e, f): 28 %

12. **ARND – Welche Auffälligkeiten weisen Kinder/Jugendliche mit alkoholbedingter entwicklungsneurologischer Störung *immer* auf? (n = 560)**

a. **Wachstumsstörungen**
b. **Beeinträchtigung in den Funktionen des zentralen Nervensystems**
c. **Fehlbildungen der inneren Organe**
d. **Schwerhörigkeit oder Sehstörungen**
e. **Auffälligkeiten des Gesichts**
f. **Wahrscheinlicher oder bestätigter Alkoholkonsum der Mutter in der Schwangerschaft**

⇨ Richtige Antworten (b, f): 57 %

13. **Welche fazialen Anomalien müssen gegeben sein, um das Kriterium „faziale Auffälligkeiten" bei der Diagnose FAS zu erfüllen? (n = 565)**

a. **Kurze Lidspalte (≤ 3. Perzentile)**
b. **Breiter Nasenrücken (> 20 % des Abstandes der Exokanthions der Augen)**
c. **Verstrichenes Philtrum (Rang 4 oder 5 auf dem Lip-Philtrum-Guide. Astley)**
d. **Ausgeprägter Epikanthus (mind. Stufe 4)**
e. **Tiefstehende Ohren (deutlich unter Augenwinkel-Linie)**
f. **Schmale Oberlippe (Rang 4 oder 5 auf dem Lip-Philtrum-Guide)**

⇨ Richtige Antworten (a, c, f): 54 %

14. Wie viele der folgenden Auffälligkeiten müssen gegeben sein, um das Kriterium „Wachstumsauffälligkeit“ zu erfüllen? (n = 552)

- **Geburtsgewicht ≤ 10. Perzentile**
- **Körpergewicht ≤ 10. Perzentile**
- **Geburtslänge ≤ 10. Perzentile**
- **Körperlänge ≤ 10. Perzentile**
- **Body Mass Index ≤ 10. Perzentile**

☐ **1**

☐ **2**

☐ **3**

☐ **4**

☐ **5**

⇨ Richtige Antwort (1): 43 %

15. Welche der folgenden Auffälligkeiten werden für die Feststellung Funktioneller ZNS-Auffälligkeiten“ bei der FASD Diagnose herangezogen? (n = 562)

a. Exekutivfunktionen
b. Rechenfertigkeiten
c. Epilepsie
d. Tourette-Syndrom
e. Legasthenie
f. Merkfähigkeit
g. Aufmerksamkeit

⇨ Richtige Antworten (a, b, c, f, g): 12 %

*Durchschnittlich wurden von Teilnehmer*innen 6 von 11 Wissensfragen korrekt beantwortet. (n = 521)*

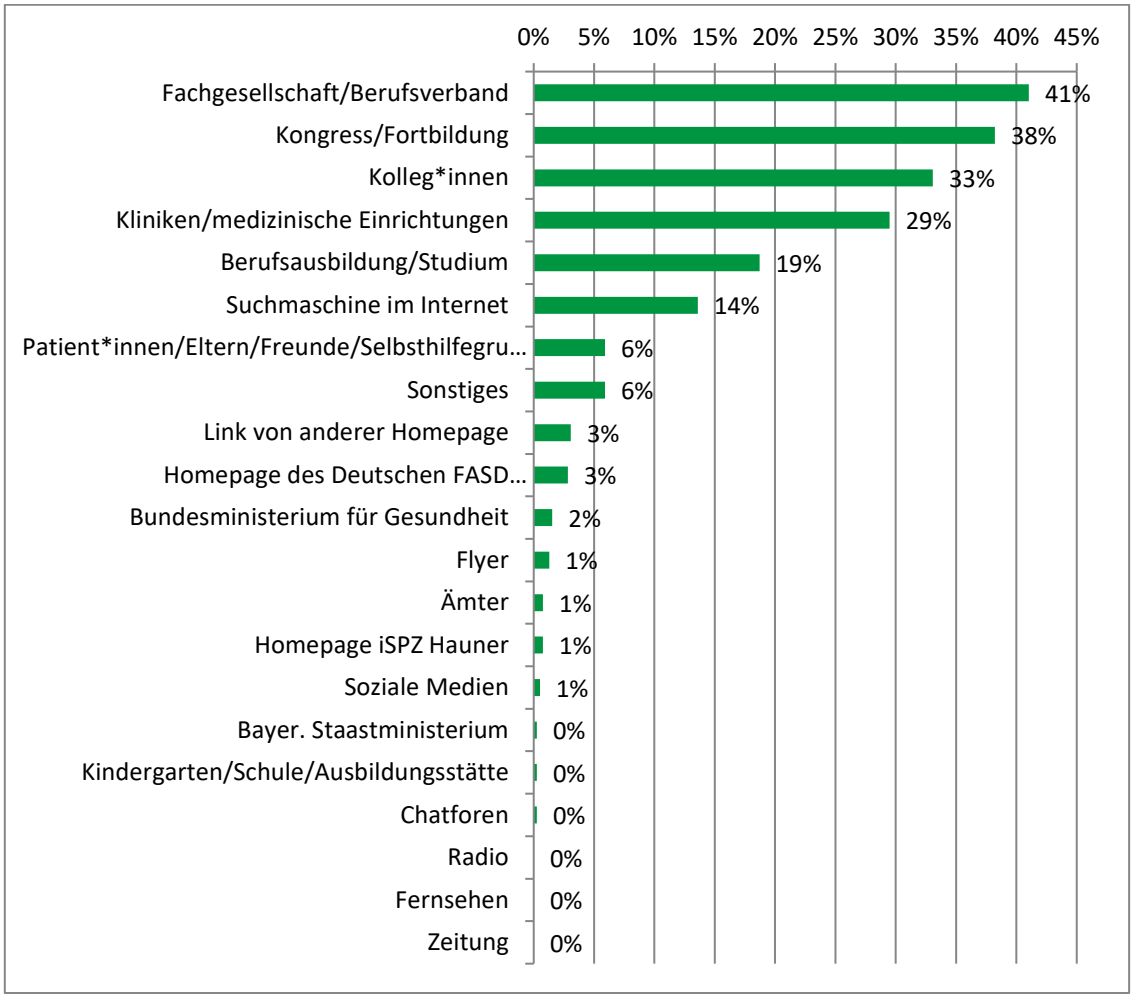
16. Welchen der folgenden Aussagen zu Leitlinien (LL) im Allgemeinen stimmen Sie zu? (n = 543)

- LL sind eine objektive Zusammenfassung des aktuellen Wissenstandes.
  ⇨ 89 % Zustimmung
- LL stellen einen strukturierten Ratgeber dar.
  ⇨ 77 % Zustimmung
- LL sind gute didaktische Mittel.
  ⇨ 42 % Zustimmung
- LL werden meist von Expert*innen entwickelt, die wenig vom Praxisalltag verstehen.
  ⇨ 3 % Zustimmung
- LL sind für meine Berufsgruppe nicht relevant.
  ⇨ 2 % Zustimmung (4 Sozialpädagog*innen/Sozialarbeiter*innen/Sozialhelfer*innen, 2 Heilpädagog*innen, 1 Psycholog*in/Psychotherapeut*in, 1 Arzt/Ärztin in der Neonatologie, 1 Systemtische*r Berater*in)
- LL stellen meine Kompetenzen in Frage.
  ⇨ 0 % Zustimmung

17. Kennen Sie die S3-Leitlinie zur Diagnose der FASD bei Kindern und Jugendlichen (von 2016)? (Ja/Nein) (n = 551)

⇨ Ja: 71 %

18. Wie sind Sie auf die S3-Leitlinie zur Diagnose FASD aufmerksam geworden? (n = 390)



19. Haben Sie bereits vor Erscheinen der „S3-Leitlinie“ Diagnostik hinsichtlich FASD durchgeführt? (Ja/Nein) (n = 552)

- ⇨ Ja: 40 %

20. Wenden Sie die diagnostischen Empfehlungen der S3-Leitlinie FASD in Ihrer Arbeit an? (Ja/nein) (n = 532)

- ⇨ Ja: 60 %

21. Wie hat sich bei Ihnen die Anwendung der S3-Leitlinie FASD insgesamt auf die Qualität Ihrer Diagnostik und Versorgung im Bereich FASD ausgewirkt? (n = 315)

- ⇨ Verbesserung: 93 %
- ⇨ Kein Einfluss: 7 %
- ⇨ Verschlechterung: 0 %

22. Wie verständlich finden Sie die Inhalte der S3-Leitlinie FASD? (Bewertung gemäß Schulnoten: 1 = sehr verständlich – 6 = überhaupt nicht verständlich) (n = 378)

⇨ Durchschnitt: 2,1 (≙ verständlich)

23. Wie übersichtlich finden Sie die Inhalte der S3-Leitlinie FASD? (Bewertung gemäß Schulnoten: 1 = sehr übersichtlich – 6 = überhaupt nicht übersichtlich) (n = 378)

⇨ Durchschnitt: 2,0 (≙ übersichtlich)

24. Wie hilfreich finden Sie die Inhalte der S3-Leitlinie FASD? (Bewertung gemäß Schulnoten: 1 = sehr hilfreich – 6 = überhaupt nicht hilfreich) (n = 378)

⇨ Durchschnitt: 1,9 (≙ hilfreich)

25. Wie gut finden Sie die Praktikabilität und Anwendbarkeit der S3-Leitlinie FASD? (Bewertung gemäß Schulnoten: 1 = sehr gut – 6 = sehr schlecht) (n = 378)

⇨ Durchschnitt: 2,2 (≙ gut)

26. Würden Sie Kollegen*innen die S3-Leitlinie FASD für Kinder und Jugendliche empfehlen? (Ja/Nein) (n = 371)

⇨ Ja: 99 %

27. Wenn nein, warum nicht?

⇨ „Sie ist auf zu wenig Kriterien aufgebaut. Körperlänge, Kopfumfang und Lidspalte ist zu wenig. Es gibt so viele körperliche Auffälligkeiten, die alle unter den Tisch fallen."

⇨ „Weil Bedarf von Patienten und die aktuellen Kriterien nicht zusammen passen. Aus meiner Sicht trifft das Konstrukt FASD nicht. Die Schnittmenge von Patienten welche die Kriterien erfüllen und die Patienten die klinische Einschränkungen haben und Unterstützung bedürfen ist erhebliche kleiner als bei anderen Störungsbildern. Insgesamt in der Praxis wenig hilfreich, bedient aber viele Klischees und Vorurteile."

28. Kennen Sie den Pocket Guide FASD, der die diagnostischen Kriterien der S3-Leitlinie FASD in einer Ultrakurz-Version veranschaulicht? (Ja/Nein) (n = 531)

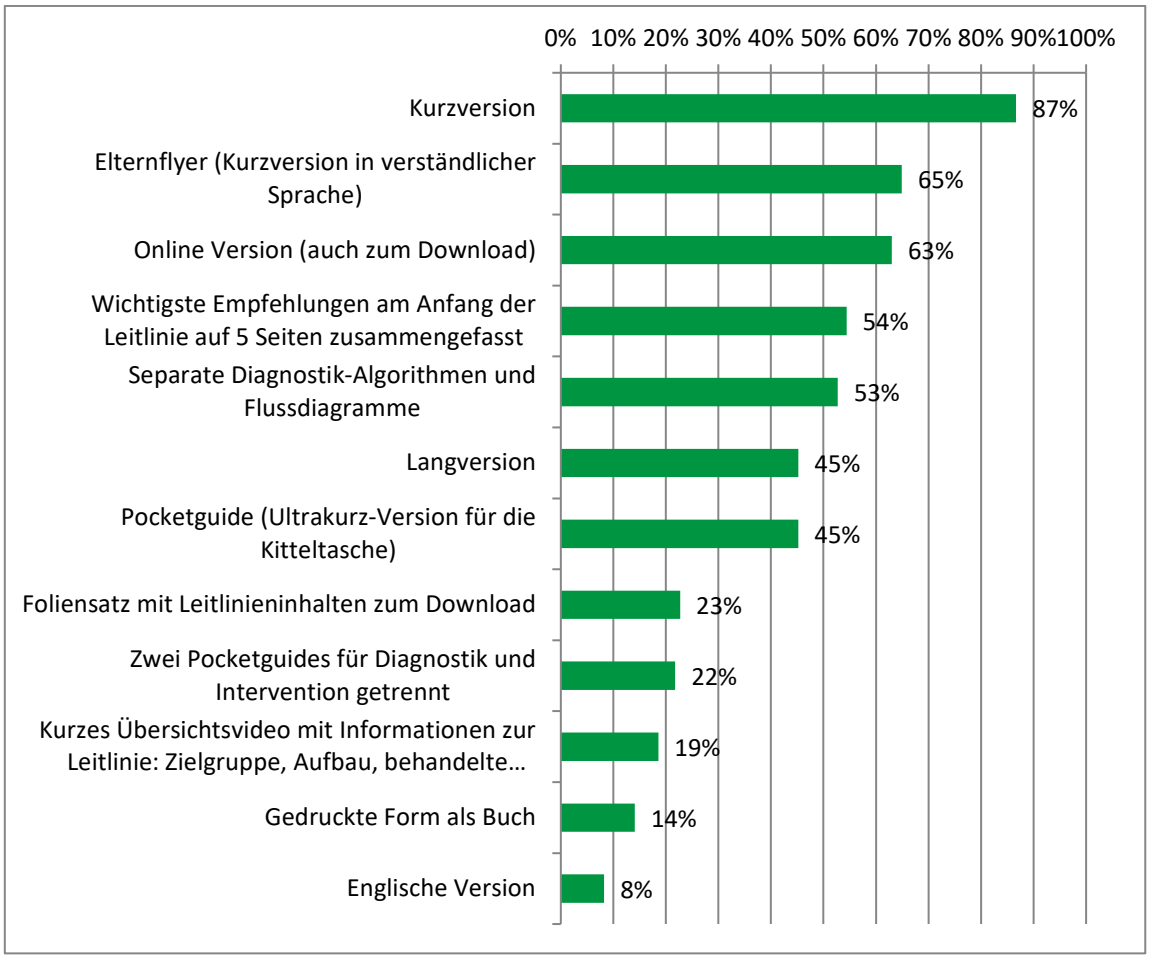
⇨ Ja: 31 %

29. Haben Sie den Pocket Guide FASD in Ihrer Arbeit bereits angewendet? (Ja/Nein) (n = 162)

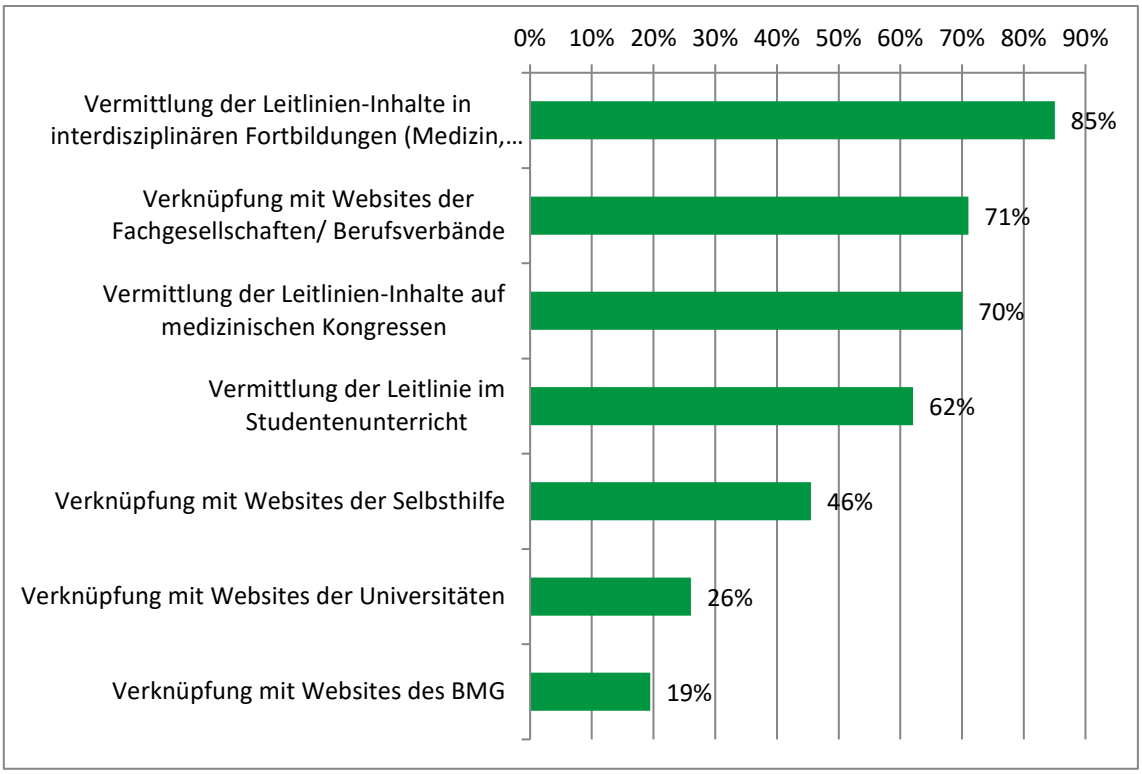
⇨ Ja: 78 %

30. Wenn nein, warum nicht? (n = 0)

31. In welchen Formaten würden Sie sich die neue „S3-Leitlinie FASD für Kinder und Jugendliche – Diagnostik und Intervention“ wünschen? (n = 533)



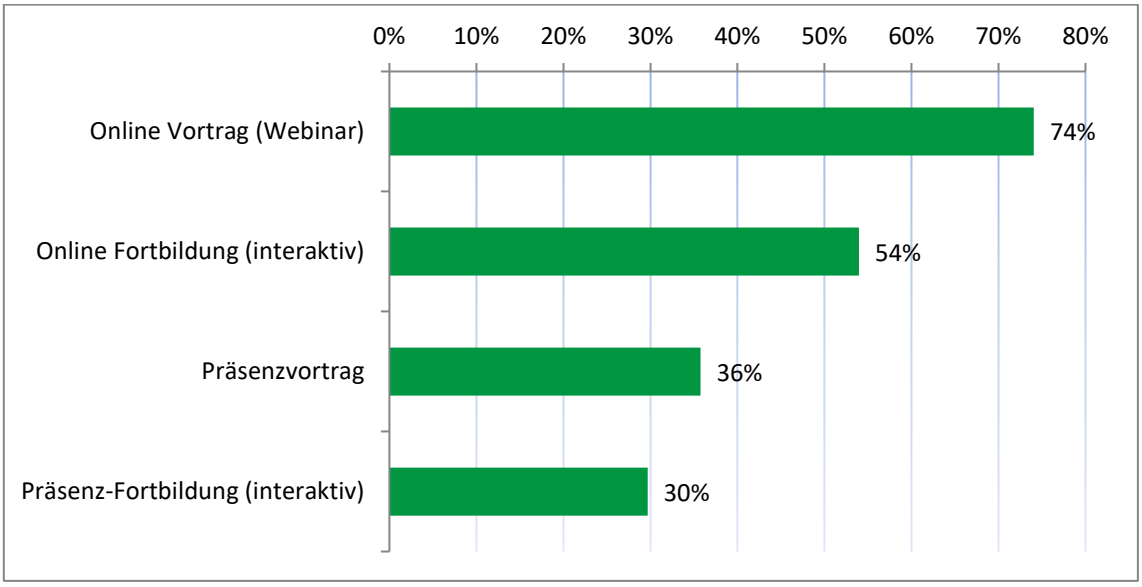
32. Welche Maßnahmen könnten aus Ihrer Sicht zu einer besseren Implementierung der S3-Leitlinie FASD führen? (n = 514)



33. Würden Sie ein Fortbildungsangebot zum Inhalt der S3-Leilinie FASD wahrnehmen? (Ja/Nein) (n = 526)

⇨ Ja: 84 %

34. In welcher Form würden Sie sich ein Fortbildungsangebot wünschen? (n = 438)



A. 9 Protokoll zur Gruppendiskussion mit Kindern und Jugendlichen mit FASD am 19.05.2023 (10:00 – 10:40 Uhr)

An der online Gruppendiskussion nahmen zwei Mädchen und vier Jungen mit FASD im Alter zwischen neun und vierzehn Jahren teil. Die Kinder wurden im Rahmen einer Familienfreizeit von FASD Deutschland e. V. rekrutiert. Alle Kinder befanden sich zusammen in einem Raum und wurden von Frau Gisela Michalowski beaufsichtigt. Fragen wurden per Videoschaltung von Frau Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf gestellt. Frau Sonja Strieker führte während der gesamten Diskussion Protokoll.

Nach einer kurzen Begrüßung und der Klärung des Alters der Kinder übernahm Frau Prof. Dr. med. Dipl.-Psych. Landgraf das Wort. Zu Beginn erklärte sie in kindgerechter Sprache, was eine Leitlinie bedeutet, welche Inhalte darin stehen und wofür diese nützlich ist. Sie betonte, wie wichtig die Perspektive von Kindern mit FASD ist, um die Leitlinie FASD zu verbessern, und ging dabei auf den Grund dieser Gruppendiskussion ein.

Danach stellt sie die erste Frage an die Kinder: Was sollen Ärzte bei der Diagnostik beachten?

Anfangs erklärten alle Kinder, sie könnten sich an ihre eigene FASD-Diagnostik nicht erinnern. Daher meinte Frau Prof. Dr. med. Dipl.-Psych. Landgraf, die Kinder sollen sich vorstellen, sie würden zum jetzigen Zeitpunkt eine FASD-Diagnostik erhalten. Zunächst gingen die Kinder darauf ein, wie wichtig ihnen das „Beraten“ und „Reden“ mit Ärzten ist. Die Ärzte sollen „Überlegen“ und die Verhaltensweisen der Kinder genau analysieren, um richtige Diagnosen stellen zu können. Schnell gingen sie auf das Thema Therapie ein, welches jedoch erst später beleuchtet werden sollte, sodass Frau Prof. Dr. med. Dipl.-Psych. Landgraf auf das aktuelle Thema Diagnostik zurückführte, indem sie fragte, ob die Kinder auch schlechte Erfahrungen bei der Diagnostik erlebt hätten. Dies verneinten alle Kinder einstimmig.

Anschließend wurden die Kinder gefragt, ob ihnen die Diagnose etwas gebracht hätte. Ein Kind antwortete, es habe anfangs nicht gewusst, was FASD ist. Nachdem ihm aber die Eltern die Bedeutung erklärt hätten, habe er es verstanden und für sich akzeptiert. Ein älteres Kind definierte daraufhin FASD in eigenen Worten und ging kurz auf die Gründe dieser Erkrankung ein. Der Nutzen der Kugy-Bücher bei der Aufklärung über FASD wurde von den Kindern betont. So hätten sie durch die Bücher die Erkrankung besser verstanden. Selbst das älteste Kind sah die Bücher auch in seinem Alter als sinnvoll an. Die Kinder meinten, sie seien über die Diagnose nicht traurig, und ein Kind ergänzte, dass es helfe, wenn man wüsste, dass man eine Krankheit hat. Ihm würde es eine „Erleichterung“ verschaffen.

Die Frage, ob ihnen die Diagnose geholfen habe, besser im Leben zurechtzukommen, führte zunächst zu keiner konkreten Antwort. Daher wurde explizit gefragt, ob ihr Umfeld („Familie“, „Lehrer“, „Mitschüler“, „Freunde“) von ihrer Diagnose wüssten. Die Kinder bejahten dies. Sie fänden es „schwierig“ und „schlecht“ die Krankheit zu „verheimlichen“. Mit anderen „darüber zu reden“ helfe ihnen dagegen. Der Redebedarf der Kinder über ihre Erkrankung wurde mehrfach betont.

Auf die Frage, ob sie von anderen anders behandelt werden würden, nachdem diese von der Diagnose FASD erfahren hätten, wurde einstimmig mit einem „nein“ geantwortet. Alle würden sie „ganz normal“ behandeln. Ein Kind, welches eine Schule für Menschen mit Behinderung besucht, führte aus, dass alle seine Mitschüler ein Problem hätten. Daher würde auch es nicht anders behandelt werden. Ein anderes Kind bekräftigte noch einmal, dass es gut ist, wenn die Diagnose gestellt werde. So lernte es seine Mitschüler vor seiner Diagnose kennen. Nachdem es die Diagnose erhalten habe und in der Klasse verkündet habe, seien die anderen Kinder ganz „zärtlich“ mit ihm umgegangen und hätten ihn sofort in die Gruppe integriert. Von schlechten Reaktionen wurde nicht berichtet.

Danach wurde das Thema Therapie mit der Frage: „ Was sollen Ärzte bei der Therapie beachten?“ eingeleitet. Hier gaben die Kinder an, dass es wichtig ist nach den „Zielen“ und „Wünschen“ der Kinder zu fragen und individuell auf diese einzugehen. Abermals wurde darauf hingewiesen, dass ihnen „Gespräche“ mit Fachpersonal über ihre „Gefühle“ wichtig seien.

Nach der Frage, welche Therapie ihnen etwas gebracht hätte, berichtete ein Kind sehr positiv von seiner Integrationshelferin, welche ihnm in der Schule und bei den Hausaufgaben unterstütze. Ein anders Kind erzählte von seiner orthopädischen Schiene, durch das es wieder besser laufen könne. Die meisten Kinder berichteten positive Erfahrungen mit Ergotherapie. Auf die Nachfrage, was sie an Ergotherapie „so toll“ fänden, erklärten die Kinder, dass man dabei „Sport“ mache und ihnen diese Art von Therapie „Spaß“ mache. Die Bedeutung des Spaßfaktors wurde auch deutlich, als von „Spielen“ bei Therapien gesprochen wurde. Ein weiteres Mal erwähnten die Kinder, dass man bei Therapien mit ihnen „reden“ solle, weil ihnen dies „gut tue“. Außerdem wurde die Logopädie als hilfreiche Therapie zur Sprachförderung angesprochen sowie die Physiotherapie als Behandlungsform genannt, welche die Kinder in Anspruch nahmen.

Auf die Frage, was die Kinder mithilfe von Therapien gerne verbessern würden, gingen die Kinder vor allem auf schulische Aspekte ein. So wurde eine Lerntherapie für Mathe erwähnt und der Wunsch in „Deutsch besser zu werden“ geäußert. Zwei Kinder erzählten von Problemen bei der „Rechtschreibung“ und dem „Verwechseln von Buchstaben“. Beim Lernen würde es ihnen vor allem helfen, klare und „einfache“ Anweisungen zu erhalten und wenn Inhalte sehr „langsam“ erklärt werden würden. Durch einfache und verständliche Sprache könnten sie sich Wissen am besten aneignen.

Die Frage nach Schwierigkeiten beim Schließen von Freundschaften verneinten die Kinder. Hier sähen sie „keine Probleme“. Eines der Kinder erklärte, es habe „viele Freunde“ und es sei „leicht, neue Freunde zu finden“, während ein anderes von seinem besten Freund erzählte, der ebenfalls FASD hätte.

Anschließend wurde von Frau Prof. Dr. med. Dipl.-Psych. Landgraf zum Thema Aggressionsprobleme übergeleitet und gefragt, was die Kinder dagegen machen würden. Ein Kind erzählte daraufhin von seinem Bruder, welcher starke Aggressionsprobleme hätte. Es selbst würde sehr unter den Wutausbrüchen des Bruders leiden und würde, auf Rat eines Psychologen, den Bruder in solchen Fällen „in Ruhe lassen“ und „ignorieren“, damit dieser das Interesse am Kind verliere. Dies deckte sich mit den Berichten der anderen Kinder, welche meinten, ihnen helfe es „sich zurückzuziehen“, wenn sie wütend seien. Auch die

Methode „Eiswürfel über den Rücken zu schütten“ wurde als effektiv bei der Bewältigung von Wutproblemen angesehen. Zum Schluss erwähnte ein Kind, es helfe ihm auch mit seinen „Freunden zu reden“, um sich zu beruhigen.

Danach fragte Frau Prof. Dr. med. Dipl.-Psych. Landgraf, was den Kindern helfe, sich zu konzentrieren. Hier stand besonders das Schaffen des richtigen Umfeldes im Vordergrund. Eine „leise Umgebung“ sei ihnen sehr wichtig. Hierbei würden auch „Kopfhörer“ helfen, um sich in der Schule von äußeren Geräuschen abzuschotten und sich bei Hausaufgaben besser fokussieren zu können. Zusätzlich wandte ein Kind „Gedächtnisaufgaben“ an, um die Konzentrationsfähigkeit zu erhöhen.

Die konkrete Frage, ob es auch Therapien gäbe, die sie schlecht fänden, verneinten die Kinder.

Auf die Frage, ob die Kinder Medikamente nehmen würden, antworteten alle Kinder mit „ja“. Es wurden unterschiedliche Medikamente genannt, die allesamt als positiv gewertet wurden. So würden ihnen die Medikamente bei der „Wut“, bei der „Konzentration“ und bei „Schlafproblemen“ helfen.

Die Frage, ob Therapien ihnen helfen würden, dass sie sich besser fühlten, wurde zuerst von den meisten Kindern bejaht. Ein Kind meldete sich jedoch zu Wort und meinte, Medikamente würden ihm „gefühlstechnisch“ nicht helfen. So seien die Medikamente sinnvoll, um „zu funktionieren“, aber nicht, dass es sich besser fühle. Für Zufriedenheit sei einem der Kinder wichtig „mehr Freiheit“ zu haben. Als Beispiel für die „Freiheit im Leben“ nannte das Kind „Freunde zu treffen“ und „mehr eigene Kontrolle“ zu haben. Auf die Frage, wie dies umgesetzt werden könnte, konnte nicht geantwortet werden. Hier standen die Kinder selbst im Konflikt mit dem Wunsch nach Unterstützung durch das Umfeld und dem Wunsch nach Freiheit.

Als nächstes fragte Frau Prof. Dr. med. Dipl.-Psych. Landgraf, wie das Umfeld sie unterstützen könne. Hier betonten die Kinder, wie wichtig ihnen „konkrete Anweisungen“ seien. So sollten „Eltern“, „Lehrer“ und „Integrationshelfer“ klare Instruktionen geben und

„auf Probleme aufmerksam machen“. Sie empfänden es als hilfreich, deutlich gesagt zu bekommen, was „gut“ und was „schlecht“ bei ihnen laufe. „Beleidigt“ wären sie durch diese klaren Aussagen nicht.

Den letzten Punkt leitete Frau Prof. Dr. med. Dipl.-Psych. Landgraf mit den Worten ein, dass man, wenn man älter wird, auch Probleme mit Depression, Drogen oder Alkohol bekommen könnte. Hier fragte sie die Kinder, ob man diese irgendwie unterstützen könne, dass sie nicht diese Probleme erhalten würden. Dabei wurde die wichtige Bedeutung einer Bezugsperson deutlich. Die Kinder erklärten, dass es ihnen helfen würde, wenn sie „nicht allein“ seien, „Hilfe in der Nähe“ hätten und wenn „eine Bezugsperson immer erreichbar“ sei.

Nach etwa 40 Minuten initiierten die Kinder selbst das Ende der Diskussion. Ein teilnehmendes Kind meldete sich, es müsse sich nun verabschieden, da es noch woanders hin müsse, und sagte abschließend, dass ihm die Diskussion gefallen hätte. Zu diesem Zeitpunkt wiesen auch die anderen Kinder bereits deutliche Konzentrationsschwächen auf, sodass die Diskussion beendet wurde.

Frau Prof. Dr. med. Dipl.-Psych. Landgraf bedankte sich herzlich bei den Kindern und alle Gesprächsteilnehmer*innen verabschiedeten sich voneinander.

Die Diskussion wurde zu Beginn von einem der Kinder leicht dominiert, welches häufig als erstes antwortete. Dies könnte die darauffolgenden Antworten der anderen Kinder beeinflusst und dadurch zu Verzerrungen geführt haben. Ein Kind ergriff nur zweimal das Wort, blieb aber sonst still im Hintergrund. Ein Kind antwortete auf keine der gestellten Fragen und hörte nur still zu, sodass ein Großteil der erhobenen Daten von vier der teilnehmenden Kinder stammte. Dies ist bei der Interpretation und Verallgemeinerung der gewonnenen Informationen zu beachten.

A. 10 Fokussierte Literaturrecherche im Rahmen des dritten Teils des Leitlinienprojektes (2022/2023)

Prävalenz des mütterlichen Alkoholkonsums während der Schwangerschaft

Die Suche nach Publikationen in deutscher und englischer Sprache umfasste den Zeitraum vom 2011 bis 2023 und wurde in folgenden Recherchequellen durchgeführt:

- Literaturdatenbank Medline über http://www.pubmed.org
- Google Scholar
- Web of Science
- EBSCO-Datenbanken

Als Recherchevokabular wurden in PubMed folgende Begriffe verwendet:

- prenatal alcohol consumption/use/drinking/exposure
- epidemiology, incidence, frequency, prevalence, occurrence, statistics

Ausschlusskriterien für die Relevanzsichtung:

- A1: andere Erkrankung
- A2: Tiere/in vitro
- A3: anderes Thema
- A4: keine echten Studien z. B. Leserbriefe etc.
- A5: anderes Land als Länder Europas, USA und Canada

Final wurden 14 Publikationen zur Auswertung eigeschlossen.

Eingeschlossene Literatur zur Prävalenz von mütterlichem Alkoholkonsum während der Schwangerschaft

1. Chiandetti, A., Hernandez, G., Mercadal-Hally, M., Alvarez, A., Andreu-Fernandez, V., Navarro-Tapia, E., Bastons-Compta, A., & Garcia-Algar, O. (2017). Prevalence of prenatal exposure to substances of abuse: questionnaire versus biomarkers. *Reproductive Health*, *14*(1). https://doi.org/10.1186/s12978-017-0385-3
2. McCarthy, R., Mukherjee, R. A. S., Fleming, K. M., Green, J., Clayton-Smith, J., Price, A. D., Allely, C. S., & Cook, P. A. (2021). Prevalence of fetal alcohol spectrum disorder in Greater Manchester, UK: An active case ascertainment study. *Alcoholism: Clinical and Experimental Research*, *45*(11), 2271-2281. https://doi.org/10.1111/acer.14705
3. Bakhireva, L. N., Sharkis, J., Shrestha, S., Miranda-Sohrabji, T. J., Williams, S., & Miranda, R. C. (2017). Prevalence of Prenatal Alcohol Exposure in the State of Texas as Assessed by Phosphatidylethanol in Newborn Dried Blood Spot Specimens. *Alcohol Clin Exp Res*, *41*(5), 1004-1011. https://doi.org/10.1111/acer.13375

4. DiBattista, A., Ogrel, S., MacKenzie, A. E., & Chakraborty, P. (2022). Quantitation of phosphatidylethanols in dried blood spots to determine rates of prenatal alcohol exposure in Ontario. *Alcohol Clin Exp Res*, *46*(2), 243-251. https://doi.org/10.1111/acer.14766
5. McCormack, C., Hutchinson, D., Burns, L., Wilson, J., Elliott, E., Allsop, S., Najman, J., Jacobs, S., Rossen, L., Olsson, C., & Mattick, R. (2017). Prenatal Alcohol Consumption Between Conception and Recognition of Pregnancy. *Alcohol Clin Exp Res*, *41*(2), 369-378. https://doi.org/10.1111/acer.13305
6. Bakhireva, L. N., Kane, M. A., Bearer, C. F., Bautista, A., Jones, J. W., Garrison, L., Begay, M. G., Ozechowski, T., & Lewis, J. (2019). Prenatal alcohol exposure prevalence as measured by direct ethanol metabolites in meconium in a Native American tribe of the southwest. *Birth Defects Res*, *111*(2), 53-61. https://doi.org/10.1002/bdr2.1427
7. Umer, A., Lilly, C., Hamilton, C., Baldwin, A., Breyel, J., Tolliver, A., Mullins, C., John, C., & Maxwell, S. (2020). Prevalence of alcohol use in late pregnancy. *Pediatr Res*, *88*(2), 312-319. https://doi.org/10.1038/s41390-019-0731-y
8. Popova, S., Lange, S., Poznyak, V., Chudley, A. E., Shield, K. D., Reynolds, J. N., Murray, M., & Rehm, J. (2019). Population-based prevalence of fetal alcohol spectrum disorder in Canada. *BMC Public Health*, *19*(1). https://doi.org/10.1186/s12889-019-7213-3
9. Popova, S., Lange, S., Probst, C., Gmel, G., & Rehm, J. (2017). Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. *The Lancet Global Health*, *5*(3), e290-e299. https://doi.org/10.1016/s2214-109x(17)30021-9
10. Bakhireva, L. N., Leeman, L., Roberts, M., Rodriguez, D. E., & Jacobson, S. W. (2021). You Didn't Drink During Pregnancy, Did You? *Alcoholism: Clinical and Experimental Research*, *45*(3), 543-547. https://doi.org/10.1111/acer.14545
11. Howlett, H., Mackenzie, S., Gray, W. K., Rankin, J., Nixon, L., & Brown, N. W. (2020). Assessing the prevalence of alcohol consumption in early pregnancy using blood biomarker analysis: a consistent pattern across north-east England? *J Public Health (Oxf)*, *42*(1), e74-e80. https://doi.org/10.1093/pubmed/fdz039
12. Adler, J., Rissmann, A., Kropf, S., Mohnicke, K., Taneva, E., Ansorge, T., Zenker, M., & Wex, T. (2021). Estimated Prevalence of Harmful Alcohol Consumption in Pregnant and Nonpregnant Women in Saxony-Anhalt (NorthEast Germany) Using Biomarkers. *Alcoholism: Clinical and Experimental Research*, *45*(4), 819-827. https://doi.org/10.1111/acer.14567
13. Dejong, K., Olyaei, A., & Lo, J. O. (2019). Alcohol Use in Pregnancy. *Clinical Obstetrics & Gynecology*, *62*(1), 142-155. https://doi.org/10.1097/grf.0000000000000414
14. Howard, J. T., Perrotte, J. K., Flores, K., Leong, C., Nocito, J. D., 3rd, & Howard, K. J. (2022). Trends in Binge Drinking and Heavy Alcohol Consumption Among Pregnant Women in the US, 2011 to 2020. *JAMA Netw Open*, *5*(8), e2224846. https://doi.org/10.1001/jamanetworkopen.2022.24846

Prävalenz der FASD

Separate Literaturrecherche für die Prävalenz der FASD in Deutschland und für die internationale Prävalenz der FASD:

Prävalenz der FASD in Deutschland

Die fokussierte Literaturrecherche zur Prävalenz der FASD in Deutschland wurde am 09.12.2022 durchgeführt:

Literaturdatenbank	Suchbegriffe	Anzahl der Treffer
Medline, Suchoberfläche: PubMed	(("fetal alcohol spectrum disorder" OR "fetal alcohol syndrome") AND (prevalence)) AND (germany)	40

Darüber hinaus wurden die Referenzlisten der identifizierten Literatur nach weiteren potentiell relevanten Daten gesichtet.

Nach der Sichtung der 40 gefundenen Publikationen wurden 3 von ihnen in die finale Auswertung eingeschlossen.

Tabelle: Übersicht zu den eingeschlossenen Publikationen zur Prävalenz der FASD in Deutschland.

Referenz	Methode	Ergebnisse
Kraus 2019	**Registerbasierte Studie** Schätzung der FASD und FAS Inzidenz in Deutschland* (Grundlage für die Inzidenzschätzung bilden Daten aus der German Health Update Study (GEDA)ǂ aus denen die Häufigkeit des Alkoholkonsums während der Schwangerschaft in Deutschland abgeleitet wurde und publizierte Prävalenzangaben aus internationalen empirischen Studien (u.a. aus Australien, Kanada, Kroatien, Frankreich, Italien, Korea und den USA) zu FASD und FAS)	**Häufigkeit bei Lebendgeburten (Jahr 2014)** basierend auf der Annahme, dass 27,6% der Schwangeren in Deutschland Alkohol konsumierenǂ **FAS** (geschätzte Prävalenz im Jahr 2014): 41 (95%-KI 24; 63) pro 10 000 Lebendgeburten *d. h. von insgesamt 714 927 Lebendgeburten im Jahr 2014, 2 930 (95%-KI 1 720; 4 500) mit FAS geboren* **FASD** (geschätzte Prävalenz im Jahr 2014): 177 (95%-KI 135-320) pro 10 000 Lebendgeburten *d. h. von insgesamt 714 927 Lebendgeburten im Jahr 2014, 12 650 (95%-KI 9 650; 23 310) mit FASD geboren*
Lange 2017	**Systematisches Review und Metaanalyse** Prävalenz von FASD bei Kindern und Jugendlichen aus der Allgemeinbevölkerung † 24 Primärstudien eingeschlossen (keine deutsche Studie)	**Prävalenz bei Kindern und Jugendlichen (0 – 16,4 Jahre) aus der Allgemeinbevölkerung (Jahr 2012)** **FASD** 230 (95%-KI 0; 550) pro 10 000 Kindern und Jugendlichen Prävalenzen für verschiedene Länder in der Publikation verfügbar: “In this meta-analysis of 24 unique studies and 1416 unique children and youth with FASD, approximately 8 of 1000 in the general population had FASD, and 1 of every 13 pregnant women who consumed alcohol during pregnancy delivered a child with FASD. The prevalence of FASD was found to be notably higher among special populations.”
Popova 2017	**Systematisches Review und Metaanalyse:** Prävalenz von FAS in der	**Prävalenz in der Allgemeinbevölkerung (Jahr 2012)** **FAS**

	Allgemeinbevölkerung § 62 Primärstudien eingeschlossen (keine deutsche Studie)	383 (95%-KI 0; 1054) pro 10 000 Personen "This study has estimated that globally, about 10% of women in the general population consume alcohol during pregnancy and 1 in 67 women delivered a child with FAS. This finding means that, on average, about 15 of every 10 000 livebirths worldwide will have FAS, translating to about 119 000 children born with FAS globally every year. In some regions (most notably in the WHO European Region) a high proportion (about a quarter) of pregnant women in the general population consume alcohol during pregnancy, which is mirrored by also having the highest FAS prevalence that is 2.6 times higher than the global average (14,6 per 10 000; 95% CI 9,4; 23,3)."

KI: Konfidenzintervall; FAS: Fetales Alkohol Syndrom; FASD: Fetale Alkoholspektrumstörungen; WHO: World Health Organization

* Zitat aus Kraus 2019: "The estimations of FAS and FASD were based on the method proposed by Popova 2017 and Lange 2017. This methodology estimates FAS and FASD indirectly using recent German prevalence data of alcohol use during pregnancy, as representative data on these diseases were not available for Germany. The incidences of FAS and FASD in countries with one or no empirical studies, including Germany, were thus predicted using data on the prevalence of alcohol use during pregnancy and estimations of the quotient for the average number of pregnant women who consumed alcohol per one case of FAS or FASD for countries with available data. The incidences of FAS or FASD were then predicted by applying this quotient to the country-specific prevalence of alcohol use during pregnancy."

ǂ Zitat aus Kraus 2019: "Data on the prevalence of alcohol use during pregnancy were obtained from the German Health Update Study (GEDA) *[Lange C, et al. Data resource profile: German Health Update (GEDA) - the health interview survey for adults in Germany. Int J Epidemiol. 2015;44:442–50.36]* for the survey years 2009 (n = 21,262), 2010 (n = 22,050), and 2012 (n = 19,294). These data were pooled and weighted to represent the distribution of the general population on December 31, 2011. At the time of their interview, n = 374 women reported being pregnant, and of those women, 27.6% (95% CI 22.5%; 33.3%) reported having consumed alcohol during their pregnancy (calculations by C. Lange, data not published)."

† Zitat aus Lange 2017: "For countries with 1 or no empirical study, we estimated the prevalence of FASD by using country-specific data on the prevalence of alcohol use during pregnancy (obtained from Popova 2017). First, we estimated a quotient of the mean number of women who consumed alcohol during pregnancy per 1 case of FASD by using the pooled estimates of the prevalence of FASD available from countries with a WHO drinking pattern score of 3 or less. […] These data were then linked to the prevalence of alcohol use during pregnancy for each respective country. Second, we applied this quotient to the country-specific prevalence of alcohol use during pregnancy to estimate the prevalence of FASD."

§ Zitat aus Popova 2017: "For countries with one or no empirical studies (or where the meta-analysis resulted in a CI of 0–100%), we predicted the prevalence of FAS using data on the prevalence of alcohol use during pregnancy. This method included the following steps: first, we estimated a quotient for the average number of pregnant women who consumed alcohol per one case of FAS for countries with available data and then we predicted prevalence of FAS by applying this quotient to the country-specific prevalence of alcohol use during pregnancy."

Eingeschlossene Literatur zur Prävalenz der FASD in Deutschland

1. Kraus L, Seitz NN, Shield KD, Gmel G, Rehm J: Quantifying harms to others due to alcohol consumption in Germany: a register-based study. BMC medicine 2019; 17: 1-9.
2. Lange S, Probst C, Gmel G, Rehm J, Burd L, Popova S: Global prevalence of fetal alcohol spectrum disorder among children and youth: a systematic review and meta-analysis. JAMA pediatrics 2017; 171: 948-56.
3. Popova S, Lange S, Probst C, Gmel G, Rehm J: Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. The Lancet Global Health 2017; 5: e290–e9.

Internationale Prävalenzen der FASD

Die Suche nach internationalen Publikationen zur Prävalenz der FASD wurde im Jahr 2023 folgendermaßen durchgeführt

1. Eingabe Stichwort „FASD-Prevalence“ bei Pubmed (1.277 Ergebnisse)
2. Suche in der Cochrane Bibliothek-Deutsch (keine weiteren Ergebnisse)
3. Screening der Ergebnisse und Setzen der Filterfunktion auf letzte 10 Jahre und Abstract (295 Ergebnisse)
4. Sichtung auf Prävalenz der FASD (nicht Alkoholkonsum in der Schwangerschaft) (45 Ergebnisse)
5. Sichtung auf ausschließlich Kinder und Jugendliche (21 bzw. 22 Ergebnisse)

Tabelle: Übersicht zu internationalen Publikationen zur Prävalenz der FASD.

Land (Region)	Autor	Jahr	Fall-zahl	Prävalenz pro 1.000	Guideline	Geschlecht	Alter (Jahre)	Besonderheiten
USA/Arizona, Colorado, New York	Fox, D.G.	2015	k.A.	0,3–0,8	k. A.		7–9	Höchste: American/Indian/Alaska Native Niedrigste: Hispanic
USA/Rocky Mountains, Midwestern, Southeastern, Pacific Southwest	May, P.A.	2018	6.639	11,3–50,0		51,9% männl., 79,3% White maternal race	6,7	Gewichtete Prävalenz 31,1
USA/South California, Indian Community	Montag, A.C.	2019	488	41		50% männl. 50% weibl.	6,6	
USA/Midwestern City	May, P.A.	2020	891	14,4–41,2	Co FASP			Kein Unterschied bei Rasse, Ethnik und sozioökonomischem Status
USA/Rocky Mountain Region City	May, P.A.	2015	1.278	10,9–25,2	Dismorphiezeichen, Fragebogen		Grundschule	
USA/Midwestern	May, P.A.	2014		24–48			6–7	70% aller Schulanfänger
Kanada/Ontario	Popova, S.	2019	2.555	29,3	Canadian Guidlines		7–9	
Kanada	Palmeter, S.	2021		1 Bei Indigenen: 12	Canadian Health Survey on Children and Youth		1–17, Median: 5,7	
Südafrika	May, P.A.	2013	747	135,1–207,5	Dismorphiezeichen, Fragebogen		6–7	Erstklässler
Südafrika/WestCup	Lubbe, M.	2017	166	127	Lesefertigkeiten, Lernfähigkeiten			1.–4. Klasse
Südafrika	May, P.A.	201		196–276	Körperliche			

		7			Auffälligkeiten, Kopfumfang, Dismorphie, Verhalten			
Südafrika	May, P.A.	2020	735	160–310	Dismorphiediagnostik und Verhaltensbeobachtung			Erstklässler
Großbritannien/Bristol	McQuire, C.	2019	223	72				
Großbritannien /Manchester	Mc Carthy, R.	2021	220	36			8-9	
Kroatien	Petković, G.	2013	824	66,7	IOM Kriterien			1.-4. Klasse
Deutschland	Kraus, L.	2019						Metaanalytischer Ansatz
Deutschland	Feldmann	2012	267	232	Diagnostik Feldmann Fragebogen			Pflegekinder
Ukraine	Colom, J.	2021	162	500			8–24	
Welt	Popova, S.	2017	328 Studien	7,7				
Weltweit Subpopulationen - Pflege/Heime - Justizanstalten - Sonderschulen - Spezialkliniken 69 Studien aus 17 Ländern	Popova, S.	2019	6.177	10- bis 40-mal höher als erwarteter globaler Wert 7,7				
Welt	Popova, S.	2017	1416	siehe Besonderheiten			0–16	Europ: 19,8/1.000 Von 187 Ländern hatte die östliche Mittelmeerregion der WHO die niedrigste

								Prävalenz von 0,1/1.000 Die höchsten Prävalenzen hatten: - Irland: 47,5/1.000 - Kroatien: 53,3/1.000 - Südafrika: 111,1/1.000
Welt	Roozen, S.	2016	188	siehe Besonderheiten				Kroatien: 43,01/1.000 Italien: 36,89/1.000 Südafrika: 28,29/1.000 Bezogen auf ARBD hatte Australien: 10,82/1.000

Eingeschlossene Literatur zur Prävalenz der FASD international

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2. May PA, Blankenship J, Marais AS, Gossage JP, Kalberg WO, Barnard R, De Vries M, Robinson LK, Adnams CM, Buckley D, Manning M, Jones KL, Parry C, Hoyme HE, Seedat S. Approaching the prevalence of the full spectrum of fetal alcohol spectrum disorders in a South African population-based study. Alcohol Clin Exp Res. 2013 May;37(5):818-30. doi: 10.1111/acer.12033. Epub 2012 Dec 14. PMID: 23241076; PMCID: PMC3610844.
3. Kraus L, Seitz NN, Shield KD, Gmel G, Rehm J. Quantifying harms to others due to alcohol consumption in Germany: a register-based study. BMC Med. 2019 Mar 19;17(1):59. doi: 10.1186/s12916-019-1290-0. PMID: 30885214; PMCID: PMC6423764.
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5. May, P. A., Chambers, C. D., Kalberg, W. O., Zellner, J., Feldman, H., Buckley, D., Kopald, D., Hasken, J. M., Xu, R., Honerkamp-Smith, G., Taras, H., Manning, M. A., Robinson, L. K., Adam, M. P., Abdul-Rahman, O., Vaux, K., Jewett, T., Elliott, A. J., Kable, J. A., . . . Hoyme, H. E. (2018). Prevalence of Fetal Alcohol Spectrum Disorders in 4 US Communities. *JAMA*, *319*(5), 474-482. https://doi.org/10.1001/jama.2017.21896
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8. May PA, De Vries MM, Marais AS, Kalberg WO, Buckley D, Adnams CM, Hasken JM, Tabachnick B, Robinson LK, Manning MA, Bezuidenhout H, Adam MP, Jones KL, Seedat S, Parry CDH, Hoyme HE. Replication of High Fetal Alcohol Spectrum Disorders Prevalence Rates, Child Characteristics, and Maternal Risk Factors in a Second Sample of Rural Communities in South Africa. Int J Environ Res Public Health. 2017 May 12;14(5):522. doi: 10.3390/ijerph14050522. PMID: 28498341; PMCID: PMC5451973.
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A. 11 Methodik systematische Literaturrecherche – Diagnostische Kriterien der FASD (dritter Teil des Leitlinienprojektes 2022)

Suchstrategien

Medline (via PubMed)

Search Date: 22-06-2022

Search	Query
#14	Search: #11 AND #13
#13	Search: "Practice Guideline" [Publication Type] OR (guideline [tiab] OR guidelines [tiab])
#12	Search: #3 AND #9 Filters: Systematic Review, from 2015/7/1 - 3000/12/12
#11	Search: #3 AND #9 Filters: from 2015/7/1 - 3000/12/12
#10	Search: #3 AND #9
#9	Search: #6 OR #7
#8	Search: (developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR deficits OR growth deficiency OR facial phenotype OR ("central nervous system" AND (damage OR dysfunction)) OR ((cognitive OR communication OR behavioral) AND (difficulties OR disabilities)) OR adverse life outcomes OR mental health concerns OR ((fluency OR articulation) AND abilities)
#7	Search: (developmental[Title/Abstract] AND (defect[Title/Abstract] OR defects[Title/Abstract] OR abnormality[Title/Abstract] OR abnormalities[Title/Abstract] OR anomaly[Title/Abstract] OR anomalies[Title/Abstract])) OR deficits[Title/Abstract] OR growth deficiency[Title/Abstract] OR facial phenotype[Title/Abstract] OR ("central nervous system"[Title/Abstract] AND (damage[Title/Abstract] OR dysfunction[Title/Abstract])) OR ((cognitive[Title/Abstract] OR communication[Title/Abstract] OR behavioral[Title/Abstract]) AND (difficulties[Title/Abstract] OR disabilities[Title/Abstract])) OR adverse life outcomes[Title/Abstract] OR mental health concerns[Title/Abstract] OR ((fluency[Title/Abstract] OR articulation[Title/Abstract]) AND abilities[Title/Abstract])
#6	Search: #4 OR #5
#5	Search: diagnos* [tiab] OR screen* [tiab]

Search	Query
#4	Search: "diagnosis"[MeSH Terms] OR "diagnosis"[MeSH Subheading]
#3	Search: #1 OR #2
#2	Search: "Fetal Alcohol Spectrum Disorder*"[tiab] OR "Foetal Alcohol Spectrum Disorder*"[tiab] OR FASD [tiab] OR FASDs [tiab] OR "Fetal Alcohol Syndrome*" [tiab] OR "Foetal Alcohol Syndrome*"[tiab] OR "Alcohol Related Birth Defect*"[tiab] OR "Alcohol Related Neurodevelopmental Disorder*" [tiab] OR "Fetal Alcohol Effect*" [tiab] OR (alcohol [tiab] AND (embryopathy [tiab] OR embryofetopathy [tiab])) OR "Foetal Alcohol Effect*"[tiab] OR "Fetal alcohol disorder*" [tiab]
#1	Search: "Fetal Alcohol Spectrum Disorders"[Mesh]

Cochrane Library via Wiley

Date Run: 22-06-22

#1	MeSH descriptor: [Fetal Alcohol Spectrum Disorders] explode any trees
#2	("Fetal Alcohol Spectrum Disorder*" OR "Foetal Alcohol Spectrum Disorder*" OR FASD OR FASDs OR "Fetal Alcohol Syndrome*" OR "Foetal Alcohol Syndrome*" OR "Alcohol Related Birth Defect*" OR "Alcohol Related Neurodevelopmental Disorder*" OR "Fetal Alcohol Effect*" OR (alcohol AND (embryopathy OR embryofetopathy)) OR "Foetal Alcohol Effect*" OR "Fetal alcohol disorder*"):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Diagnosis] explode any trees 444924
#5	MeSH descriptor: [] explode any trees and with qualifier(s): [diagnosis - DI]
#6	(diagnos* OR screen*):ti,ab,kw
#7	#4 OR #5 OR #6
#8	((development* AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR deficit OR deficits OR growth deficien* OR facial phenotype OR ("central nervous system" AND (damage OR dysfunction*)) OR ((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disabilit*)) OR adverse life outcomes OR mental health concerns OR ((fluen* OR articulat*) AND abilit*)):ti,ab,kw
#9	#7 OR #8
#10	#3 AND #9 with Cochrane Library publication date Between Jul 2015 and Jul 2022

PsycINFO/PsycARTICLES/PSYNDEX via EBSCO

Search Date 06-07-22

#	Query	Limiters/Expanders	
S9	(TX (("systematic review" or "meta analysis"))) AND (S7 AND S8)	Expanders - Apply equivalent subjects Search modes - Find any my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo
S8	TX ("systematic review" or "meta analysis")	Expanders - Apply equivalent subjects Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo
S7	(S4 OR S5) AND (S1 AND S6)	Expanders - Apply equivalent subjects Search modes - Find any my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo
S6	S4 OR S5	Expanders - Apply equivalent subjects Search modes - Find any my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo

S5	((TI development* OR AB development*) AND ((TI defect OR AB defect) OR (TI defects OR AB defects) OR (TI abnormality OR AB abnormality) OR (TI abnormalities OR AB abnormalities) OR (TI anomaly OR AB anomaly) OR (TI anomalies OR AB anomalies))) OR (TI deficit OR AB deficit) OR (TI deficits OR AB deficits) OR (TI "growth deficien*" OR AB "growth deficien*") OR (TI "facial phenotype" OR AB "facial phenotype") OR ((TI "central nervous system" OR AB "central nervous system") AND ((TI damage OR AB damage) OR (TI dysfunction* OR AB dysfunction*))) OR (((TI cognitive OR AB cognitive) OR (TI communication OR AB communication) OR (TI behavioral OR AB behavioral) OR (TI behavioural OR AB behavioural)) AND ((TI difficult* OR AB difficult*) OR (TI disabilit* OR AB disabilit*))) OR (TI "adverse life outcomes" OR AB "adverse life outcomes") OR (TI "mental health concerns" OR AB "mental health concerns") OR (((TI fluen* OR AB fluen*) OR (TI articulat* OR AB articulat*)) AND (TI abilit* OR AB abilit*))	Expanders - Apply equivalent subjects Search modes - Find any my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo
S4	S2 OR S3	Expanders - Apply equivalent subjects Search modes - Find any my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo
S3	(TI diagnos* OR AB diagnos*) OR (TI screen* OR AB screen*)	Expanders - Apply equivalent subjects Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo
S2	DE "Diagnosis" OR DE "Anthropometry" OR DE "Computer Assisted Diagnosis" OR DE "Diagnosis Related Groups" OR DE "Differential Diagnosis" OR DE "Dual Diagnosis" OR DE "Educational Diagnosis" OR DE "Galvanic Skin Response" OR DE "Medical Diagnosis" OR DE "Misdiagnosis" OR DE "Neuroimaging" OR DE "Psychodiagnosis"	Expanders - Apply equivalent subjects Search modes - Find any my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo

S1	(TI "Fetal Alcohol Spectrum Disorder*" OR AB "Fetal Alcohol Spectrum Disorder*") OR (TI "Foetal Alcohol Spectrum Disorder*" OR AB "Foetal Alcohol Spectrum Disorder*") OR (TI FASD OR AB FASD) OR (TI FASDs OR AB FASDs) OR (TI "Fetal Alcohol Syndrome*" OR AB "Fetal Alcohol Syndrome*") OR (TI "Foetal Alcohol Syndrome*" OR AB "Foetal Alcohol Syndrome*") OR (TI "Alcohol Related Birth Defect*" OR AB "Alcohol Related Birth Defect*") OR (TI "Alcohol Related Neurodevelopmental Disorder*" OR AB "Alcohol Related Neurodevelopmental Disorder*") OR (TI "Fetal Alcohol Effect*" OR AB "Fetal Alcohol Effect*") OR ((TI alcohol OR AB alcohol) AND ((TI embryopathy OR AB embryopathy) OR (TI embryofetopathy OR AB embryofetopathy))) OR (TI "Foetal Alcohol Effect*" OR AB "Foetal Alcohol Effect*") OR (TI "Fetal alcohol disorder*" OR AB "Fetal alcohol disorder*")	Expanders - Apply equivalent subjects Search modes - Find any of my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - APA PsycInfo

TRIP Database https://www.tripdatabase.com/

Search Date: 06/07/2022

(title:diagnos* title:or title:screen*) AND ("fetal alcohol spectrum disorders" OR "fetal alcohol spectrum disorder*" OR "foetal alcohol syndrome*")

Epistemonikos www.epistemonikos.org

Search Date: Jun 22, 2022

(title:((title:((diagnos* OR detect* OR screen*) OR ((title:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR abstract:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies))) OR (title:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes") OR abstract:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes")) OR (title:("central nervous system" AND (damage OR dysfunction)) OR abstract:("central nervous system" AND (damage OR dysfunction))) OR (title:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*)) OR abstract:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*))) OR (title:("adverse life outcomes" OR "mental health concern" OR "mental health concerns") OR abstract:("adverse life outcomes" OR "mental health concern" OR "mental health concerns")) OR (title:((fluen* OR articulat*) AND (able OR abilit*)) OR abstract:((fluen* OR articulat*) AND (able OR abilit*))))) OR abstract:((diagnos* OR detect* OR screen*) OR ((title:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR abstract:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies))) OR (title:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes") OR abstract:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes")) OR (title:("central nervous system" AND (damage OR dysfunction)) OR abstract:("central nervous system" AND (damage OR dysfunction))) OR (title:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR

disab*)) OR abstract:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*))) OR (title:("adverse life outcomes" OR "mental health concern" OR "mental health concerns") OR abstract:("adverse life outcomes" OR "mental health concern" OR "mental health concerns")) OR (title:((fluen* OR articulat*) AND (able OR abilit*)) OR abstract:((fluen* OR articulat*) AND (able OR abilit*)))))) AND (title:("Fetal Alcohol Spectrum Disorder" OR "Foetal Alcohol Spectrum Disorder" OR "Fetal Alcohol Syndrome" OR "Foetal Alcohol Syndrome" OR FASD OR "Alcohol Related Birth Defect" OR "Alcohol Related Neurodevelopmental Disorder" OR "fetal alcohol effect" OR "fetal alcohol effects" OR (alcohol* AND (embryopathy OR embryofetopathy))) OR abstract:("Fetal Alcohol Spectrum Disorder" OR "Foetal Alcohol Spectrum Disorder" OR "Fetal Alcohol Syndrome" OR "Foetal Alcohol Syndrome" OR FASD OR "Alcohol Related Birth Defect" OR "Alcohol Related Neurodevelopmental Disorder" OR "fetal alcohol effect" OR "fetal alcohol effects" OR (alcohol* AND (embryopathy OR embryofetopathy))))) OR abstract:((title:((diagnos* OR detect* OR screen*) OR ((title:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR abstract:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies))) OR (title:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes") OR abstract:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes")) OR (title:("central nervous system" AND (damage OR dysfunction)) OR abstract:("central nervous system" AND (damage OR dysfunction))) OR (title:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*)) OR abstract:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*))) OR (title:("adverse life outcomes" OR "mental health concern" OR "mental health concerns") OR abstract:("adverse life outcomes" OR "mental health concern" OR "mental health concerns")) OR (title:((fluen* OR articulat*) AND (able OR abilit*)) OR abstract:((fluen* OR articulat*) AND (able OR abilit*))))) OR abstract:((diagnos* OR detect* OR screen*) OR ((title:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies)) OR abstract:(developmental AND (defect OR defects OR abnormality OR abnormalities OR anomaly OR anomalies))) OR (title:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes") OR abstract:(deficit* OR "growth deficiency" OR "facial phenotype" OR "facial phenotypes")) OR (title:("central nervous system" AND (damage OR dysfunction)) OR abstract:("central nervous system" AND (damage OR dysfunction))) OR (title:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*)) OR abstract:((cognitive OR communication OR behavioral OR behavioural) AND (difficult* OR disab*))) OR (title:("adverse life outcomes" OR "mental health concern" OR "mental health concerns") OR abstract:("adverse life outcomes" OR "mental health concern" OR "mental health concerns")) OR (title:((fluen* OR articulat*) AND (able OR abilit*)) OR abstract:((fluen* OR articulat*) AND (able OR abilit*)))))) AND (title:("Fetal Alcohol Spectrum Disorder" OR "Foetal Alcohol Spectrum Disorder" OR "Fetal Alcohol Syndrome" OR "Foetal Alcohol Syndrome" OR FASD OR "Alcohol Related Birth Defect" OR "Alcohol Related Neurodevelopmental Disorder" OR "fetal alcohol effect" OR "fetal alcohol effects" OR (alcohol* AND (embryopathy OR embryofetopathy))) OR abstract:("Fetal Alcohol Spectrum Disorder" OR "Foetal Alcohol Spectrum Disorder" OR "Fetal Alcohol Syndrome" OR "Foetal Alcohol Syndrome" OR FASD OR "Alcohol Related Birth Defect" OR "Alcohol Related Neurodevelopmental Disorder" OR "fetal alcohol effect" OR "fetal alcohol effects" OR (alcohol* AND (embryopathy OR embryofetopathy))))))

The Oxford 2011 Levels of Evidence

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

A. 12 Evidenztabellen zur eingeschlossenen Literatur über Diagnostik der FASD (dritter Teil des Leitlinienprojektes 2022)

Leitlinien und diagnostische Systeme

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
S3-LL 2017(1) (Deutschland)	**FASD**	Keine gesonderte Empfehlung				S3-LL
	FAS (starker Konsensus, Empfehlungs-grad A, nur ZNS Auffälligkeiten B)	**Mind. 1 Auffälligkeit:** ▪ Geburts-/ Körpergewicht ▪ Geburts-/ Körperlänge ▪ BMI für jedes Kriterium: ≤ 10ter P. **Soll Empfehlung**	**Alle 3 Auffälligkeiten:** ▪ **Lidspalten (kurz)** ≤ 3ter P., 2 SA unter Norm ▪ **Philtrum (verstrichen)** ▪ **Oberlippe (schmal)** Rang 4/5 Lip Philtrum Guide **Soll Empfehlung**	**Mind. 1 strukturelle <u>oder/und</u> funktionelle Auffälligkeit** **A. Strukturell: Mikrozephalie ≤ 10ter P.** **B. Funktionell** - Globale Intelligenzminderung (mind. **2** SA unter Norm) ***oder*** kombinierte Entwicklungsverzögerung (bei ≤ 2 J.) **oder/und** mind. 3 Auffälligkeiten (mind. 2 SA unter Norm) *oder* mind. 2 Auffälligkeiten, wenn **Epilepsie** vorliegt: - Sprache - Fein-/Graphomotorik oder grobmotorische Koordination - Räumlich-visuelle Wahrnehmung oder räumlich-konstruktive Fähigkeiten - Exekutive Funktionen - Lern-/ Merkfähigkeit - Rechenfertigkeiten - Aufmerksamkeit	**Kein Kriterium** (d. h. bei anderen Auffälligkeiten)	

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
				- Soziale Fertigkeiten oder Verhalten **Sollte Empfehlung**		
	pFAS (starker Konsensus außer für PAE)	**Kein Kriterium**	**Mind. 2 Auffälligkeiten:** ▪ **Lidspalten (kurz)** ≤ 3ter P. bzw. 2 SA unter Norm ▪ **Philtrum (verstrichen)** ▪ **Oberlippe (schmal)** Rang 4/5 Lip Philtrum Guide	**Mind. 3 Auffälligkeiten** (Aufzählungspunkte sind gleichwertig): - Mikrozephalie ≤ 10ter P. - Epilepsie - Globale Intelligenzminderung[a] *oder* kombinierte Entwicklungsverzögerung bei Kindern ≤ 2 J. - Sprache[a] - Fein- /Graphomotorik oder grobmotorischer Koordination[a] - Räumlich-visuelle Wahrnehmung oder räumlich-konstruktive Fähigkeiten[a] - Exekutive Funktionen[a] - Lern-/ Merkfähigkeit[a] - Rechenfertigkeiten[a] - Aufmerksamkeit[a] - Soziale Fertigkeiten oder Verhalten [a]*mind. 2 SA unter Norm* **Soll Empfehlung**	**Mindestens wahrscheinliche Alkoholexposition** (wenn faciale oder ZNS Auffälligkeit)	
	ARND (Konsensus)	**Kein Kriterium**	**Kein Kriterium**		**Kriterium/ Bestätigt**	
Broccia 2017 (2) (Dänemark)	**FASD**	Keine gesonderte Empfehlung				LL bezieht sich in erster Linie auf kanadische LL Keine Literatursuche angegeben **Expertenkonsens**
	FAS	**Mind. 1 Auffälligkeit:** ▪ **Geburts-/ Körpergewicht** ▪ **Geburts-/ Körperlänge** für jedes Kriterium: ≤ 10ter P.	Identisch zur dt. LL	**Mind. 1 der folgenden Auffälligkeiten:** - Mikrozephalie ≤ 10ter P. - Abnormale Gehirnstruktur - Fokal neurologische Defizite inkl. Epilepsie - Gehirnfunktionen (beurteilt anhand psychologischer Gutachten und psychometrischer Tests)	Identisch zur dt. LL	
	pFAS	**Kein Kriterium**		**Mind. 1 der folgenden Auffälligkeiten:** - Mikrozephalie ≤ 10ter P.		

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
	ARND			- Abnormale Gehirnstruktur - Gehirnfunktionen (beurteilt anhand psychologischer Gutachten und psychometrischer Tests)		
Okulicz-Kozaryn 2021 (3) (Polen)[#]	**At risk for FASD***	Keine Kriterien			**Kriterium/ Bestätigt** **Oder** **Kein Kriterium** (d. h. unbekannte PAE, bei 3 facialen Auffälligkeiten)	Anerkennung der fehlenden Evidenz im Hinblick auf Kriterien Bewertung und Einschätzung der kanadischen LL und IOM Kriterien und 4-Digit Code auf das polnische Gesundheitssystem durch interdisziplinäres Team Empfehlung: „3-stage Algorithm“ basiert auf **Expertenkonsensus,** vorhandene LL (4-6), SRs (7, 8) und Primärstudien publiziert vor 2015 Keine Literatursuche/-bewertung beschrieben **Expertenkonsens**
	FAS (pFAS wird nicht berücksichtigt)	**Mind. 1 Auffälligkeit:** ▪ Geburts-/ Körpergewicht ▪ Geburts-/ Körperlänge für jedes Kriterium: ≤ 10ter P.	Identisch zur dt. LL	**Neurodevelopmental disorders**: - deficits in ≥3 cognitive areas or if neurological symptoms (e.g. Epilepsy) are found in ≥2 cognitive areas **and** - irregularities in ≥3 areas from the emotional and social sphere, adaptation disorders, or psychopathological symptoms - significant impact of the above-mentioned irregularities in daily life activities and functioning in school, pre-school, or work	**Kein Kriterium** (d. h. bei anderen Auffälligkeiten)	
	ARND (ND-PAE)	**Kein Kriterium**			**Kriterium/ Bestätigt**	
Hoyme 2016 (6) **IOM Kriterien°** (USA)	**FAS**	**Mind. 1 Auffälligkeit:** ▪ **Geburts-/ Körpergewicht** ▪ **Geburts-/ Körperlänge** für jedes Kriterium: ≤ 10ter P.	**Mind. 2 Auffälligkeiten:** **Lidspalten (kurz)** ≤ 10 P. (Messung mit Lineal empfohlen) **Philtrum (verstrichen)** **Oberlippe (schmal)**	**A. <u>Mind. 1 der folgenden Auffälligkeiten:</u>** - Mikrozephalie ≤ 10ter P. - Gehirnanomalien (strukturell) - Neurophysiologisch (Epilepsie) **und**	**Kein Kriterium** (d. h. bei anderen Auffälligkeiten)	“These guidelines were formulated by the authors over a 12-month period. The following working subgroups were organized to revisit diagnostic criteria:

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
			Rang 4/5 Lip Philtrum Guide	**B. <u>„Neurobehavioural disorder"/Verhaltensstörung</u>** **Kinder ≥ 3 J.; entweder kognitiv oder verhaltensbezogen:** **(i) kognitive:** globale Intelligenzminderung (mind. 1,5 SA unter Norm) ***oder*** *mind. 1 der folgenden* Einschränkungen (jeweils mind. 1,5 SA unter Norm): exekutive Funktion, spezifische Lernbehinderung, Einschränkungen des Gedächtnisses, visuell-räumliche Defizite *oder* **(ii) verhaltensbezogene** *(mind.* 1,5 SA unter Norm) in mind. 1 der folgenden Bereiche: Stimmung oder Verhaltensregulation Aufmerksamkeitsdefizit Impulskontrolle **Kinder < 3 J.:** „Evidence of developmental delay" (mind. 1,5 SA unter Norm)		dysmorphology evaluation, neurobehavioral assessment, and definition of significant documented PAE." Recommendations from the working committees were brought back to the larger group for discussion and revision. The guidelines presented herein are the result of a thorough review of the literature and the longstanding collective expertise of the authors and the evaluation of >10 000 children for potential FASD in clinical settings and in epidemiologic studies"
	pFAS mit PAE	**<u>Diagnosis of pFAS with PAE requires features A and B:</u>** **A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:** 1. Short palpebral fissures (≤10th centile) 2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available) 3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available) AND **B. Neurobehavioral impairment (Adaptive skills should be assessed, but such deficits cannot stand alone for diagnosis)**				Trotz dieses Statements keine Literatursuche und -bewertung beschrieben **Expertenkonsens**

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
		B1. For children ≥3 y of age (a or b): a. WITH COGNITIVE IMPAIRMENT: −Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or spatial IQ ≥1.5 SD below the mean) or −Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment or visual-spatial impairment) OR b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT: −Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control) ***B2. For children <3 y of age:*** −Evidence of developmental delay ≥1.5 SD below the mean				
	pFAS ohne PAE	**<u>Diagnosis of pFAS without documented PAE requires all features (A–C):</u>** **A. A characteristic pattern of minor facial anomalies, including ≥2 of the following:** 1. Short palpebral fissures (≤10th centile) 2. Thin vermilion border of the upper lip (rank 4 or 5 on a racially normed lip/philtrum guide, if available) 3. Smooth philtrum (rank 4 or 5 on a racially normed lip/philtrum guide, if available) AND **B. Growth deficiency or deficient brain growth, abnormal morphogenesis, or abnormal neurophysiology** B1. Height and/or weight ≤10th centile (plotted on a racially or ethnically appropriate growth curve, if available), or B2. Deficient brain growth, abnormal morphogenesis or neurophysiology, including ≥1 of the following: a. Head circumference ≤10th percentile b. Structural brain anomalies c. Recurrent non-febrile seizures (other causes of seizures having been ruled out) AND **C. Neurobehavioral impairment (Adaptive skills should be assessed, but such deficits cannot stand alone for diagnosis)** ***C1. For children ≥3 y of age (a or b):*** a. WITH COGNITIVE IMPAIRMENT: −Evidence of global impairment (general conceptual ability ≥1.5 SD below the mean, or performance IQ or verbal IQ or				

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
		spatial IQ ≥1.5 SD below the mean) OR −Cognitive deficit in at least 1 neurobehavioral domain ≥1.5 SD below the mean (executive functioning, specific learning impairment, memory impairment, or visual-spatial impairment) b. WITH BEHAVIORAL IMPAIRMENT WITHOUT COGNITIVE IMPAIRMENT: −Evidence of behavioral deficit in at least 1 domain ≥1.5 SD below the mean in impairments of self-regulation (mood or behavioral regulation impairment, attention deficit, or impulse control) ***C2. For children <3 y of age:*** −Evidence of developmental delay ≥1.5 SD below the mean				
	ARND	**Kein Kriterium**	**Kein Kriterium**	**Kriterium** **1 Beeinträchtigung kognitiv oder behavioral** (siehe pFAS)	**Kriterium/ Bestätigt**	
	ARBD**	**Kein Kriterium**	**Kein Kriterium**	**Kein Kriterium**		
SIGN 2019 (9) (Schottland)	Keine eigenständige LL, bezieht Evidenz auf die australische bzw. kanadische LL					**Expertenkonsens**
Bower 2017 (10, 11) (Australien)	Identisch zu kanadischer LL Nicht transparent berichtet, Referenzen beziehen sich auf andere LL oder selektiv ausgewählte diagnostische Instrumente					**Expertenkonsens**
Cook 2016 (5) (Kanada)	**FASD** (Unterschied: FASD mit/ohne faciale Auffälligkeit)	**Kein Kriterium**§ (Wachstumsauffälligkeiten wurden im Vergleich zur ursprünglichen Empfehlung aus dem Jahr 2005 gestrichen; es gibt jedoch die Empfehlung, dass Auffälligkeiten dokumentiert werden sollen)	**<u>FASD mit facialen Auffälligkeiten:</u>** **Alle 3 Auffälligkeiten** (bei unbekannter PAE): **Lidspalten (kurz)** ≤ 3ter P., 2 SA unter Norm (computerbasierte Messung empfohlen) **Philtrum (verstrichen)** **Oberlippe (schmal)** Rang 4/5 Lip Philtrum Guide **<u>FASD ohne faciale</u>**	**Mind. 3 Auffälligkeiten** (≤ 3ter P. bzw. 2 SA unter Norm): - Motorik (einschl. Schreiben, Zeichnen, Gleichgewicht) - Neuroanatomie/Neurophysiologie - Kognitiv (z. B. Lernschwäche) - Sprache - akademische Errungenschaften - Gedächtnis - Aufmerksamkeit - Exekutive Funktionen (inkl. Impulskontrolle, Hyperaktivität, Organisationsdefizit) - Affektregulation	**Kein Kriterium** (bei facialer Auffälligkeit) **Kriterium/ Bestätigt** (bei < 3 facialen Auffälligkeiten)	Insgesamt wurde die LL nach etablierten Standards durchgeführt: "The guideline was developed according to AGREE II framework, The literature review was conducted by 2 committee […]. Relevant reports published from 2005 to September 2014 were identified. Once the recommendations were drafted by the steering

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
			<u>Auffälligkeiten:</u> **< 3 Auffälligkeiten**	- Adaptives Verhalten, soziale Fertigkeiten / Kommunikation - Mikrozephalie (2 SA unter Norm; nur bei Kindern, die alle 3 facialen Merkmale aufweisen, aber (noch) keine eindeutige entwicklungsneurologische Auffälligkeit, weil zu jung)		committee, they were appraised independently by the same two researchers using GRADE. " **Domäne: Wachstum,** Evidenzeinschätzung: *Low* ("Following an analysis of historical clinical reports, basic science, and clinical research, the committee supported the recommendation to remove growth as a diagnostic criterion") **Geringe (low) Vertrauenswürdigkeit in die Evidenz**
	At risk for FASD*	Kein Kriterium	<u>Nicht</u> vorhanden	Wenn die entwicklungsneurologische Beurteilung aufgrund situationaler Faktoren und/oder des Alters uneindeutig ist, aber eine PAE bestätigt.t	**Kriterium/ Bestätigt**	
4-Digit Code 2000 (4, 12)	**FAS**	**Mind. 1 Auffälligkeit:** ▪ **Geburts-/ Körpergewicht** ▪ **Geburts-/ Körperlänge** für jedes Kriterium: ≤ 10ter P. (verschiedene Kombinationen von Größe und Gewicht möglich)	**Alle 3 Auffälligkeiten:** ▪ **Lidspalten (kurz)** ≤ 3ter P., 2 SA unter Norm (Messung: Lineal, Foto) ▪ **Philtrum (verstrichen)** ▪ **Oberlippe (schmal)** Rang 4/5 Lip Philtrum Guide [Für die Diagnose pFAS reicht wenn 2 der Merkmale mit 4/5 bewertet werden und eines mit 3 (=moderat)]	**A. Mind. 1 der folgenden strukturellen bzw. neurologischen Auffälligkeiten (Rank 4):** - Mikrozephalie ≤ 3ter P. oder ≥2 SD (strukturell) - Gehirnanomalien, die vermutlich pränatal sind (strukturell) - "hard" neurological findings likely to be of prenatal origin **UND/ ODER** **B. Mind. 3 funktionelle Auffälligkeiten (Rank 3)** (≥ 2 SA unter Norm)	„keine PAE", „unbekannt", „bestätigt" und „bestätigt hoch". Bei „keiner PAE (Nicht-Exposition bestätigt)" kann keine Diagnose aus dem FASD Spektrum vergeben werden (jedoch anderer Code); bei unbekannter	Insgesamt sehr komplexes System Insgesamt 256 verschiedene Codes, die zu 22 diagnostischen Kategorien zusammengefasst wurden Klare Beschreibung von PAE **Expertenkonsens**

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
				mind. 3 funktionelle Auffälligkeiten Rank 3 reicht schon für die Diagnose von FAS aus	Exposition ist eine Diagnose möglich	
CDC 2004 (13)	**FAS**	**Mind. 1 Auffälligkeit:** ▪ **Geburts-oder Körpergewicht** ▪ **Geburts- oder Körperlänge** für jedes Kriterium: ≤ 10ter P. (adjustiert nach Alter, Geschlecht, Geburtswoche, ethischer Herkunft)	**Alle 3 Auffälligkeiten:** ▪ **Lidspalten (kurz)** ≤ 10ter P. (Messung mit Lineal oder Foto) ▪ **Philtrum (verstrichen)** ▪ **Oberlippe (schmal)** Rang 4/5 Lip Philtrum Guide	**A. Mind. 1 der folgenden strukturellen bzw. neurologischen Auffälligkeiten:** - Mikrozephalie ≤ 10ter P. (strukturell) - Gehirnanomalien (strukturell, diagnostiziert mit bildgebenden Verfahren)) - "Neurological problems not due to a postnatal insult or fever, or other soft neurological signs outside normal limits" **UND/ ODER** **B. funktionelle Auffälligkeiten** -globales oder kognitives Defizit (< 3ter P., 2 SA unter Norm) *oder* - Defizit (< 16ter P., 1 SA unter Norm) in mind.3 der folgenden Domänen a) kognitiv oder entwicklungsbezogen b) exekutive Funktionen c) Verzögerungen der motorischen Entwicklung d) Aufmerksamkeitsprobleme oder Hyperaktivität e) soziale Fähigkeiten f) andere wie z. B. sensorische Fähigkeiten, pragmatisches Sprachverständnis, Gedächtnisdefizite usw.)	**Kein Kriterium** "[…] effort should be made to obtain the necessary information, but lack of confirmation of alcohol use during pregnancy should not preclude an FAS diagnosis if all other criteria are present."	Klare Beschreibung von PAE[##] **Expertenkonsens**
DSM-5 (14, 15) §§	**ND-PAE**	Kein Kriterium	Kein Kriterium	**<u>Neurokognitiv</u>, mind. 1 Auffälligkeit:** - Einschränkung des globalen	**Kriterium/ Bestätigt**	"No detailed description of criteria in the DSM-5."

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
				intellektuellen Funktionsniveaus (IQ oder anderer Standardwert bei einer umfassenden entwicklungsbezogenen Einschätzung von 70 Punkten oder weniger) - Einschränkung der Exekutiven Funktionen (z. B. schlechte Planungs- und Organisationsfähigkeit; Inflexibilität: Schwierigkeiten mit Verhaltenshemmung) - Lernschwierigkeiten (z. B. geringere akademische Erfolge als durch das intellektuelle Niveau erwartbar, spezifische Lernbehinderungen) - Einschränkungen des Gedächtnisses (z. B. Probleme kürzlich gelernte Informationen zu erinnern; wiederholt dieselben Fehler machen; Probleme umfangreichere mündliche Instruktionen zu erinnern) - Einschränkungen im visuell-räumlichen Denken (z. B. desorganisierte, schlecht geplante Zeichnungen oder Konstruktionen; Probleme Links und Rechts auseinanderzuhalten) **UND** **<u>Selbstregulation,</u> mind. 1 Auffälligkeit:** - Einschränkung in der Emotionsregulation oder der Regulation von Verhalten (z. B. labile Stimmung, negativer Affekt oder Reizbarkeit, häufige Wutausbrüche) - Aufmerksamkeitsdefizit (z. B.	(> 1 PAE)	"(Expert) Consensus of this criteria are based on 3 major areas of impairment: neurocognition, self-regulation, and adaptive functioning." "These areas of deficit, along with evidence of in utero exposure to PAE, formed the basis of the ND-PAE diagnostic criteria." "Criteria established due to diversity of many do not conduct physical examinations and do not have the capacity to independently obtain neuroimaging studies […] without providing evidence based on clinical studies why criteria shortened." "Criteria for DSM-5 disorders are behavioral-based symptoms that could be applied to case conceptualizations by all mental health professionals. Although this is somewhat dissatisfying to professionals who are used to using these indices

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
				Schwierigkeiten die Aufmerksamkeit zu verlagern, Schwierigkeiten mentale Anstrengung aufrecht zu erhalten) - Beeinträchtigungen der Impulskontrolle (z. B. warten bis man an der Reihe ist, Schwierigkeiten, sich an Regeln zu halten **UND** **<u>Adaptive Funktion,</u> mind. 2 Auffälligkeiten (wobei eine der beiden erstgenannten dabei sein muss):** - Defizite bei der Kommunikation (z. B. verspätetes Erlernen von Sprache, Schwierigkeiten, gesprochene Sprache zu verstehen) - Einschränkung in der sozialen Kommunikation und Interaktion (z. B. übermäßige Zutraulichkeit gegenüber Fremden, Schwierigkeiten soziale Hinweisreize zu verstehen, Schwierigkeiten soziale Konsequenzen zu verstehen) - Beeinträchtigungen bei Fertigkeiten des alltäglichen Lebens (z. B. verspätete Sauberkeit, Nahrungsaufnahme oder Reinlichkeitsverhalten; Schwierigkeiten eine Alltagsroutine aufrecht zu erhalten) - Beeinträchtigungen in motorischen Fähigkeiten (z. B. schlechte Entwicklung der Feinmotorik, verspätetes Erreichen großer motorischer Meilensteine oder andauernder Defizite bei der Gesamtmotorik; Defizite in Koordination und Balance)		in their FASD case conceptualization, individuals with small head sizes or abnormal MRI findings are unlikely to not have functional neurobehavioral consequences associated with these physical alterations." **Expertenkonsens**

Quelle	FASD Form	Wachstums-auffälligkeiten	Faciale Auffälligkeiten	ZNS Auffälligkeiten	PAE	Kommentar und Empfehlungsstärke
				Die Höhe der Funktionseinschränkungen in den 3 Bereichen ist nicht definiert, also keine Festlegung von SD o.ä.		
Young 2016 (16) (England)	**ADHS (ADHD) with associated FASD**	Es sollte routinemäßig nach FASD gescreent werden, wenn ADHS diagnostiziert wurde und umgekehrt sollte nach ADHS gescreent werden, wenn eine Form von FASD festgestellt wurde. Für die Diagnose von ADHS mit FAS sollten die DSM-5 und die ICD-10[$] Kriterien verwendet werden, für alle anderen Diagnosen aus dem FASD-Spektrum sollte die Kanadische LL von 2005 verwendet werden bis die DSM-5 und ICD-11[$$] Kriterien für die Diagnosen weiter spezifiziert wurden. Alkoholkonsum während der Schwangerschaft sollte standardmäßig im Rahmen der ADHS-Diagnostik erhoben werden. Darüber hinaus sollte bei der ADHS-Diagnostik (und Behandlung) auf folgende Warnsignale („red flags“) geachtet werden: - mögliche oder bestätigte Alkoholexposition während der Schwangerschaft - primäres Auftreten des unaufmerksamen Subtypus von ADHD in Verbindung mit einigen („some“) impulsiven Verhaltensweisen - keine Therapieresponse oder vermehrte behaviorale Störungen bei Verschreibung von Methylphenidat - schlechte Therapieresponse auf Psycho Stimulantien bei Kindern mit einem IQ unter 50 - Physische Indikatoren von FAS oder pFAS, einschließlich Wachstumsverzögerungen und/ oder spezifische faciale Merkmale (z. B. verstrichenes Philtrum. Schmale Oberlippe und schmale Lidspalten) - eine mangelhafte Therapiereaktion auf typische behaviorale Interventionen bei ADHS				Nicht bewertet, da nicht unmittelbar FASD

ADHD: Attention Deficit Hyperactivity Disorder; ADHS: Aufmerksamkeitsdefizit-Hyperaktivitätsstörung; AGREE: Appraisal of Guidelines, Research and Evaluation; ARND: Alcohol-Related Neurodevelopmental Disorder; BMI: Body Mass Index; CDC: Centers for Disease Control; DSM: Diagnostisches und Statistisches Manual Psychischer Störungen; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; ICD-10/11: International Classification of Diseases, 10th./11th. Revision; IOM: Institute of Medicine; IQ: Intelligence Quotient; LL: Leitlinie; MRI: Magnetic Resonance Imaging; ND-PAE: Neurodevelopmental Disorders associated with Prenatal Alcohol Exposure, ND-PAE wird bisher nicht in ICD-10 Klassifizierung gelistet, es wird jedoch eine Klassifikation unter „other specified disorders of the CNS“ empfohlen; PAE: Pränatale Alkoholexposition; pFAS: partial FAS; P: Percentile; SA/SD: Standardabweichung/Standard Deviation; SIGN: Scottish Intercollegiate Guidelines Network; SR: Scoping Review; ZNS: Zentrales Nervensystem

*** At risk FASD (in polnischer und kanadischer LL):** keine Diagnose, nur Hinweis, dass Kind zu späterem Zeitpunkt noch einmal evaluiert werden sollte.

**** ARBD (IOM Kriterien)**: Kriterium lässt sich nicht in vorliegenden Säulen abbilden: „Eine oder mehrere wesentliche, spezifische Missbildungen, die in Tiermodellen und in klinischen Studien (mit Menschen) bei pränatalen PAE aufgezeigt wurden.“ „One of more specific major malformations without any neurodevelopmental impairments.”

° Hoyme 2016 (IOM Kriterien) USA: bei bestätigter PAE müssen Wachstums- u. strukturelle Auffälligkeiten nicht vorliegen. Description of 4 Subtypes: FAS: „growth deficiency, with height or weight below the 10th percentile, facial characteristics (e.g., small eyes, smooth philtrum, and thin upper lip), CNS damage (structural, neurological, and/or functional impairment)“; partial FAS:

„some but not all of the physiological symptoms of FAS“; ARND: Patients do not present with any facial deformities but have symptoms of CNS damage associated with FAS; ARBD: „physical defects, such as malformations of the heart, bone, kidney, vision, or hearing systems“; ARND in Kindern < 3 Jahre schwierig zu diagnostizieren → Gefahr, dass Therapie zu spät eingeleitet wird.

 # Polnische LL: verwendet nicht den Begriff ARND, sondern ND-PAE; Kriterien ähnlich, aber etwas strenger (vergleiche 4-Digit Code).

CDC Kriterien: PAE sehr klar beschrieben: Confirmed PAE (…requires documentation of the alcohol consumption patterns of the birth mother during the index pregnancy based on clinical observation; self-report; reports of heavy alcohol use during pregnancy by a reliable informant; medical records documenting positive blood alcohol levels, or alcohol treatment; or other social, legal, or medical problems related to drinking during the index pregnancy.); unknown PAE (…indicates that there is neither a confirmed presence nor a confirmed absence of exposure. Examples include: the child is adopted and prenatal exposure(s) is unknown; the birth mother is an alcoholic, but confirmed evidence of exposure during pregnancy does not exist; and conflicting reports about exposure exist that cannot be reliably resolved.); confirmed absence of PAE (…. in very rare instances, there will be confirmed absence of exposure. Documentation that the birth mother did not drink any amount of alcohol from conception through birth would indicate that the FAS diagnosis is not appropriate. This typically implies that the birth mother knew the date of conception (e.g., a planned pregnancy) and did not consume alcohol from that day forward, or she was prevented from drinking for some reason (e.g., incarceration)).

§ Entwicklung der kanadischen LL: “Canadian Guidelines for Diagnosis was originally established in conjunction and consultation with the CDC, the IOM Criteria and 4-Digit Code. IOM terminology was used, and the 4-Digit approach to describing, assessing, and measuring features indicative of FAS was adopted. The guidelines recommend review by a multidisciplinary team, a neurobehavioral assessment, analysis and documentation of maternal alcohol history, and a differential diagnosis.“ *Guideline update:* „The use of FASD as a diagnostic term. The inclusion of special considerations for diagnosing FASD in infants, young children, and adults. The deletion of “growth” as a diagnostic criterion. The addition of a new “at-risk” category for FASD. Revision and refinement of brain domains evaluated in the neurodevelopmental assessment“. **Kanadische LL, Mikrozephalie:** Mikrozephalie ist eigentlich nur dann relevant, wenn Kinder zu jung für die Durchführung entwicklungsneurologischer Tests sind. Dann darf beim Vorliegen aller drei auffälligen Gesichtsmerkmale UND Mikrozephalie die Diagnose FASD mit sentinal facial features vergeben werden. Bei Kindern, bei denen eine Testung möglich ist, sind die Einschränkungen in mindestens 3 der genannten Domänen entscheidend**.** *Lt. LL Autoren geht das Vorliegen aller 3 facialen Merkmale und Mikrozephalie praktisch immer auch mit entwicklungsneurologischen Auffälligkeiten einher.* **Kanadische LL, Wachstum:** „[…] the importance of growth in the overall presentation of alcohol-related effects has been debated. The predictive value of growth deficiency especially in the absence of documented PAE has been queried. Evidence (O’Leary 2009 (17)), plus clinical experience suggest that growth is neither sensitive nor sufficiently specific to indicate an FASD diagnosis. Other contemporary diagnostic approaches have relaxed the criterion for growth deficiency in making the diagnosis, although not removing it entirely. Following an analysis of historical clinical reports, basic science, and clinical research, the committee supported the recommendation to remove growth as a diagnostic criterion.“

Ergebnisse bisheriger Studien zu Zusammenhängen zwischen PAE und Wachstumsauffälligkeiten geben kein klares Bild, manche Studien fanden Zusammenhänge, andere nicht. In der Studie von O’Leary 2009 (17) fand sich zunächst ein Zusammenhang zwischen geringem Geburtsgewicht und moderatem oder hohem Alkoholkonsum, aber dieser Zusammenhang verschwand, wenn für Tabakkonsum kontrolliert wurde. Das Fazit von O’Leary 2009: „There was no association between alcohol consumption during pregnancy and SGA infants after taking into account smoking status.“ Allerdings betonen sie, dass die Stichprobe bei Schwangeren mit hohem Alkoholkonsum so gering war, dass keine abschließenden Schlussfolgerungen gezogen werden können. Astley 2016 (18) hat eine Studie durchgeführt, um diesen „approach“ zu wiederlegen.

§§ DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition): „ND-PAE describes the range of neuro-disabilities associated with prenatal alcohol exposure (PAE). ND-PAE can be diagnosed regardless of the presence or absence of the physical effects of PAE. Confirmation of maternal alcohol consumption is required. Although ND-PAE is mentioned under ‘other specified neurodevelopmental disorder’, no diagnostic criteria or detailed description is provided in the DSM-5. Further reference is made under ‘conditions needing further study’. The proposed criteria for ND-PAE do not include criteria for recognizing facial deformities characteristic of more severe cases, nor do they recognize FASD subtypes. „The proposed criteria emphasize psychometric measurements over features that might arguably be attributed to familial genetics (e.g., head circumference, facial dysmorphic features, and body length and weight).“ DSM-5 requires

confirmation PAE: above “minimal” levels (>13 drinks/month and >2 drinks/occasion). This threshold was suggested in reflection of a high base rate of drinking amongst women of child-bearing years, as a minimum level, to avoid over-use of diagnosis.

$ ICD-10: P04.3 - New-born (suspected to be) affected by maternal use of alcohol (excludes FAS): Q86.0 - FAS (dysmorphic) *no further description offered for this specific code; F06.30 - Mood disorder due to known physiological condition, unspecified; P00.4 - New-born (suspected to be) affected by maternal nutritional disorders; P01.9 - New-born (suspected to be) affected by maternal complication of pregnancy, unspecified G93.4 - Encephalopathy, other and unspecified (static); G96.8 - Other specified disorders of central nervous system; G96.9 - Disorder of central nervous system, unspecified.

$$ ICD-11: LD2F.00 Foetal alcohol syndrome: Fetal alcohol syndrome is a malformation syndrome caused by maternal consumption of alcohol during pregnancy. It is characterized by prenatal and/or postnatal growth deficiency (weight and/or height <10th percentile); a unique cluster of minor facial anomalies (short palpebral fissures, flat and smooth philtrum, and thin upper lip) that presents across all ethnic groups, is identifiable at birth, and does not diminish with age. Affected children present severe central nervous system abnormalities including: microcephaly, cognitive and behavioral impairment (intellectual disability, deficit in general cognition, learning and language, executive function, visual-spatial processing, memory, and attention).

Neurodevelopmental syndrome due to prenatal alcohol exposure (6A0Y): no detailed description found, “This category is an 'other specified' residual category.”

Bewertung der Leitlinien nach DELBI (https://www.Leitlinien.de/hintergrund/Leitliniengrundlagen#delbi)

(Domäne 8 des DELBI Instrument wurde nicht berücksichtigt, da redundant)

Erfüllt + / Nicht erfüllt - / Unklar ?

Kritische Bewertung der Leitlinien und diagnostischen Systeme (eine Gesamtbewertung ist in dieser Bewertung nicht vorgesehen)

	Dänische LL	Polnische LL	USA / IOM Kriterien	Kanadische LL	Australische LL	Schottische LL	4-Digit Code	CDC	DSM-5
Domäne 1: Geltungsbereich und Zweck									
1. Das / die Gesamtziel(e) der LL ist / sind eindeutig beschrieben	+	+	+	+	Basiert auf kanadische LL	Basiert auf kanadische LL	+	+	-
2. Die in der LL behandelte(n) gesundheitsrelevante(n) Frage(n) ist (sind) eindeutig beschrieben	+	+	+	+			+	+	-
3. Die Zielpopulation der LL ist eindeutig beschrieben	+	+	+	+			+	+	-
Domäne 2: Beteiligung von Interessengruppen									
4. Die Entwicklergruppe der LL schließt Mitglieder aller relevanten Berufsgruppen ein	?	+	+	+			?	?	?
5. Die Ansichten und Präferenzen der Zielpopulation (z. B. Patienten, Bevölkerung) wurden ermittelt	-	+ (zum Teil)	?	?			-	-	-
6. Die Anwenderzielgruppe(n) der LL ist (sind) eindeutig beschrieben	?	+	?	+			-	-	-
7. Die LL wurde in einer Pilotstudie von Mitgliedern der Anwenderzielgruppe getestet	-	+	?	?			-	-	-
Domäne 3: Genauigkeit (methodische Exaktheit) der LL-entwicklung									
8. Es wurde systematisch nach Evidenz gesucht.	-	-	-	+			+	+	-
9. Die Kriterien für die Auswahl der Evidenz sind eindeutig beschrieben	-	?	-	+			?	?	-
10. Das methodische Vorgehen bei der Formulierung der Empfehlungen ist eindeutig beschrieben	-	?	?	+			-	-	-
11. Der gesundheitliche Nutzen, Nebenwirkungen und Risiken wurden bei der Formulierung der Empfehlungen berücksichtigt	-	?	?	+			-	-	-
12. Die zugrunde liegende Evidenz kann den Empfehlungen eindeutig zugeordnet werden	-	?	?	+			-	-	-
13. Die LL wurde vor ihrer Veröffentlichung durch externe Experten begutachtet	?	?	?	+			+	+	+

14. Es existiert ein Verfahren zur Aktualisierung der LL	-	-	-	-			-	-	-
Domäne 4: Klarheit der Gestaltung									
15. Die Empfehlungen sind spezifisch und eindeutig	+ (zum Teil)	+ (zum Teil)	+ (zum Teil)	+			+ (zum Teil)	+ (zum Teil)	+ (zum Teil)
16. Die unterschiedlichen Alternativen des Gesundheitsproblems sind eindeutig dargestellt	-	-	-	-			-	-	-
17. Die Schlüsselempfehlungen sind einfach zu finden	+	+	+	+			+	+	+
18. Es existieren Instrumente bzw. Materialien, die die Anwendung der LL unterstützen	+	+	+	+ (zum Teil)			+	+	□
Domäne 5: Anwendbarkeit									
19. Mögliche förderliche und hinderliche Faktoren für die Anwendung der LL werden beschrieben	-	-	-	-			-	-	-
20. Die möglichen finanziellen Auswirkungen der LL-empfehlungen wurden berücksichtigt	-	-	-	-			-	-	-
21. Die LL nennt Messgrößen für die Bewertung der Prozess- und / oder Ergebnisqualität der LL	-	-	-	-			-	-	-
Domäne 6: Redaktionelle Unabhängigkeit									
22. Die finanzierende Organisation hat keinen Einfluss auf die Inhalte der LL genommen	□	□	□	+			□	□	□
23. Interessenkonflikte der Mitglieder der Entwicklergruppe wurden dokumentiert und berücksichtigt	□	□	□	+			□	□	□
Domäne 7: Anwendbarkeit im deutschen Gesundheitssystem									
24. Es liegen Empfehlungen zu präventiven, diagnostischen, therapeutischen u. rehabilitativen Maßnahmen vor	-	-	-	□			-	-	-
25. Es existieren Angaben, welche Maßnahmen unzweckmäßig, überflüssig oder obsolet erscheinen	-	-	-	-			-	-	-
26. Die klinische Information der LL ist so organisiert, dass der Ablauf nachvollzogen wird	-	-	-	+			-	-	-

27. Es ist eine Strategie für die einfache Zugänglichkeit und für die Verbreitung der LL dargelegt	-	-	-	+			-	-	-
28. Ein Konzept zur Implementierung wird beschrieben	-	-	-	-			-	-	-
29. LL enthält Beschreibung zum methodischen Vorgehen				+					

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Übersicht über die systematischen Reviews

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
Poitras 2017: Fetal Alcohol Spectrum Disorders: A Review of Diagnostic Test Accuracy, Clinical and Cost-effectiveness of Diagnosis and Treatment, and Guidelines								
Poitras 2017 (1)§	Canada	04/17	SRs (3) DTA studies (10) Guideline (1) + studies evaluating clinical effectiveness (1)	Individuals of any age with suspected or diagnosed FASD	- Decision tree model - Second trimester fetal ultrasound measures - Regression model developed from a test battery - Fetal Alcohol Syndrome Diagnostic Checklist - Computer-assisted morphometric facial analyses - Narrative analysis (not further defined)	**<u>Various clinical diagnoses with "unknown accuracy":</u>** - 4-Digit Code - Structural features and growth deficiency consistent with the revised IOM criteria - Dysmophological examination at birth and neurobehavioural evaluation at age 6 and/or 12 months - Astley Lip-Philtrum Guide - Dysmorphology and behaviour problems (with confirmation of PAE) - Clinical diagnosis (based on unspecified criteria) **<u>Case-control study:</u>** PAE history obtained through retrospective maternal report, social service, or legal or medical records	"Overall, there was insufficient evidence to suggest an optimal diagnostic test for FASD, and there remains no gold standard for FASD diagnosis." "One evidence-based Canadian guideline was identified providing recommendations regarding the diagnosis of FASD. Based on predominantly high-quality evidence, the guidelines provide strong recommendations for multi-disciplinary diagnosis based on criteria related to facial features, PAE, and neurodevelopmental effects."	Literature search described? Yes Study selection criteria described? Yes Quality assessment performed? Yes Reporting of diagnostic study sufficient? No (missing data such as DTA effect estimates and number of participants) Selective reporting in favour of Canadian guideline (2) **LoE: Systematic review, Level 2**

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
Brown 2019: This review analyses discrepancies in existing diagnostic tools for FASD, and the repercussions these differences have on research, public health, and government policy								
Brown 2019 (3) [10] [10]	Canada	NR	unclear	Individuals of any age suspected or having, or diagnosed with FASD	**Indextest / Comparator test not defined** - IOM criteria (developed in 1996, up-date 2005 and 2016) - CDC 2004 guideline (only FAS) - 4-Digit Code (developed in 1997, update 1999, 2004) - Canadian Guidelines (2005, reviewed 2015) - DSM-5 (ND-PAE) (2013) - ICD-10		**<u>Physical (facial) features (for FAS)</u>** 4-Digit Code: requires 3 facial features Canadian guidelines: requires 3 facial features CDC guidelines: requires 3 facial features Hoyme (modified IOM criteria): requires 2 facial features **<u>Mental disorders</u>** DSM-5 criteria: ND-PAE neurocognitive impairments (but not the presence/absence of dysmorphic physical symptoms) Brown 2019 also refers to the review of Del Campo 2017 (4) that argues "that **the physical (facial) features are the only substitute for PAE** and that the pattern of physical features of FAS is considered specific enough that a diagnosis of FAS can be established (in the absence of confirmation PAE). But it is also acknowledged that physical features may only be found in the most severe subset of patients with FASD (=FAS)." Brown 2019 concludes: "objective measurement of the timing and level of PAE is a key to bride these gaps; however, there is conflicting or limited evidence to support the use of existing tools."	Literature search described? Yes Study selection criteria described? No Quality assessment performed? No Reporting of diagnostic study sufficient? No **LoE: Systematic review, Level 3 (low quality)**
Lim 2022: The aims of this systematic review are to identify FASD screening tools and examine their performance characteristics								
Lim 2022 (5) [11] [11]	Australia	01/21	16 (comprising 5 FAS,	Individuals with FASD or PAE	**Indextest / Comparator test not defined** <u>FAS Screening Tools (N=5)</u>		**<u>FAS (studies published between 1995-2003)</u>** **1) Tools linked to** IOM criteria, "Gestalt method", 4-Digit Code => Main focus of these	Literature search described? Yes

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
			7 FASD screening tools)		- FAS Screening Tool - Craniofacial Measurements - FAS Photographic Screening Tool - FAS Diagnostic Checklist - FAS Screen <u>FASD Screening Tools (N=7)</u> - Eye movement behavior tasks) - FASD brief Checklist (adults) - FASD risk assessment question (adults) - FASD Screening and Referral Tool for Youth Probation Officers (adults) - Life History Screen – 11 items (adults) - Neurobehavioral Screening Test - Tally reference errors in narrative tasks		tools on facial features with Se 89-100% and Sp 72-100% to identify FAS in individuals at risk of FAS) **2) Craniofacial Measurements:** Moore (2001) (6): Se 100%, Sp 100% **3) FAS Photographic Screening Tool:** Astley (1996) (7) Se 100%, Sp 100% **4) FAS Diagnostic Checklist:** Burd (2003) (8): Se 89%, Sp 72% **5) FAS Screen:** Burd (1999) (9): PPV 9, NPV 100; Poitra (2003) (10=: Se 100%, Sp 94-95% **<u>FASD (studies published between 2005 and 2020)</u>** **1) Tools linked to** IOM criteria, Canadian Guideline and 4-Digit Code: Se 100%, Sp 89% **2) FASD eye movement behavior tasks** Tseng (2013) (11), Zhang (2019) (12): Se 73-77%, Sp 79-91%, time to complete: 17-20 min **3) Neurobehavioral Screening Test** Breiner (2013) (13), LaFrance (2014) (14), Nash (2006) (15) and (2011) (16): Se 63-98%, Sp 42-100% **4) Tally reference errors in narrative tasks** Thorne (2017) (17): Se 54%, Sp 96%	Study selection criteria described? Yes Quality assessment performed? Yes (QUADAS-2) Reporting of diagnostic study sufficient? No (authors report Se and Sp, but it's not always clear to which study they refer to) **LoE: Systematic review, Level 2**

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
							"FAS Screening Tools demonstrated high accuracy in identifying individuals at risk of FAS while FASD Screening Tools demonstrated limited accuracy in identifying individuals at risk of FASD. […] Call for biomarkers […]"	
Maya-Enero 2021: Neurocognitive and behavioral profile of FASD								
Maya-Enero 2021 (18)	Spain	NR	NR	Diagnostic tools and criteria of FASD, especially neurocognitive and behavioural profile	**Indextest / Comparator test not defined** **I. IOM criteria and comparison of guidelines** **II. Biomarkers to identify PAE** **III. Differential diagnostic and neurocognitive/neuropsychological profile of FASD**		**I. Overview IOM criteria and other guidelines** Not presented here, because we established own overview of guidelines for this update of the S3-LL**. Moreover, the overview presented in this review was not conclusive.** **II. Biomarkers to identify PAE** „Detection of biomarkers of alcohol in biological matrices allows diagnosis of PAE. The diagnosis of alcohol use during pregnancy is based on the detection of fatty acid ethyl esters or ethyl glucuronide (EtG) in placental tissue, meconium or maternal hair or nails. […] The presence of EtG in maternal hair allows retrospective identification of alcohol exposure in the entire pregnancy period, and detection in meconium exposure in the second and third trimester of gestation" **III. Differential diagnostic and neurocognitive/neuropsychological profile (FASD):** „Phenotypic diagnostic (dysmorphic features, abnormal growth) are easy to identify, but neurocognitive and behavioural features are shared by other neurodevelopmental and psychiatric disorders (attention-deficit	Literature search described? No Study selection criteria described? No Quality assessment performed? No Reporting of diagnostic study sufficient? No (this is more like an overview; there are inconsistency between presented tables and information provided in the text) **LoE: Systematic review, Level 4 (very low quality)**

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
							hyperactivity, autism spectrum disorder, global developmental delay, intellectual disability, oppositional-defiant disorder, conduct disorder, mood disorders, reactive attachment disorder, post-traumatic stress, sleep disturbances, substance use, schizophrenia).“	
Grubb 2021: Analyses of available evidence on FASD screening tools and approaches across age groups and settings (20 tools, 45 studies considered).								
Grubb 2021 (19)	Canada (SR)	05/20	45	Children (>5y.), adolescents, adults #	**Neurobehavioral Screening Tool (Nash 2006)** (15) (5 case-control studies published before 2015, 1 cross-sectional study published in 2020)		**Outcome / Indication of Interest: FASD** **FASD vs. control (5 case-control studies)** Se (50-98%), Sp (42-100%) **Cross-sectional study from Patel 2020** “Of those who screened positive, positive predictive value=78%”	Literature search described? Yes Study selection criteria described? Yes Quality assessment performed? Yes (QUADAS-2 and GRADE assessment but with very limited information) Reporting of diagnostic study sufficient? Partly (not always clear what is the reference test and how reported Se and Sp should be interpreted in
					FASD screening program (1 cross-sectional study published in 2001)		**Outcome / Indication of Interest: FASD** „Nearly all eligible children were screened when consent was passive compared with 25% screened when consent was active; 40% who screened positive and attended a diagnostic clinic were identified as having an alcohol-related condition.“	
					FAS Screen (2 cross-sectional studies published before 2004)		**Outcome / Indication of Interest: FAS and pFAS** Se (100% (in both studies), Sp (94-95%)	

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
					Children's Aid Society of Toronto screening tool (1 case-control study published 2016)		**Outcome / Indication of Interest: FASD** "One item differed between the FASD and control groups. Use of the tool was unsupported"	terms of test comparison) **LoE: Systematic review, Level 1-2**
					FASD Screening and Referral Tool for Youth Probation Officers (1 cross-sectional study published in 2018 and 1 published in 2010)		**Outcome / Indication of Interest: FASD** "High rate of incomplete screens limited evaluation"	
					Red Flag Method (1 cross-sectional study published in 2018)		**Outcome / Indication of Interest: FASD** "70.9% agreement on cases between the Red Flag Method and the FASD Screening and Referral Tool for Youth probation officers"	
					Measurements based on facial features (3 studies)		**Outcome / Indication of Interest: FAS** Astley and Clarren (1995) (20) cross-sectional study: Se (100%), Sp (89%) **Outcome / Indication of Interest: Facial features** Lee (2016) (21) cross-sectional study in high risk setting in South Korea:	
							"Of those who screened positive, 14.9% met criteria for facial features of FAS, 50.6% were deferred, and 34.5% were classified as No FAS" **Outcome / Indication of Interest: FAS and pFAS and PAE** Moore (2001) (6) cases (PAE)-controls (non-PAE) wide age range up to over 30 y. of age, N=131: Se (98%), Sp (90%)	
					Facial Photographic Analysis Software (2D		**Outcome / Indication of Interest: FAS**	

Year published	Country*	Last search	Studies (N)	Population	Diagnostic systems/test evaluated		Outcomes reported	Critical Appraisal of SR modified after AMSTAR° and LoE after OCEBM†
					Indextest	Comparator test		
					images) (3 studies published before 2015))		Astley and Clarren (1996) (7) case-control study: Se (100%), Sp (100%) **Outcome / Indication of Interest: FAS** Astley (2002) (22) cross-sectional study: Se (100%), Sp (99.8%) **Outcome / Indication of Interest: Short PFL and philtrum smoothness** Avner (2014) (23) cross-sectional study: Se (100%), Sp (64%)	
					Emerging Biomarker Approaches: Serum Protein Analysis (2 studies), Dermatoglyphics (2 studies), Functional Near-Infrared Spectroscopy(1 Study), Respiratory Sinus Arrhythmia (1 study), 3D Facial Photographic Analysis(6 studies), Eye Movement Control (7 studies), DNA Methylation (1 study)			
					Overall Conclusion of diagnostic tools „Several tools and approaches for identifying FASD in children, adolescents, and adults, designed for use in specific settings are currently available for use by a range of professionals. Some tools show early potential promise for use in identifying individuals who may have PAE or FASD. However, limited overall evidence regarding the validity, reliability, and utility of screening tools and approaches, combined with methodological limitations across studies to date, render it difficult to consider any individual tool or approach as being psychometrically established.“			

AMSTAR: Assessing the Methodolgoical Quality of Systmeatic Reviews (https://amstar.ca/Amstar_Checklist.php); CDC: Centers for Disease Control and Prevention (guidelines); DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition); DTA: Diagnostic Test Accuracy; EtG: Ethyl Glucuronide; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; GRADE: Grading of Recommendations, Assessment, Development and Evaluation; ICD-10: International Classification of Diseases, 10th./11th. Revision; IOM: Institute of Medicine (criteria); LoE: Levels of Evidence ND-PAE: Neurobehavioral Disorder associated with Prenatal Alcohol Exposure; NPV: Negative Predictive Value; NR: Not Reported; OCEBM: Oxford Centre for Evidence-Based Medicine (2011 Levels of Evidence); PAE: Prenatal Alcohol Exposure; pFAS: partial FAS; PFL: Palpebral Fissure Length; PPV: Positive Predictive Value; QUADAS 2: Quality Assessment of Diagnostic Accuracy Studies, revised; Se: Sensitivity; Sp: Specificity; SR: Systematic Review

* Country of corresponding review author.

° Die Bewertung erfolgte in Anlehnung an das Manual Cochrane Deutschland, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften - Institut für Medizinisches Wissensmanagement. „Bewertung von systematischen Übersichtsarbeiten: ein Manual für die Leitlinienerstellung“. 1. Auflage 2017. Verfügbar: Cochrane Deutschland: http://www.cochrane.de/de/review-bewertung-manual, AWMF: http://www.awmf.org/leitlinien/awmf-regelwerk/ll-entwicklung.html.

† Die Bewertung erfolgte in Anlehnung an die Empfehlungen des Oxford Centre for Evidence-Based MEdicine (OCEBM) (2011 Levels of Evidence) Critical Appraisal tools — Centre for Evidence-Based Medicine (CEBM), University of Oxford.**§ Poitras 2017:** also conducted clinical effectiveness and cost-effectiveness assessment. “Limited evidence […] suggested that multi-dimensional treatment strategies (that include physical, mental health, behavioural, cognitive, and/or pharmacologic components) that are individually tailored for patients may be clinically effective.”

 # Grubb 2020: Screening Tools bzw. Studien, die nur Erwachsene betrachten, wurden nicht abgebildet.

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Studien zur Genauigkeit von Diagnosetests – Merkmale

Reference	Study design	Country, Setting	Population			Diagnostic systems compared	
			Patient population	N	Age (years) mean±SD	Indextest (diagnostic systems)	Reference test (patient records)
Comparison of different diagnostic systems, N=3 studies							
Astley 2017 (1)	cross-sectional (analysis of patients records, retrospective)	USA, Seattle (Washington) patient records from 1993-2012 reassessed	"The records of 1392 patients were drawn from 1522 consecutive patients that received an FASD diagnostic evaluation at the FASDPN using **the FASD 4-Digit Code** (2)."	1392 (total)	0-19+ (range) (19+: 4%)	(i) 4-Digit Code 2004 (2) (ii) Hoyme 2016, IOM Criteria (3)	Patient records
Astley Hemingway 2019 (4)	cross-sectional (analysis of patients records, retrospective)	USA, Seattle (Washington) patient records from 1993-2012 reassessed	"The records of 1392 patients were drawn from 1522 consecutive patients that received an FASD diagnostic evaluation at the FASDPN using the **FASD 4-Digit Code** (2)."	1392 (total)	0-19+ (range) (19+: 4%)	(i) 4-Digit Code 2004 (2) (ii) Hoyme 2016, IOM Criteria (3) (iii) Canadian Guideline 2016 (5) (iv) Australian Guideline 2016 (6)	Patient records
Coles 2016 (7)	cross-sectional (analysis of patients records, retrospective)	USA, Atlanta (Georgia) patient records from 1995-2011 reassessed	"Records of consecutively registered patients applying for a multidisciplinary evaluation (pediatric, social, psychological) at a university-based clinic treating alcohol and drug-exposed children were abstracted and diagnostic criteria for all **5 systems** were applied."	1581 (total)	0-21 (range) 6.06±3.27 (age at diagnosis 5.98±3.99)	(i) 4-Digit Code 2000 (8) (ii) Hoyme 2005, IOM Criteria (9) (iii) CDC and FAS Task Force 2004 (10) (iv) Emory FAS Clinic 2000 (11, 12) (v) Canadian Guideline 2005 (13)	Patient records

Studien zur Genauigkeit von Diagnosetests – Ergebnisse

Reference	Disease to identify	4-Digit Code (Astley)		IOM criteria (Hoyme)		Emory-2000	CDC guideline	Canadian guideline		Australian guideline	Overall findings
		2004 (2)	**2000** (8)	**2016** (3)	**2005** (3)	**2000** (11, 12)	**2004** (10)	**2016** (5)	**2005** (13)	**2016** (6)	
Astley 2017 (1)	FASD*	1092/1392 (78.4%)	-	558/1392 (40.1%)	-	-	-	-		-	**FASD (4-Digit Code: higher prevalence):** 35% (379/1092) of the patients who received a diagnosis of FASD using the 4-Digit Code did not receive a diagnosis of FASD using the Hoyme system. They all had confirmed PAE (e.g., birth mother reported drinking throughout the pregnancy), but their record of PAE did not meet the more stringent criteria by Hoyme (e.g., intoxication confirmed by BAC; positive biomarker test; positive outcome on a validated screening tool like the T-ACE (Tolerance, Annoyance, Cut down, Eye opener) or AUDIT; or number of drinks/ week or occasion reported) or the level of PAE (e.g., 6 drinks/week for 2 weeks or 2 drinks/occasion on 2 occasions). **FAS (IOM: higher prevalence):** The prevalence of FAS (6%; n=89) and pFAS (15%, n=208) generated by the Hoyme system was 3-to 4-fold greater than the prevalence of FAS and pFAS generated by the 4-Digit Code. In some cases, patient diagnosed with **severe FAS (4-Digit Code) did not receive a diagnosis under the umbrella of FASD using the Hoyme system** because the PAE level reported directly by the birth mother was not high enough to meet the Hoyme criteria (6 drinks/week for 2 weeks during pregnancy). **<u>Diagnostic concordance:</u>** Diagnostic concordance was observed in 38% (528/1392). Diagnostic discordance was observed in 62% (864/1392). The 2 systems ruled-out FASD in 239 patients and both rendered the same diagnosis under the umbrella of FASD in 289 cases. The discordance ranged from subtle differences (e.g. patients received a diagnosis of FAS by 1 system and pFAS by the other) to marked contrasts (e.g., the patient received a diagnosis of FAS by 1 system and no FASD
	FAS	28/1392 (2.0%)	-	89/1392 (6.4%)	-	-	-	-		-	
	pFAS	53/1392 (3.8%)	-	208/1392 (15.0%)	-	-	-	-		-	
	SE-PAE§	388/1392 (27.9%)	-	-	-	-	-	-		-	
	ND-PAE§	623/1392 (44,8%)	-	-	-	-	-	-		-	
	ARND	-§	-	261/1392 (18.8%)	-	-	-	-		-	
	FASD* (subset < 3 y.)	98/141 (70.0%)	-	21/141 (14.9%)	-	-	-	-		-	
	FAS (subset < 3 y.)	7/141 (5.0%)	-	10/141 (7.1%)	-	-	-	-		-	
	pFAS (subset < 3 y.)	4/141 (2.8%)	-	11/141 (7.8%)	-	-	-	-		-	
	SE-PAE (subset < 3 y.)	29/141 (20.6%)	-	-	-	-	-	-		-	
	ND-PAE (subset < 3 y.)	58/141 (41,1%)	-	-	-	-	-	-		-	
	ARND (subset < 3 y.)	-§	-	does not permit a diagnosis < 3 y.	-	-	-	-		-	

Reference	Disease to identify	4-Digit Code (Astley)		IOM criteria (Hoyme)		Emory-2000	CDC guideline	Canadian guideline		Australian guideline	Overall findings
		2004 (2)	**2000** (8)	**2016** (3)	**2005** (3)	**2000** (11, 12)	**2004** (10)	**2016** (5)	**2005** (13)	**2016** (6)	
											diagnosis by the other).
Astley Hemingway 2019 (4) **	FASD	1094/1392 (78.6%)	-	613/1392 (44.0%)	-	-	-	226/1392 16.2%)	-	397/1392 28.5%	**<u>Prevalence of FASD diagnostic outcomes by system:</u>** The proportion of patients diagnosed with **FAS or FASD** varied significantly across the systems: 4-Digit 2.1% (FAS) and 79% (FASD); Australian 1.8% and 29%; Canadian 1.8% and 16%; Hoyme 6.4% and 44%. Even though the proportion of patients diagnosed with FAS (1.8%-2.1%) by the 4-Digit, Canadian and Australian systems was comparable, the patient population that made up the 2% within each system were not comparable. **Subset:** The distribution of diagnoses also varied substantially across the four systems among the subset of patients <6 years of age at the time of diagnosis. **<u>Diagnostic concordance:</u>** Very little diagnostic concordance was observed across systems: Of the 1,392 patients, 1,138 (82%) were diagnosed with FASD by at least 1 of the 4 systems.
	FAS (4-Digit Code, IOM), FASD with facial features (Canadian and Australian guideline)$	29/1392 (2.1%)	-	89/1392 (6.4%)	-	-	-	25/1392 (1.8%)	-	25/1392 (1.8%)	
	No FASD (includes at risk$$)	299/1392 (21.4%)	-	779/1392 (56.0%)	-	-	-	1166/1392 (83.8%)	-	995/1392 (71.5%)	

Reference	Disease to identify	4-Digit Code (Astley)		IOM criteria (Hoyme)		Emory-2000	CDC guideline	Canadian guideline		Australian guideline	Overall findings
		2004 (2)	**2000** (8)	**2016** (3)	**2005** (3)	**2000** (11, 12)	**2004** (10)	**2016** (5)	**2005** (13)	**2016** (6)	
	FASD (subset < 6 y.)	346/455 (76%)	-	159/455 (35.0%)	-	-	-	51/455 (11.2%)	-	94/455 (20.7%)	In contrast, only 152 (11%) were diagnosed with FASD by all 4 systems. Of the 107 (8%) diagnosed with FAS by at least 1 of the 4 systems, only 12 (1%) were diagnosed FAS by all 4 systems. Of the 1,392 patients, concordant diagnoses (including those being classified as "**Not FASD**") were as follows: 4-Digit vs.. Canadian: 31%; 4-Digit vs. Hoyme: 38%; 4-Digit vs. Australian: 45%; Canadian vs. Hoyme 39% Canadian vs. Australian: 82%.
	FAS (4-Digit Code, IOM), FASD with facial features (Canadian and Australian guideline)[$] **(subset < 6 y.)**	15/455 (3.3%)	-	35/455 (7.7%)	-	-	-	13/455 (2.9%)	-	13/455 (2.9%)	
	No FASD (includes at risk[$$]) **(subset < 6 y.)**	109/455 (24.0%)	-	296/455 (65.1%)	-	-	-	404/455 (88.8%)	-	362/455 (79.6%)	
Coles 2016 (7) [§§]	FAS	-	4/1581 (0.3%)	-	193/1581 (12.2%)	217/1581 (13.7%)	75/1581 (4.7%)	-	29/1581 (1.8%)	-	**<u>Agreement Among Systems</u>** **FAS:** […] the CDC system shows fair to moderate agreement with the Canadian (0.506), Hoyme (0.407), and Emory-20 (0.329) systems and slight agreement with the 4-Digit Code (0.097). The Emory-20 and the Hoyme systems show moderate agreement (0.535), while the Canadian system shows only "slight" agreement with all the systems except the CDC. The 4-Digit Code shows only slight agreement with other systems. **FASD vs. no diagnosis:** Agreement between the 4-Digit Code, Hoyme, and the Emory-20 system is "moderate", while the Canadian system is in the "fair" to "moderate range. The greatest agreement is between the Emory and 4-Digit Code, while the least is between the Canadian and the Hoyme systems ("fair").
	pPFAS	-	205/1581 (13.0%)	-	361/1581 (22.8%)	255/1581 (16.1%)	does not permit a diagnosis	-	163/1581 (10.3%)	-	

Reference	Disease to identify	4-Digit Code (Astley)		IOM criteria (Hoyme)		Emory-2000	CDC guideline	Canadian guideline		Australian guideline	Overall findings
		2004 (2)	**2000** (8)	**2016** (3)	**2005** (3)	**2000** (11, 12)	**2004** (10)	**2016** (5)	**2005** (13)	**2016** (6)	
	ARND	-	384/1581 (24.3%)	-	388/1581 (24.5%)	252/1581 (15.9%)	does not permit a diagnosis	-	206/1581 (13.0%)	-	**Agreement across FASD spectrum:** When the diagnostic outcomes are considered individually, as FAS, pFAS, "ARND," or no Diagnosis, agreement is lower. **Concordance of specific criteria among systems:** **Growth:** […] growth was found concordant at an "almost perfect" level, […]. **Facial (physical) features:** […] "no agreement" between 4-Digit Code and the Hoyme and Emory systems; "almost perfect agreement" between the Canadian and the CDC systems. […] discordance among the other systems was not expected, as they all rely on occurrence of the same 3 facial features (PFL, philtrum, thinned upper lip). Absence of norms for children under 6 y. contribute to discrepancies. **Neurobehavioral criteria:** […] systems for neurobehavior showed significant discrepancies. This criterion is defined differently among systems and agreement ranges "slight" between the Canadian, Hoyme systems and CDC and Hoyme systems to a high between the Emory and CDC systems and between the Canadian and 4-Digit Code (both in the "moderate" range). **PAE:** In all systems, knowledge of alcohol use greatly increased diagnosis of FASD.
	No FASD diagnosis	-	988/1581 (62.5%)	-	639/1581 (40.4%)	857/1581 (54.2%)	1506/1581 (95.3%)	-	1183 (74.8%)	-	

ARND: Alcohol-Related Neurodevelopmental Disorder; AUDIT: Alcohol Use Disorders Identification Test; BAC: Blood Alcohol Concentration; CDC: Centers for Disease Control and PreventionEM; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; FASDPN: (University of Washington) Fetal Alcohol Syndrome Diagnostic & Prevention Network; IOM: Institute of Medicine; ND-PAE: Neurobehavioral disorder associated with prenatal alcohol exposure; PAE: Prenatal Alcohol Exposure; pFAS: partial FAS; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies, revised; SD: Standard Deviation; SE-PAE: Static Encephalopathy associated with Prenatal Alcohol Exposure

Astley 2017 (1) / 2019 (4): "All patients with one or both birth parents African American (130 of the 1,522) were excluded from the study because it was unclear which PFL normal growth chart to use for African Americans when applying the IOM criteria (3) […]. Historically, all records resulting from each patient's FASD diagnostic evaluation have been entered into a research database since 1992 […]. Patients' records include the following standardized 4-Digit Code data forms: the New Patient Information Form, the FASD Diagnostic Form, digital facial photos, and the FAS Facial Photographic Analysis Report (2, 14). These data are entered into a research database shortly after the patient's FASD diagnostic evaluation reflecting the tools and growth norms available at that time. Over the decades the 4-Digit Code has evolved (1st edition 1997, 3rd edition 2004) (2, 8, 15, 16), new tools have been developed like the FAS Facial Photographic Analysis Software (Version 1.0 in 2004, Version 2.1 in 2016) (14), and new more accurate growth norms have been adopted […]." In die erste Leitlinie von Landgraf 2015 (17) wurde Astley 2006 (Vorgängerstudie) (18) eingeschlossen.

* FASD is including FAS, pFAS, SE-PAE and ND-PAE. NOTE: 4-Digit Code (2) includes FAS and pFAS under the FASD umbrella, but notes SE-PAE and ND-PAE are only FASDs if PAE caused their SE or ND.
** Astley Hemingway 2019 (4): This study is an extension of Astley 2017 (1) using the same population, but comparing more diagnostic systems including the Canadian Guideline 2016 (5) and Australian Guideline 2016 (6).
§ 4-Digit Code: (refers to Astley 2017 (1)) does not use the term ARND, but states that their categories of SE-PAE and ND-PAE are equivalent (compare also to Polish guideline (19)).
§§ Coles 2016 (7): Only percentages given by Coles 2016 (7), absolute figures calculated subsequently.
$ Canadian 2016 (5) and Australian 2016 (6) Guidelines: 3 facial features and microcephaly required.
$$ Astley Hemingway 2019 (4): FASD criteria not met at time of assessment, but nevertheless there is a potential for FASD (category used in Canadian (5) and Australian Guidelines (6)).

Studien zur Genauigkeit von Diagnosetests / Qualitätsbeurteilung durch QUADAS-2[#]

		Astley 2017 (1)	Astley Hemingway 2019 (4)	Coles 2016 (7)
Patient selection	Was a consecutive or random sample of patients enrolled?	+	+	-
	Was a case-control design avoided?	+	+	+
	Did the study avoid inappropriate exclusions?	?	?	?
Index-test	Could the conduct or interpretation of the index test have introduced bias?	-[£,£]	-[£,£]	?[£,£]
	If a threshold was used, was it pre-specified? (RoB)	+	+	+
	Were the index test results interpreted without knowledge of the results of the reference test?	?	?	?
Reference-test[£]	**Could the reference standard, its conduct, or its interpretation have introduced bias?[£]**	+	+	+
	Is the reference standard likely to correctly classify the target condition?	+	+	+
	Were the reference standard results interpreted without knowledge of the results of the index test?	+	+	+
Flow + Timing	Was there an appropriate interval between index test(s) and reference standard?	-	-	-
	Did patients receive the same reference standard? (differential verification bias)?	?	?	?
	Did all patients receive a reference standard? (partial verification bias)?	?	?	?
	Were all patients included in the analysis?	?	?	?
	Could the patient flow have introduced bias?	?	?	?

+ yes (fulfilled); **-** no (not fulfilled); **?** unclear (no or not sufficient information)

After the methods presented in Whiting, PF; Rutjes, AW; Westwood, ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009.

£ Different Indextests (test systems) are compared to each other using records of consecutive patients that received an FASD diagnostic evaluation at different clinics as reference test. Of note: most individuals presented for diagnosis without accurate information on PAE. Valid and reliable dose information is difficult to obtain (but this issue refers to both index- and reference test).

ﬀ Astley 2017 (1) and Astley Hemingway 2019 (4): The 4-Digit Code (one of Index tests) has been developed by Astley. Coles 2016 (7) is from Emory University School of Medicine, Atlanta, Georgia (Emory-System).

Studien zur Genauigkeit von Diagnosetests / Zusammenfassung von QUADAS-2[#] und Levels of Evidence after Oxford

Study	Risk of Bias				Applicability			LoE
	Patient selection	Index-test	Reference-test	FLOW AND TIMING	Patient Selection°	Index-test°°	Reference-test°°°	
Astley 2017 (1)	+	-	+	?	+	?	+	3
Astley Hemingway 2019 (4)	+	-	+	?	+	?	+	3
Coles 2016 (7)	-	?	+	?	-	?	+	3

LoE: Levels of Evidence after the Oxford 2011 Levels of Evidence; die Bewertung erfolgte in Anlehnung an die Empfehlungen des Oxford Centre for Evidence-Based MEdicine (OCEBM). Critical Appraisal tools — Centre for Evidence-Based Medicine (CEBM), University of Oxford.

After the methods presented in Whiting, PF; Rutjes, AW; Westwood, ME et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009.

° Are there concerns that the included patients and setting do not match the review question?

°° Is there concern that the index test, its conduct, or interpretation differ from the review question?

°°° Is there concern that the target condition as defined by the reference standard does not match the review question?

Coles 2016 (7)**:** the sample used was patients applying consecutively for services and, therefore, self-selected. The characteristic of the individuals in the sample reflect the characteristics of the region in which they live rather than the general population of the US. The sample is 47% African American […].

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Merkmale von Studien, die sich mit Wachstumsdefiziten bei PAE und/oder FASD befassen

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
O'Leary 2009 (1)**: No association between SGA and PAE** **Risk of bias***: **CONFOUNDING:** moderate RoB (authors adjusted confounders such as maternal smoking, illicit drug use during pregnancy, maternal age, parity, ethnicity and income [all self-reported] but unmeasured or residual confounding cannot be excluded); **SELECTION of PARTICIPANTS:** moderate RoB (random-sample of births retrospectively selected); **CLASSIFICATION of FASD:** not applicable (PAE considered in study); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** high RoB (multiple subgroups (alcohol consume for different trimester and different PAE classifications) making interpretation difficult) **OVERALL: high risk of bias; concerns of the applicability of the results (due to the Western Australian setting, higher prevalence of alcohol consumption in Australian women); LoE: 4**						
O'Leary 2009 (1) (identified by reference screening; reference was used to justify that growth is not an important criteria in Canadian guideline)	cross-sectional design (retrospective evaluation of a population at a single time point)	Western Australia no clinical setting (midwives notification)	A 10% random sample of births restricted to nonindigenous women who had delivered a singleton infant in 1995–1997. These women were invited by a letter at 12 weeks postpartum to participate in a postal survey of health-related behaviours and events during pregnancy and infancy.	4719 (total) 54-57.4% (no PAE) 38-44% (low to moderate PAE) 2-5% (high PAE, binge drinking) (% across all trimesters)	newborns	**SGA and PAE** **PAE status:** Information on maternal alcohol consumption was collected retrospectively by self-administered questionnaire for the *3-month period pre-pregnancy and for each trimester separately*. For each period, women were asked how often they drank [….] level of alcohol consumption was categorised […].# **Overall proportion of SGA (< 10th P. of optimal birth weight):** 421/4719 (8.9%) **Association between SGA and PAE:** "Low levels of alcohol consumed during pregnancy (levels less than 60 g/week and not more than two standard drinks per occasion) **were not associated** with SGA, and there was little difference in SGA between women who drank low levels of alcohol during pregnancy and women who were abstinent during pregnancy. Higher levels resulted in a non-significant increase in odds ratios.

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
Hasken 2021 (2)**: The risk for being diagnosed with FASD in children born SGA is increased in comparison to children being born AGA (OR 2.2, 95% CI: 1.4 to 3.5)** **Risk of bias*: CONFOUNDING:** moderate RoB (authors adjusted for confounders such as maternal age at pregnancy, education, tobacco during pregnancy, number of trimester of drinking, drinks per drinking but unmeasured or residual confounding cannot be excluded); **SELECTION of PARTICIPANTS:** moderate RoB (case-control study); **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB(authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** low RoB (outcome measure (SGA) cannot be influenced by knowledge of the exposure/intervention received by study participants, any error in measuring the outcome is only minimally (or not at all) related to exposure/intervention status); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: moderate RoB; concerns of the applicability of the results (due to the South African setting, not applicable to more economically advantaged populations); LoE: 3-4**						
Hasken 2021 (2)	case-control study	South Africa school setting	737 randomly selected children (from 5 cohorts) within population-based school studies received full screening for FASD and other known anomalies in 3 tiers of assessment […] Additionally, the mothers of the children were asked in structured interviews about general social, demographic, medical and childbearing history including details on the quantity, frequency and timing of alcohol, tobacco and other drugs use 6-8 years prior **Afterwards** the children were categorised either in FASD or controls (no FASD and no other anomalies). Some of the controls were born to women who consumed alcohol prenatally and others who were abstainers. Physicians assigned the final diagnosis for each child using the revised IOM guideline (3).	737 (total) 96 (FAS) 81 (pFAS) 78 (ARND) 482 (controls, normal developed)	FASD diagnostic at 7	**SGA in FASD** **FASD diagnostic:** after IOM criteria (3) (assignment at age 7) **Growth data at birth:** originated from clinical records **Is growth a predictor of FASD?** Being born SGA increased the odds ratio (OR) of being diagnosed with any of the three common diagnoses on the continuum of FASD at 7 y of age. FASD: OR 2.16, 95% CI: 1.35 to 3.45 FAS: OR 3.13, 95% CI: 1.64 to 5.99 pFAS: OR 2.09, 95% CI: 1.08 to 4.03 ARND: OR 2.03, 95% CI: 1.09 to 3.76 This effect was independent of drinks per drinking day in the first trimester, number of trimester of drinking, maternal education, tobacco use and maternal age. Being born SGA to mothers who used to drink alcohol heavily during the prenatal period significantly increased the odds of postnatal growth deficiency, dysmorphic features, and, therefore, a diagnosis with an FASD **Proportion of children with SGA:** FASD 51.4% vs. non-FASD 27.7%

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
Carter 2016 (4)**: Higher prevalence of SGA in children with heavy PAE than in control children with mild PAE** **Risk of bias*: CONFOUNDING:** unclear RoB (confounding factors not sufficiently considered/described); **SELECTION of PARTICIPANTS:** moderate RoB (inclusion, exclusion criteria for mother and child reported, prospective); **CLASSIFICATION of FASD:** not applicable (PAE considered in study); **MISSING DATA:** moderate RoB (authors acknowledged that growth data were available from at least 92.5%); **MEASUREMENT of OUTCOMES:** moderate RoB (PAE was classified during pregnancy when "outcome" was not known and standardised protocols used); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: moderate RoB; concerns of the applicability of the results (due to the South African setting, not applicable to more economically advantaged populations); LoE: 3-4**						
Carter 2016 (4)	case-control study	South Africa, Cape Town clinical setting	„Children of women (recruited between 07/99-01/02 at initiation of prenatal care that serves an economically disadvantaged, predominantly Cape Coloured population) were included and categorized in heavy exposure and controls (mild exposure; women who drank <0.5 oz. AA/day and did not binge drink, among them 96.8% abstained during pregnancy). *PAE was classified after interviews conducted at recruitment during pregnancy.* Newborns were followed-up up to 13 y of age"	157 (total) 94 (heavy PAE) 63 (mild or no PAE)	birth, 6.5 months, 1, 5, 9, 13 years	**Growth restriction (over time) and PAE:** "Children born SGA (defined as birth weight <10th P.) were exposed to higher levels of alcohol than children born AGA. A linear relation was seen between PAE and growth trajectory: those born AGA with normal postnatal growth had the lowest levels of exposure; those born SGA followed by catch-up growth, intermediate levels; those born SGA without catch-up growth had the highest. These findings validate the use of growth restriction in the diagnosis of FASD and identify growth trajectory as a biomarker of which heavily exposed children are at greatest risk for cognitive developmental deficits." **Prevalence of SGA (N, %):** Heavy PAE: 52/94 (55.3) vs. controls (mild PAE): 12/63 (19.0), p <0.001
Astley 2016 (5)**: Growth deficiency is associated with PAE** **Risk of bias*: CONFOUNDING**: moderate RoB (authors adjusted for confounders but unmeasured or residual confounding cannot be excluded); **SELECTION of PARTICIPANTS**: moderate RoB (consecutive, retrospectively selected); **CLASSIFICATION of FASD:** low RoB (4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described) **SELECTION of REPORTED RESULTS:** high RoB (e.g. multiple results reported and underlying data base including outcome definition often unclear) **OVERALL: high risk of bias; concerns of the applicability of the results (due to wide age range and patient records from 1993-2012 reassessed – diagnostic may have changed); LoE: 4**						
Astley 2016 (5)	cross-sectional design	USA, Seattle (Washington)	"Data from 1814 patients with FASD (across the full spectrum) evaluated consecutively from 01/1993 through 12/2012 at one of the FASDPN	1814 (with PAE and all with a FASD	0.2-50.9 (range)	**GD (height and/or weight) and PAE over a wide age range** **FASD diagnostic:** after 4-Digit Code (all PAE in this

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
	(retrospective evaluation of a population at a single time point)	clinical setting	clinics were used. All patients were diagnosed in accordance with (or upgraded to) the 2004 FASD 4-Digit Code (6).“	diagnosis)	(60% between 6 and 18)	sample) **1) Is there evidence of an association between GD and PAE?** “Significant linear correlation of GD and PAE, controlled for risk factors such as physical abuse, sexual abuse, foster care, prenatal tobacco exposure” **2) Is GD sufficiently prevalent among individuals with PAE to warrant its inclusion as a diagnostic criterion?** 639/1814 (35.2%) ≤10th P. for GD (most prevalent form of GD with 69% was postnatal short stature). “GD was as prevalent as the other core diagnostic features (facial and CNS abnormalities). GD (any extent) occurred in all FASD diagnoses and increased in prevalence with increasing severity of diagnosis.” **3) Does GD aid the diagnostic team in identifying and/or predicting which individuals will be most impaired by PAE?** **(i) GD and brain dysfunction:** “GD was highly correlated with, and predictive of severe brain dysfunction “ - Individuals with GD: 2-3-fold increased risk for severe brain dysfunction. - 60% of patients with severe GD had severe brain dysfunction **(ii) Subgroup: GD and facial features (n=1162 with a diagnosis at birth and later in life):** „GD is highly correlated, but not highly concordant with the FAS facial phenotype. Mean height and weight percentiles at birth and at the age of diagnosis decreased significantly with increasing severity of the FAS facial features Rank.“

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
						4) Subgroup: tobacco exposure vs. no tobacco exposure: „Logistic regression documented that subjects with exposure to prenatal tobacco (90% of sample) were at a 2.1-fold increased risk (95% CI 1.1–4.3) for birth weight ≤ 10th P. compared to subjects with no tobacco exposure."
Kalberg 2019 (7)**: Growth deficiency and total dysmorphology scores differed between children with and without FASD as early as 9 months (but results are influenced by confounding)** **Risk of bias*: CONFOUNDING:** high RoB (significant confounder described in study: height of the mother, BMI and dose of alcohol intake during pregnancy, moreover, other confounding cannot be excluded); **SELECTION of PARTICIPANTS:** moderate RoB (consecutive sample, prospective); **CLASSIFICATION of FASD:** unclear/low RoB (IOM criteria [may be adapted, not clear described in study]); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** moderate RoB (standardised protocols were used to assess outcomes); **SELECTION of REPORTED RESULTS:** moderate RoB **OVERALL: high risk of bias; concerns of the applicability of the results (due to the South African setting, not applicable to more economically advantaged populations); LoE: 4**						
Kalberg 2019 (7)	longitudinal prospective design	South Africa no clinical setting (communities)	"A cohort of pregnant South African women attending primary health care clinics or giving birth in provincial hospitals was enrolled and their children were followed longitudinally from birth to 5 years […] using standardized protocols"	155 (total) 79 (FAS, pFAS) 76 (no FASD)	6 weeks, 9, 18, 42, and 60 months	**GD and dysmorphology scores in FASD and controls** **FASD diagnostic:** after CoFASP Consensus Clinical Diagnostic Guidelines for FASD adapted from revised IOM criteria (8) **PAE status:** The percentages of women who reported drinking during pregnancy were 90% for FAS, 100% for pFAS, 100% for ARND, and 51.4% for no FASD. **GD and dysmorphology score over time (FASD vs. no FASD):** „Growth restriction and total dysmorphology scores differentiated among children with and without FASD as early as 9 months (area under the receiver operating characteristic curve = 0.777; p < .001; 95% CI: 0.705–0.849)" **High confounding:** "Mothers of children with FASD were significantly smaller, with lower BMIs and higher alcohol intake during pregnancy, than mothers of children without FASD."

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
May 2022 (9)**: Height, weight, BMI, and head circumference differed between children with and without FASD (at school age)** **Risk of bias*: CONFOUNDING:** moderate RoB (authors adjusted for tobacco and illicit drugs used during pregnancy but unmeasured or residual confounding such as age cannot be excluded); **SELECTION of PARTICIPANTS:** moderate RoB (random-sample, prospective); **CLASSIFICATION of FASD:** low RoB (blinded diagnostic teams, IOM criteria applied); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** moderate RoB; **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: moderate risk of bias; no concerns of the applicability of the results; LoE: 2-3**						
May 2022 (9) (also in facial abnormalities and in CNS structural)	cross-sectional design (prospective evaluation of a population at a single time point)	USA school setting	"[…] this was a population-based study that began by sampling all consented children enrolled in first grade in 6 school cohorts. Then randomly selected children from this sample received full screening for FASD and other known anomalies in 3 Tiers of assessment […]. Additionally, the mothers of the children were asked in structured interviews about general social, demographic, medical and childbearing history including details on the quantity, frequency and timing of alcohol, tobacco, mother's height and weight, nutrition […]. Afterwards the children were categorised by physicians (using IOM criteria (3)) either in FAS, pFAS, ARND or controls (no FASD and no other anomalies). "	1343 (total) 23 (FAS) 61 (pFAS) 47 (ARND) 1212 (controls)	6-7 (range)	**Physical characteristics in school children with FASD and controls** **FASD diagnostic:** after IOM criteria (3) **Growth deficiency:** "GD was a primary differentiator among the diagnostic groups of subjects within this study. Children who met diagnostic criteria for any diagnosis on the continuum of FASD were indeed significantly smaller in height, weight, BMI[§] and head circumference than typically developing children. Furthermore, children with one of the specific diagnoses within FASD were significantly different in size from one diagnostic group to another (e.g., FAS vs. pFAS, pFAS vs. ARND, etc.). These data confirm the observations of other investigators that validate the use of growth restriction in the diagnosis of FASD." **Height centile (mean±SD):** FAS 7.1±7.9 pFAS 33.2±25.4 ARND 50.3±30.9 controls 55.9±27.9 p <0.001 for each FASD category vs. control; except for ARND vs. controls **Weight percentile (mean±SD):** FAS 13.0±14.0

Reference	Study design	Country, Setting	Population			Diagnostic aspects and findings
			Population included	N	Age (years) mean±SD	
						pFAS 39.6±26.7 ARND 52.5±34.2 controls 59.7±27.5 p <0.001 for each FASD category vs. control; except for ARND vs. controls **BMI percentage (mean±SD):** FAS 36.9±30.6 pFAS 50.2±30.6 ARND 53.0±33.5 controls 60.0±27.6 p <0.001 for FAS vs. control

AA: Absolute Alcohol; AGA: Appropriate for Gestational Age; ARND: Alcohol Related Neurodevelopmental Disorder; BMI: Body Mass Index; CI: Confidence Interval; CNS: Central Nervous System; CoFASP: Collaboration on FASD Prevalence; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; FASDPN: (University of Washington) Fetal Alcohol Syndrome Diagnostic & Prevention Network; GD: Growth Deficiency; IOM: Institute of Medicine; LoE: Levels of Evidence after the Oxford 2011 Levels of Evidence; OR: Odds Ratio; P: Percentile; PAE: Prenatal Alcohol Exposure; pFAS: partial FAS; RoB: Risk of Bias; SD: Standard Deviation; SGA: Small for Gestational Age

*** Biasbewertung (RoB)** in Anlehnung an das „Manual zur Bewertung des Biasrisikos in Interventionsstudien". 2. Auflage, 2021. Verfügbar unter: https://www.cochrane.de/de/literaturbewertung oder https://www.leitlinien.de/methodik. **For all studies assessing PAE status:** CLASSIFICATION of PAE EXPOSURE is generally associated with a high RoB (PAE, recall bias, outcome was known when women were questioned, the longer the time between the interviews and the pregnancy, the higher the risk for recall bias**). Confounders** including age of mother and/or child, BMI, sex of child, socioeconomic status and PAE (except for studies focusing only on PAE, PAE is considered as exposure).
 # O'Leary 2009 (1)**:** 10 g = 1 standard drink in Australia, 50 g per occasion = binge drinking. Classification of maternal alcohol consumption is complex and presented in Table 1 in the study of O'Leary 2009.
§ May 2022 (9)**:** "Height, weight, and body mass index (BMI) were all significantly different among the four groups, with height and weight significantly different in all bivariate comparisons among groups except ARND vs. controls. Bivariate comparisons of BMI were only significant between the children with FAS and the control group."

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Merkmale von Studien, die sich mit Gesichtsmerkmalen bei PAE und/oder FASD befassen

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
Kesmodel 2019 (1)**: PAE associated with presence of facial features, prevalence of all facial features (3.2%) in this population, OR of risk for facial features differs with drinking level** **Risk of bias*: CONFOUNDING:** moderate RoB (authors adjusted for confounders such as age, maternal age, BMI and PAE, however, unmeasured or residual confounding cannot be excluded); **SELECTION of PARTICIPANTS:** high RoB (oversampling of PAE; high proportion of excluded subjects for analysis without explanation); **CLASSIFICATION of FASD:** low RoB (4-Digit Code); **MISSING DATA:** high RoB (high proportion of excluded subjects for analysis but were measured without explanation); **MEASUREMENT of OUTCOMES:** moderate RoB (testers were blinded to exposure); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high RoB; no concerns of the applicability of the results; LoE: 3-4**						
Kesmodel 2019 (1)	cross-sectional design (prospective evaluation of a population at a single time point)	Denmark data from national birth cohort	Population derived from stratified sample of the Danish National Birth Cohort. „The objective of the present analysis was[…] to assess the potential effects of low-to-moderate average weekly alcohol consumption and binge drinking in early pregnancy on facial features associated with FAS among children 5 y of age.“	366 (total) 308 (PAE) 58 (non-PAE reported but all 3 facial features measured)	5.2 (median)	**<u>Facial features and PAE</u>** 366 with photographs of sufficient quality, 308 with PAE - PAE / drinking level assessed through maternal interviews. - Subgroups built to differ between drinking levels and presence of facial features. -Diagnostic by 4-Digit Code: „[…] standardized digital facial photographs were taken of each mother and child to allow subsequent measurement of (dysmorphic) facial features, including the philtrum, the upper lip, and PFL.“ **Prevalence of facial features:** **3.2%** (10/308) with confirmed PAE presented with the 3 features of FAS/pFAS facial phenotypes (face ranks 3-4) when mothers had low-to-moderate alcohol intake **Presence of all facial features (Face Rank 3-4) and the association with different PAE levels:** Children with PAE vs. no PAE showed higher OR for facial features. The highest OR was found at drinking level “1-4 drinks per week” (not for > 5 drinks a week) followed by “single binge exposure in week 3-4”. Other binge drinking episodes showed no significant differences. → **Anmerkung:** diese Ergebnisse sind pathophysiologisch nicht erklärbar **Other results:** „Although 10 children in the current study presented with the Rank 3

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
						or 4 FAS/pFAS facial phenotypes, none met the diagnostic criteria for FAS or pFAS (in accordance with the 4-Digit Code) at the young age of 5 years.“ That means none of the 10 children had a growth deficiency or microcephaly which is obligatory in the 4-Digit-diagnostic Code.
May 2022 (2)**: Height, weight, BMI, and head circumference differed between FASD and typically developing children** **Risk of bias*: CONFOUNDING:** moderate RoB (authors adjusted for tobacco and illicit drugs used during pregnancy but unmeasured or residual confounding such as age cannot be excluded); **SELECTION of PARTICIPANTS:** moderate RoB (random-sample, prospective); **CLASSIFICATION of FASD:** low RoB (blinded diagnostic teams, IOM criteria applied); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** moderate RoB; **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: moderate risk of bias; no concerns of the applicability of the results; LoE: 2-3**						
May 2022 (2) (also in CNS structural and GD)	cross-sectional design (prospective evaluation of a population at a single time point)	USA school setting	“[…] this was a population-based study that began by sampling all consented children enrolled in first grade in 6 school cohorts. Then randomly selected children from this sample received full screening for FASD and other known anomalies in 3 Tiers of assessment […]. Additionally, the mothers of the children were asked in structured interviews about general social, demographic, medical and childbearing history including details on the quantity, frequency and timing of alcohol, tobacco, mother’s height and weight, nutrition […]. Afterwards the children were categorised by physicians (using IOM criteria (3)) either in FAS, pFAS, ARND or controls (no FASD and no other anomalies). “	1343 (total) 23 (FAS) 61 (pFAS) 47 (ARND) 1212 (controls)	6-7 (range)	**<u>Physical characteristics in school children with FASD (+PAE) and controls</u>** **FASD diagnostic:** after IOM criteria (3) **Palpebral fissure length, smooth philtrum and arrow vermillion p < 0.001 for the following groups:** FAS vs. ARND, pFAS vs. ARND, FAS vs. controls, pFAS vs. controls (not significant for FAS vs. pFAS) **Palpebral Fissure Length Percentile (mean±SD):** FAS 9.9 (12.3), pFAS 14.6±15.6, ARND 31.1±14.1, controls 30.6±15.7 **Smooth Philtrum (rank 4 or 5 on lip-philtrum guide) (% yes):** FAS 82.6, pFAS 78.7, ARND 17.0, controls 14.6 **Narrow Vermillion (% yes):** FAS 82.6, pFAS 85.2, ARND 12.8, controls 17.2 **Total dysmorphology scores (mean±SD):** Children with FAS had the highest scores (15.9±3.3), followed by those diagnosed with pFAS (10.9±3.3), ARND (4.9±3.8), and controls (4.1±3.0)

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
						"Overall, the mean total dysmorphology scores of children formed a continuum that was statistically significantly different among each of the FASD diagnostic groups, and all were significantly different from the comparison group of controls (except for children with ARND). Among other features useful in differentiating children with FASD from controls were: ptosis, hypoplastic nails, fifth finger clinodactyly, and altered palmar creases. These observations validate the inclusion of these features in the total dysmorphology scoring system."
Suttie 2018 (4)**: Higher prevalence of facial anomalies in FAS group** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** unclear RoB (no information about how the study sample was selected from the database); **CLASSIFICATION of FASD:** low RoB (IOM criteria used); **MISSING DATA:** low RoB (secondary data analysis led to no loss of data); **MEASUREMENT of OUTCOMES:** unclear RoB (methods and used software cannot be evaluated by us due to the need of specific knowledge for machine learning); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: unclear or high RoB; no concerns of the applicability of the results; LoE: 3-4**						
Suttie 2018 (4)	cross-sectional design (retrospective evaluation of a population at a single time point)	USA clinical setting	„The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) consortium has recruited several thousand participants who completed clinical examinations, neurobehavioral profiles, 3D face images and MRI scans. 119 participants were available, the majority from a recently described Caucasian cohort, and some additional subjects of Latin American descent. For each participant in this analysis, we required clinical data, a 3D facial image and an MRI image acquired at a time point close to that of the face images."	119 (total) 22 (FAS) 50 (PAE) 47 (controls)	12.3-12.6 (range)	Initial diagnosis of FAS after IOM Criteria **<u>Analysis of 3D facial images</u>** **PFL (N, %):** FAS: 9 (86.4%) vs. PAE: 8 (16%) vs. controls: 4 (8.5%), p< 0.001 **Smooth Philtrum anomalies (N, %):** FAS: 12 (54.5%) vs. PAE: 11 (22%) vs. controls: 9 (19.1%), p< 0.01 **Thin vermillion anomalies (N, %):** FAS: 12 (54.5%) vs. PAE: 14 (28%) vs. controls: 11 (23.4%), p< 0.05 „[…] Our study demonstrates the relationships that exist between face and brain by combining localised regions of facial morphology with the corpus callosum."
Gomez 2020 (5)**: Comparison of ocular measurements of FASD and controls: Interpupilary distance percentiles were sig. lower in FAS, pFAS and ARND; inner canthal distance showed no sig. difference** **Risk of bias*: CONFOUNDING:** moderate RoB (sex considered, age-matched controls but unmeasured or residual confounding cannot be excluded); **SELECTION of PARTICIPANTS:** low RoB (use of recent data of Fetal Alcohol Syndrome Epidemiologic Research (FASER) database); **CLASSIFICATION of FASD:** low RoB (dysmorphologist blinded to PAE status, IOM criteria applied for diagnosis); **MISSING DATA:** low RoB (almost no missing data: 19 cases from > 2000); **MEASUREMENT of OUTCOMES:** low RoB (valid diagnostic procedure, valid measurements, outcomes sufficiently reported); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely)						

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
OVERALL: (low to) moderate RoB; concerns of the applicability of the results (due to the South African setting, not applicable to more economically advantaged populations); LoE: 3						
Gomez 2020 (5)	cross-sectional design (retrospective evaluation of a population at a single time point)	South Africa FASER database based on school setting	„This database comprises information compiled from a long-term epidemiological study of first grade students (ages 5 to 9 y) in five communities in South Africa. As has been previously described, school-age participants were studied in entire schools where they were screened for deficiencies in growth parameters (height, weight, and head circumference) and an additional random sample was also drawn in these studies to ensure population representativeness." „Dysmorphology examinations were conducted on all individuals with growth parameters at or below the 25th centile and on the additional random sample. Children with normal growth parameters (above the 10th centile) comprised the age-matched controls."	583 (FAS) 481 (pFAS) 332 (ARND) 604 (controls, non-FASD)	6.9±8.1	Diagnosis of FASD after IOM Criteria Ocular features measured with plastic ruler **Inner canthal distance percentiles:** "[…] provided no significant addition to the prediction of an FASD diagnosis after accounting for that provided by IPD centile." **Interpupilary distance (IPD) percentiles (Mean±SD):** FAS: 38.18±23.87, pFAS: 50.75±24.68, ARND: 49.13±24.69, controls: 63.13±23.79; sig. differences between groups showing lower percentiles in FASD groups with lowest result in the FAS group. „IPD is an easier measure to obtain than PFL because the landmarks (centre of the pupil) are less challenging to identify during an exam in young children when compared to the landmarks for palpebral fissure length."
Abell 2016 (6)**: Association of maxillar and mandibular arc growth and FASD diagnosis** **Risk of bias*: CONFOUNDING:** high RoB (authors considered sex but not age and other possible confounders); **SELECTION of PARTICIPANTS:** unclear RoB (use of data from the Fetal Alcohol Syndrome Epidemiologic Research (FASER) database but not clear if all cases from the database or a subset was used for analysis); **CLASSIFICATION of FASD:** low RoB (FASER database→ cases (FASD diagnosis) and controls (non FASD) already given, additional control groups built from database); **MISSING DATA:** unclear RoB (missing values not reported); **MEASUREMENT of OUTCOMES**: moderate RoB (outcomes sufficiently reported, consistently and concordant results); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high RoB; no concerns of the applicability of the results; LoE: 3-4**						
Abell 2016 (6)	cross-sectional design (retrospective evaluation of	South Africa, Italy, and the United States	„The Fetal Alcohol Syndrome Epidemiologic Research (FASER) database contains information from extensive screenings of school-age children for FASD. For this report, we analysed variables reported in the FASER database to investigate the	273 (FASD including 94 FAS, 129 pFAS, 50 ARND)	5-9 (range)	Diagnosis of FASD after IOM Criteria Arc measurements were made with a flexible measuring tape **FASD vs. non FASD:** „When compared to non-FASD controls, we found that for all FASD diagnosis groups, both males and females showed significantly

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
	a population at a single time point)	FASER database based on school setting	effects of prenatal alcohol exposure on facial growth." „[…] we first established normative arc measurements. These were taken from individuals with a diagnosis of non-FASD, and height, weight, and OFC >10th centile (n = 544 male, 436 female)." control population: comprising non-FASD individuals whose height, weight, and OFC were not necessarily >10th centile	1388 (controls)		decreased maxillary and mandibular arcs. The arc ratio was not significantly altered in all comparisons. The arc ratio significantly increased in full FAS males." "[…] we matched non-FASD controls and FASD cases by reduced growth parameters, specifically microcephaly, in order to control for the variable of reduced growth. We found that the arc measurements and arc ratio did not differ significantly between these cases and controls […]. From this, we conclude that the reduction of maxillary and mandibular arc lengths seen in individuals with prenatal alcohol exposure is primarily due to alcohol's effect of the growth parameters of the individual in general and less on the growth of the maxilla and mandible themselves." „If alcohol primarily affected the arc growth, we would have expected to see a further decrease in the arc measurements in the microcephalic FASD cases when compared to the microcephalic controls. "
Black-Lubarsch 2019a (7)**: Association of FAS and dimensions of the maxilla and facial length compared to non FAS children: no sig. differences for palatal height measures but sig. differences in vertical proportions** **Risk of bias* (applies to all studies of Blanck-Lubarsch): CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB (consecutive sample, prospective but unclear how controls were sampled); **CLASSIFICATION of FASD:** low RoB (specialist diagnosed children, German diagnostic guideline applied for FAS diagnosis); **MISSING DATA:** low RoB (no missing values); **MEASUREMENT of OUTCOMES:** moderate RoB (orthodontist was blinded to FAS status); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high RoB; concerns of the applicability of the results (due to missing information on the validity of the used Software and Tools); LoE: 4**						
Blanck-Lubarsch 2019a (7)	cross-sectional design (prospective evaluation at a single time point)	Germany, Münster clinical setting	„Children with FAS were recruited from 2012 to 2016 by a specialist in the Pediatric Department of the University Clinic Münster, who introduced our study to patients diagnosed with FAS according to the German FAS diagnostic guidelines (8)." „The control group consisted of children from local schools prospectively included	30 (FAS) 30 (controls)	8.8±1.5 (FAS) 8.2±1.8 (controls)	FAS diagnosed before 3D scan measurement (by a specialist using the German Diagnostic Guideline) 3D scan (for the measurements of facial features, a 3D scan of the face was taken using a photogrammetry-based, contact-free method) **5 measured face points (FP)/lengths:** FP1 (transition point of the hairline to the forehead), FP2 (the central point between the eyebrows just above the nose), FP3 (transition

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
			and examined during the same time period.“			point from the nose to the upper lip), FP4 (transition point between the upper and the lower lip), FP5 (most caudal point of the chin) **Mean palatal depth (FAS vs. controls):** not sig. (p= 0.708) **Measurements for total facial length (FAS vs. controls):** not sig. (p= 0.737) **Vertical distance between FP1 and FP2 (mean±SD):** FAS 53.4±4.5 mm vs. controls: 50.8±4.2 mm, p = 0.042 **Distance from FP2 to FP3 (mean±SD):** FAS 42.6±3.6 mm vs. controls: 49.1±3.1 mm, p < 0.001 **Distance FP3 to FP4 (represents philtrum lengths in mm) (mean±SD):** FAS 19.6±2.3 vs. controls: 16.5±1.9, p < 0.001 **Distance FP3 to FP5 in mm (mean±SD):** FAS group 55.1±4.4 vs. controls 51.9±3.7, p < 0.011 „Our study showed that for patients with an average age of 8.5 years, palatal height measurements may not be suitable for verification of FAS(D) diagnostics.“ „Vertical measurements of the face based on 3D facial scans, however, showed significant differences in all subdivisions with the exception of FP4 to FP5, and thus clarified that children with FAS have abnormal vertical proportions.“
Blanck-Lubarsch 2019b (9)**: Some additional facial features could be indicators of FAS such as inner canthal distance**						
Blanck-Lubarsch 2019b (9)	see above			28 (FAS) 30 (controls)	8.7±1.4 (FAS) 8.2±1.8 (controls)	“ […] metrical differences concerning various facial features in the regions of the eyes, nose and mouth as additional evidence and improvement for the diagnostic process in the sense of a better dysmorphology diagnosis in children with FAS […]” 3D scan (same as in Blanck-Lubarsch 2019a (7))

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
						Measured points P1-P10: P1–P2: right and left angulus oris (mouth breadth); P3–P4: distance between right and left alar nasi; P5–P6: distance between right and left sulcus alaris; P8–P9: inner canthal distance; P7–P8: right palpebral fissure length; P9–P10: left palpebral fissure length. **Differences between FAS and control in mm:** mouth breadth (P1–P2): not sig. p = 0.267 alares nasi (P3–P4): not sig. p = 0.260 **Sulci alares nasi at transition point to philtrum (P5–P6 in mm, mean±SD):** FAS: 16.9 (2.2) vs. controls: 21.2 (2.0), p< 0.001 **Inner canthal distance (P8–P9 in mm, mean, SD):** FAS 28.8±2.3 vs. controls 31.0±2.3, p< 0.001 **Palpebral fissure length right (P7–P8 in mm, mean±SD):** FAS: 21.7±1.5 vs. controls: 24.0±1.6, p = 0.003 **Palpebral fissure length left (P9–P10 in mm, mean±SD):** FAS 21.6±2.0 vs. controls 23.9±1.6, p< 0.001 **Sensitivity and specificity of 3D scans for FAS diagnosis:** „Using the analyzed parameters (e.g. sulci alares, inner canthal distance and palpebral fissure length) 92.6% of the FAS patients can be diagnosed correctly and 93.3% of the healthy children can be diagnosed correctly.“ FAS was verified for the cases but FAS status was blinded for examination of the images „Mouth breadth and breadth between nasal wings cannot be used as parameters for FAS diagnostics. In contrast, nose breadth at the transition point of the sulcus alaris to the philtrum, inner canthal distance (only for males) and palpebral fissure length are potential indicators for identification of children with FAS“

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
						„3D facial scans can be easily included into the diagnostic process of FAS(D) as 3D scans are fast, contactless and easily accepted by the patients.“
Blanck-Lubarsch 2019c (10)**: Mean Philtrum Depth was shallower in FAS**						
Blanck-Lubarsch 2019c (10)	see above			25 (FAS with rank 4 or 5 smooth philtrum) 30 (controls)	8.7±1.4 (FAS) 8.2±1.8 (controls)	„ […] we aimed to identify possible metric differences in philtrum depth in children with fetal alcohol syndrome (FAS) compared to healthy controls […]. “ 3D scan (for the measurements of facial features, a 3D scan of the face was taken using a photogrammetry-based, contact-free method). **Differences in mean philtrum depth at P1/P2/P3/P4:** (4 horizontal intersection lines resulting of calculation of intersections of the horizontal planes and the facial surface contour) FAS: 0.13/0.41/0.21/−0.16 mm vs. controls 0.47/0.75/0.58/0.22 mm „ […] mean philtrum depth P1–P4 ($p < 0.001$). Compared to controls, the philtrum was shallower in patients with FAS by on average 0.4 mm at each of the respective points. Whereas no differences could be determined for body height and weight, head circumference was significantly smaller in patients with FAS ($p = 0.001$) […].”
Blanck-Lubarsch 2019d (11)**: FAS group showed greater malocclusion and higher prevalence of cross-bites**						
Blanck-Lubarsch 2019d (11)	see above			30 (FASD) 30 (controls)	9.0±1.6	„To further clarify and support the diagnosis of FASD in affected patients based on oral manifestations, this study aims investigating possible associations between FASD and malocclusion as characterized by the PAR (peer assessment rating) index.“ All patients were examined according to a standardized orthodontic diagnostic protocol. **Mean difference (±SD) for total PAR index (with 11 domains for**

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
						malocclusions): FASD: 21±7.1 vs. controls: 15.5±5.3, p = 0.002 „When taking a closer look at the 11 components of the PAR index, 2 of them showed significant intergroup differences: occlusal features in the anterior segment (crowding, spacing, impacted teeth) and transversal dimension of the right side. “ **Prevalence of cross-bites:** Cross-bite, yes (%): FASD: 18/30 (60) vs. controls: 8/30 (26.7), p = 0.018 „Malocclusions (cross-bites as well as edge-to-edge bite and higher PAR scores for the upper anterior segment) can give additional hints for diagnosing FASD in later life, when some facial characteristics may have become less obvious. Early and regular orthodontic supervision of children with FASD is recommended in order to detect and treat malocclusions that can lead to facial asymmetry. Characteristic developmental deficits of FAS children regarding body weight, height and head circumference at birth show only a limited tendency to improve until the mean age of 9 years.“
Blanck-Lubarsch 2020 (12)**: No sig. group differences in facial asymmetrie; but facial proportions differ sig. between groups (p<0.001)**						
Blanck-Lubarsch 2020 (12)	see above			30 (FAS) 30 (controls)	8.8±1.4 (FAS) 8.2±1.8 (controls)	“The aim of our study was to assess differences in facial morphology of children with FAS—being the most severe form of the spectrum of FASD—as compared to normal controls and to find new reliable, objective parameters for improvement of FAS diagnosis based on non-invasive diagnostic 3D scans of the face.“ 3D scans (orthodontic facial analysis methods) to evaluate profile type differences **Mean profile angle (±SD):** FAS 20.9±4.1 vs. controls 17.8±4.4, p = 0.009

Reference	Study design	Country, Setting	Population			Diagnostic aspects addressed in studies
			Patient population	N	Age (years) mean±SD	
						Facial proportions all p< 0.001: -shorter middle facial third: FAS (24/30) vs. controls (9/30) -normal facial subdivision only: FAS (4/0) vs. controls (14/30) -shorter lower third/longer middle third: FAS (2/30) vs. controls (7/30) -normal lower third: FAS (3/30) vs. controls (21/30) **Facial types:** no stat. sig. differences between groups **Asymmetry index:** no stat. sig. differences between groups **Sensitivity and specificity of 3D scans for FAS diagnosis** (using e.g. profile angle, Kollmann's proportions, lower facial third): Sensitivity: 86.7%; Specificity: 93.3%; FAS was verified for the cases but FAS status was blinded for examination of the images

ARND: Alcohol Related Neurodevelopmental Disorder; BMI: Body Mass Index; CNS: Central Nervous System; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; FASER: Fetal Alcohol Syndrome Epidemiology Research; FP: Facial Points; IOM: Institute of Medicine; IPD: Interpupilary Distance; MRI: Magnetic Resonance Imaging; LoE: Levels of Evidence after the Oxford 2011 Levels of Evidence; OFC: Occipital Frontal Circumference; OR: Odds Ratio; PAE: Prenatal Alcohol Exposure; PAR: Peer Assessment Rating; pFAS: partial Fetal Alcohol Syndrom; PFL: Palpebral Fissure Length, RoB: Risk of Bias; SD: Standard Deviation

*** Biasbewertung (RoB)** in Anlehnung an das „Manual zur Bewertung des Biasrisikos in Interventionsstudien". 2. Auflage, 2021. Verfügbar unter: https://www.cochrane.de/de/literaturbewertung oder https://www.leitlinien.de/methodik. For all studies assessing PAE status: CLASSIFICATION of PAE EXPOSURE is generally associated with a high RoB (PAE, recall bias, outcome was known when women were questioned, the longer the time between the interviews and the pregnancy, the higher the risk for recall bias**). Confounders** including age of mother and/or child, BMI, sex of child, socioeconomic status and PAE (except for studies focusing only on PAE, PAE is considered as exposure).

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Merkmale von Studien, die sich mit strukturellen ZNS-Auffälligkeiten bei PAE und/oder FASD befassen

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
May 2022 (1)**: Occipital Frontal Circumference (OFC)** **Risk of bias*: CONFOUNDING:** moderate RoB (authors adjusted for tobacco and illicit drugs used during pregnancy but unmeasured or residual confounding such as age cannot be excluded); **SELECTION of PARTICIPANTS:** moderate RoB (random-sample, prospective); **CLASSIFICATION of FASD:** low RoB (blinded diagnostic teams, IOM criteria applied); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** moderate RoB; **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **Other concerns:** control group much larger than FASD group, last author of this publication is Hoyme who also developed IOM criteria (co-authors Hasken, Kalberg) **OVERALL: moderate risk of bias; no concerns of the applicability of the results; LoE: 2-3**						
May 2022 (1) (also in GD and facial abnormalities)	cross-sectional design (prospective evaluation at a single time point)	USA school cohorts	"[…] this was a population-based study that began by sampling all consented children enrolled in first grade in 6 school cohorts. Then randomly selected children from this sample received full screening for FASD and other known anomalies in 3 Tiers of assessment […]. Additionally, the mothers of the children were asked in structured interviews about general social, demographic, medical and childbearing history including details on the quantity, frequency and timing of alcohol, tobacco, mother's height and weight, nutrition […]. Afterwards the children were categorised by physicians (using IOM criteria (2)) either in FAS, pFAS, ARND or controls (no FASD and no other anomalies). "	1343 (total) 23 (FAS) 61 (pFAS) 47 (ARND) 1212 (controls)	6-7 (total) (range)	**OFC:** significantly different among all groups except for pFAS vs. ARND **OFC ≤ 3rd P.:** FAS: 56.5% pFAS: 9.8% ARND: 17.0% controls: 2.1% **OFC ≤ 10th P.:** FAS: 100% pFAS: 26.2% ARND: 27.7% controls: 6.3%
Chandran 2021 (3)**: OCF and MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** not applicable (PAE considered in study); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely)						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
OVERALL: high risk of bias; concerns of the applicability of the results (due to the low socioeconomic setting in India); LoE: 4						
Chandran 2021 (3)	cross-sectional design (evaluation at a single time point, unclear if retrospective or prospective)	India, Bangalore "low socioeconomic setting"	"Children between the ages of 6 and 16 years were recruited for the study with the assistance of health workers and field workers working in a community comprising low socioeconomic strata of urban Bengaluru. […] Families were interviewed in detail and assessed for alcohol consumption by mothers before and during the pregnancy of these children." "Thirty age, sex, and education matched children whose mothers did not consume any alcohol during pregnancy and had no regular use of alcohol before pregnancy, hailing from the same socioeconomic background were chosen as controls. All of them were ascertained not to have any significant medical/neurological conditions […], and any heritable neurological problems in the family using detailed history and physical examination before recruitment."	58 (total) 28 (PAE, no FASD) 30 (controls)	9±2 (PAE, no FASD) 10±2 (controls)	**OFC (mean±SD):** PAE 49.5±1.2 cm vs. controls 49.6±1.3 (p=0.7) **MRI:** "Midbody of Corpus callosum (CC) was found to be significantly smaller in children exposed to alcohol during the prenatal period. CC is a sensitive white matter structure to neurotoxic effects of alcohol during prenatal life. This impact could be visible in developmental age even in those without any clinically detectable features of alcohol exposure." **Area of midbody CC:** significant deficit in PAE compared to controls (p=0.038) **Intracranial volume**: no significant difference between PAE and controls (p=0.068) **Total area of CC:** no significant difference between PAE and controls (p=0.425) **Other areas of CC:** no significant differences
Lange 2019 (4)**: OCF findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guidelines); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
Lange 2019 (4) also in CNS functional	cross-sectional design (prospective evaluation at a single time point)	Canada, Toronto clinical setting	"A secondary analysis was conducted on data obtained from the Canadian component of the WHO International Study on the Prevalence of FASD (5). The Canadian FASD prevalence study employed a cross-sectional, observational design using active case ascertainment, along with retrospective collection of prenatal alcohol exposure information, to identify cases of suspected FASD […]." "The study procedures followed a step-wise approach, where only those students meeting predetermined criteria proceeded to the subsequent phase." Final diagnostic screening conclusions were made using the 2005 Canadian guidelines (6)." "[…] a group of typically developing control children was randomly selected from a list of all students who completed Phase I and who did not meet the criteria for Phase II using a systematic sampling technique; these students underwent a complete assessment in Phase II."	86 (total) 21 (FASD including 3 FAS, 2 pFAS, 16 ARND) 28 (ADHD/ASD) 37 (controls)	9.7±0.8 (FASD) 9.3±1.0 (ADHD/ASD) 9.0±1.0 (controls)	Difference between FASD and controls and compared to children with other neurodevelopmental disorders **OFC:** "The three groups of children differed from one another with respect to […] OFC ≤ 10th P., p=0.011." **OFC ≤ 10th percentile:** FASD n=5/21 (23.8%) ADHD/ASD n=5/28$^{\#}$ (17.9%) controls n=0/37 (0.0%) $^{\#}$ n=8 children with ADHD/ASD were also diagnosed with FASD, no further information regarding FASD diagnosis for the 5 ADHD/ASD children with OFC ≤ 10th percentile
Astley-Hemingway 2020 (7)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely)						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
OVERALL: high RoB; no concerns of the applicability of the results; LoE: 3-4						
Astley Hemingway 2020 (7) also in CNS functional	cross-sectional design (retrospective evaluation at a single time point)	USA, Seattle (Washington) patient records reassessed	"Study participants diagnosed with FASD by the University of Washington using the FASD 4-Digit Code (8-10) were compared to typically-developing peers with no PAE." "[…] data collected from a 2009 neuropsychological and magnetic resonance imaging (MRI) study (11-14) […]" "[…] a control child matched on age (within 6 months), gender, and race was randomly invited."	50 (total 11 (FAS/pFAS) 12 (SE-PAE) 11 (ND-PAE) 16 (controls)	12.9±2.4 (FAS/pFAS) 12.5±2.7 (SE-PAE) 11.8±2.7 (ND-PAE) 12.4±2.7 (controls)	**MRI findings:** "PAE accounted for up to 34% of the variance in regional brain volumes [total brain, frontal lobe, caudate, hippocampus and corpus callosum]." No separate description for PAE-FASD and PAE-non FASD. "Of the various measures of quantity, frequency and timing of PAE available for entry into the regressions: days per week of drinking during pregnancy and drank all three trimesters demonstrated the strongest, significant correlations with brain outcomes." "All correlations between risk factors and brain outcomes were in the direction anticipated (the more severe the risk factor, the more severe the brain outcome)." "Prenatal risks include: maternal use of tobacco, marijuana, cocaine, any illicit drugs and no prenatal care (all measured on a yes/no scale)." "Postnatal risks included: not living with either birth parent, number of foster placements, physical abuse, sexual abuse, SES of current caregiver" "Other prenatal and postnatal risk factors that met criteria for entry into the regression equations each explained an additional 5–15% of the variance."
McLachlan 2019 (15)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guideline); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD,						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
McLachlan 2019 (15)	cross-sectional design (retrospective evaluation at a single time point)	Canada, Vancouver clinical, school and community setting	"Participants were drawn from the Kids Brain Health Network FASD study cohort (16) from a single site in Vancouver, British Columbia, Canada […]." "Typically developing children were recruited from the same geographic region at a variety of community sites (e.g., community centers, schools, hospitals, and Web-based advertising) and were excluded if they had a neurological, genetic, or psychiatric disorder, or any reported PAE." "All study participants in the PAE group were assessed for FASD prior to study enrolment by interdisciplinary teams using the Canadian Diagnostic Guidelines (2005) (6) for FASD and had confirmed PAE […]."	24 (total) 10 (PAE including 9 with FASD diagnosed after Canadian guideline 2005) 14 (controls)	13.9±3.9 (PAE with/without FASD) 13.2±2.1 (controls)	**<u>Mean MWF (Myelin Water Fraction):</u>** **No significant difference between PAE vs. controls:** - internal capsule (left p=0.074; right p=0.395) - splenium (p=0.652) - genu (p=0.256) - major forceps (left p=0.391; right p=0.846) - minor forceps (left p=0.319) - putamen (left p=0.741; right p=0.127) - caudate nucleus (left p=0.146; right p=0.217) **Significant difference between PAE vs. controls:** - minor forceps right (p=0.023)
Treit 2017 (17)**: DTI and MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** unclear RoB (different classification systems used); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (study also included adults); LoE: 4**						
Treit 2017 (17) (also in CNS functional)	cross-sectional design	Canada, Alberta clinical and school setting	"Alcohol-exposed participants were primarily recruited (n = 40) through two FASD diagnostic clinics at the Glenrose Rehabilitation Hospital in Edmonton,	144 (total) 70	5-32 (range) 14.2±6.3	**<u>DTI of white matter tracts:</u>** "No main effects of group (FASD and controls) were found for FA [fractional anisotropy] or MD [mean diffusivity] of any of the 9 tracts."

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
	(evaluation at a single time point, unclear if prospective or retrospective)		Alberta, and were previously diagnosed according to the Canadian Guidelines (6) and the 4-Digit Code (8). The remaining FASD participants (n = 30) were recruited through school and social work services, and were diagnosed clinically by primary care physicians and practitioners in other developmental disability clinics." "Controls were recruited through advertising on public bulletin boards in locations such as community centres, hospitals, recreation centres etc., by letters sent home from several public schools, and by word of mouth." "Twenty of the 70 FASD participants were included in previous publications on volume and cortical thickness, and 50 were newly recruited for this study. The second scans of the 17 FASD participants in our previous longitudinal study (18) are included here […]"	(FASD including 10 FAS, 6 pFAS, 54 ARND/FASD without further specification) 74 (controls)	(FASD) 13.2±6.0 (controls)	**<u>MRI findings:</u>** **(i) Brain volumes:** **Significantly reduced volumes in FASD (FASD vs. controls):** "Main effect of group indicated significantly reduced volume [brain volumes left and right combined] of nearly all structures (p<0.001-0.033) in the FASD group, except the amygdala" **<u>(ii) Cortical thickness (left and right combined):</u>** **Significantly thicker cortex in controls (FASD vs. controls):** - middle frontal gyrus p=0.031 - inferior occipital gyrus p=0.007 - lingual gyrus p=0.008 - fusiform gyrus p<0.001 - middle temporal gyrus p=0.026 - inferior temporal gyrus p=0.022
Treit 2020 (19)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** unclear RoB (different classification systems used); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Treit 2020 (19)	cross-sectional design	Canada clinical setting	"Participants with PAE were recruited through multidisciplinary FASD diagnostic clinics across Canada, had confirmed	327 (total)	13±6 (PAE with/ without FASD)	**<u>MRI findings:</u>** **<u>(i) Incidental findings:</u>**

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
	(retrospective evaluation at a single time point)		PAE, and were assessed according to the Canadian Guidelines (6) for the Diagnosis of FASD and the 4-Digit Code (8)." "Healthy controls had been originally recruited through advertising and were screened for parent-reported history of neurological, psychiatric or developmental disorders, and contraindications to MRI." -both populations and MRI scans retrospectively sampled	164 (PAE including 33 PAE without FASD; 94 non-dysmorphic FASD; 37 dysmorphic FASD) 163 (controls)	12±5 (controls)	**No incidental findings[§] (any kind) on MRI (i.e. overall no incidental findings):** PAE 73% (PAE without FASD 64%; nondysmorphic FASD 81%; dysmorphic FASD 59%) vs. controls 75% > no significant difference between PAE and controls **Clinically significant[$] incidental findings:** PAE 3% (PAE without FASD 6%, nondysmorphic FASD 0%; dysmorphic FASD 8%) vs. Controls 1% => no significant difference between PAE and controls "The overall proportion of findings in each category (nonclinically significant incidental finding, or clinically significant incidental finding) did not differ between the control and total PAE group. However, when the PAE group was subdivided by diagnostic category (PAE without FASD, nondysmorphic FASD, and dysmorphic FASD), there were significant differences in the proportion of subjects with at least one or more than 1 finding. Post hoc analysis revealed that this difference was primarily driven by the dysmorphic FASD group (pFAS/FAS), in which 41% of subjects had at least 1 finding (vs. 25% of controls) and 19% had 2 or more findings (vs. 6% of controls." **<u>(ii) Specific findings with significant differences between PAE with FASD and controls:</u>** **Low-lying cerebellar tonsils**: PAE without FASD n=0 (0%); nondysmorphic FASD n=0 (0%), dysmorphic FASD n=3 (8%), controls n=4 (3%)

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						Ventricular asymmetry and/or enlargement: PAE without FASD n=0 (0%); nondysmorphic FASD n=1 (1%), dysmorphic FASD n=5 (14%), controls n=3 (2%); p < 0.001) **Polymicrogyria:** PAE without FASD n=1 (3%), nondysmorphic FASD n=0 (0%), dysmorphic FASD n=2 (6%), controls n=0 (0%) "When the PAE group was split by diagnosis, low-lying cerebellar tonsils, polymicrogyria, and ventricular asymmetry/enlargement were all most prevalent in subjects with fetal alcohol syndrome/partial fetal alcohol syndrome. In addition, the overall rate of incidental findings was higher (41%) in participants with FAS/pFAS, compared to 25% in controls. No participants in this relatively large sample had corpus callosum agenesis." → all more prevalent in dysmorphic FASD group
Zhou 2018 (20)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guideline); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no a priori protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Zhou 2018 (20) also in CNS functional	cross-sectional design (prospective evaluation at a single time point)	Canada, clinical setting	"Brain MRI was acquired in a newly recruited sample of 157 participants across four Canadian sites in the NeuroDevNet project (16). […] Typically developing control children were recruited from the same geographic regions, matched as closely as possible for age and sex."	157 (total) 78 (PAE including 22 confirmed PAE without FASD, 7 FAS, 12	1.8±3.3 (PAE with/ without FASD) 12.1±3.3 (controls)	**<u>MRI findings:</u>** **<u>(i) PAE vs. controls:</u>** **Brain Volumes:** "All brain regions showed reductions of volume in PAE relative to controls." - intracranial volume (cerebrum + cerebellum + brain stem + cerebrospinal fluid in crania cavity): Diff. -4%

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
			"The diagnosis of FASD was made by experienced multidisciplinary teams using the Canadian Guidelines from 2005 (6) […]" "The alcohol history is confirmed from reliable sources such as birth records, child welfare reports, legal documents, and direct interview with the birth mother if available. In most cases, the exact amount and pattern of alcohol use in that pregnancy is not reported or recalled."	pFAS, 37 ARND) 79 (controls)		(=PAE less,; p=0.005 - total cerebrum volume (total gray matter + total white matter): Diff. -5.6%; p<0.001 - volume of other structures: Diff. -4.1% to -12.1%, p= 0.03 to p<0.001 **Cortical Thickness:** "The PAE group showed reductions in global and regional cortical thickness […]." (significantly lower by >5% in PAE) **Cortical Thickness Asymmetry:** "[…] the pattern and degree of cortical thickness asymmetry were preserved in PAE participants […]. This persistent asymmetry reflects that the homologous left and right cortical regions followed typical relative developmental patterns in the PAE group despite being thinner bilaterally than controls." **<u>(ii) Analysis for PAE subgroups (vs. controls):</u>** **FAS:** "All brain volumes were reduced except the intracranial volume in FAS, but there were no reductions in regional cortical thickness." **pFAS:** "No brain volume was altered except the caudate that was significantly reduced and all regional cortical thickness was significantly reduced in pFAS." **ARND:** "ARND showed reductions in all brain volumes except cerebellum white matter and amygdala, and all regional

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						cortical thickness." **Confirmed PAE without FASD Diagnosis:** "All the brain volumes were reduced except intracranial, cortex, cerebellum white matter, and putamen. […] The regional cortical thickness values were reduced in the frontal, parietal, and temporal lobes, but not in the occipital lobe." **Diagnosed FASD only:** "[…] all regions showed reductions of volume and cortical thickness."
Roediger 2021 (21)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB the (outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to a low socio-economic setting); LoE: 4**						
Roediger 2021 (21) based on CIFASD (22)	cross-sectional design (prospective evaluation at a single time point)	USA, Minnesota; California; San Diego; Georgia low socioeconomic setting	Participants were recruited between 2017 and 2019 […]. PAE group: history of heavy PAE (> 13 drinks/week or >4 drinks per occasion at least once per week during pregnancy) or when such exposure was suspected in a child with a FAS diagnosis based on dysmorphology. "[…] modified IOM criteria (23) were used to determine FASD classifications." PAE histories were obtained through retrospective maternal report, social	79 (total) 40 (PAE; 38/40 were also diagnosed with FASD) 39 (controls)	12.0±2.49 (PAE with/without FASD) 12.21±2.67 (controls)	**<u>MRI findings:</u>** **Repeated-measures (ANCOVA):** "significant differences between PAE and controls on adjusted hippocampal subfield volumes (p = 0.003)" - CA1 (p=0.015) - CA4 (p=0.034) - subiculum (p=0.001) - presubiculum (p=0.003) - hippocampal tail (p=0.012)

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			service, legal, and medical records.			
Hendrickson 2018 (24)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** not applicable (PAE considered in study); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to a low socio-economic setting); LoE 4**						
Hendrickson 2018 (24) (based on CIFASD (22)	longitudinal design (unclear if prospective)	USA, Minnesota; California; San Diego; Georgia low socioeconomic setting	"[…] participants were […] scanned between 2012 and 2014. Follow-up scans took place between 2014 and 2017 approximately 2 years after the initial scan. PAE group: history of heavy PAE (> 13 drinks/week or >4 drinks per occasion at least once per week during pregnancy) or when such exposure was suspected in a child with a FAS diagnosis based on dysmorphology.	110 (total) 58 (PAE) 52 (controls)	12.44±2.74 (PAE) 13.71±2.29 (controls)	**MRI findings:** "Across the age range, control participants showed a curvilinear pattern when modelled as a quadratic function (individual change in Local Gyrification Index over two years was greatest in the youngest controls but there was also an increase in the rate of change in the 16–18-year-old controls). In contrast, participants with PAE showed a relatively flat pattern […]." "Cortical surface area did not differ between groups."
Donald 2015 (25)**: DTI findings** **Risk of bias*: CONFOUNDING:** moderate RoB; **SELECTION of PARTICIPANTS:** moderate RoB; **CLASSIFICATION of FASD:** not applicable (PAE considered in study); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** unclear RoB; **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: moderate risk of bias; concerns of the applicability of the results (due to a South African setting, not applicable to more economically advantaged populations); LoE: 3**						
Donald 2015 (25)	cross-sectional design (prospective	South Africa, West Cape low socioeconomic	"The current investigation […] included infants enrolled in a larger population-based birth cohort study, the Drakenstein Child Lung Health Study (26)." "For the group with PAE, mothers were	56 (total) 28 (PAE)	**(in days)** 20.71±5.29 (PAE) 19.96 ±4.92	**<u>DTI findings:</u>** **(i) Diffusion parameters (whole brain):** "[…] no significant group differences in any diffusion parameter." (e.g., axial diffusity)

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
	evaluation at a single time point)	setting	screened based on a minimum score of 11 (indicating that a participant is at moderate to high risk of experiencing severe problems as a result of their current pattern of use) on the alcohol questions on the ASSIST questionnaire (27) […]. In addition to this initial screen, mothers were required to give a positive history of alcohol use in any of the three trimesters of pregnancy at levels consistent with WHO moderate to severe alcohol use (either drinking two or more times a week or two or more drinks per occasion)." FAS assessed through dysmorphologies but not reported how many subjects received diagnosis in this population	28 (controls)	(controls)	**(ii) Diffusion parameters (for different regions of interest):** "[…] significant difference in diffusion by group in major white matter fibres that interconnect temporal, frontal and parietal regions."
Jacobson 2017 (28)**: MRI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to a South African setting, not applicable to more economically advantaged populations); LoE: 4**						
Jacobson 2017 (28)	case-control	South Africa, Cape Town clinical setting "clinic for economically disadvantaged population"	"The infants were born to women who were recruited between 2011 and 2013 at their first antenatal visit from 2 midwife obstetrical clinics that serve an economically disadvantaged Cape Coloured community." "Two groups of women were recruited as	43 (total) 8 (FAS) 21 (heavy PAE, no	**(age at scan in weeks)** 2.8±1.3 (FAS and heavy PAE) 1.9±1.2	**<u>MRI findings on Corpus Callosum (CC):</u>** **(i) Association of CC Area and FASD Diagnosis:** - significant relation CC area with FASD diagnosis (p=0.023) "Post hoc comparisons showed that the CC area was significantly smaller in infants diagnosed with FAS than controls, p=0.006.

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			follows: heavy drinkers, who consumed 14 or more standard drinks/wk (≈1.0 oz AA/day) and/or engaged in binge drinking (4 or more drinks/occasion), and controls, who abstained or drank only minimally during pregnancy." "In 2013, we organized a clinic in which the infants were examined for growth and FAS anomalies independently by 2 expert dysmorphologists […]." IOM criteria (2) used for diagnosis.	FASD) 11 (mild or no PAE, controls)	(controls)	CC area was intermediate in size for the heavily PAE group (p=0.056 between FAS and heavily PAE, although not significantly smaller than controls, p=0.166)." **(ii) Association of CC Area and continuous measures of PAE:** alcohol use at conception and alcohol use across pregnancy (any frequency) → all negatively related to CC area and significant relation even after adjustment for total intracranial volume (p<0.05)
Fan 2016 (29)**, Biffen 2018** (30) **und Robertson 2016** (31) **(3 studies based on the same cohort); MRI and DTI findings** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to a South African setting not applicable to more economically advantaged populations); LoE: 4**						
Fan 2016 (29)	cross-sectional design (retrospective evaluation at a single time point)	South Africa, Cape Town clinical setting "clinic for economically disadvantaged population"	"Children of pregnant women recruited between 1998 to 2002 into the Cape Town Longitudinal Cohort (32) were included." "the children in the study were each independently examined […] using a standard protocol based on the revised IOM criteria (2)." "Detailed alcohol exposure data collected prospectively during pregnancy were available for all of these children."	54 (total) 7 (FAS) 19 (pFAS) 15 (non-syndromal heavy PAE, no FASD)	10.4±0.5 (FAS, pFAS) 10.5±0.3 (heavy PAE, no FASD) 10.4±0.4 (controls)	**DTI findings:** "Using voxelwise analyses, children with FAS/pFAS showed significantly lower fractional anisotropy (FA) [compared to controls] in four white matter regions and higher mean diffusivity (MD) in seven; three regions of FA and MD differences (left inferior longitudinal fasciculus (ILF), splenium, and isthmus) overlapped, and the fourth FA cluster was located in the same white matter bundle (right ILF) as an MD cluster. Heavily PAE children showed lower FA and higher MD [compared to controls] in a subset of these regions. Significant correlations were observed between three continuous alcohol measures and DTI values at cluster peaks, indicating that white matter

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			Newborns were followed-up up to 13 y of age.	13 (controls)		damage in several regions is dose dependent. Lower FA in the regions of interest was attributable primarily to increased radial diffusivity rather than decreased axonal diffusivity, suggesting poorer axon packing density and/or myelination."
Biffen 2018 (30) (identifed by reference searching)				71 (total) 9 (FAS) 19 (pFAS) 24 (heavy PAE, no FASD) 19 (controls)	10.4±0.9 (FAS, pFAS) 11.0±0.7 (heavy PAE, no FASD) 10.6±0.5 (controls)	**<u>MRI findings:</u>** **Brain volumes:** "Total brain volumes were smaller in the children with FAS compared to all other groups." "Children in the FAS/pFAS group had smaller right hippocampi compared to both the non-syndromal PAE and control children, but this effect was no longer significant after adjustment for total intracranial volume." **PAE and brain volumes:** "Higher levels of PAE were associated with reductions in CC volume after adjustment for total intracranial volume. Although the effect of PAE on CC was confounded with smoking and lead exposure, additional analyses showed that it was not accounted for by these exposures." "In addition, higher levels of PAE were associated with bilateral volume reductions in caudate nuclei and hippocampi, effects that remained significant after control for total intracranial volume, child sex and age, socioeconomic status, maternal smoking during pregnancy, and childhood lead exposure."

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
Robertson 2016 (31)				78 (total) 28 (FAS/pFAS) 28 (heavy PAE, no FASD) 22 (controls)	10.7±0.6 (total)	**<u>MRI findings:</u>** **Intracranial Volume:** "Although the intracranial volume for the children with FAS/pFAS was smaller than for PAE and control groups, this difference fell short of levels of significance p<0.1." **Association of diagnostic group to cortical thickness:** "[…] revealed no significant clusters where cortical thickness differed by FASD diagnostic group." **Relation of continuous PAE measures to Cortical Thickness:** "After multiple comparison correction, there were no significant clusters in analyses relating cortical thickness to AA/day or drinking days/week. However, there were 3 regions in the right hemisphere in which AA/drinking occasion was inversely related to cortical thickness." - occipital cortex cluster: cuneus, pericalcarine cortex - occipitotemporal cluster: parts of fusiform and lingual gyri - parietal cluster: supramarginal/postcentral gyrus

AA: Absolute Alcohol; ADHD: Attention Deficit Hyperactivity Disorder; ANCOVA: Analysis of Covariance; ARND: Alcohol Related Neurodevelopmental Disorder; ASD: Autism Spectrum Disorder; CA: Cornu Ammonis; CC: Corpus Callosum; CIFASD: Collaborative Initiative on Fetal Alcohol Spectrum Disorders Study; CNS: Central Nervous System; DTI: Diffusion Tensor Imaging; FA: Fractional Anisotropy FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; GD: Growth Deficiency; ILF: Inferior Longitudinal Fascilus; IOM: Institute of Medicine; LoE: Levels of Evidence after the Oxford 2011 Levels of Evidence; MD: Mean Diffusivity; MRI: Magnetic Resonance Imaging; MWF: Myelin Water Fraction; ND-PAE: Neurodevelopmental Disorders associated with Prenatal Alcohol Exposure; OFC: Occipital Frontal Circumference; P: Percentile; PAE: Prenatal Alcohol Exposure; pFAS: partial FAS; RoB: Risk of Bias; SD: Standard Deviation; SE-PAE: Static Encephalopathy associated with Prenatal Alcohol Exposure; SES: Socioeconomic Status; WHO: World Health Organization

*** Biasbewertung (RoB)** in Anlehnung an das „Manual zur Bewertung des Biasrisikos in Interventionsstudien". 2. Auflage, 2021. Verfügbar unter: https://www.cochrane.de/de/literaturbewertung oder https://www.leitlinien.de/methodik. For all studies assessing PAE status: CLASSIFICATION of PAE EXPOSURE is generally associated with a high RoB (PAE, recall bias, outcome was known when women were questioned, the longer the time between the interviews and the pregnancy, the higher the risk for recall bias**). Confounders** including age of mother and/or child, BMI, sex of child, socioeconomic status and PAE (except for studies focusing only on PAE, PAE is considered as exposure).

§ Treit 2020 (19)**:** "[…] previously undiagnosed structural brain anomalies found unintentionally […]."; "Incidental findings were categorised as normal variants, non-clinically significant incidental findings, or clinically significant incidental findings."

$ Treit 2020 (19)**:** "Clinically significant incidental findings were anything considered to require further consultation, monitoring, and/or clinical follow-up."

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Merkmale von Studien, die sich mit funktionellen Aspekten bei PAE und/oder FASD befassen

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
Focus on a wide range of functional aspects N=15						
Branton 2022 (1)**: Motor abilities and intelligence** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** unclear RoB; **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 4**						
Branton 2022 (1)	cross-sectional design (retrospective evaluation at a single time point)	Canada, Alberta clinical setting	Children with confirmed PAE, scores for motor skills and intelligence, no genetic or other neurological diagnosis that precluded a diagnosis of FASD were included.	73 (23 only PAE, 50 with FASD)	total 10.5±2.9	**<u>Association of motor abilities and intelligence in PAE:</u>** **Tools of interest:** - Movement Assessment Battery for Children (MABC-2) - Wechsler Intelligence Scale for Children (WISC-4) **Findings:** "The study did not support the presence of a relationship between motor abilities and intelligence indicating that motor assessment and intelligence should be considered distinct constructs when investigating an FASD diagnosis. This finding contradicts the clinical assumption of a positive relationship between motor abilities and intelligence, which can lead to the clinical practice of excluding motor assessment from the diagnostic process. These results suggest that intelligence scores should not be used as a proxy for motor abilities, nor should they dictate when motor testing be completed. […] (p = 0.67 for the relationship between motor skills and intelligence)."
Zhou 2018 (2)**: Cognitive scores** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guideline, 4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Zhou 2018 (2) also in CNS structural	cohort study (prospective) **NeuroDevNet project** (3)	Canada, University of British Columbia, University of Alberta, University of Manitoba, Queens University clinical setting	"Brain MRI was acquired in a newly recruited sample of 157 participants across four Canadian sites in the NeuroDevNet project (3). […] Typically developing control children were recruited from the same geographic regions, matched as closely as possible for age and sex." "The diagnosis of FASD was made by experienced multidisciplinary teams using the Canadian Guidelines (4) from 2005 with 4-Digit Code that incorporates an objective method of evaluating core fields of growth deficiency, facial dysmorphology, brain impairment, alcohol exposure, and other pre and postnatal adverse factors (4)" "The alcohol history is confirmed from reliable sources such as birth records, child welfare reports, legal documents, and direct interview with the birth mother if available. In most cases, the exact amount and pattern of alcohol use in that pregnancy is not reported or recalled."	157 (total) 78 (PAE including 22 confirmed PAE without FASD, 7 FAS, 12 pFAS, 37 ARND) 79 (controls)	PAE 12.8±3.3 controls 12.1±3.3	**<u>Differences between PAE and controls in cognitive scores:</u>** **Test battery of interest:** Test battery included 5 major evaluations of core functions affected in PAE such as math, reading, executive function, memory, and inhibition: - WJ-III Tests of Academic Achievement - WRMT-R (reading ability, word identification [word ID]) - BRIEF (everyday executive function) - WMTB-C (standardized test battery to assess working memory, 2 subsets: digit recall measuring verbal/phonological working memory and block recall assessing visuospatial working memory) - NEPSY-II standardised neuropsychological test battery including the subsets: Animal Sorting; Auditory Attention; Response Set; Inhibition; Memory for Names **Key finding:** "The combined group of PAE participants performed worse than the controls in all cognitive scores [p<0.01]." *(Statistics not performed on the PAE subtypes; multiple numbers / data are provided in Table II in the publication of Zhou 2018* (2)*)*
Stevens 2017 (5)**: Social perception (RME test)** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB (questionable recruitment strategy); **CLASSIFICATION of FASD:** unclear RoB (different classification systems used); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclearRoB (there was no *a priori* protocol and selections based on outcome is not unlikely)						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4						
Stevens 2017 (5)	cross-sectional design (prospective evaluation at a single time point)	Canada, Toronto clinical setting	"The primary aim of the current study is to investigate social perception in children with FASD using the RMET-C and a similar scoring approach […]. Specifically, FASD controls are compared on overall RMET-C performance, as well as on difficulty level (Easy and Hard) and emotional valence (Positive, Negative, Neutral)." "The FASD group was recruited from two sources: letters mailed to families of past patients diagnosed at the Hospital for Sick Children (SickKids) FASD Clinic in Toronto, Canada and postings at local FASD parent support groups." "…all had documented evidence corroborating excessive maternal alcohol consumption and daily or frequent binges during pregnancy with alcohol as the primary cause of exposure." "Children in the control group were recruited from community postings or were biological children of the adoptive or foster parents of a participating child with FASD."	56 (total) 35 (FASD) 21 (controls)	FASD 9.9±1.3 controls 10.5±1.2	**<u>Social perception in FASD:</u>** **Tool of Interest:** Reading the Mind in the Eyes (RME) Test (Children's Version) **Findings (total RME score (mean±SD)):** FASD 18.24±2.4 vs. control 14.86±3.9; p<0.001 (Subscore for emotional valence, difficulty and Gender control Task displayed in Table 2 in the publication of Stevens 2017 (5)) "The results reveal that the children with FASD performed below the control children on the RME Total score, Easy items, and Positive, Negative, and Neutral emotional valence scores." "When the effects of age and IQ were further investigated, the results indicated that the Positive item scores increase with age in the control group only. Interestingly, children in the FASD group with ARND performed below those with pFAS/FAS on the Positive emotional valence items." "The current results suggest that compared with controls, children with FASD display significant difficulty in understanding emotional cues portrayed through the eye region, regardless of whether this information signals positive, negative, or neutral cues." "[…] the current findings show that the older control children scored higher than the younger children on the positive items, whereas this result is not observed in the FASD group. This

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						suggests that children with FASD may not undergo the typical improvements in social processing related to understanding facial cues and emotions […]."
Lange 2019 (6)**: Neurobehavioural status** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guidelines); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Lange 2019 (6) also in CNS structural	cross-sectional design (prospective evaluation at a single time point)	Canada, Toronto school setting	"A secondary analysis was conducted on data obtained from the Canadian component of the WHO International Study on the Prevalence of FASD (7). The Canadian FASD prevalence study employed a cross-sectional, observational design using active case ascertainment, along with retrospective collection of prenatal alcohol exposure information, to identify cases of suspected FASD […]." "The study procedures followed a step-wise approach, where only those students meeting predetermined criteria proceeded to the subsequent phase." Final diagnostic screening conclusions were made using the 2005 Canadian Guidelines (4)." "[…] a group of typically developing control children was randomly selected from a list of all students who completed Phase I and who did not meet the criteria for Phase II using a	86 (total) 21 (FASD including 3 FAS, 2 pFAS, 16 ARND) 28 (ADHD/ASD) 37 (controls)	FASD 9.7±0.8 (FAS) ADHD/ASD 9.3±1.0 controls 9.0±1.0	Neurodevelopmental status and behavior were derived from a battery of standardized tests and the Child Behavior Checklist (CBCL) **<u>Test battery / checklist:</u>** - **Neurodevelopmental assessments:** were conducted by using the WHO International Study on the Prevalence of FASD test battery (WASI-II, **WISC-IV,** NEPSY-II) - **Behavioral observations/ratings by parents:** Parents were asked to complete the CBCL to evaluate their child's social competencies and identify any behavioural problems. **<u>Findings:</u>** **FASD vs. controls:** When children with FASD were compared with typically developing control children, a "2-class model" fit the data best and resulted in a sensitivity of 95.2% (95% CI: 84.2–100.0%), specificity of 89.2% (95% CI: 78.4–97.5%) **FASD vs. ADHD/ASD + controls:** When children with FASD were compared with typically developing control children and children with other neurodevelopmental disorders, the neurodevelopmental profile (behavior, Subtests of IQ, spatio-visual, attention,

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			systematic sampling technique; these students underwent a complete assessment in Phase II."			language (word genereation, vocabulary, language comprehension, processing speed) correctly identified only 56.9% (95% CI: 45.1–69.2%) of typically developing children and children with other neurodevelopmental disorders as not having FASD, and thus the profile was found not to be specific to children with FASD. **Overall conclusion:** "The findings question the uniqueness of children with FASD with respect to their neurodevelopmental impairments and behavioural manifestations. […] the neurodevelopmental profile identified was sensitive to FASD, but it was not specific to FASD, suggesting that a neurodevelopmental profile that can differentiate children with FASD from children with other neurodevelopmental disorders may not exist. However, the findings are limited by the measures used in the analyses, as the inclusion of additional measures may have resulted in a more specific FASD neurodevelopmental profile. Also, data on the use of psychotropic medications were not available. […]
Treit 2017 (8)**: Cognitive test scores** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guidelines, 4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (study also included adults); LoE: 4**						
Treit 2017 (8) (also in CNS structural)	cohort study (mixture of prospective and retrospective data)	Canada, Alberta clinical and school setting	"PAE participants were primarily recruited through two FASD diagnostic clinics at the Glenrose Rehabilitation Hospital in Edmonton, Alberta, and were previously diagnosed according to the Canadian Guidelines (4) (2005) and the 4-Digit Code (9) (2004). The remaining FASD participants (n = 30)	144 (total) 70 (FASD including 10 FAS, 6 pFAS, 54	FASD 14.2±6.3 controls 13.2±6.0	**<u>Comparison of cognitive test scores between FASD and controls:</u>** **Age-standardized test scores provided in FASD vs. controls:** (higher scores reflect better performance in all tests) - **Wide Range Intelligence Test (WRIT):** (verbal and visual IQ): FASD<controls, p<0.001

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			were recruited through school and social work services, and were diagnosed clinically by primary care physicians and practitioners in other developmental disability clinics." "Twenty of the 70 FASD participants were included in previous studies […], and 50 were newly recruited. […]" "Controls were recruited through advertising on public bulletin boards in locations such as community centres, hospitals, recreation centres etc., by letters sent home from several public schools, and by word of mouth."	ARND/FASD without further specification) 74 (controls)		- **Woodcook Reading Mastery Test (WRMT-R):** (reading): FASD<controls, p<0.001 - **Woodcok Johnson subtest (WJ):** (Quantitative concepts – number series, knowledge about mathematic concepts): FASD<controls, p<0.001 - **Comprehensive Receptive and Expressive Vocabulary (CREVT):** (Receptive & expressive vocabulary): FASD<controls, p<0.001 - **NEPSY/D-KEFS:** (Executive function composite): FASD<controls, p<0.001 - **Working Memory Test Battery (WMTB-C):** (number-working-memory Digit): FASD<controls, p<0.001 - **WMTB-C:** (Block recall – Memory): FASD<controls, p<0.001 "No significant effects of group on Rey Complex Figure Test RCFT (age 6+) in immediate recall and delayed recall and recognition […]" (Rey Complex Figure Test for visual-spatial abilities and memory)
Kerns 2015 (10)**: Emotion recognition abilities** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guidelines, 4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to non-standardized tools (validity unclear)); LoE: 4-5**						
Kerns 2015 (10)	cross-sectional design (retrospective evaluation at a single time point)	Canada, British Columbia clinical and school setting	"Two samples of children were recruited for this study: children with a diagnosis of Fetal Alcohol Spectrum Disorder secondary to PAE and a typically developing control group." "To ensure that all children had sufficient cognitive abilities to understand the tasks, children with full-scale intelligence quotients outside of the average range (less than 70)	44 (total) 22 (FASD including 4 FAS, 6 pFAS, 4 ARND, 3 FASD brain and	FASD 11.2±2.2 controls 11.2±2.1	**<u>Emotion recognition abilities:</u>** - The tasks included measures of emotion recognition from 3 non-linguistic modalities: facial expressions, emotional tone of voice, and body positioning and movement - Participant's parents completed measures of adaptive and behavioural function that were related to children's performance on aspects of emotion recognition. **Test battery of interest:**

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			were excluded from the study." "[…] children in the FASD group were required to have a previously confirmed diagnosis from a qualified medical practitioner, and they either had at the time of diagnosis a 4-Digit Code that meet Canadian Diagnostic Guidelines for FASD (4) or had adequate testing to confirm a diagnosis if it was completed before these guidelines were adopted. Diagnostic labels such as [FAS], Fetal Alcohol Effects, [pFAS], or [ARND] were all accepted as confirmed diagnoses."	*alcohol code of 3 or 4)* 22 (controls)		- **Measures of Intelligence:** WASI; FAB; DANVA-2; Dynamic Faces Task; Point-light Walker Measure - **Perception Control Tasks:** FAB Facial Identity, Nonprosody Discrimination; created perceptual control condition for DANVA-2 Postures subtest; nonemotional point-light displays depicting nonemotional actions for Point-light Walker Measure **Findings:** - "Overall, the results show that children with FASD have more difficulties with emotion recognition than typically developing age-matched peers, but these difficulties may not be clinically significant (e.g., smaller effect size) or may be specific to the age of the individual exhibiting the emotion (i.e., child vs.. adult.") - WASI (Full-scale Intelligence): "[…] the two participant groups differed significantly […], though both groups scored within the average range of intellectual function." FASD<controls, p<0.01 - Perception Control Tasks: "As noted, to rule out the possibility that difficulties on tasks of emotion recognition could be secondary to differences in basic perceptual abilities or task understanding, all participants completed simple perceptual tasks […]. On these control tasks, children with FASD scored similarly to typically developing children with no differences noted between the groups." - Emotion Recognition – Faces: "The Facial Affect discrimination task, Child and Adult Faces subtests of the DANVA-2 and Dynamic Faces total error scores […] with Group (FASD vs.. controls) as independent variable and Age as a covariate to control for developmental

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						differences." → marginally significant group differences - Emotion Recognition – Prosody: Emotional Prosody Task and DANVA-2 Child and Adult Paralanguage task →"[…] significant group differences for emotion recognition based on prosody […]." - Emotion Recognition – Human Movements: "The MANOVA for the DANVA-2 Postures and the Emotional Point-Light display data did not reveal any significant group differences […]."
Rockhold 2021 (11)**: Executive and social functioning** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** not applicable (only PAE); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to non-standardized tools (validity unclear)); LoE: 4-5**						
Rockhold 2021 (11) CIFASD-4 (12)	case-control study	USA, Minnesota clinical setting	The post-hoc analyses described here analysed data from eighty-three preschool-age children with PAE (early childhood group; ages 2.5–5.0) and ninety-five adolescents (49 with PAE, 46 controls; ages 8–16). Each child completed executive function tasks as part of several prior studies. Children's parents completed social and communication inventories about their child's abilities. Thirty-three participants from the early childhood group returned for a four-year follow-up and completed both social and executive function measures. *PAE status:* Preschool children: partly	83 preschool children (all PAE) 95 adolescents (49 with PAE, 46 controls)	preschool children 2.5-5 (range) adolescents 8-16 (range)	**<u>Magnitude of executive and social functioning deficits in PAE:</u>** "Both the early childhood and adolescent groups with PAE showed deficits in social and executive functions." - "Within the early childhood PAE cohort, scores on all measures of executive and social funcitons were significantly different than test norms, […]." - "For this cohort at the 4-year follow-up, all executive and social functions standard scores were significantly different than test norms […]" - […] "the adolescent PAE group showed below-average mean scores across all executive and social functions measurements. The control group showed average mean scores in all domains." There was a relationship between social function and executive function within the adolescent PAE group that was not present

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			confirmed partly unconfirmed; adolescents: confirmed through maternal interviews or medical records in case-control-study			in the adolescent control group or the early childhood PAE group. However, at the four-year follow-up (mean age= 8.45 y), those originally in the early childhood PAE group also demonstrated this relationship."
Astley Hemingway 2020 (13)**: Risks for the impairment of brain functions** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Astley Hemingway 2020 (13) (also in CNS structural)	cross-sectional design (retrospective evaluation at a single time point)	USA, Seattle (Washington) clinical setting	"Study participants diagnosed with FASD by the University of Washington using the FASD 4-Digit Code (9, 14, 15) were compared to typically-developing peers with no PAE." (PAE confirmed in all FASD subjects and absence of PAE reported for all controls per birth mother report) "[…] data collected from a neuropsychological and magnetic resonance imaging (MRI) study from the year 2009 […] (6-19)" "Key outcome measures (composite and subtest scores) from the battery of assessments were selected in the original study (16-19) to represent the different domains of deficit (Figure 2). These same outcome measures served as the primary dependent variables for brain function in the current study"	50 (total with PAE) 11 (FAS/pFAS) 12 (SE-PAE) 11 (ND-PAE) 16 (controls)	FAS/pFAS 12.9±2.4 SE-PAE 12.5±2.7 ND-PAE 11.8±2.7 controls 12.4±2.7	**<u>Proportion of variance in function explained by pre- and postnatal risks:</u>** **Test Battery of interest:** (see also Fig. 2 in original study of Astley Hemingway 2020 (13)) - Soft Neurologic Signs: QNST-II - General Intellectual Function: WISC III - Academic Achievement: WIAT Basic Reading, KeyMath Revised - Visuospatial Skills, Visual Memory, Organization: VMI, RCFT - Executive Function: D-KEFS (Trail Making, Tower, Color-Word Interference, Verbal Fluency), WCST Computer Version (3rd Edition) - Visual Memory: CVLT-C - Attention: IVA CPT - Language: TOLD-I:3 - Sentence Combining, TLC (1-Expanded, 2-Expanded), TOWK Conjunctions and Transition Words - Adaptive Behavior: VABS - Behavioral Problems: CBCL 6-18 - Caregiver Report of Behavior: BRIEF

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			"[…] a control child matched on age (within 6 months), gender, and race was randomly invited."			Prenatal risks for alteration of brain function: maternal use of tobacco, marijuana, cocaine, any illicit drugs and no prenatal care (all measured on a yes/no scale). Postnatal risks for alteration of brain function: not living with either birth parent, number of foster placements, physical abuse, sexual abuse, SES of current caregiver **Findings:** - "PAE was the dominant risk factor explaining the largest proportion of variance in […] brain function (intellect, achievement, memory, language, executive-function, motor, adaptation, behavior-attention and mental health symptoms)." - "PAE accounted for […] up to 52% of the variance in CNS function […]. […] the number of days/week of drinking during pregnancy explained the greatest proportion of variation (43%) in the WISC-III Full Scale Intelligence Quotient (FSIQ) score and thus was the first statistically significant risk factor to enter into the regression equation. - Caregiver's years of education explained the 2nd greatest and statistically significant proportion of variance of the FSIQ (an additional 8% of variance). These two risk factors together explained 54% of the variance in the FSIQ. - Maternal drinking through all three trimesters was the third and final statistically significant risk factor to enter the equation, explaining an additional 4% of variance. - The three risk factors together explained a total of 58% of the variance in the FSIQ. […] Higher levels of prenatal alcohol use were correlated with lower FSIQ scores. Higher parental education levels were correlated with higher FSIQ scores."

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
Fuglestad 2015 (20)**: Executive functioning** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Fuglestad 2015 (20)	cross-sectional design (retrospective evaluation at a single time point)	USA clinical setting	We evaluated Executive Functioning in 39 children with FASD (3.0-5.5 years) and a comparison group of 50 age-matched, nonexposed controls. Exclusion criteria were developmental disorder (e.g., Autism, Down Syndrome), neurological disorder, traumatic brain injury […], or other medical condition affecting the brain or senses. Data on growth, facial dysmorphology, cognition, and alcohol exposure were collected and modified IOM criteria (21) were applied.	89 (total) 39 (FASD including 32 with PAE) 50 (controls)	total 3.0-5.5 (range)	**<u>Executive function measures:</u>** - Executive Functioning Scale for Early Childhood - Delay of Gratification - FASD group: The Mullen Scales of Early Learning [IQ-Measure] - Control group: Abbreviated IQ Battery of the Stanford-Binet Intelligence Scales [IQ-Measure] **<u>Findings:</u>** **Preschool children with FASD vs. controls:** Compared to age-matched controls, preschool children with FASD had impairments on the executive function Scale and showed more impulsivity on the Delay of Gratification task. […] IQ was correlated with the executive function scale (p=.001) and Delay of Gratification (p=.005).” **Pre-school children with PAE:** Executive function performance did not differ significantly across levels of FASD severity (FAS, pFAS, ARND). **Overall conclusion:** “These novel data show that executive function deficits manifest well before the age of 6 years in children with FASD, that they occur across the spectrum, and that executive function may be most impaired in children with more severe forms of FASD and/or lower IQs.”

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
Pinner 2021 (22)**: Behavioural and neuropsychological aspects** **Risk of bias*: CONFOUNDING:** unclear RoB; **SELECTION of PARTICIPANTS:** unclear RoB (not sufficiently described); **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** unclear RoB (not sufficiently described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: unclear risk of bias; concerns of the applicability of the results (due to non-standardizes tools (validity unclear)); LoE: 4**						
Pinner 2020 (22)	cross-sectional design (retrospective evaluation at a single time point)	USA, New Mexico clinical setting	"Data for this study were collected as part of a larger, multimodal neuroimaging study (23)." "Participants were classified as having an FASD using the IOM criteria (24) […]and also had IQ scores above the cut-off for intellectual disability <70." "Healthy controls had IQ scores above the cut-off for intellectual disability <70 and did not have known PAE or other substances; nor did they have histories of developmental delays or neurological or psychological problems."	33 (total) 13 (FASD) 20 (controls)	FASD 16.1±2.5 controls 16.5±2.1	**<u>Neuropsychological Evaluations and Behavior in FASD and controls:</u>** **Test battery of interest:** - WASI-II (IQ) - GPB (visual motor coordination) - CANTAB Spatial Working Memory (spatial working memory maintenance); CANTAB Cambridge Gambling Task (impulsive decision-making and risk taking); CANTAB Intra-Extra Dimensional Set Shift (reversal learning) **Findings:** "[Controls] performed significantly higher on the vocabulary subtest of the WASI-II, expressed higher overall IQ computed from the vocabulary and matrix reasoning subtests of the WASI-II, had less deliberation time on the Cambridge Gambling Task (a.e. Exekutivfunktionen) […], and had lower levels of impulsivity as assessed by the CGT relative to the FASD group […]." "No other neuropsychological evaluations and no saccadic behavioral measures showed significant group differences after FDR LSU correction for multiple comparisons (p's > 0.05)." (FDR LSU: False Discovery Rate Linear Step Up procedure= Stat. correction procedure because of multiple group comparisions)."
Lindinger 2022 (25)**: Reading Mind in Eye (RME) and executive functions**						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
Risk of bias*: CONFOUNDING: high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to a South African setting (not applicable to more economically advantaged populations)); LoE: 4**						
Lindinger 2022 (25)	longitudinal design (unclear if prospective)	South Africa, Cape Town clinical setting	"Participants were 42 prenatally heavily PAE adolescents […] and 20 controls from the same community […], who are participating in our Cape Town Longitudinal Cohort study (26) and had been administered the Reading the Mind in the Eyes (RME) test during late childhood […]." "The mothers of the study participants were recruited between 1999 and 2002 at their first antenatal care visit […].At recruitment, each mother was interviewed orally […] using a timeline follow-back interview regarding her drinking on a day-by-day basis during the preceding 2 weeks and during a typical week around time of conception. […]The timeline follow-back interview was repeated at mid-pregnancy and again at 1-month postpartum […]." Diagnostic: Revised IOM criteria (21)	62 (total) 8 (FAS) 15 (pFAS) 19 (only heavy PAE, no syndromes) 20 (controls)	total 11.0-17.2 (range)	**<u>Reading Mind in Eye (RME) test across age and executive functions:</u>** **Test battery of interest:** - RME test *(main test)* - IQ: WISC-IV *(at childhood);* WASI *(at adolescence)* - Working Memory *(both ages)*: WISC-IV Digit Span Backward - Cognitive Control: D-KEFS Colour-Word Interference Test (Inhibition; Inhibition/Switching; Trails *(additionally only at adolescence)* subtests) - Verbal Fluency *(both ages)*: D-KEFS - Verbal Fluency subtests (Letters; Categories; Switching) **Findings:** **Reading the Mind in the Eyes (RME) across age:** - "Children with FAS […] and pFAS […] performed worse on the RME than heavy PAE […] and control individuals […].By adolescence, the pFAS group performed similarly to heavy PAE and controls, whereas the FAS group continued to perform more poorly. - No deficits were seen for positively "valenced" items in any of the groups. For negative and neutral items, in late childhood individuals with FAS and pFAS performed more poorly than heavy PAE and controls, but by adolescence only the FAS group continued to perform more poorly. - Test–retest reliability was moderate across the two ages. At both time points, the effects in the FAS group were partially mediated by Verbal Fluency but not by other aspects of

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						executive function." **Executive function across age:** - "Higher levels of PAE, measured in terms of AA/day, were associated with poorer *Verbal Fluency* at both ages and with poorer *Cognitive Control* at 17 years. - At 11 years, the FAS and pFAS groups performed more poorly than the heavy PAE on Cognitive Control and Verbal Fluency. - At 17 years, the FAS group performed more poorly than the control group on *Verbal Fluency* and marginally more poorly than the heavy PAE, but the pFAS group no longer differed from the heavy PAE group. - The pFAS group performed more poorly than the heavy PAE and control groups on *Cognitive Control*."
Lucas 2016a (27)**: Gross motor performance** and **Lucas 2016b** (29)**: Soft neurological signs (SNS)** **Risk of bias*: CONFOUNDING:** moderate RoB; **SELECTION of PARTICIPANTS:** moderate RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guideline); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** moderate RoB; **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: moderate risk of bias; concerns of the applicability of the results (due to a remote Australian setting (aboriginal population)); LoE: 3-4**						
Lucas 2016a (27)	cross-sectional design (retrospective evaluation at a single time point)	Australia, Fitzroy Valley remote area / setting	"[…] in the current study, we report gross motor outcomes of children in the Lililwan Project (28)." "The Canadian Guidelines (4) for the diagnosis of FASD will be used to assign specific diagnoses along the FASD spectrum […]." (28) "The Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) is a standardised, validated, self-report tool that	108 (total) 65 (PAE including 21 FASD) 43 (no PAE)	total 7.5–9.6 (range)	**<u>Gross motor performance:</u>** **Test of interest:** Bruininks–Oseretsky Tests of Motor Proficiency Complete Form (BOT-2) **Findings:** **PAE vs. no PAE:** - "Children with PAE in comparison to no PAE had lower mean scores or score ranges in all composite subtests and most (70%) Subtasks." - "there was no significant difference in scores between

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
			estimates risk from maternal alcohol intake during pregnancy and was used as a proxy for PAE." "In the Lililwan Project, we assessed motor performance as part of the FASD diagnostic assessment using the Bruininks–Oseretsky Tests of Motor Proficiency Complete Form, Second Edition (BOT-2) based on recommendations from the Canadian Guidelines (4)." "All children born in 2002 or 2003 and living in the Fitzroy Valley during 2010/2011 were eligible to participate in the Lililwan Project; a population based study with active case ascertainment." Fritzroy valley: very remote communities with 4500 inhabitants			children with and without PAE for the three gross motor Composites or four gross motor Subtests. There was no dose relationship between the gross motor score and alcohol exposure (details see Table 5 in publication)" - "No significant difference in impairment rates was found between children with and without PAE." **FASD vs. no FASD:** - "Gross motor performance was significantly poorer in children with an FASD diagnosis than in those without, as indicated by the overall Gross Motor Composite score. Significantly lower scores were found in children with FASD for the Strength and Agility Composite, Running Speed and Agility and Strength Subtest and most (73.1%; 19/26) of the median Subtasks" - "In children with FASD compared with children without, a high prevalence of severe gross motor impairment was found in all Composite categories (9.5%, at least four times higher) and Subtest categories (range: 4.8–14.3%, at least 2-7 times higher)"
Lucas 2016b (29)						**<u>Neurological signs (soft):</u>** **Test of interest:** Quick Neurological Screening Test (QNST-2), Soft neurological signs (SNS) **Findings:** **PAE vs. no PAE:** - "The median QNST-2 Total Score was significantly higher (p=0.045) in children with PAE (20.0, range 4–66) than without PAE (16.5, range 4–66)." - "Children with PAE had significantly higher scores in two QNST tasks: Eye Tracking and Tandem Walk."

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						FASD vs. no FASD: - "The median QNST-2 Total Score was significantly higher (r=0.3, p=0.004) in children with FASD (22.0, range 11– 66) than in those without FASD (18.0, range 4–40)." - "For six QNST-2 tasks, children with FASD had significantly higher scores (poorer performance): Hand Skills, Figure Recognition and Production, Eye Tracking, Rapidly Reversing Repetitive Hand Movements, Left– Right Discrimination, and Behavioural Irregularities."
Ronen 2022 (30)**: Neurobehavioral screening tool (NST)** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (IOM criteria); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to a mixed population (children with FASD and comorbidities such as ADHD and other behavioural deficits)); LoE: 4**						
Ronen 2022 (30)	cross-sectional design (retrospective evaluation at a single time point)	Israel clinical setting	151 children and young adults of whom 40 were diagnosed with FASD with the updated clinical guidelines for diagnosing fetal alcohol spectrum (IOM criteria (31)) (original sample size 202, but children with known prenatal exposure to other substances were excluded) „Prenatal alcohol consumption was determined either by reports from the primary caregiver or by maternal history documented in medical records."	151 (total) 40 (FASD including 3 FAS, 22 pFAS, 15 ARND; 36 of the FASD group had a comorbid ADHD diagnosis) 111 (non-FASD; individuals	FASD 9.32±3.12 non-FASD 11.83±4.25	**<u>External validity of the Neurobehavioral Screening Tool (NST) (to identify additional characteristics of FASD):</u>** - The NST questionnaire results did not differ significantly between the FASD and the non-FASD group for any age range - NST demonstrated 72%-73% sensitivity, and 34%-36% specificity, in identifying FASD - Items 4 and 5 ('Lies or cheats', 'Lacks guilt after misbehaving') were the most predictive items in the NST - Other variables that were characteristic of the FASD group included: emotional regulation difficulties (p value <0.01), being born and adopted in Israel (vs. other countries) (p value <0.01) and younger age at the first visit to the clinic (p

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
				who were assessed for FASD, but did not reach the threshold for diagnostic criteria)		value <0.01) - Low specificity is explained by the use of the NST in a high-risk population of PAE with significant comorbidities such as ADHD and other behavioural deficits
Coles 2021 (32)**: Nonverbal battery for cognitive problems** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** not applicable (only PAE); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to the Ukranian setting and a "special" test battery for this population); LoE: 4**						
Coles 2021 (32)	cross-sectional design (prospective evaluation at a single time point)	Ukraine, Rivne and Khmelnitky clinical setting	For n = 10 children, there is no explanation why they were not included. "This cohort study (33) originally recruited 686 women of whom half drank alcohol at moderate to heavy levels, and half were controls reporting low drinking levels or abstaining. […] When infants were born, information was collected from medical records and direct examination on growth, physical features associated with prenatal alcohol exposure, and other factors affecting development. A subsample of mothers/children […] were followed into the preschool period drawn from those […] who had participated in follow-up at 6 and/or 12 months."	291 (total) 113 (PAE) 178 (without PAE)	PAE 4.02±0.42 without PAE 3.93±0.31	**<u>Nonverbal battery in early identification of cognitive problems in PAE:</u>** **Test battery focusing on:** - early executive functioning - visuospatial skills - areas of cognitive development **Included tests:** Differential Ability Scales, 2(nd) Edition (DAS-2) and several NEPSY/NEPSY-II subtests; other tests were adapted from commonly used non-standardized neuropsychological measures of executive functions (Preschool Spatial Span, Imitation Hand Game, A not B, Delayed Attention, Subject Ordered Pointing) **Findings:** "Although most children performed within the average range, PAE children had lower scores on DAS-II Summary Scores as well as on specific subtests. To evaluate the effects of alcohol

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
						dose during the pre-pregnancy recognition period and during mid-gestation of pregnancy, generalized linear regression models were used controlling for demographic and individual variables. In addition to DAS-II variables, measures reflecting sustained attention, working memory and ability to shift cognitive set were impacted by alcohol dose. Early executive function appears to subsume these performance differences." (DAS-II= nonverbal processing/ problem solving, spatial processing)." "Findings indicate that the effects of PAE can be identified in the preschool period and reliably measured using tests assessing nonverbal and spatial skills supported by executive functioning."
Focus on ND-PAE N= 5						
Kable 2018 (34)**: Validation of ND-PAE as a (possible) psychiatric disorder in FASD** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** unclear (dysmogphology checklist); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; concerns of the applicability of the results (due to non-standardizes tools (validity unclear)); LoE: 4**						
Kable 2018 (34)	cross-sectional design (retropsective evaluation at a single time point)	USA, Atlanta clinical setting	The internal validity of the proposed Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) was evaluated in children diagnosed with either FAS or pFAS who were 3–10 years of age and had enrolled in a math intervention study. Participants were identified from medical records under a HIPAA partial waiver and recruited and were required to have been	56 (with FAS or pFAS)	total 3-10 (range)	**<u>Validation of ND-PAE as a psychiatric disorder in FASD:</u>** **(i) Neurocognitive measures** (≥ 2 symptom: impairment in global intellectual functioning, executive functioning, learning, memory, or visual-spatial reasoning) **(ii) Self-regulation domain** (≥1 symptom: impairment in mood or behavioral regulation, attention deficits, or impulse control) **(iii) Adaptive Functioning** (≥2 symptoms: impairments in

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	**N**	**Age (years)** mean±SD	
			diagnosed with FAS or pFAS. A physical examination was conducted on all participants by a pediatric geneticist using a standard pediatric dysmorphology checklist (35), where characteristics associated with the disorder are listed and weighted based on their saliency for the FAS diagnosis (e.g., hypoplastic philtrum, small palpebral fissures, and thin vermillion receive 3 points and clindactyly receives 1 point). Scores ≥ 10 are assumed to indicate significant alcoholrelated dysmorphology.			communication, social, daily living skills and motor skills with at least one of the two symptoms being either communication or social impairments) "Symptoms were coded as present or absent using assessments conducted in the study, including standardized measures of neurocognitive and behavioral functioning, parent interview, and direct observations of the child. The number of endorsed ND-PAE symptoms was not related to environmental factors but was moderately related to the child's age. ND-PAE symptoms were highly consistent and this did not vary by age. Evidence suggested the ND-PAE adaptive symptoms may be too restrictive and only one symptom from this domain may be sufficient. Impulsiveness was not related to an endorsement of the ND-PAE disorder but research is needed with other clinical groups to establish the discriminative validity of this symptom." "The rate of endorsement for each symptom, domain, and ND-PAE disorder were computed […] for both cut-off values and methods of endorsing the adaptive functioning (AF) symptoms. Using AF 1 of 4 criteria, 82.1% received an endorsement for the ND-PAE disorder using cut-off value of 1.5 SD and 89.3% using a cut-off value of 1.0 SD. Using the AF 2 of 4 criteria, 60.7% received an endorsement for the disorder using cut-off value of 1.5 SD and 83.9% using a cut-off value of 1.0 SD."
Coles 2020 (36)**: Characterisation of ARND (behavioural and cognitive)** **Risk of bias*: CONFOUNDING:** high RoB (e.g. wide age range); **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** not applicable (only ARND, PAE); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
Coles 2020 (36)	cross-sectional design (retrospective evaluation at a single time point)	USA, Rocky Mountains, Midwest, Southeast, Pacific Southwest community and school setting	A total of 1.842 children seen as part of a surveillance study were evaluated for alcohol exposure and physical characteristics of FAS, and completed neurodevelopmental testing. 91 were identified as either ARND/behavioral or ARND/cognitive and contrasted with other groups to further identify distinguishing patterns. Alcohol criteria: - 6 or more standard drinks per week for 2 or more weeks during pregnancy and/or - 3 or more standard drinks per occasion on 2 or more occasions during pregnancy and/or - Documentation of alcohol-related social or legal problems in proximity to (prior to or during) the index pregnancy	409 (total) 47 (ARND/ behavioural) 44 (ARND/ cognitive) 49 (alcohol criterion met, but not FASD) 99 (any alcohol use (alcohol criterion not met, random sample)) 88 (children classified as low risk for developmental problems)	Not reported	**<u>Characterisation of ARND (PAE and the spectrum of outcomes):</u>** **Test battery of interest and focus:** - Cognitive and academic aspects (Differential Ability Scale (DAS): verbal and visual working memory, immediate and delayed recall, visual recognition and matching, processing and naming speed, phonological processing, and understanding of basic number concepts) - Emotional and behavioral aspects (CBCL) - Emotional and behavioral aspects (Teacher report) **Findings:** Multinomial logistic regression was used to examine the accuracy of classification and to identify factors contributing to such classification Children described as ARND/cognitive were distinct from other groups based on cognition and behavior as well as demographic factors (e.g., age, race, SES), child characteristics (e.g., gestational age; sex), and other drug exposures, while those described as ARND/behavioural differed only on behavior and other drug exposures. Logistic regression successfully discriminated ARND groups from children in other groups with accuracy ranging from 79% (Higher Risk) to 86.7% (Low Risk). Analysis suggests the effects of alcohol on behavior and cognition even in the absence of the characteristic facial features and growth deficiency
Johnson 2018 (37)**: Overlaps between ND-PAE and ARND** **Risk of bias*: CONFOUNDING:** high RoB (e.g. wide age range); **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** not applicable (only ARND, PAE); **MISSING DATA:** unclear RoB						

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
(authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Johnson 2018 (37)	cross-sectional design (retrospective evaluation at a single time point)	USA, North Dakota clinical setting	Clinical charts from 06/2013 to 07/2016 were reviewed to identify patients with an evaluation for ARNDs and where the criteria for ND-PAE were also available. Inclusion criteria were all children from birth through 18 years of age, both sexes, all levels of intellectual functioning who were seen and given a diagnosis of ARNDs with confirmed prenatal alcohol exposure, and had both the ARND and neurodevelopmental disorders associated with prenatal alcohol exposure (ND-PAE) criteria in the chart.	86 (ARND and ND-PAE)	total 7.9±4.5 (range 0-18)	**<u>Diagnostic criteria for ND-PAE (from DSM-5) in comparison to the ARND Behavioral Checklist (=reference checklist):</u>** **Findings:** "The review found 86 charts with a diagnosis of ARNDs, which included the ARND Checklist and the ND-PAE criteria. We then calculated the sensitivity and specificity comparing the ND-PAE with the ARND Checklist as the comparison standard. The sensitivity was 95.0%, specificity was 75.0%, and the ND-PAE diagnosis correctly classified 89.5% of cases identified as meeting criteria for ARNDs by the checklist. […]The 2 diagnostic constructs of ARNDs and ND-PAE seem to be very similar." **Differences for age groups:** 0-6 y: sensitivity: 93%, specificity: 100%, accuracy: 94.6% 7-18 y: sensitivity: 97%, specificity 57%, accuracy: 85.7%
Sanders 2020 (38)**: Validation of ND-PAE as a psychiatric disorder** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guideline); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influcenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Sanders 2020 (38)	cross-sectional design (prospective evaluation at a single time	Canada, Alberta clinical setting	Children age 7–15 (53% female) with confirmed PAE who underwent multidisciplinary FASD assessments from 2016 to 2019 in a clinic in Alberta, Canada Canadian Guidelines (39) for FASD diagnosis DSM-5 (40) for ND-PAE	53 (total) 41 (FASD) 24 (ND-PAE)	total 7-15 (range)	**<u>Validation of ND-PAE as a psychiatric disorder in FASD:</u>** "Construct and factorial validity of ND-PAE were assessed, and associations between domains and symptoms described. Post hoc analysis assessed external validity of factors: ND-PAE demonstrated weak construct validity with variable convergence and divergence within and between symptoms.

Reference	Study design	Country, Setting	Population			Diagnostic procedures
			Patient population	N	Age (years) mean±SD	
	point)					Factor analysis revealed one strong factor consisting of abilities associated with adaptive behavior and general cognitive ability. Relative contribution of symptoms and domains were variable. This study provides an evidence-based approach to assessing ND-PAE symptoms and is a starting point to elucidating its neurobehavioral pattern."
Sanders 2017 (41)**: Diagnostic classification of ND-PAE using DSM-5 and Canadian guideline** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD: low RoB (Canadian Guideline); MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 3-4**						
Sanders 2017 (41)	cross- cross-sectional design (retrospective evaluation at a single time point)	Canada, Alberta clinical setting	Diagnostic FASD: Canadian FASD diagnostic guidelines (4) Diagnostic ND-PAE: DSM-5 criteria (40) 82 patients underwent multidisciplinary clinical evaluations between 2011 and 2015 […]. Two clinicians independently reviewed patient files for evidence of diagnostic criteria for ND-PAE when applying an impairment cut-off level of 2 or more SD below the mean, or clinically significant impairment in the absence of standardized norm-referenced measures. Confirmation of alcohol exposure was obtained from direct maternal self-report or professional documentation such as hospital, social work or police records.	82 (total) 79 (PAE including 60 FASD, 1 FAS, 13 pFAS, 46 ARND) 3 (no PAE)	total 7-47 (range) (of 60 FASD: 43 children, 17 adults)	**<u>Diagnostic classification of ND-PAE (DSM-5</u>** (40)**<u>) with the Canadian FASD guidelines</u>** (4) **<u>(=reference guideline):</u>** **ND-PAE (DSM-5** (40)**) vs. Canadian guideline** (4)**:** specificity 100% (95% CI 87.7%–100%); sensitivity 47% (95% CI 33.7%–60%) "Although there is considerable overlap between the areas assessed in DSM-5 and those assessed in the Canadian FASD guidelines, the DSM-5 criteria for ND-PAE were less likely to identify patients who met the Canadian neurobehavioral criteria for FAS, partial FAS and ARND while using a threshold of 2 or more SDs on norm referenced measures. Of particular note, ND-PAE criteria failed to reliably identify the presence of pFAS and FAS, which diagnoses incorporate cardinal facial features that are highly specific to the effects of PAE."

AA: Absolute Alcohol; ADHD: Attention Deficit Hyperactivity Disorder; AF: Adaptive Functioning; ARND: Alcohol Related Neurodevelopmental Disorder; ASD: Autism Spectrum Disorder; BOT: Bruininks–Oseretsky Tests of Motor Proficiency; BRIEF: Behavior Rating Inventory of Executive Function; CANTAB: Cambridge Neuropsychological Test Automated Battery; CBCL: Child behaviour Checklist; CCTT: Children's Colour Trails Task; CGT: Cambridge Gambling Task; CI: Confidence Interval; CIFASD: Collaborative Initiative on Fetal Alcohol Spectrum Disorders; CNS: Central Nervous System; CREVT: Comprehensive Receptive and Expressive Vocabulary Test; CVLT-C: California Verbal Learning Test-Children's Version; DANVA: Diagnostic Analysis of Nonverbal Accuracy; DAS: Differential Ability Scales; D-KEFS: Delis-Kaplan Executive Functioning System; DSM: Diagnostic and Statistical Manual of Mental Disorders; FAB: Florida Affect Battery; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; FDR LSU: False Discovery Rate Linear Step Up procedure; FSIQ: Full Scale Intelligence Quotient; GPB: Grooved Pegboard; HIPAA: Health Insurance Portability and Accountability Act; IOM: Institute of Medicine; IQ: Intelligence Quotient; IVA CPT: Integrated Visual and Auditory Continuous Performance Test; LoE: Levels of Evidence after the Oxford 2011 Levels of Evidence; MABC: Movement Assessment Battery for Children; MANOVA: Multivariate Analyses of Variance; ND-PAE: Neurobehavioral Disorder associated with Prenatal Alcohol Exposure; NEPSY: "A Developmental NEuroPSYchological Assessment"; NST: Neurobehavioral Screening Tool; PAE: Prenatal Alcohol Exposure; pFAS: partial FAS; QNST: Quick Neurological Screening Test; RCFT: Rey Complex Figure Test; RME/RMET-C: "Reading the Mind in the Eyes" / Test – Children's Version; RoB: Risk of Bias; SD: Standard Deviation; SE-PAE: Static Encephalopathy associated with Prenatal Alcohol Exposure; SES: Socioeconomic Status; SNS: Soft Neurological Signs; TLC: Test of Language Competence; TOLD-I:3: Test of Language Development – Intermediate 3rd Edition; TOWK: Test of Word Knowledge; VABS: Vineland Adaptive Behavior Scales; VMI: Developmental Test of Visual-Motor Integration; WASI: Wechsler Abbreviated Scale of Intelligence; WCST: Wisconsin Card Sorting Test; WHO: World Health Organization; WIAT: Wechsler Individual Achievement Test; WISC: Wechsler Intelligence Scale for Children; WJ: Woodcock Johnson; WMTB-C: Working Memory Test Battery for Children; WRIT: Wide Range Intelligence Test; WRMT-R: Woodcock Reading Mastery Test Revised

*** Biasbewertung (RoB)** in Anlehnung an das „Manual zur Bewertung des Biasrisikos in Interventionsstudien". 2. Auflage, 2021. Verfügbar unter: https://www.cochrane.de/de/literaturbewertung oder https://www.leitlinien.de/methodik. For all studies assessing PAE status: CLASSIFICATION of PAE EXPOSURE is generally associated with a high RoB (PAE, recall bias, outcome was known when women were questioned, the longer the time between the interviews and the pregnancy, the higher the risk for recall bias**). Confounders** including age of mother and/or child, BMI, sex of child, socioeconomic status and PAE (except for studies focusing only on PAE, PAE is considered as exposure).

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Merkmale von Studien, die sich mit pränataler Alkoholexposition befassen

Reference	Study design	Country, Setting	Population			Findings
			Population included	N	Age (years) mean±SD	
Astley 2019 (1)**: Correlation between the FAS facial phenotype and PAE** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (4-Digit Code); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; unclear concerns of the applicability of the results (authors also refer to an animal study from 1992 in their result section); LoE: 4**						
Astley Hemingway 2019 (1)	cross-sectional design (retrospective evaluation at a single time point)	USA, Seattle (Washington) patient records from 1993-2012 reassessed	"The records of 1392 patients were drawn from 1522 consecutive patients that received an FASD diagnostic evaluation at the FASDPN using the FASD 4-Digit Code (2)."	1392 (total with FASD)	total 0-19+ (range) (19+: 4%)	**Of note:** Importance of PAE selective and often unclear reported by the authors **<u>Correlation between the FAS Facial Phenotype and PAE:</u>** **Hypotheses of the authors:** "[…] If the FAS facial phenotype is specific to PAE, validation studies should confirm the FAS facial phenotype is more prevalent among those with higher exposure and does not occur in individuals with confirmed absence of PAE. One would also expect that the majority of (if not all) individuals presenting with the FAS facial phenotype would meet criteria for a diagnosis under the umbrella of FASD." **Findings:** "[…] the 4-Digit Code Rank 4 FAS face was 5 times more prevalent in the Rank 4 high exposure group than the Rank 3 moderate exposure group (p=0.000) . […] The association between the 4-Digit FAS face and alcohol was weakened substantially when the Hoyme criteria (3) for alcohol exposure were used (p=0.02). The 4-Digit FAS face was only 2-fold more prevalent in the Hoyme exposed group relative to the Hoyme unknown/too-low exposure group." **<u>Does PAE cause moderate dysfunction?</u>**

Reference	Study design	Country, Setting	Population			Findings
			Population included	N	Age (years) mean±SD	
						Methods used of the authors to address this question: "To address this question, the 4-Digit Code was applied to our nonhuman-primate model of FASD (4) to document the distribution of diagnostic (FAS/pFAS, SE-PAE, ND-PAE and Not FASD/PAE) outcomes when the only risk factor present was PAE. The primates had been exposed weekly to binge exposures equivalent to a six-pack of beer for the first 3, 6 or entire 24 weeks of gestation (mean maternal peak plasma ethanol concentrations ranged from 176 to 271 mg/dl)." **Findings:** " The primate model confirmed PAE causes a spectrum of outcome (FAS/pFAS 5%, SE-PAE 31%, ND-PAE 59%, and Not FASD/PAE 5%) with moderate dysfunction (ND-PAE/PAE) being the most prevalent. The 4-Digit Code was the only system that produced a near identical distribution of diagnoses across the full spectrum (including 53% ND-PAE). The Australian and Canadian outcomes were in greatest contrast with the primate model due to their exclusion of moderate dysfunction from the spectrum. The Australian, Canadian and Hoyme systems placed 51% to 81% of patients with PAE in the "Not FASD" category, in contrast to the 5% observed in the primate model." **General comment on this study:** Inconclusive if (i) more pronounced PAE results in more severe FAS and less alcohol in pFAS/ARND and inconclusive if (ii) PAE confirmation is required for FASD.
Petryk 2019 (5)**: "Setting a PAE threshold for diagnosis requires a level of detail and accuracy that does not exist"** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD: low RoB (Canadian Guideline); MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely)						

Reference	Study design	Country, Setting	Population			Findings
			Population included	N	Age (years) mean±SD	
OVERALL: high risk of bias; unclear concerns of the applicability of the results (children involved in a youth service); LoE: 4						
Petryk 2019 (5)	cross-sectional (retrospective, mixed-method study)	Canada setting children involved in child and youth service	146 patient charts referred for an FASD assessment applying the 2015 Canadian Guidelines (6) for PAE to those already diagnosed with FASD	146 (FASD including 2 FAS, 10 pFAS, SE-PAE 82, 51 ND-PAE, 1 diagnoses is missing) (87/146 with confirmed PAE)	total 9-10 (range)	**Background of this review:** The revised 2015 Canadian Guidelines (6) requires a more specific PAE threshold for a FASD diagnosis. The unintended consequences of adhering to the suggested PAE threshold for an FASD diagnosis and the challenges professionals face in obtaining an accurate PAE history were explored using a mixed methods study design. […], the study was carried out in two parts (Quantitative and Qualitative). PAE history and FASD diagnosis was reviewed retrospectively from 146 patient charts referred for an FASD assessment between 2011 and 2016. The challenges experienced when collecting the PAE history were explored through interviews with 23 professionals. **Findings:** • Of 146 assessments, only 21.9% met the revised 2015 PAE guidelines while 79.4% met the previous 2005 PAE criteria. • Of 146 clients, 54.1% met brain criteria for FASD yet of those only 29.1% met the revised PAE criteria whereas 70.9% did not and therefore could lose their FASD diagnosis under a diligent application of PAE level suggested in the 2015 Guidelines (1 of 2 client with full FAS and 6 of 10 with pFAS would lose their diagnoses). • Thematic analysis of the interview data indicated that obtaining a reliable PAE history was challenging and a combination of methods are employed to get credible

Reference	Study design	Country, Setting	Population			Findings
			Population included	N	Age (years) mean±SD	
						information. Three out of every four individuals in the present study lost their FASD diagnosis following implementation of 2015 Canadian FASD Guidelines (6).
Lange 2019 (7)**: "FASD: Neurodevelopmentally and behaviourally indistinguishable from other neurodevelopmental disorders"** **Risk of bias*: CONFOUNDING:** high RoB; **SELECTION of PARTICIPANTS:** high RoB; **CLASSIFICATION of FASD:** low RoB (Canadian Guidelines); **MISSING DATA:** unclear RoB (authors did not provide sufficient information regarding missing data); **MEASUREMENT of OUTCOMES:** high RoB (the outcome measurement can be influenced by knowledge of the exposure or the definition of FASD, no blinding described); **SELECTION of REPORTED RESULTS:** unclear RoB (there was no *a priori* protocol and selections based on outcome is not unlikely) **OVERALL: high risk of bias; no concerns of the applicability of the results; LoE: 4**						
Lange 2019 (7) (also in CNS functional and structural)	cross-sectional design (for outcome PAE: retrospective evaluation at a single time point)	Canada, Toronto clinical setting	"A secondary analysis was conducted on data obtained from the Canadian component of the WHO International Study on the Prevalence of FASD (8). The Canadian FASD prevalence study employed a cross-sectional, observational design using active case ascertainment, along with retrospective collection of prenatal alcohol exposure information, to identify cases of suspected FASD […]." "The study procedures followed a step-wise approach, where only those students meeting predetermined criteria proceeded to the subsequent phase." Final diagnostic screening conclusions were made using the 2005 Canadian Guidelines (9)." "[…] a group of typically developing control children was randomly selected from a list of all	86 (total) 21 (FASD including 3 FAS, 2 pFAS, 16 ARND) 37 (controls) 28 (ADHD/ASD)	9.7±0.8 (FASD) 9.3±1.0 (ADHD/ASD) 9.0±1.0 (controls)	**Overall author conclusion of this study:** "The findings question the uniqueness of children with FASD with respect to their neurodevelopmental impairments and behavioural manifestations. […] the neurodevelopmental profile identified was sensitive to FASD, but it was not specific to FASD, suggesting that a neurodevelopmental profile that can differentiate children with FASD from children with other neurodevelopmental disorders may not exist. However, the findings are limited by the measures used in the analyses, as the inclusion of additional measures may have resulted in a more specific FASD neurodevelopmental profile. […]" **General comment on this study:** Study may indicate that PAE is important to confirm ARND, because the neurodevelopmental profile is not specific for FASD. Inconclusive for pFAS and FAS (because of the presence of other diagnostic columns).

Reference	Study design	Country, Setting	Population			Findings
			Population included	N	Age (years) mean±SD	
			students who completed Phase I and who did not meet the criteria for Phase II using a systematic sampling technique; these students underwent a complete assessment in Phase II."			

ADHD: Attention Deficit Hyperactivity Disorder; ARND: Alcohol Related Neurodevelopmental Disorder; ASD: Autism Spectrum Disorder; CNS: Central Nervous System; FAS: Fetal Alcohol Syndrome; FASD: Fetal Alcohol Spectrum Disorder; FASDPN: (University of Washington) Fetal Alcohol Syndrome Diagnostic & Prevention Network; LoE: Levels of Evidence after the Oxford 2011 Levels of Evidence; ND-PAE: Neurobehavioral Disorder associated with Prenatal Alcohol Exposure; PAE: Prenatal Alcohol Exposure; pFAS: partial FAS; RoB: Risk of Bias; SE-PAE: Static Encephalopathy associated with Prenatal Alcohol Exposure; WHO: World Health Organization

*** Biasbewertung (RoB)** in Anlehnung an das „Manual zur Bewertung des Biasrisikos in Interventionsstudien". 2. Auflage, 2021. Verfügbar unter: https://www.cochrane.de/de/literaturbewertung oder https://www.leitlinien.de/methodik. For all studies assessing PAE status: CLASSIFICATION of PAE EXPOSURE is generally associated with a high RoB (PAE, recall bias, outcome was known when women were questioned, the longer the time between the interviews and the pregnancy, the higher the risk for recall bias**). Confounders** including age of mother and/or child, BMI, sex of child, socioeconomic status and PAE (except for studies focusing only on PAE, PAE is considered as exposure).

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A. 13 Eingeschlossene Studien der systematischen Literaturrecherche zu Diagnostik der FASD (dritter Teil des Leitlinienprojektes 2022)

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A. 14 Methodik systematische Literaturrecherche – Interventionen für Kinder und Jugendliche mit FASD (2022)

Einschlusskriterien mit Relevanzbewertung der Endpunkte

P	Kinder und Jugendliche mit Fetalen Alkoholspektrumstörungen FASD (0–18 Jahre)
I	- Medikamentöse Therapien des Kindes/Jugendlichen: • Stimulanzien • Neuroleptika • Nahrungsergänzungsmittel • Medikamente zur Regulierung des Schlafrhythmus - Nicht-medikamentöse Therapien: • Psychoedukation des Kindes/Jugendlichen • Psychoedukation der Eltern/Sorgeberechtigten/Bezugspersonen • Funktionelle, nicht-medikamentöse Intervention beim Kind/Jugendlichen: ○ Ergotherapie ○ Physiotherapie ○ Sprachtherapie ○ Psychotherapie ○ Training spezifischer schulischer Fertigkeiten (z. B. Mathematik) - Kombiniert medikamentös-nicht-medikamentöse Interventionen - Andere funktionelle Therapien
C	- Keine Intervention - Placebo - Kontexteffekt - Alternative Intervention - Vorher-Nachher-Vergleich
O	- Verbesserung des neuropsychologischen Funktionsniveaus/ Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD z. B. (Relevanz 8): • Kognitive Leistung/Intelligenz • Entwicklung • Epilepsie • Sprache • Fein-/Graphomotorik oder grobmotorische Koordination • Räumlich-visuelle Wahrnehmung oder räumlich-konstruktive Fähigkeiten • Exekutivfunktionen

	• Rechenfertigkeiten • Lern- und Merkfähigkeit • Aufmerksamkeit • Soziale Fertigkeiten und Verhalten - Vermeidung von Nebenwirkungen der Interventionen (Relevanz 9) - Reduktion von Komplikationen/Sekundärerkrankungen z. B. (Relevanz 8): • Somatische Erkrankungen • Psychiatrischen Erkrankungen inkl. Suchterkrankungen • Risikoverhalten (riskanter Alkohol-/Drogenkonsum, Eigen-/Fremdgefährdung, suizidale Handlungen) • Schulversagen und -abbruch (bzw. höhere Rate an Schulabschlüssen und Berufsausbildungen) • Delinquenz • Misshandlung • Krankenhaus- oder sonstigen stationären Aufenthalten - Verbesserung der Partizipation der Kinder/Jugendlichen mit FASD (Relevanz 9) • Lernen und Wissensanwendung • Allgemeine Aufgaben und Anforderungen • Kommunikation • Mobilität • Selbstversorgung • Häusliches Leben • Interpersonelle Interaktion und Beziehungen • Bedeutende Lebensbereiche • Gemeinschafts-, soziales- und staatsbürgerliches Leben - Verbesserung der Lebensqualität der Kinder/Jugendlichen mit FASD (Relevanz 9) - Entlastung der Bezugspersonen (biologische, Pflege- und Adoptiv-Eltern, Bezugsbetreuer*innen) und Verbesserung der Lebensqualität der gesamten betroffenen Familie/Einrichtung (Relevanz 8) - Verbesserung des Wissens um den abweichenden Gesundheitszustand/die Erkrankung/Störung/Behinderung und Verbesserung der Krankheitseinsicht (Relevanz 8) - Verbesserung der Krankheitsbewältigung/Coping und Selbstwirksamkeit (Relevanz 8)

P: Patient*innen, I: Intervention (hier Indextest), C: Comparator (hier Vergleichstest), O: Outcomes

Ausschlusskriterien auf Abstrakt- und Volltextebene

A1	andere Erkrankung
A2	Studien an Tieren/in vitro
A3	Keine Intervention
A4	Methodik der Publikation, anderer Publikationstyp
A5	unsystematischer Review
A6	Alter der Probanden überwiegend >18 Jahre
A7	Publikationsjahr vor 2012
A8	Doppelpublikationen (Dubletten)

Die systematische Literaturrecherche umfasste den Zeitraum von 01.01.2012 bis 09.08.2022.

Im Folgenden sind die genutzten Datenbanken für die systematische Suche sowie die Trefferzahlen der einzelnen Datenbanken aufgelistet:

- Medline über PubMed (n = 2.112)
- Wiley Online Library über Cochrane Library (n = 56)
- PsycINFO, PsycARTICLES, PSYNDEX über Ebsco (n = 319)
- Epistemonikos (n = 431)

Nach Sichtung von Titel und Abstract der identifizierten Publikationen wurden insgesamt 203 Publikationen eingeschlossen und zur Volltextsichtung zugelassen. Nach der Volltextsichtung wurden 32 Publikationen zur Evidenzbewertung eingeschlossen. Eine anschließende Handrecherche am 31.10.2022 ergab keine weiteren Publikationen, die alle Suchkriterien erfüllten.

Recherchestrategie in Pubmed am 09. August 2022

((fetal alcohol spectrum disorder*[tw] OR (FASD*[tiab] AND alcohol*[tiab]) OR alcoholic related birth defect*[tiab] OR alcoholic related neurodevelopmental disorder*[tiab] OR (("fetus"[MH] OR fetus[tiab] OR foetus[tiab] OR fetal[tiab] OR foetal[tiab] OR embryopathy[tiab] OR prenatal*[tiab] OR antenatal*[tiab]) AND (alcohol*[tiab] OR ethanol[tiab]) AND (disease*[tiab] OR disorder*[tiab] OR syndrome*[tiab] OR deficit*[tiab] OR effect*[tiab] OR expos*[tiab]))))

AND

((“therapeutics”[MH] OR “therapeutic use”[SH] OR “therapy”[SH] OR therap*[tiab] OR intervention*[tiab] OR treatment*[tiab] OR training*[tiab] OR stimulat*[tiab] OR program*[tiab] OR workshop*[tiab] OR support*[tiab] OR “education”[MH] OR education*[tiab] OR ergotherap*[tiab] OR physiotherap*[tiab] OR “Motor Activity”[MH] OR “Sports”[MH] OR sport*[tiab] OR exercise*[tiab] OR physical activit*[tiab] OR

hippotherap*[tiab] OR horseback*[tiab] OR “Psychotherapy”[MH] OR psychotherap*[tiab] OR psychoeducation*[tiab] OR neurofeedback*[tiab] OR biofeedback*[tiab] OR rehabilitation*[tiab] OR “Relaxation”[MH] OR “Relaxation Therapy”[MH])

OR

(“Chemicals and Drugs Category”[MH] OR Drug*[tiab] OR medication*[tiab] OR stimulant*[tiab] OR hormon*[tiab] OR “Pharmacological and Toxicological Phenomena”[MH] OR (drug*[tiab] AND (therap*[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR (medic*[tiab] AND (therap*[tiab] OR treatment*[tiab] OR intervention*[tiab])) OR pharmaco*[tiab] OR psychotropic*[tiab] OR psychoactiv*[tiab] ORpsychiatric*[tiab] OR adrenergic*[tiab] OR antipsychotic*[tiab] OR analeptic*[tiab] OR psychostimulant*[tiab] OR (tranquilizing[tiab] AND (drug*[tiab] OR agent*[tiab] OR medicin*[tiab] OR medication*[tiab])) OR tryptamin*[tiab] OR melatonin*[tiab] OR methylphenidat*[tiab] OR amphetamin*[tiab] OR amfetamin*[tiab] OR dextroamphetamin*[tiab] OR dextroamfetamin*[tiab] OR dexedrin*[tiab] OR lisdexamphetamine Dimesylate*[tiab] OR lisdexamfetamine Dimesylate*[tiab] OR guanidin*[tiab] OR guanfacin*[tiab] OR atomoxetin*[tiab] OR bupropion*[tiab] OR neuroleptic*[tiab] OR risperidon*[tiab] OR pipamperon*[tiab] OR metylperon*[tiab] OR methylperon*[tiab] OR melperon*[tiab] OR benzodiazepin*[tiab] OR olanzapin*[tiab] OR aripiprazol*[tiab] OR quetiapine Fumarat*[tiab] OR seroquel*[tiab] OR chlorprothixen*[tiab] OR chlorprotixen*[tiab] OR methotrimeprazin*[tiab] OR levomepromazin*[tiab] OR promethazin*[tiab] OR prometazin*[tiab] OR chloral hydrat*[tiab] OR clonidin*[tiab] OR SSRI*[tiab] OR SNRI*[tiab] OR inhibitor*[tiab] OR fluoxetin*[tiab] OR citalopram*[tiab] OR cytalopram*[tiab] OR sertralin*[tiab] OR mood stabilizer*[tiab] OR valproic acid*[tiab] OR divalproex*[tiab] OR lamotrigin*[tiab] OR nutrition*[tiab] OR "Dietary Supplements"[MH] OR ((food*[tiab] OR diet*[tiab]) AND supplement*[tiab]) OR "plants, medicinal"[MH] OR probiotic*[tiab] OR vitamin*[tiab] OR mineral*[tiab])))

NOT

(animal study[ti] OR animals study[ti] OR animal survey[ti] OR animals survey[ti] OR animal model*[ti] OR mice[MH] OR mice[ti] OR mouse[ti] OR rats[MH] OR rats[ti] OR rat[ti] OR zebrafish[ti] OR drosophila[ti] OR in vitro[ti])

Filter: Humans, English, German, since 2012

Recherchestrategie in Ebsco am 09. August 2022

#1:

SU (fetal alcohol syndrome* or fasd or fetal* alcohol spectrum disorder* or prenatal* alcohol exposure* or alcohol* related fetal damage* or alcohol* related birth defect* or alcohol* related neurodevelopmental disorder* or fetal alcohol exposure*) OR TI (fetal alcohol syndrome* or fasd or fetal* alcohol spectrum disorder* or prenatal* alcohol exposure* or alcohol* related fetal damage* or alcohol* related birth defect* or alcohol* related neurodevelopmental disorder* or fetal alcohol exposure*) OR AB (fetal alcohol syndrome* or fasd or fetal* alcohol spectrum disorder* or prenatal* alcohol exposure* or alcohol* related fetal damage* or alcohol* related birth defect* or alcohol* related neurodevelopmental disorder* or fetal alcohol exposure*)

#2:

SU (therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR motor Activit* OR sport* OR

exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR Relaxation) OR TI (therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR motor Activit* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR Relaxation)

#3:

SU (Drug therapy OR Drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR Dietary Supplements OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*) OR TI (Drug therapy OR Drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR Dietary Supplements OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*)

#4:

SU (animal research* OR animal stud* OR animal survey OR animal model* OR mice OR mouse OR rat* OR zebrafish OR drosophila OR in vitro) OR TI (animal research* OR animal stud* OR animal survey OR animal model* OR mice OR mouse OR rat* OR zebrafish OR drosophila OR in vitro)

#5:

(#1 AND (#2 OR #3)) NOT #4

Limited: since 2012

Recherchestrategie in Epistemonikos am 09. August 2022

((title:((FASD AND alcohol*) OR "alcohol related birth defect" OR "alcohol related neurodevelopmental disorder" OR ((fetus OR foetus OR fetal* OR foetal* OR embryopathy OR prenatal* OR antenatal*) AND (alcohol* OR ethanol*) AND (disease* OR disorder* OR syndrome* OR deficit* OR effect* OR expos*))) OR abstract:((FASD AND alcohol*) OR "alcohol related birth defect" OR "alcohol related neurodevelopmental disorder" OR ((fetus OR foetus OR fetal* OR foetal* OR embryopathy OR prenatal* OR antenatal*) AND (alcohol* OR ethanol*) AND (disease* OR disorder* OR syndrome* OR deficit* OR effect* OR expos*))))

AND

(title:(therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR relaxation) OR abstract:(therapeutic* OR therap* OR intervention* OR treatment* OR training* OR stimulat* OR program* OR workshop* OR support* OR education* OR ergotherap* OR physiotherap* OR sport* OR exercise* OR physical activit* OR hippotherap* OR horseback* OR psychotherap* OR psychoeducation* OR neurofeedback* OR biofeedback* OR rehabilitation* OR relaxation))

OR

(title:(drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*) OR abstract:(drug* OR medication* OR stimulant* OR hormon* OR (drug* AND (therap* OR treatment* OR intervention*)) OR (medic* AND (therap* OR treatment* OR intervention*)) OR pharmaco* OR psychotropic* OR psychoactiv* OR psychiatric* OR adrenergic* OR antipsychotic* OR analeptic* OR psychostimulant* OR (tranquilizing AND (drug* OR agent* OR medicin* OR medication*)) OR tryptamin* OR melatonin* OR methylphenidat* OR amphetamin* OR amfetamin* OR dextroamphetamin* OR dextroamfetamin* OR dexedrin* OR lisdexamphetamine Dimesylate* OR lisdexamfetamine Dimesylate* OR guanidin* OR guanfacin* OR atomoxetin* OR bupropion* OR neuroleptic* OR risperidon* OR pipamperon* OR metylperon* OR methylperon* OR melperon* OR benzodiazepin* OR olanzapin* OR aripiprazol* OR quetiapine Fumarat* OR seroquel* OR chlorprothixen* OR chlorprotixen* OR methotrimeprazin* OR levomepromazin* OR promethazin* OR prometazin* OR chloral hydrat* OR clonidin* OR SSRI* OR SNRI* OR inhibitor* OR fluoxetin* OR citalopram* OR cytalopram* OR sertralin* OR mood stabilizer* OR valproic acid* OR divalproex* OR lamotrigin* OR nutrition* OR ((food* OR diet*) AND supplement*) OR probiotic* OR vitamin* OR mineral*)))

NOT

(title:("animal study" OR "animals study" OR "animal survey" OR "animals survey" OR "animal model" OR "animal models" OR mice OR mouse OR rats OR rat OR zebrafish OR drosophila OR "in vitro"))

Limited: since 2012 => 431 results

Limited: systematic reviews => 168 results

Recherchestrategie in Cochrane Library am 09. August 2022

[[Keywords: fetal* alcohol* syndrome*] OR [Keywords: fasd] OR [Keywords: fetal* alcohol* spectrum disorder*] OR [Keywords: prenatal* alcohol* exposure*] OR [Keywords: alcohol* related fetal* damage*] OR [Keywords: alcohol* related birth defect*] OR [Keywords: alcohol* related neurodevelopmental disorder*] OR [Keywords: fetal* alcohol* exposure*]] AND [[Keywords: therapeutic*] OR [Keywords: therap*] OR [Keywords: intervention*] OR [Keywords: treatment*] OR [Keywords: training*] OR [Keywords: stimulat*] OR [Keywords: program*] OR [Keywords: workshop*] OR [Keywords: support*] OR [Keywords: education*] OR [Keywords: ergotherap*] OR [Keywords: physiotherap*] OR [Keywords: motor activit*] OR [Keywords: sport*] OR [Keywords: exercise*] OR [Keywords: physical activit*] OR [Keywords: hippotherap*] OR [Keywords: horseback*] OR [Keywords: psychotherap*] OR [Keywords: psychoeducation*] OR [Keywords: neurofeedback*] OR [Keywords: biofeedback*] OR [Keywords: rehabilitation*] OR [Keywords: relaxation] OR [Keywords: drug therap*] OR [Keywords: drug*] OR [Keywords: medication*] OR [Keywords: stimulant*] OR [Keywords: hormon*] OR [[Keywords: drug*] AND [[Keywords: therap*] OR [Keywords: treatment*] OR [Keywords: intervention*]]] OR [[Keywords: medic*] AND [[Keywords: therap*] OR [Keywords: treatment*] OR [Keywords: intervention*]]] OR [Keywords: pharmaco*] OR [Keywords: psychotropic*] OR [Keywords: psychoactiv*] OR [Keywords: psychiatric*] OR [Keywords: adrenergic*] OR [Keywords: antipsychotic*] OR [Keywords: analeptic*] OR [Keywords: psychostimulant*] OR [[Keywords: tranquilizing] AND [[Keywords: drug*] OR [Keywords: agent*] OR [Keywords: medicin*] OR [Keywords: medication*]]] OR [Keywords: tryptamin*] OR [Keywords: melatonin*] OR [Keywords: methyl*enidat*] OR [Keywords: am*etamin*] OR [Keywords: dextroam*etamin*] OR [Keywords: dexedrin*] OR [Keywords: lisdexam*etamine dimesylate*] OR [Keywords: guanidin*] OR [Keywords: guanfacin*] OR [Keywords: atomoxetin*] OR [Keywords: bupropion*] OR [Keywords: neuroleptic*] OR [Keywords: risperidon*] OR [Keywords: pipamperon*] OR [Keywords: metylperon*] OR [Keywords: methylperon*] OR [Keywords: melperon*] OR [Keywords: benzodiazepin*] OR [Keywords: olanzapin*] OR [Keywords: aripiprazol*] OR [Keywords: quetiapine fumarat*] OR [Keywords: seroquel*] OR [Keywords: chlorprothixen*] OR [Keywords: chlorprotixen*] OR [Keywords: methotrimeprazin*] OR [Keywords: levomepromazin*] OR [Keywords: promethazin*] OR [Keywords: prometazin*] OR [Keywords: chloral hydrat*] OR [Keywords: clonidin*] OR [Keywords: ssri*] OR [Keywords: snri*] OR [Keywords: inhibitor*] OR [Keywords: fluoxetin*] OR [Keywords: citalopram*] OR [Keywords: cytalopram*] OR [Keywords: sertralin*] OR [Keywords: mood stabilizer*] OR [Keywords: valproic acid*] OR [Keywords: divalproex*] OR [Keywords: lamotrigin*] OR [Keywords: nutrition*] OR [Keywords: dietary supplement*] OR [[[Keywords: food*] OR [Keywords: diet*]] AND [Keywords: supplement*]] OR [Keywords: probiotic*] OR [Keywords: vitamin*] OR [Keywords: mineral*]] AND [Earliest: (01/01/2012 TO 08/31/2022)]

A. 15 Summary of Findings Tabellen (GRADE-Tabellen) zur Qualität der Evidenz für die Empfehlungen zu den FASD-Interventionen

In den folgenden Tabellen ist die Bewertung der Qualität der Evidenz für jedes Outcome nach den GRADE-Kriterien dargestellt.

Da aufgrund der unterschiedlichen Zusammensetzung der Interventions- und Kontrollgruppen, der verschiedenen Testverfahren zur Beurteilung des Interventionseffektes und der Verwendung unterschiedlicher methodischer Vorgehensweisen sowie der divergierenden Berichterstattung der herangezogenen Studien keine sinnvolle oder standardisierte Berechnung eines Effektschätzers möglich war, sind in den folgenden Tabellen keine relativen und antizipierten absoluten Effekte dargestellt.

Tabelle 1: Summary of findings, Medikation

Population†: Kinder mit FASD oder hohem pränatalem Alkoholkonsum

Setting†: unbekannt

Intervention†: Methylphenidat, Stimulanzien, Neuroleptika

Vergleich†: diverse Medikamente, keine Vergleichsgruppe, Placebo

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Epilepsie[a] **(kritisch)**	N = 10 (1x Kontrollstudie) [1]	1x sehr hoch	Nein	Nein	Nein	Nein	Nein	Nein	Nein	1 systematischer Review; nur 1 Studie; sehr kleine Stichprobe	Sehr niedrig ⊖⊖⊖⊖
Soziale Fertigkeiten und Verhalten[a] **(kritisch)**	N† [1–3]	2x niedrig, 1x sehr hoch	Nein	Ja	Nein	Nein	Nein	Nein	Nein	2 systematische Reviews; 13 Studien; hohe Datenmenge; nur milde Nebenwirkungen	Hoch ⊕⊕⊕⊕

Aufmerksamkeit[a] (kritisch)	N > 125 (1x RCT; 1x unkontrollierte Interventionsstudie)[†] [3]	1x niedrig, 1x sehr hoch	Nein	Ja	Nein	Nein	Nein	Nein	Nein	1 systematischer Review; teilweise sehr kleine Stichproben (N = 10); unterschiedliche Art an Medikamenten	Hoch ⊕⊕⊕⊕
Nebenwirkungen[b] (kritisch)	N = 114 (unkontrollierte Interventionsstudie) [3]	1x niedrig	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; keine Placebo-Gruppe; kein Fokus auf Nebenwirkungen	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[b] Vermeidung von Nebenwirkungen der Interventionen

[†] Aufgrund der Berichterstattung der Systematischen Reviews nicht genau ermittelbar

Literatur:

1. Mela, M., Okpalauwaekwe, U., Anderson, T., Eng, J., Nomani, S., Ahmed, A., & Barr, A. M. (2018). The utility of psychotropic drugs on patients with Fetal Alcohol Spectrum Disorder (FASD): a systematic review. Psychiatry and Clinical Psychopharmacology, 28(4), 436-445. https://doi.org/10.1080/24750573.2018.1458429
2. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001

3. Smiarowska, M., Brzuchalski, B., Grzywacz, E., Malinowski, D., Machoy-Mokrzynska, A., Pierzchlinska, A., & Bialecka, M. (2022). Influence of COMT (rs4680) and DRD2 (rs1076560, rs1800497) Gene Polymorphisms on Safety and Efficacy of Methylphenidate Treatment in Children with Fetal Alcohol Spectrum Disorders. Int J Environ Res Public Health, 19(8). https://doi.org/10.3390/ijerph19084479

Tabelle 2: Summary of findings, Nahrungsergänzungsmittel

Population: Kinder mit FASD

Setting: Zuhause

Intervention: Cholinsupplementation in unterschiedlicher Dosierung

Vergleich: Placebo

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Kognitive Leistung / Intelligenz[a] (kritisch)	N = 91 (2x RCT) [1, 2]	2x niedrig	Nein	Nein	Nein	Nein	Ja	Nein	Nein	Fischgeruch als Nebenwirkung; nur Teilbereich der Kognition; Verbesserung nur mit Latenz; unterschiedliche Testverfahren; hohes Lost-to-Follow-up	Hoch ⊕⊕⊕⊕
Exekutivfunktionen[a] (kritisch)	N = 86 (2x RCT) [2, 3]	2x niedrig	Nein	Nein	Ja	Nein	Nein	Nein	Nein	Nur 2 Studien mit jeweils anderem Alter der Kinder, Dauer und Dosis der Medikation; 1 Follow-up; Fischgeruch als Nebenwirkung	Hoch ⊕⊕⊕⊕

Lern- und Merkfähigkeit[a] (kritisch)	N = 168 (4x RCT) [1–4]	4x niedrig	Nein	Ja	Ja	Nein	Nein	Nein	Nein	Kein direkter Effekt, auch nicht im Langzeitgedächtnis; Verbesserung nur des nonverbalen Arbeitsgedächtnisses und nur mit Latenz von einigen Jahren; Fischgeruch als Nebenwirkung	Moderat ⊕⊕⊕⊖
Aufmerksamkeit[a] (kritisch)	N = 86 (2x RCT) [2, 3]	2x niedrig	Nein	Ja	Nein	Nein	Ja	Nein	Nein	Hohes Lost-to-Follow-up; Fischgeruch als Nebenwirkung; positiver Effekt nur mit Latenz	Hoch ⊕⊕⊕⊕
Nebenwirkungen[b] (kritisch)	N = 132 (3x RCT) [1, 3, 5]	3x niedrig	Nein	Ja	Nein	Nein	Nein	Ja	Nein	Nur Fischgeruch als Nebenwirkung	Hoch ⊕⊕⊕⊕

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[b] Vermeidung von Nebenwirkungen der Interventionen

Literatur:

1. Wozniak, J. R., Fuglestad, A. J., Eckerle, J. K., Fink, B. A., Hoecker, H. L., Boys, C. J., Radke, J. P., Kroupina, M. G., Miller, N. C., Brearley, A. M., Zeisel, S. H., & Georgieff, M. K. (2015). Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr, 102(5), 1113-1125. https://doi.org/10.3945/ajcn.114.099168
2. Wozniak, J. R., Fink, B. A., Fuglestad, A. J., Eckerle, J. K., Boys, C. J., Sandness, K. E., Radke, J. P., Miller, N. C., Lindgren, C., Brearley, A. M., Zeisel, S. H., & Georgieff, M. K. (2020). Four-year follow-up of a randomized controlled trial of choline for neurodevelopment in fetal alcohol spectrum disorder. J Neurodev Disord, 12(1), 9. https://doi.org/10.1186/s11689-020-09312-7
3. Nguyen, T. T., Risbud, R. D., Mattson, S. N., Chambers, C. D., & Thomas, J. D. (2016). Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders. Am J Clin Nutr, 104(6), 1683-1692. https://doi.org/10.3945/ajcn.116.142075
4. Wozniak, J. R., Fuglestad, A. J., Eckerle, J. K., Kroupina, M. G., Miller, N. C., Boys, C. J., Brearley, A. M., Fink, B. A., Hoecker, H. L., Zeisel, S. H., & Georgieff, M. K. (2013). Choline supplementation in children with fetal alcohol spectrum disorders has high feasibility and tolerability. Nutr Res, 33(11), 897-904. https://doi.org/10.1016/j.nutres.2013.08.005
5. Smith, S. M., Virdee, M. S., Eckerle, J. K., Sandness, K. E., Georgieff, M. K., Boys, C. J., Zeisel, S. H., & Wozniak, J. R. (2021). Polymorphisms in SLC44A1 are associated with cognitive improvement in children diagnosed with fetal alcohol spectrum disorder: an exploratory study of oral choline supplementation. Am J Clin Nutr, 114(2), 617-627. https://doi.org/10.1093/ajcn/nqab081

Tabelle 3: Summary of findings, Transkranielle Gleichstromstimulationen (tDCS)

Population: Kinder mit FASD

Setting: Klinisches Setting

Intervention: Transkranielle Gleichstromstimulation (tDCS)

Vergleich: Sham

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Exekutivfunktionen[a] (kritisch)	N = 38 (RCT) [1]	1x niedrig	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; hoher Aufwand; mögliche Schäden überwiegen möglichen Nutzen	Hoch ⊕⊕⊕⊕
Lern- und Merkfähigkeit[a] (kritisch)	N = 38 (RCT) [1]	1x niedrig	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; hoher Aufwand; mögliche Schäden überwiegen möglichen Nutzen	Hoch ⊕⊕⊕⊕
Aufmerksamkeit[a] (kritisch)	N = 38 (RCT) [1]	1x niedrig	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; hoher Aufwand; mögliche Schäden überwiegen möglichen Nutzen	Hoch ⊕⊕⊕⊕

Nebenwirkungen[b] (kritisch)	N = 38 (RCT) [1]	1x niedrig	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; hoher Aufwand; mögliche Schäden überwiegen möglichen Nutzen	Hoch ⊕⊕⊕⊕

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[b] Vermeidung von Nebenwirkungen der Interventionen

Literatur:

1. Boroda, E., Krueger, A. M., Bansal, P., Schumacher, M. J., Roy, A. V., Boys, C. J., Lim, K. O., & Wozniak, J. R. (2020). A randomized controlled trial of transcranial direct-current stimulation and cognitive training in children with fetal alcohol spectrum disorder. Brain Stimul, 13(4), 1059-1068. https://doi.org/10.1016/j.brs.2020.04.015

Tabelle 4: Summary of findings, Somatosensorische Trainings

Population: Kinder mit FASD

Setting: unbekannt

Intervention: The Neurosequential Model of Therapeutics (NMT) zur Bestimmung der Interventionselemente aus einer Eltern-Kind-Psychotherapie (CPP) und Mindful Parenting Education (MPE)

Vergleich: keine Vergleichsgruppe

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Entwicklung[a] (kritisch)	N = 10 (unkontrollierte Interventionsstudie) [1]	1x hoch	Nein	ja	Ja	Nein	Ja	Nein	nein	nur 1 Studie; kleine Stichprobe; kein Follow-up; keine Unterscheidung der Unterkategorien der Entwicklung	Sehr niedrig ⊕⊖⊖⊖

Elternstress[f] (kritisch)	N = 10 (unkontrollierte Interventionsstudie) [1]	1x hoch	Nein	ja	Ja	Nein	Ja	Nein	nein	nur 1 Studie; kleine Stichprobe; kein Follow-up	Sehr niedrig ⊕⊖⊖⊖
Wissensvermittlung[g] (kritisch)	N = 10 (unkontrollierte Interventionsstudie) [1]	1x hoch	Nein	ja	Ja	Nein	Ja	Nein	nein	nur 1 Studie; kleine Stichprobe; kein Follow-up	Sehr niedrig ⊕⊖⊖⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[f] Entlastung der Bezugspersonen (biologische, Pflege- und Adoptiv-Eltern, Bezugsbetreuer*innen) und Verbesserung der Lebensqualität der gesamten betroffenen Familie/Einrichtung

[g] Verbesserung des Wissens um den abweichenden Gesundheitszustand/die Erkrankung/Störung/Behinderung und Verbesserung der Krankheitseinsicht

Literatur:

1. Zarnegar, Z., Hambrick, E. P., Perry, B. D., Azen, S. P., & Peterson, C. (2016). Clinical improvements in adopted children with fetal alcohol spectrum disorders through neurodevelopmentally informed clinical intervention: A pilot study. Clin Child Psychol Psychiatry, 21(4), 551-567. https://doi.org/10.1177/1359104516636438

Tabelle 5: Summary of findings, Gleichgewichtstrainings

Population: Kinder mit FASD

Setting: Universität, Labor, zuhause

Intervention: STABEL

Vergleich: inaktive Vergleichsgruppe

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Fein-/Graphomotorik oder grobmotorische Koordination[a] (kritisch)	N = 45 (1x nicht randomisierte Kontrollstudie; 1x nicht kontrollierte Studie) [1, 2]	1x niedrig, 1x hoch	Nein	Ja	Ja	Nein	Nein	Nein	Nein	zuhause möglich; wenig Zeitaufwand; klinische Signifikanz ungewiss; Verschlechterung der Haltungsstabilität und der sensorischen Aufmerksamkeit (Ermüdungserscheinungen?); kein Follow-up	Niedrig ⊕⊕⊖⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

Literatur:

1. McCoy, S. W., Jirikowic, T., Price, R., Ciol, M. A., Hsu, L. Y., Dellon, B., & Kartin, D. (2015). Virtual Sensorimotor Balance Training for Children With Fetal Alcohol Spectrum Disorders: Feasibility Study. Phys Ther, 95(11), 1569-1581. https://doi.org/10.2522/ptj.20150124
2. Jirikowic, T., Westcott McCoy, S., Price, R., Ciol, M. A., Hsu, L. Y., & Kartin, D. (2016). Virtual Sensorimotor Training for Balance: Pilot Study Results for Children With Fetal Alcohol Spectrum Disorders. Pediatr Phys Ther, 28(4), 460-468. https://doi.org/10.1097/PEP.0000000000000300

Tabelle 6: Summary of findings, Sprachtrainings

Population: Kinder mit FASD

Setting†: unbekannt

Intervention: Language and literacy training

Vergleich: inaktive Vergleichsgruppe, Kinder ohne FASD

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen					Faktoren, die zur Heraufstufung der Qualität führen			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Sprache[a] (kritisch)	N = 59 (Kontrollstudie) [1]	1x moderat	Nein	Nein	Nein	Nein	Nein	Nein	Nein	Systematischer Review mit nur 1 Studie; Outcome nicht rezeptive/expressive Sprache	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[†] Aufgrund der Berichterstattung der Systematischen Reviews nicht genau ermittelbar

Literatur:

1. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001

Tabelle 7: Summary of findings, Training zur Förderung rechnerischen Denkens

Population: Kinder mit FASD

Setting: Schule, zuhause, klinisches Setting

Intervention: MILE

Vergleich: The Social Skills Improvement System Intervention, inaktive Kontrollgruppe, Elternedukation

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Räumlich-visuelle Wahrnehmung oder räumlich-konstruktive Fähigkeiten[a] (kritisch)	N = 28 (Kontrollstudie) [1]	1x moderat	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; kein Follow-up	Moderat ⊕⊕⊕⊖
Exekutivfunktionen[a] (kritisch)	N = 28 (Kontrollstudie) [1]	1x moderat	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; kein Follow-up; keine klare Überlegenheit einer Intervention	Moderat ⊕⊕⊕⊖

Rechenfertigkeiten[a]	N = 190‡ (3x RCT, 1x Kontrollstudie) [1–4]	2x niedrig, 2x moderat	Ja	Nein	Nein	Nein	Ja	Nein	Nein	2 systematische Reviews; 4 Studien; 2x dieselbe Stichprobe; Vergleich mit Kompetenztraining; 2x Follow-up; mit und ohne Elternbeteiligung; Abhängigkeit von individuellen Faktoren unklar; englischsprachiges Programm	Hoch ⊕⊕⊕⊕
Lern- und Merkfähigkeit[a] **(kritisch)**	N = 60 (RCT) [3]	1x moderat	Nein	Ja	Ja	Nein	Nein	Nein	Nein	Nur 1 Studie; nur Elternbeurteilung des Lernvermögens des Kindes	Niedrig ⊕⊕⊖⊖
Aufmerksamkeit[a] **(kritisch)**	N = 28 (Kontrollstudie) [1]	1x moderat	Nein	Ja	Ja	Nein	Nein	Nein	Ja	Nur 1 Studie; kein Follow-up; keine klare Überlegenheit einer Intervention	Sehr niedrig ⊕⊖⊖⊖
Lernen und Wissensanwendung[d] **(kritisch)**	N = 60 (RCT) [3]	1x moderat	Nein	Ja	Ja	Nein	Nein	Nein	Nein	Nur 1 Studie; nur subjektive Erfassung des Lernverhaltens; Übertragbarkeit auf Alltag unklar	Niedrig ⊕⊕⊖⊖
Wissensvermittlung[g] **(kritisch)**	N = 60 (RCT) [3]	1x moderat	Nein	Ja	Ja	Nein	Nein	Nein	Nein	Nur 1 Studie; interventionsspezifischer Effekt unklar	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[d] Unterpunkt des Outcomes: Verbesserung der Partizipation der Kinder/Jugendlichen mit FASD

[g] Verbesserung des Wissens um den abweichenden Gesundheitszustand/die Erkrankung/Störung/Behinderung und Verbesserung der Krankheitseinsicht

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Kully-Martens, K., Pei, J., Kable, J., Coles, C. D., Andrew, G., & Rasmussen, C. (2018). Mathematics intervention for children with fetal alcohol spectrum disorder: A replication and extension of the math interactive learning experience (MILE) program. Res Dev Disabil, 78, 55-65. https://doi.org/10.1016/j.ridd.2018.04.018
2. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
3. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2015). Community translation of the Math Interactive Learning Experience Program for children with FASD. Res Dev Disabil, 39, 1-11. https://doi.org/10.1016/j.ridd.2014.12.031
4. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903

Tabelle 8: Summary of findings, Serious Games

Population: Kinder mit FASD

Setting: Schule

Intervention: The Caribbean Quest, Virtual Reality Game zum Brandschutz, Virtual Reality Game zur Verkehrssicherheit

Vergleich: keine Vergleichsgruppe, Vergleich zwischen zwei Serious Games

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Rechenfertigkeiten[a] (kritisch)	N = 17 (unkontrollierte Interventionsstudie) [1]	1x moderat	Nein	Ja	Ja	Nein	Nein	Nein	Nein	Nur 1 Studie; kleine Stichprobe; Gruppe bestand aus Kindern mit FASD und ASD – kein Gruppenunterschied gerechnet; nur subjektive Verbesserung	Sehr niedrig ⊕⊖⊖⊖

Lern- und Merkfähigkeit[a] (kritisch)	N = 17 (unkontrollierte Interventionsstudie) [1]	1x moderat	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; kleine Stichprobe; Gruppe bestand aus Kindern mit FASD und ASD – kein Gruppenunterschied gerechnet	Sehr niedrig ⊕⊖⊖⊖
Eigen-/Fremdgefährdung[c] (kritisch)	N = 21 (2x Kontrollstudien) [1]	1x niedrig	Nein	Nein	Nein	Nein	Nein	Nein	Nein	1 systematischer Review; sehr kleine Stichproben	Niedrig ⊕⊕⊖⊖
Lernen und Wissensanwendung[d] (kritisch)	N = 17 (unkontrollierte Interventionsstudie) [1]	1x moderat	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; kleine Stichprobe; Gruppe bestand aus Kindern mit FASD und ASD – kein Gruppenunterschied gerechnet; subjektive, qualitative Einschätzung der Lehrer	Sehr niedrig ⊕⊖⊖⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[c] Unterpunkt des Outcomes: Reduktion von Komplikationen/Sekundärerkrankungen

[d] Unterpunkt des Outcomes: Verbesserung der Partizipation der Kinder/Jugendlichen mit FASD

Literatur:

1. Kerns, K. A., Macoun, S., MacSween, J., Pei, J., & Hutchison, M. (2017). Attention and working memory training: A feasibility study in children with neurodevelopmental disorders. Appl Neuropsychol Child, 6(2), 120-137. https://doi.org/10.1080/21622965.2015.1109513

Tabelle 9: Summary of findings, Neurokognitive Trainings

Population: Kinder mit FASD

Setting†: Klinisches Setting, zuhause, Universität, Gemeinschaftsstandort

Intervention: (adaptiertes) Alert-Programm mit/ohne Elterntraining, GoFAR, The Caribbean Quest; Computerised progressive attention program CPAP, Training basierend auf dem Pay Attention Training Protocol

Vergleich: inaktive Kontrollgruppe, Warteliste, Training zur Emotionserkennung (FACELAND), keine Vergleichsgruppe

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Exekutivfunktionen[a] (kritisch)	N = 151 (1x RCT, 2x Kontrollstudie) [1–3]	2x moderat, 1x hoch	Ja	Nein	Ja	Nein	Ja	Nein	Ja	3 Studien; Übertragbarkeit auf Alltag unklar; 2 Studien der gleichen Arbeitsgruppe; hohe Teilnehmerzahl	Moderat ⊕⊕⊕⊖

Aufmerksamkeit[a] (kritisch)	N = 105 (2x RCT, 2x Kontrollstudie 1x unkontrollierte Interventionsstudie) [4–8]	2x niedrig, 3x moderat	Ja	Ja	Ja	Nein	Ja	Nein	Nein	2 systematische Reviews; 5 Studien; Überschneidung mit anderen Therapien; Einfluss der Eltern unklar; englischsprachige Trainings	Moderat ⊕⊕⊕⊖
Lebensqualität[e] (kritisch)	N = 27 (RCT) [9]	1x moderat	Ja	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; nur allgemeine Beeinträchtigung ermittelt	Niedrig ⊕⊕⊖⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[e] Verbesserung der Lebensqualität der Kinder/Jugendlichen mit FASD

[†] Aufgrund der Berichterstattung der Systematischen Reviews nicht genau ermittelbar

Literatur:

1. Nash, K., Stevens, S., Greenbaum, R., Weiner, J., Koren, G., & Rovet, J. (2015). Improving executive functioning in children with fetal alcohol spectrum disorders. Child Neuropsychol, 21(2), 191-209. https://doi.org/10.1080/09297049.2014.889110
2. Soh, D. W., Skocic, J., Nash, K., Stevens, S., Turner, G. R., & Rovet, J. (2015). Self-regulation therapy increases frontal gray matter in children with fetal alcohol spectrum disorder: evaluation by voxel-based morphometry. Front Hum Neurosci, 9, 108. https://doi.org/10.3389/fnhum.2015.00108

3. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
4. Kerns, K. A., Macoun, S., MacSween, J., Pei, J., & Hutchison, M. (2017). Attention and working memory training: A feasibility study in children with neurodevelopmental disorders. Appl Neuropsychol Child, 6(2), 120-137. https://doi.org/10.1080/21622965.2015.1109513
5. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
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7. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
8. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
9. Petrenko, C. L. M., Pandolfino, M. E., & Robinson, L. K. (2017). Findings from the Families on Track Intervention Pilot Trial for Children with Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 41(7), 1340-1351. https://doi.org/10.1111/acer.13408

Tabelle 10: Summary of findings, Emotionsregulationstrainings

Population: Kinder mit FASD, Kinder mit hoher pränataler Alkoholexposition

Setting: Klinisches Setting, zuhause, Universität, Gemeinschaftsstandort

Intervention: GoFAR, Alert, The Caribbean Quest, Families on Track

Vergleich: inaktive Kontrollgruppe, Warteliste, Training zur Emotionserkennung (FACELAND), keine Vergleichsgruppe, Feedback an Bezugspersonen

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Soziale Fertigkeiten und Verhalten[a] (kritisch)	N = 259 (6x RCT, 1x Kontrollstudie, 1x unkontrollierte Interventionsstudie) ‡ [1–8]	8x moderat	Nein	Ja	Nein	Nein	Ja	Nein	Ja	8 Studien; hohe Datenmenge; Follow-ups; Langzeiteffekt fraglich; 3x dieselbe Stichprobe; 2x dieselbe Stichprobe; Abhängigkeit von individuellen Faktoren unklar	Hoch ⊕⊕⊕⊕

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Kerns, K. A., Macoun, S., MacSween, J., Pei, J., & Hutchison, M. (2017). Attention and working memory training: A feasibility study in children with neurodevelopmental disorders. Appl Neuropsychol Child, 6(2), 120-137. https://doi.org/10.1080/21622965.2015.1109513
2. Nash, K., Stevens, S., Greenbaum, R., Weiner, J., Koren, G., & Rovet, J. (2015). Improving executive functioning in children with fetal alcohol spectrum disorders. Child Neuropsychol, 21(2), 191-209. https://doi.org/10.1080/09297049.2014.889110
3. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
4. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
5. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
6. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. C. (2015). A metacognitive strategy for reducing disruptive behavior in children with fetal alcohol spectrum disorders: GoFAR pilot. Alcohol Clin Exp Res, 39(11), 2224-2233. https://doi.org/10.1111/acer.12885
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8. Petrenko, C. L. M., Demeusy, E. M., & Alto, M. E. (2019). Six-Month Follow-up of the Families on Track Intervention Pilot Trial for Children With Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 43(10), 2242-2254. https://doi.org/10.1111/acer.14180

Tabelle 11: Summary of findings, Soziales Kompetenztraining

Population: Kinder mit FASD

Setting: Klinisches Setting

Intervention: Children's Friendship Training mit/ohne Neuroleptika

Vergleich: Standardversorgung

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Soziale Fertigkeiten und Verhalten[a] (kritisch)	N = 567[‡] (6x Kontrollstudie) [1–4]	3x niedrig, 1x moderat	Nein	Ja	Ja	Nein	Ja	Nein	Ja	2 systematische Reviews; 6 Studien; teilweise dieselben Stichproben; gute Umsetzbarkeit; geringer Aufwand; hohe Teilnehmerzahl	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja", wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
2. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903
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Tabelle 12: Summary of findings, Neurokognitive Trainings kombiniert mit Elterntrainings

Population: Kinder/Jugendliche mit FASD und deren Bezugspersonen

Setting: Universität, klinisches Setting

Intervention: Project Step-up, GoFAR, Alert, Children's Friendship Training, Families on Track

Vergleich: schriftliche Information, FACELAND, inaktive Vergleichsgruppe, Standardversorgung, Feedback an Bezugspersonen

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Aufmerksamkeit[a] (kritisch)	N = 60 (2x RCT) [1, 2]	2x moderat	Nein	Ja	Ja	Nein	Ja	Nein	Nein	Nur 2 Studien; 2x gleiche Studienpopulation; kleine Gruppengrößen; hohe Elternzufriedenheit	Moderat ⊕⊕⊕⊖
Riskanter Alkohol-/Drogenkonsum[c] (kritisch)	N = 54[‡] (2x RCT) [3, 4]	1x niedrig, 1x moderat	Nein	Ja	Nein	Nein	Ja	Nein	Ja	2x dieselbe Studie; Follow-up; gute Umsetzbarkeit; hohe Zufriedenheit	Hoch ⊕⊕⊕⊕

Interpersonelle Interaktion und Beziehungen[d] (kritisch)	N = 145 (1x RCT, 1x Kontrollstudie) [5, 6]	2x moderat	Nein	Ja	Nein	Nein	Ja	Nein	Ja	2 Studien; hohe Teilnehmerzahl; Langzeiteffekte unklar; Übertragbarkeit unklar	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[c] Unterpunkt des Outcomes: Reduktion von Komplikationen/Sekundärerkrankungen

[d] Unterpunkt des Outcomes: Verbesserung der Partizipation der Kinder/Jugendlichen mit FASD

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
2. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
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6. O'Connor, M. J., Laugeson, E. A., Mogil, C., Lowe, E., Welch-Torres, K., Keil, V., & Paley, B. (2012). Translation of an evidence-based social skills intervention for children with prenatal alcohol exposure in a community mental health setting. Alcohol Clin Exp Res, 36(1), 141-152. https://doi.org/10.1111/j.1530-0277.2011.01591.x

Tabelle 13: Summary of findings, Emotionsregulationstraining kombiniert mit Elterntrainings

Population: Kinder mit FASD, Kinder mit hoher pränataler Alkoholexposition

Setting: Klinisches Setting, zuhause, Universität, Gemeinschaftsstandort

Intervention: GoFAR, Alert, Families on Track

Vergleich: inaktive Kontrollgruppe, Warteliste, Training zur Emotionserkennung (FACELAND), Feedback an Bezugspersonen

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Soziale Fertigkeiten und Verhalten[a] (kritisch)	N = 217‡ (6x RCT) [1–6]	6x moderat	Nein	Ja	Nein	Nein	Ja	Nein	Nein	6 Studien; hohe Datenmenge; Follow-ups; Langzeiteffekt fraglich; teilweise dieselben Stichproben; Abhängigkeit von individuellen Faktoren unklar	Hoch ⊕⊕⊕⊕
Wissensvermittlung[g] (kritisch)	N = 51‡ (2x RCT) [5, 6]	2x moderat	Nein	Ja	Nein	Nein	Ja	Nein	Nein	2x dieselbe Stichprobe; Follow-up; Langzeiteffekte	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[g] Verbesserung des Wissens um den abweichenden Gesundheitszustand/die Erkrankung/Störung/Behinderung und Verbesserung der Krankheitseinsicht

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Wells, A. M., Chasnoff, I. J., Schmidt, C. A., Telford, E., & Schwartz, L. D. (2012). Neurocognitive habilitation therapy for children with fetal alcohol spectrum disorders: an adaptation of the Alert Program(R). Am J Occup Ther, 66(1), 24-34. https://doi.org/10.5014/ajot.2012.002691
2. Kable, J. A., Taddeo, E., Strickland, D., & Coles, C. D. (2016). Improving FASD Children's Self-Regulation: Piloting Phase 1 of the GoFAR Intervention. Child Fam Behav Ther, 38(2), 124-141. https://doi.org/10.1080/07317107.2016.1172880
3. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263
4. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. C. (2015). A metacognitive strategy for reducing disruptive behavior in children with fetal alcohol spectrum disorders: GoFAR pilot. Alcohol Clin Exp Res, 39(11), 2224-2233. https://doi.org/10.1111/acer.12885
5. Petrenko, C. L. M., Pandolfino, M. E., & Robinson, L. K. (2017). Findings from the Families on Track Intervention Pilot Trial for Children with Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 41(7), 1340-1351. https://doi.org/10.1111/acer.13408
6. Petrenko, C. L. M., Demeusy, E. M., & Alto, M. E. (2019). Six-Month Follow-up of the Families on Track Intervention Pilot Trial for Children With Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 43(10), 2242-2254. https://doi.org/10.1111/acer.14180

Tabelle 14: Summary of findings, Soziales Kompetenztraining kombiniert mit Elterntrainings

Population: Kinder mit FASD und deren Bezugspersonen

Setting: Klinisches Setting

Intervention: Children's Friendship Training mit/ohne Neuroleptika

Vergleich: Standardversorgung

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Soziale Fertigkeiten und Verhalten[a] (kritisch)	N = ca. 567[‡] (6x Kontrollstudie) [1–4]	3x niedrig, 1x moderat	Nein	Ja	Ja	Nein	Ja	Nein	Ja	2 systematische Reviews; 6 Studien; teilweise dieselben Stichproben; gute Umsetzbarkeit; geringer Aufwand; hohe Teilnehmerzahl	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja", wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Ordenewitz, L. K., Weinmann, T., Schluter, J. A., Moder, J. E., Jung, J., Kerber, K., Greif-Kohistani, N., Heinen, F., & Landgraf, M. N. (2021). Evidence-based interventions for children and adolescents with fetal alcohol spectrum disorders - A systematic review. Eur J Paediatr Neurol, 33, 50-60. https://doi.org/10.1016/j.ejpn.2021.02.001
2. Reid, N., Dawe, S., Shelton, D., Harnett, P., Warner, J., Armstrong, E., LeGros, K., & O'Callaghan, F. (2015). Systematic Review of Fetal Alcohol Spectrum Disorder Interventions Across the Life Span. Alcohol Clin Exp Res, 39(12), 2283-2295. https://doi.org/10.1111/acer.12903
3. O'Connor, M. J., Laugeson, E. A., Mogil, C., Lowe, E., Welch-Torres, K., Keil, V., & Paley, B. (2012). Translation of an evidence-based social skills intervention for children with prenatal alcohol exposure in a community mental health setting. Alcohol Clin Exp Res, 36(1), 141-152. https://doi.org/10.1111/j.1530-0277.2011.01591.x
4. Regehr, E. (2015). The Impact of an Intervention on Social Skills of Young Children with Prenatal Alcohol Exposure [Master's Thesis, University of Alberta]. Alberta. https://dx.doi.org/10.7939/r3b56dc77

Tabelle 15: Summary of findings, Psychoedukationen der Eltern/Bezugspersonen

Population: Kindern mit FASD und ihre Bezugspersonen

Setting: zuhause, klinisches Setting

Intervention: schriftliche Information, Gruppenworkshop, online Workshop, GoFAR

Vergleich: Vergleich zwischen verschiedenen Formen untereinander, FACELAND, inaktive Kontrollgruppe

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Soziale Fertigkeiten und Verhalten[a] (kritisch)	N = 59 (RCT) [1]	Moderat	Nein	Ja	Ja	Nein	Ja	Nein	Ja	Nur 1 Studie; gute Anwendbarkeit; auf Deutschland übertragbar; geringer Aufwand, niedrige Kosten	Moderat ⊕⊕⊕⊖
Häusliches Leben[d] (kritisch)	N = 30 (RCT) [2]	1x moderat	Nein	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; Elternbeurteilung; kleine Gruppengröße; gute Anwendbarkeit; Auf Deutschland übertragbar	Moderat ⊕⊕⊕⊖

Elternstress[f] (kritisch)	N = 231[‡] (2x RCT, 1x unkontrollierte Studie) [3–5]	3x moderat	Nein	Ja	Nein	Nein	Ja	Ja	Nein	3 Studien; 2x dieselbe Stichprobe; Follow-up; Langzeiteffekte unklar; von individuellen Faktoren abhängig; hohe Teilnehmerzahl	Moderat ⊕⊕⊕⊖
Wissensvermittlung[g] (kritisch)	N = 59 (RCT) [1]	1x moderat	Nein	Nein	Ja	Nein	Ja	Nein	Nein	Nur 1 Studie; gute Anwendbarkeit; auf Deutschland übertragbar; geringer Aufwand, niedrige Kosten	Hoch ⊕⊕⊕⊕

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[d] Unterpunkt des Outcomes: Verbesserung der Partizipation der Kinder/Jugendlichen mit FASD

[f] Entlastung der Bezugspersonen (biologische, Pflege- und Adoptiv-Eltern, Bezugsbetreuer*innen) und Verbesserung der Lebensqualität der gesamten betroffenen Familie/Einrichtung

[g] Verbesserung des Wissens um den abweichenden Gesundheitszustand/die Erkrankung/Störung/Behinderung und Verbesserung der Krankheitseinsicht

[‡] Aufgrund von Überschneidungen durch dieselbe Studienpopulation nicht genau ermittelbar

Literatur:

1. Kable, J. A., Coles, C. D., Strickland, D., & Taddeo, E. (2012). Comparing the Effectiveness of On-Line versus In-Person Caregiver Education and Training for Behavioral Regulation in Families of Children with FASD. Int J Ment Health Addict, 10(6), 791-803. https://doi.org/10.1007/s11469-012-9376-3
2. Coles, C. D., Kable, J. A., Taddeo, E., & Strickland, D. (2018). GoFAR: improving attention, behavior and adaptive functioning in children with fetal alcohol spectrum disorders: Brief report. Dev Neurorehabil, 21(5), 345-349. https://doi.org/10.1080/17518423.2018.1424263

3. Petrenko, C. L. M., Pandolfino, M. E., & Robinson, L. K. (2017). Findings from the Families on Track Intervention Pilot Trial for Children with Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 41(7), 1340-1351. https://doi.org/10.1111/acer.13408
4. Petrenko, C. L. M., Demeusy, E. M., & Alto, M. E. (2019). Six-Month Follow-up of the Families on Track Intervention Pilot Trial for Children With Fetal Alcohol Spectrum Disorders and Their Families. Alcohol Clin Exp Res, 43(10), 2242-2254. https://doi.org/10.1111/acer.14180
5. Leenaars, L. S., Denys, K., Henneveld, D., & Rasmussen, C. (2012). The impact of fetal alcohol spectrum disorders on families: evaluation of a family intervention program. Community Ment Health J, 48(4), 431-435. https://doi.org/10.1007/s10597-011-9425-6

Tabelle 16: Summary of findings, Extrinsische Verstärkungen

Population: Kinder mit pränataler Alkoholexposition

Setting: Klinisches Setting

Intervention: Extrinsische Verstärkung

Vergleich: Kinder mit ADHD, Kinder ohne Erkrankung, Aufgabe ohne extrinsische Verstärkung

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Aufmerksamkeit[a] (kritisch)	N = 88 (Kontrollstudie) [1]	1x moderat	Ja	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; niedriger Aufwand; keine Kosten; gute Anwendbarkeit; keine Negativfolgen zu erwarten; keine inaktive Kontrollgruppe; Übertragbarkeit auf Alltag unklar	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

Literatur:

1. Graham, D. M., Glass, L., & Mattson, S. N. (2016). The Influence of Extrinsic Reinforcement on Children with Heavy Prenatal Alcohol Exposure. Alcohol Clin Exp Res, 40(2), 348-358. https://doi.org/10.1111/acer.12959

Tabelle 17: Summary of findings, Trainings mit Fokus auf psychischer Gesundheit

Population: Kinder mit FASD/Autismus-Spektrum-Störungen/Intelligenzminderung

Setting: Schule

Intervention: "The Brain Unit mental health literacy program" und „Dialectical behavior therapy skill-building"

Vergleich: inaktive Vergleichsgruppe

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Krankheitsbewältigung[h] (kritisch)	N = 133 (RCT) [1]	1x niedrig	Ja	Nein	Nein	Nein	Nein	Nein	Nein	1 systematischer Review, nur 1 Studie; hohe Teilnehmerzahl; Umsetzbarkeit unklar	Moderat ⊕⊕⊕⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja", wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[h] Verbesserung der Krankheitsbewältigung/Coping und Selbstwirksamkeit

Literatur:

1. Flannigan, K., Coons-Harding, K. D., Anderson, T., Wolfson, L., Campbell, A., Mela, M., & Pei, J. (2020). A Systematic Review of Interventions to Improve Mental Health and Substance Use Outcomes for Individuals with Prenatal Alcohol Exposure and Fetal Alcohol Spectrum Disorder. Alcohol Clin Exp Res, 44(12), 2401-2430. https://doi.org/10.1111/acer.14490

Tabelle 18: Summary of findings, Tiergestützte Therapien

Population: Kinder mit FASD

Setting: Klinisches Setting

Intervention: Therapieprogramm mit Therapiehunden

Vergleich: Standardversorgung

Outcomes (Relevanz)	Teilnehmerzahl (Studiendesign)[4]	Faktoren, die zur Herabstufung der Qualität führen:					Faktoren, die zur Heraufstufung der Qualität führen:			Weitere Faktoren, die bei den Empfehlungen zu beachten sind[3]	Qualität der Evidenz (Certainty of the evidence - GRADE)
		Risk of Bias[1]	Indirektheit[2]	Inkonsistenz	mangelnde Präzision[2]	Publikations-Bias[2]	Effektstärke[2]	Dosis-Wirkungs-Beziehung[2]	Residuelle/plausible Störgrößen[2]		
Soziale Fertigkeiten und Verhalten[a] (kritisch)	N = 33 (1x RCT) [1]	1x moderat	Nein	Ja	Nein	Nein	Ja	Nein	Nein	Nur 1 Studie	Moderat ⊕⊕⊕⊖
Lebensqualität[e] (kritisch)	N = 33 (1x RCT) [1]	1x moderat	Ja	Ja	Nein	Nein	Nein	Nein	Nein	Nur 1 Studie; nur Schweregrad der Erkrankung ermittelt	Niedrig ⊕⊕⊖⊖

[1] Bewertung: Randomisiert kontrollierte Studien: ROB 2; Nicht-randomisiert kontrollierte Studien: ROBINS-I; Nicht-kontrollierte Studien: angepasste Form des ROBINS-I; Systematische Reviews: AMSTAR-2

[2] „Ja“, wenn mindestens eine Publikation dieses Kriterium erfüllt

[3] Anmerkungen betreffen teilweise nur einzelne Publikationen

[4] Bei systematischen Reviews sind hier die Teilnehmerzahlen und Studiendesigns der relevanten Studien des Reviews abgebildet

[a] Unterpunkt des Outcomes: Verbesserung des neuropsychologischen Funktionsniveaus/Gehirnfunktionsniveaus der Kinder/Jugendlichen mit FASD

[e] Verbesserung der Lebensqualität der Kinder/Jugendlichen mit FASD

Literatur:

1. Vidal, R., Vidal, L., Ristol, F., Domenec, E., Segu, M., Vico, C., Gomez-Barros, N., & Ramos-Quiroga, J. A. (2020). Dog-Assisted Therapy for Children and Adolescents With Fetal Alcohol Spectrum Disorders a Randomized Controlled Pilot Study. Front Psychol, 11, 1080. https://doi.org/10.3389/fpsyg.2020.01080

A. 16 Evidenztabellen zur eingeschlossenen Literatur über Interventionen bei Kinder und Jugendlichen mit FASD (2022)

Originalstudien

Reference Study Type	Participants (Number and Characteristics)	Drop-outs	Intervention	Control	Outcomes	Results	Comments	RoB
´Smiarowska et al. (2022) (1) **Uncontrolled intervention study**	- Inclusion criteria: children (> 6 years old) with ADHD and hPAE who did not benefit from cognitive behavioural therapy for last 6 months or who have severe ADHD symptoms and dysfunctional environmental functioning - Exclusion criteria: psychiatric or developmental disorders - Enrolled: n = 303 - Included: n = 114 - Age: > 6 years	NA	MPH: - 20 mg MPH hydrochloride or 36 mg MPH - Maximum dose (60 mg MPH hydrochloride or 36 mg MPH) was used only in individual cases - Daily doses for 4 weeks	NA	- Tolerability (depending on polymorphisms) - Severity of ADHD symptoms (depending on polymorphisms)	Tolerability: 104 successfully treated: 3 without improvement, 7 discontinued due to adverse effects (occurred at the time of drug introduction and decreased after introduction of a modified form of MPH); no cardiotoxic effects or life-threatening symptoms; Boderline significance between adverse effects and the COMT rs4680 minor allele (G > A) ($p < 0.049$) Severity of ADHD: - All children: treatment was effective in > 90 % of children - Children with morphological features of FASD: significant reduction in symptoms of hyperactivity and impulsivity ($p < 0.0001$); no improvement in attention deficits ($p = 0.2024$) - Children without morphological features of FASD: significant improvement in attention ($p < 0.001$); reduction in hyperactivity ($p = 0.0163$); no significant reduction in impulsivity ($p = 0.1274$) No association of the studied polymorphisms: DRD2 rs1076560: C > A or DRD2 rs1800497: G > A with the	- No specific age range - Missing source of recruitment and recruitment process - Very short treatment period - No international diagnostic valid instrument for severity questionnaire - Genomic DNA was extracted and genotyping for COMT rs4680, DRD2 rs1076560, and rs1800497 SNPs was used - No monitoring of adherence - Children with morphological features of FASD had	Low for effectiveness Moderate for adverse effects (ROBINS-I modified

							efficacy or safety of MPH	significantly higher doses of MPH - No subanalyses of sex, medicine	
Nguyen et al. (2016) (2) **RCT (multisite, randomized, double-blinded, placebo-controlled, parallel-group clinical trial)**	- Inclusion criteria: children with confirmed hPAE; primary English speakers - Exclusion criteria: head injury, substantial physical or psychiatric disability; any other causes of mental deficiency; prescription of medication with risk of atherosclerosis - 5–10 years old Choline group: - Assigned: n = 30 - Received: n = 29 - Lost to follow-up: n = 1 - Completed: n = 28 - Analysed with intention-to-treat: n = 29 Placebo group: - Assigned: n = 28 - Received: n = 26 - Lost to follow-up: n = 2 - Completed: n = 24 - Analysed with intention-to-treat: n = 26		Discontinued intervention: n = 0		Choline: - 625 mg choline (in form of a glycerophosphocholine liquid concentrate (5.25 ml/d)) - Daily doses for 6 weeks	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 6 weeks	- Neuropsychological measures of memory, executive function, attention and hyperactivity - Association between treatment compliance/dietary choline intake and outcomes - Tolerability	Cognitive performance: - Choline group did not differentially improve in any cognitive performance domain (no group or group x time interaction) - Treatment compliance and mean dietary choline intake were not predictive of cognitive performance - No significant interaction of group x time x age group in any cognitive outcome variable Compliance: high treatment compliance in both groups (about 96 %) Tolerability and adverse events: - Significantly more children in choline group reported at least 1 adverse event - No serious adverse events	- Very small sample size in subgroup analyses of age - Intention-to-treat analyses (subanalyses of children completing the study did not change results) - Children without FASD diagnosis included	Low (RoB-2)
Wozniak et al. (2013) (3)	- Inclusion: Children with FASD diagnosis - Exclusion: developmental or neurological disorder; other medical conditions affecting the brain.	Choline: Discontinued: n = 1	Placebo: Discontinued:	Choline: - 1.25 g choline bitartrate powder	Placebo: - Equivalent doses of an oral	- Feasibility of parental administration - Tolerability	Feasibility: - Compliance: 82 % - 87 % - No evidence for dietary confounding	- No child living with biological parents - Prenatal drug use was suspected with alcohol being the	Low (RoB-2)

RCT (double-blind, randomized, placebo-controlled trial) pilot study	- No exclusion: psychiatric co-morbidities (ADHD) - 2,5–4,9 years old Choline group: - Assigned: n = 13 - Received: n = 10 - Lost to follow-up: n = 0 - Completed: n = 9 - Analysed with intention-to-treat: n = 10 Placebo group: - Assigned: n = 12 - Received: n = 10 - Lost to follow-up: n = 1 - Completed: n = 8 - Analysed with intention-to-treat: n = 10	(refused to test agent for more than 1 month)	n = 1 (declined to continue)	delivering 500 mg choline - Daily doses for 9 months	inactive placebo treatment - Daily doses for 9 months	- Serum choline levels	Tolerability: - Minimal adverse effects: no group differences on all adverse events except for a fishy body odor in the choline group (p = 0.011) - In both groups: taste problems at least once (55 %); non-standard administration at least once (75 %) Serum choline level: - Choline group increased choline at all time points: 1 month (p = 0.004), 6 months (p < 0.001), and 9 months (p < 0.001) - Choline group increased betaine concentration at all time points: 1 month (p = 0.04), 6 months (P = 0.03), and 9 months (p = 0.04) - No changes in phosphatidycholine - Choline group had higher sphingomyelin concentrations at baseline (p = 0.04) and months 1 (p = 0.05), but no differences in months 6 (p = 0.25) and 9 (p = 0.91)	dominant substance (n = 14) - Reasons for drop-out: not related to study; lost to follow-up; refused dose after one time trying it - Potential unblinding due to fishy body odor - Not all children at each testing point	
Wozniak et al. (2015) (4) **RCT (randomized, double-blind, placebo-controlled pilot**	- Inclusion: Children with confirmed hPAE or suspected hPAE with dysmorphic faces and cognitive deficits - Exclusion: developmental or neurological disorder; traumatic brain injury; other medical conditions. - No exclusion: psychiatric co-morbidity (ADHD or learning disorder) - 2,5–5 years old	Choline: Discontinued: n = 5 (declined to continue: n = 4; refused intervention: n = 1)	Placebo: Discontinued: n = 3 (declined to continue)	Choline: - 1.25 g choline bitartrate powder delivering 500 mg choline - Daily doses for 9 months	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 9 months	- Neurocognitive functioning (particularly hippocampal-dependent memory) - Feasibility - Serum choline levels	Global cognitive functioning: no main effects of treatment and no interaction effect The Mullen Early Learning Composite was correlated (with age controlled for) with EI delayed performance for items (partial r = 0.56, P < 0.001) and ordered pairs (partial r = 0.47, P < 0.001) at baseline but not at the 9-month visit (p > 0.17 for all). Hippocampus-dependent long-term memory: - No significant main effects of treatment on EI delayed memory performance - race and FASD diagnosis as no moderators - Age as a moderator: ○ subanalysis: splitting participants into a younger	- All children received the same dosage regardless their weight - Intention-to-treat analysis - Due to different group distributions age, race, and FASD diagnosis were included as covariates - Immediate recall performance showed	Low (RoB-2)

trial)	Choline: - Assigned: n = 34 - Received: n = 31 - Lost to follow-up: n = 0 - Completed: N = 26 - Analysed with intention-to-treat: n = 31	Placebo: - Assigned: n = 31 - Received: n = 29 - Lost to follow-up: N = 1 - Completed: n = 25 - Analysed with intention-to-treat: n = 29					- Tolerability	group consisting of 2.5 to ≤ 4.0-year-olds (n = 30; placebo: n = 13; choline: n = 17) and an older group consisting of > 4.0–5.0-year-olds (n = 30; placebo: n = 16; choline: n = 14) ○ Largest improvement in delayed EI performance in the young choline group. - For items: t test [t(28) = -2.41, p = 0.023]; d = 0.54 => young choline group showed an increase of 21 % compared with 7 % in the young placebo group - For ordered pairs: [t(28) = -2.18, p = 0.038]; d = 0.50 => young choline group showed an increase of 28 % compared with 16 % in the young placebo group ○ No significant differences for the older age groups Feasibility: - Compliance: dose on 88 % of days - Diet: no group differences regarding compliance or dietary changes Serum choline levels: Significant increase in serum choline (102 %; p < 0.0001) and betaine (106 %; p < 0.0001) in choline group Tolerability: fishy body odor as the only adverse event	no improvement in choline group for items; but for ordered pairs the choline group performed worse than placebo - Improvements in delayed memory in the young group was only present after controlling for immediate recall performance - Potential ceiling effect in EI: young choline group had slightly lower delayed EI performance than the other groups at baseline	
Wozniak et al. (2020) (5) **4-year follow-up of a RCT (randomized, double-**	- Inclusion: Children with confirmed hPAE or suspected hPAE with dysmorphic faces and cognitive deficits; supplement adherence in initial trial > 50 % of days - Exclusion: developmental or neurological disorder; traumatic brain injury; other medical conditions. - No exclusion: psychiatric co-morbidity (ADHD or learning disorder) - 2,5–5 years old in initial trial		Choline: Initial trial: Discontinued: n = 5 (declined to continue: n = 4; refused intervent	Placebo: Initial trial: Discontinued: n = 3 (declined to continue)	Choline: - 1.25 g choline bitartrate powder delivering 513 mg choline - Daily doses for 9 months	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 9 months	Potential long-term cognitive and behavioural implications (intelligence, memory, executive functioning, and behaviour)	General cognitive functioning: - Choline group had higher non-verbal IQ (8 % difference; (F1, 28) = 5.17; p = 0.03; ηp2 = 0.17); and higher working memory scores (11.7 % difference; F(1, 28) = 7.74; p = 0.01; ηp2 = 0.23) - Components of non-verbal IQ: significant group effects in 2 of 5 components: non-verbal Visual-Spatial Reasoning with Choline group showing better performance (28.9 % difference; F(1, 29) = 9.93; p = 0.004), and non-verbal Working Memory with Choline group showing better performance (26.8 % difference; F(1, 29) = 6.37; p = 0.018) - No significant differences in Verbal IQ; Fluid	- No measures of serum choline level - Dietary intake as a potential mediator	Low (RoB-2)

blind, placebo - controlled trial)	Choline: Initial trial: - Assigned: n = 34 - Received: n = 31 - Lost to follow-up: n = 0 - Completed: n = 26 - Analysed with intention-to-treat: n = 31 Follow-up: - Lost to follow-up: n = 9 - Analysed: n = 15	Placebo: Initial trial: - Assigned: n = 31 - Received: n = 29 - Lost to follow-up: n = 1 - Completed: n = 25 - Analysed with intention-to-treat: n = 29 Follow-up: - Lost to follow-up: n = 8 - Analysed: n = 16	ion: n = 1)					Reasoning; Knowledge; Quantitative Reasoning; Visual-Spatial Processing and Full-Scale IQ Memory functioning: No significant group differences regarding the EI paradigm; age was not a significant modulator; In NEPSY-II choline group scored significantly higher in Memory for Names Delayed (37.9 % difference; p = 0.04; d = 0.77) Executive functioning: No group differences in the Dimensional Change Card Sort Test; but a trend toward higher performance in the Flanker Inhibitory Control Test in the choline group compared to placebo (13.5 % difference; p = 0.08; d =0.66) Behavioural and emotional functioning: Choline group had significantly lower scores in the parent-reported scale for ADHD problems (estimated marginal mean = 62.1; SE = 2.1) compared to placebo group (estimated marginal mean = 69.0; SD = 2.0) (10.5% difference; F(1,28)=5.57; p=0.026; ηp2 =0.17)		
Smith et al. (2021) (6) **Retrospective analysis of a RCT (randomized, double-blind, placebo - controlled trial)**	- Inclusion: Children with confirmed hPAE or suspected hPAE with dysmorphic faces and cognitive deficits; supplement adherence in initial trial > 50 % of days; providing blood sample for genomics - Exclusion: developmental or neurological disorder; traumatic brain injury; other medical conditions. - No exclusion: psychiatric co-morbidity (ADHD or learning disorder) - 2,5–5 years old in initial trial		Choline: Initial trial: Discontinued: n = 5	Placebo: Initial trial: Discontinued: n = 3	Choline: - 1.25 g choline bitartrate powder delivering 500 mg choline - Daily doses for 9 months	Placebo: - Equivalent doses of an oral inactive placebo treatment - Daily doses for 9 months	Correlation between choline-related SNPs and memory and cognition (at study terminus, and 4 year follow-up)	14 SNPs within the choline transporter gene SLC44A1 were significantly associated with the change-score (pre-/post) on an EI sequential memory task (p = 0.04969) Same 14 SNPs + 2 SNPs within SLC44A1 were associated with change scores for adjacent pairs of items from the sequence (p = 0.023) Only participants in the choline group who had these variants were more likely to show improvement in the memory task (pre-/post). Some SNPs were associated with improved performance in the working memory measure of the Stanford-Binet Intelligence Scale, version 5, at 4 year follow-up, in the EI immediate memory task at baseline, in the NIH Toolbox Dimensional Card Sort Test at 4 year follow-up, and in change-score measures from baseline to 9 months for the Immediate Memory Task in the EI	Small number of participants with specific SNPs	Low (RoB-2)
	Choline: Initial trial: - Assigned: n = 34 - Received: n =	Placebo: Initial trial: - Assigned: n = 31 - Received: n = 29 - Lost to follow-up:								

	31 - Lost to follow-up: n = 0 - Completed: n = 26 - Blood sample: n = 26 - Analysed with intention-to-treat: n = 31 Follow-up: - Lost to follow-up: n = 11 - Analysed: n = 15	n = 1 - Blood sample: n = 26 - Completed: n = 25 - Analysed with intention-to-treat: n = 29 Follow-up: - Lost to follow-up: n = 9 - Analysed: n = 16								
Boroda et al. (2020) (7) **RCT**	- Inclusion criteria: documented history of heavy PAE; or suspected of heavy PAE with full-FAS diagnosis based on dysmorphology; at baseline characterized according to modified IOM criteria - Age: 9–16 years		tDCS: Discontinued: n = 1 (stimulation discomfort)	Sham: Discontinued: n = 3 (stimulation discomfort: n = 1, time commitment: n = 2)	tDCS group: 2 parallel components: - Cognitive training: 5 tasks from BrainHQ focussing on working memory and attention. Tasks were completed 4 times (total of 46 minutes) during each of 5 weekly sessions. - tDCS: transcranial stimulation was initiated 30s (at 2mA intensity) prior cognitive training and	Sham: 2 parallel components: - Cognitive training: 5 tasks from BrainHQ focussing on working memory and attention. Tasks were completed 4 times (total of 46 minutes) during each of 5 weekly sessions.	- Feasibility - Tolerability - Cognitive gains (near/far transfer)	Tolerability: No significant differences for tDCS related side-effects between the groups and no serious adverse events Near transfer of cognitive gains: - For visuospatial working memory, a significant effect of time was observed (F (1, 144) = 2.46, p = 0.047), with both groups showing improvement over the visits, but no significant effect for tDCS versus sham (F(1, 39) = 0.017, p = 0.911) or an interaction effect (F(1, 144) = 4.41, p = 0.612). No meaningful between group effect size. - In the continuous performance test tDCS performed significantly better over time than sham (F(1, 39) = 4.31, p = 0.043). No significant overall effect of time (F(1, 144 = 1.36, p = 0.247) or an interaction (F(1, 144) = 1.46, p = 0.221). Posthoc contrast analyses: significant tDCS versus sham differences at visit 3 (p = 0.033), visit 4 (p = 0.043), and visit 5 (p = 0.046). Medium between group effect size (d = 0.64). Far transfer of cognitive gains: - For the verbal fluency test, no significant effects of tDCS were seen for either letter VF (F(1, 36) = 0.067, p = 0.797), nor category verbal fluency (F(1, 36) = 0.049, p = 0.826). - No treatment effect was seen for the trail making	- Main effect of treatment was only marginally significant and would likely not remain significant after correction for multiple-comparisons. - In cognitive training attention was emphasised and working memory was only trained in 2 tasks - Effects of more training sessions unclear	Low (RoB-2)
	tDCS: - Assigned: n = 20 - Lost to follow-up: n = 0 - Analysed: n = 19	Sham stimulation augmented (sham): - Assigned: n = 24 - Lost to follow-up: n = 2 - Analysed: n = 19								

					lasted 13 min. Afterwards, it turned off and stayed off for 20 min. Then it turned on again for 13 min.	- Sham: transcranial stimulation ramped up to 2mA over the course of 30s, ramped down to 0mA over 30s and remained at 0mA.		test performance for number sequencing (F(1, 36) = 0.064, p = 0.801), letter sequencing (F(1, 36) = 2.75, p = 0.107), nor combined letter and number sequencing (F1(1, 36) = 0.197, p = 0.659).		
Vidal et al. (2020) (8) **RCT (randomized, rater-blinded, controlled pilot trial)**	- Inclusion: FASD diagnosis (FAS, pFAS, ARND); 6-18 years of age; with stabilized doses of medication for at least 2 months before the study - No exclusion: comorbidities, borderline IQ/intellectual disability DAT: - Assigned: n = 19 - Completed: n = 17 - Lost at post-treatment: n = 0 - Analysed: n = 17	TAU: - Assigned: n = 20 - Completed: n = 16 - Lost at post-treatment: n = 1 - Analysed: n = 16	DAT: Discontinued medication: n = 2	TAU: Dropped-out: n = 1; Discontinued medication: n = 2	DAT: - 12 manualized sessions in 2 phases (6 individual sessions, 6 group activity sessions - Sessions included 2 certified therapy dogs - Groups of 3-4 patients - Weekly 45-miniute sessions for about 3 months - Pharmacological treatment as usual	TAU: Pharmacological treatment as usual	- Social skills - Internalized symptomatology - Externalized symptomatology - Severity of FASD symptoms.	Social Skills: - A main effect on time [F(1.30) = 15.54, p = 0.001] and an interaction time x group with the DAT group being the one who improved more [F(1.30) = 13.82, p = 0.02, d = 0.8]. - Problem behaviour: no interaction of time x group Internalizing symptoms: Main effect of time [F(1.30) = 10.45, p = 0.001], but there was no significant interaction of time x group Externalizing symptoms: Main effect of time [F(1.30) = 12.35, p = 0.001] and also a significant interaction on time x group [F(1.30) = 11.59, p = 0.03, d = 0.56 Severity of FASD Symptoms: Main effect of time [F(1.30) = 12.549, p = 0.001] and also a main effect on time x group interaction with FASD severity decreasing significantly more in the DAT group [F(1.30) = 16.54, p = 0.001, d = 0.5].	- Low power - All participants had ADHD - Effects of DAT only with pharmacological treatment - Maintenance of the results is unclear - No definition of TAU - No clear description of DAT - Results might be due to the intensive treatment sessions and not due to the dogs involved - Big range of age (6-18 years)	Moderate (RoB-2)

Kerns et al. (2017) (9) **Uncontrolled intervention study**	- Inclusion: Children with diagnosed FASD or Autism Spectrum Disorder who receive Educational Assistant Support within their school program - Exclusion: history of traumatic brain injury, chronic health problem, inability to verbally communicate or diagnosis of an intellectual disability based on information provided by special education staff and parent or caregiver - Age: 6–13 years old - Enrolled: n = 23 - Completed: n = 17 - Analysed: n = 17 (Children with FASD: n = 10 Children with Autism Spectrum Disorder: n = 7)	Discontinued: n = 6 (Education Assistant scheduling difficulties)	Caribbean Quest: - Video game with one-to-one support by a trained and tested educational assistant using metacognitive strategies - Game consisting of 5 hierarchically structured self-adjusting mini-games to improve attention and working memory - 30-minute sessions, 2–3 times a week over a 10-12 week span	NA	- Everyday problem behaviour and attention skills - Emotional and behavioural strengths - Utility and feasibility - Attention - Working Memory - Academic skills - Children's respond to training	- Everyday problem behaviour and attention skills: BRIEF and CRS-3 could not be analysed due to very low questionnaire return rates - Emotional and behavioural strength: BERS-2 could not be analysed due to very low questionnaire return rates - Utility and feasibility: 80% reported easy incorporation in school schedule - Attention: sign. reductions in total errors on the KiTAP for distractibility (p = 0.002, d = 0.87) and divided (p = 0.001, d = 0.91) tasks, and no significant reduction of total errors in the flexibility task (p = 0.226, d = 0.31); no differences on the total correct responses of any KiTAP task - Working Memory: significant improvement on the Listening Recall (p = 0.003, d = 0.45) and Counting Recall (p = 0.001, d = 0.61) verbal working memory tasks from WMTB-C; no significant changes on the WISC-IV verbal and spatial span tasks - Academic skills (AIMSweb): significant reductions in errors on the oral reading fluency task (p = 0.002, d = 1.30); total number of correct words did not change (children read less quickly, but the read words were more likely to be correct) - Academic skills (interview with Educational Assistants): spelling, reading, and math were ameliorated (no quantitative testing) - Children's respond to training (interview with Educational Assistants): functional improvements in the classroom (improved focus and alertness, decreased hyperactivity, less resistance to engaging in new/challenging activities, increased academic engagement and mastery); emotional and social improvements	- Potential bias due to additional support services - Possible practice effect - No sub-analysis of disorder type - No manualized version of the Caribbean Quest intervention protocol that includes evidence-based guidelines to assist in metacognitive training - Impact of components of intervention unclear (serious game vs metacognitive training)	Moderate (ROBINS-I modified)

Kable et al. (2015) (10) **RCT**	- Inclusion: clinical diagnosis of FAS/pFAS or significant levels of alcohol-related dysmorphia - Exclusion: IQ < 50; diagnosis of mental health problems interfering with learning; no stable placement - Parents needed to complete two workshops (education about neurodevelopmental characteristics of FASD; strategies to deal with behavioural regulation problems) - Age: 3–10 years old - Recruited: n = 68	Centre MILE: Discontinued: n = 1 (session 3-travel and time)	Community MILE: Discontinued: n = 1 (session 4-scheduling conflicts/travel)	Parents Instruction: Discontinued: n = 0	MILE: - Parents completed workshops and received a manual discussing math learning in children with FASD and strategies for facilitating math learning at home - MILE: Program targeting learning behaviour and math development and focussing on core deficit of mathematical competence (metacognitive control strategies adapted from FAR) - One-on-one individualized tutorial sessions by trained instructor - Weekly home assignments - Weekly sessions for 15 weeks	Parents Instruction: Parents completed workshops and received a manual discussing math learning in children with FASD and strategies for facilitating math learning at home	- Instructor satisfaction - Instructor knowledge - Instructor fidelity - Child's academic outcomes - Parent satisfaction	Instructor satisfaction, knowledge, and fidelity: - High satisfaction and willingness to recommendation - Significant group effect on the knowledge scores ($F(2, 48) = 8.21$, $p < 0.001$, $\eta p2 = 0.255$) with centre-based employees who were not trained in the MILE program receiving lower scores (X = 8.00, STD = 1.92) than both instructors trained at the centre (X = 9.83, STD = 0.76) or in the community (X = 9.39, STD = 0.41), but no difference between centre-instructors and community-instructors - The session number was positively related to the fidelity score (r = 0.36, p 0.005), suggesting that instructors were improving over the course of sessions. A significant effect was found for block ($F(2, 52) = 4.26$, $p < 0.019$) but was not found for site. Higher ratings of fidelity were obtained in the final block of five sessions relative to the initial block of sessions. Child's academic outcomes: - No significant group*time effect on the individual tests - Using the math summary score from summing the raw scores from Bracken, TEMA, and Handwriting measure: significant time*group effect with MILE groups demonstrating more positive gains in math skills than Parent Instruction group ($F(2, 41) = 3.4$, $p < 0.04$, $\eta p2 = 0.139$)	- Original treatment plan of 6 weeks was extended to 15 weeks - Detailed instruction training with feedback on the sessions and mock sessions - Children were evaluated by a psychologist or psychology trainee blind to group status - Possible impact of maturation effects as groups differed in days of completion - KeyMath only administered to children ≥ 5 years (N's: Centre = 9; Community = 14; Parent Instruction = 12) - No results for the instrument adapted from math concepts administered as part of the Bayley Scales of Infant Development 2nd Edition (for children < 5 years) - Raw and standardized scores were analysed - Broad age span (possible floor effects with younger children)	Moderate (RoB-2)

								- Within in the MILE groups, fidelity ratings were significantly positively correlated with change on the total score of KeyMath (standard score D: r = 0.48, p < 0.02) and the TEMA (raw score D: r = 0.35, p < 0.04; standard score D: r = 0.45, p < 0.04), but no significant correlations with the raw scores of KeyMath, the number of writing score or the total scores from Bracken. Parent satisfaction: - Compared to MILES groups, the Parent Instruction group reported less agreement that child improved in math skills (p < 0.001) and that their ability to help child to study had improved (p < 0.01) - Centre-MILES group reported more favourable rating than Parent Instruction group on: informative (p < 0.05), helpful (p < 0.05), improved understanding of FAS/pFAS (p < 0.01), and helped child's study habits (p < 0.05); - Community-MILE group and Parent Instruction group did not differ significantly		
Kully-Martens et al. (2018) (11) **CCT (not randomized)**	- Inclusion: confirmed PAE or FASD diagnosis - No exclusion: common mental health comorbidities - Enrolled: n = 29 - Age: 4–10 years MILE: - Assigned: n = 15 - Received: n = SSIS: - Assigned: n = 13 - Received: n = 13 - Lost to		MILE: Discontinued: n = 0	SSIS: Discontinued: n = 0		MILE: - No parent workshops - MILE: Program targeting learning behaviour and math development	SSIS: - The Social Skills Improvement System Intervention: Program	- Mathematical skills - Executive functioning - Working memory - Visuospatial functioning	Mathematical skills: - MILE group improved significantly more on total KeyMath score from pre-to post-testing compared to contrast group (F(1, 27) = 5.89,p < 0.05, η2 = 0.19); - MILE group gained significantly more raw points on the Basic Concepts composite than contrast group (F(1, 27) = 4.98, p < 0.05, η2 = 0.16) but the overall MANOVA of the 5 subtests of the Basic Concepts composite was not significant (F(5, 27) = 2.01, p > 0.05);	- Post-testing by a blinded research assistant - Working Memory Test Battery for Children suitable for children aged 5-15 years - No assessment of executive functioning, working	Moderate (ROBINS-I)

	15 - Lost to immediate follow-up: n = 0 - Analysed (immediate): n = 15 - Lost to 6-months follow-up: n = 3 - Analysed (6-months): n = 12	immediate follow-up: n = 0 - Analysed (immediate): n = 13 - Lost to 6-months follow-up: n = 6 - Analysed (6-months): n = 7			and focussing on core deficit of mathematical competence (metacognitive control strategies adapted from FAR) - One-on-one individualized tutorial sessions by trained instructor - Weekly home assignments - 10–30-minute sessions once/twice a week for 6-8 weeks	focussing on social skills - One-on-one individualized tutorial sessions Weekly home assignments - 10–30-minute sessions once/twice a week for 6–8 weeks	- Influence of participant's characteristics	- MILE group did not gain significantly more points on Operations and Problem Solving than contrast group; - MILE group showed greater increases in total math achievement than control group from pre-test to 6-months follow-up ($F(1, 18) = 5.47$, $p < 0.05$, $\eta 2 = 0.24$) Executive functioning: No significant differences in raw scores on Auditory Attention and Response set, but trend: MILE group had larger gains in total correct in Auditory Attention ($p = 0.18$, total correct in Response ($p = 0.13$) and in Omission errors in Response ($p = 0.13$) compared to control group. Working Memory: No significant treatment effect Visuospatial functioning: No significant treatment effect Influence of participant's characteristics: - Within the MILE group: Older age was associated with higher KeyMath Total and Operations raw change scores. PAE 'diagnosis' was strongly associated with greater raw point gains in Operations, Problem Solving, and Total Score. A lower Verbal IQ was associated with greater change in KeyMath Operations and Problem Solving raw scores. A strong negative relationship was observed between overall IQ and KeyMath Problem Solving raw change score ($r(13) = -0.54, p < 0.05$). Sex was not significantly related to KeyMath Total raw change score. SES was not significantly correlated with changes math achievement - Within the SSIS group: PAE 'diagnosis' was not associated with greater raw point gains in Operations, Problem Solving, and Total Score. A higher Verbal and Visual IQ was associated with more raw changes in Problem Solving. IQ was strongly positively related to KeyMath Problem Solving raw change score ($r(11) = 0.85$, $p < 0.01$). Sex was not significantly related to KeyMath Total raw change score. SES was not significantly correlated with changes math achievement.	memory and visuospatial functioning at 6-months follow-up - N at follow-up: 19 - Possible effect of control intervention on outcomes - Possible practice effect - MILE group had lower Math scores at pre-test (greater improvement potential)	

Wells et al. (2012) (12) **RCT (rater-blinded)**	- Inclusion: confirmed PAE, FAS or ARND diagnosis - Exclusion: serious head trauma; current/historical lead poisoning; genetic/dysmorphic syndrome (other than FAS) - No exclusion: exposures to other drugs (marijuana/cocaine) - Age: 6–11 years - Eligible for enrolment: n = 90 - Enrolled: n = 78 Neurocognitive habilitation therapy (NHT): n = 40 Control: n = 38		NA	NHT: - Parents received feedback and recommendations regarding child's behaviour, learning and emotional functioning - Parent training: psychoeducation in group setting - Children's' training: - NHT: program in group setting teaching children to recognize individual deficits and to develop strategies to compensate for them (integration of techniques of therapy of traumatic brain injury, and Alert Program: analogy of car engine) - Conjoined parent and children	Control: - Parents received feedback and recommendations regarding child's behaviour, learning and emotional functioning - No further intervention	- Executive functioning - Emotional and social problem-solving skills	Executive functioning: - Significant interaction between group and time, F(8, 57) = 3.09, p = 0.006, ηp2 = 0.30); significant main effect for group, F(8, 57) = 2.61, p = 0.02 with treatment group showing more improvement; nonsignificant main effect for time, F(8, 57) = 1.93, p = 0.07 - No specific subtest was responsible for the significant effect, but the combination of the subtests Emotional problem solving: - Significant interaction between group and time, F(7, 52) = 2.92, p = 0.012, ηp2 = 0.28; significant main effect for group, F(7, 52) = 3.54, p = 0.003 with treatment group showing more improvement; and significant main effect of time, F(7, 52) = 492.88, p < 0.001 - Specific subtest was responsible for significant effect: treatment group did not rely on easy or unrealistic solutions to problems	- Only children living with foster or adoptive caregivers - No predetermined allocation sequence for randomization, but randomization through random numbers - Transformation of the data to eliminate skewness by extreme outliers - Outcome differences might be muted by the extensive feedback and comprehensive recommendations the assessment psychologist provided to all	Moderate (RoB-2)

				training at the end of each session - Weekly 75-minute sessions for 12 weeks					
Nash et al. (2015) (13) **CCT (not randomized)**	- Inclusion: Children with FASD diagnosis - Exclusion: IQ < IQ 70 - Age: 8-12 years TXT: - Assigned: n = 14 - Completed: n = 12 - Received: n = 15 - Analysed (immediate): n = 12 - Lost to 6-months follow-up: n = 3 - Analysed (6-months): n = 9	Delayed treatment control group (DTC): - Assigned: n = 15 - Completed: n = 13 - Received: n = 15 - Analysed (immediate): n = 13	No completion: n = 4 (3 children (1 TXT, 2 DTC) had custody access issues and did not continue after baseline testing; and 1 child was lost to follow-up between the initial screening interview and scheduling of baseline testing)	TXT: - Alert: Program targeting self-regulation skills through sensory integration and cognitive processing activities (analogy of a car engine) in three stages: awareness, self-regulation strategies, independent usage - 12 1-hour sessions for 14 weeks	DTC: Waiting list	- Cognitive executive functioning - Socio-affective executive functioning - Emotional/ behavioural functioning - Social skills	- Significant improvements of TXT compared to DTC in inhabitation naming (F(2, 20) = 6.12, p = 0.001, effect size = 0.283) with scores changing into the normal range - No significant changes in Inhibition-Inhibition score (F(2, 18) = 3.27, p = 0.15, effect size = 0.060) or Inhibition-Switching (F(2, 18) = 2.12, p = 0.30, effect size = 0.010) in TXT compared to DTC For attention, trend-level effect for the TEA-Ch Score (F(2, 22) = 2.89, p = 0.15; effect size = 0.047) - No group differences in attention switching or planning from CANTAB - Significant treatment effect for NEPSY Affect recognition (F(2, 21) = 4.82, p = 0.05, effect size = 0.103) with scores improving into the normal in TXT - For social cognition, trend level effect for Strategic Control of Emotions (F(2, 21) = 6.49, p = 0.07, effect size = 0.004) with TXT showing improvement and Personalized Emotions (F(2, 21) = 5.46, p = 0.09, effect size = 0.002) with DTC showing improvements - Sign. treatment effect in behavioural regulation (F(2, 21) = 22.6, p = 0.01, effect size = 0.189) and trend-level in General Executive Functioning (F(2, 21) = 21.7, p = 0.06, effect size = 0.103) with TXT showing improvements - Sign. treatment effect for Emotional control (F(2, 21) = 4.29 , p = 0.03, effect size = 0.170) with TXT showing improvements - Trend-level for Inhibition control (F(2, 21) = 1.96, p = 0.09, effect size =0 .085) and CBCL Externalizing Problems (F(2, 21) = 34.6, p = 0.08, effect size = 0.095) with TXT showing improvements - No treatment effects were observed for the CBCL Total Behaviour Problems or SSIS Social Skills scores. - Results from parent-questionnaire data obtained at	- Different tests for similar outcomes - did not reach significance - Differences in the groups regarding ADHD diagnosis, and alcohol and secondary drugs - No correction for comorbidities - Child with IQ = 70 did not master the third stage	Moderate (ROBINS-I)

								6-month follow-up in nine TXT cases revealed that treatment effects observed at first posttest were sustained after 6 months, while an improvement on the Inhibit subscale of the BRIEF was also noted (M posttest (SD): 78.9 (8.7); M follow-up (SD) 74.6 (10.6); p = 0.01)			
Soh et al. (2015) (14) **CCT (not randomized)**	Treatment and waiting list group: - Inclusion: Children with FASD included in clinic files or children in FASD support groups - Exclusion: Head injury requiring hospitalization, other neurological abnormalities, a debilitating or chronic medical condition, contraindications to MRI (e.g. braces, other implanted metal devices) - No exclusion: ADHD Healthy control group: - Inclusion: Children without PAE, psychiatric diagnosis (e.g. ADHD) or learning disability In total: - Age: 8–12 years - Recruited: n = 65		TXT: Before pretest: n = 3 (drop-out: 1; refused scan: 2) After pretest: Drop-out: n = 1; refused scan: n = 1)	DTC: Before pretest: n = 1 (refused scan) After pretest: n = 1 (movement) After posttest: n = 2 (movement)	CT: After posttest: n = 7 (undisclosed exposure: 1; low IQ/learning disability: 2, technical problems: 1; movement: 1; braces: 2) After posttest: n = 1 (movement)	TXT: - Alert: Program targeting self-regulation skills through sensory integration and cognitive processing activities (analogy of a car engine) in three stages: awareness, self-regulation strategies, independent usage - 12 1,5-hour sessions for 14 weeks	DTC: waiting list	CT: no intervention	- Emotion regulation - Inhibition - Brain structure and - function	Emotion regulation: BRIEF: significant group*time interaction with TXT having the largest improvement (p = 0.04) (TXT > CT > DTC) Inhibition: NEPSY-II: sign. group*time interaction in inhibition subscale with improvements in TXT and CT (p = 0.01) (CT, TX > DTC) Brain structure and function: MRI: - While controlling for multiple comparisons: no significant changes among groups - Uncorrected data: Significant increase in grey matter volumes in some brain regions (e. g. related to self-regulation) in TXT compared to DTC (p between < 0.0001 and 0.005) - Increase in grey matter volume in TXT, DTC and CT in different areas (p between 0.0001 and 0.001) - TXT still differed from CT group regarding neuroanatomy after treatment	- 2 children without FASD diagnosis in TXT - Only 1 children with FAS in DTC and no child in TXT - 1 family in TXT was reassignment to DTC after pretest - No between and within group differences with false discovery rate applied (only uncorrected) - Large number of comparisons (possible false-positive/type 1 errors) - Group differences in time between pre- and post-testing (TXT > DTC > CT) - More females in DTC than TXT (differences in neurodevelopmental peaks) - Normal brain changes during this age - No examination of structure-function correlations on DTC and CT (placebo	High (ROBINS-I)

										effect) - Mask was relatively large and allowed for a large number of voxel comparisons	
Coles et al. (2015) (15) **RCT**	- Inclusion: Children with PAE with significant levels of alcohol-related physical features or with a clinical diagnosis of FAS/pFAS - Age: 5–10 years - Recruited: 30 children	GoFAR: Drop-out: n = 3 (unknown)	FACELAND: Drop-out: n = 3 (family crisis: 2; unknown: 1)	Control: Drop-out: n = 1 (unknown)	GoFAR with 3 components: - Children: Children learn metacognitive control strategies (FAR methodology) through computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-	FACELAND with 3 components: - Children: Children learn to identify emotions through a computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to	Control: no intervention	Disruptive behaviour	- No overall time point effect, F(5, 90) < 1, but a significant treatment group*time point effect on the disruptive behaviour composite, F(4, 36) = 2.903, p < 0.035, ηp2 = 0.244. - No time point differences in the Control - GoFAR had significant improvements in disruptive behaviour at Mid-Treatment after the Game learning - FACELAND had significant improvements in disruptive behaviour at Posttreatment, after completing the BAT sessions - Intent to treat analysis: trend for the treatment group*time point interaction, F(4, 42) = 1.823, p < 0.142, ηp2 = 0.148	- Maintenance of the behavioural change is unknown. - Generalisability to other situations is unknown. - Parents and observers were not blinded	Moderate (RoB-2)

					hour sessions parallel to children's sessions) - Children + Parents: Behaviour analog therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training)	facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour analog therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training)					

Coles et al. (2018) (16) **RCT**	- Inclusion: Children with PAE with significant levels of alcohol-related physical features or with a clinical diagnosis of FAS/pFAS - Parents needed to attend a group workshop on the impact of PAE on neurodevelopmental functioning before enrolment - Age: 5–10 years - Recruited: n = 30 - Completed: n = 25	NA	GoFAR with 3 components: - Children: Children learn metacognitive control strategies (FAR methodology) through computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour analog therapy (BAT): Children and parents apply the FAR methodology in everyday	FACELAND with 3 components - Children: Children learn to identify emotions through a computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural	Control: no intervention	- Neurocognition - Adaptive functioning - Behaviour - Parents' satisfaction and fidelity to treatment protocol	Neurocognition (attention regulation): - Only GoFAR showed significant improvements in summary score of TOVA = Attention Performance Index (API) that measures efficiency in sustaining attention and inhibiting impulsive responding. On this measure, children who received the GoFAR intervention showed significant improvement at Post Test while the other two groups did not (Wald χ (2)= 6.09, $p < 0.05$) - Control group performed significantly better in NEPSY-Auditory Attention-SS than intervention groups Adaptive functioning: FACELAND and GoFAR had significant improvements in the Vineland Dailiy Living Skills, Domestic subscale that reflects adaptive functioning in the home (in contrast to control) (Wald χ (1) =5.39, $p < 0.02$) Behaviour: On the CBQ, which measures Temperamental Functioning, Fear, one of the elements of Negative Affect was significantly reduced both when the three groups are compared (Wald χ (2) = 8.59, $p < 0.01$) and when both intervention groups were combined (Wald χ (1) = 7.91, $p < 0.005$) Fidelity: - Significant improvements in parent fidelity in carrying out the FAR methodology in FACELAND and GoFAR group ($F(4, 13) = 8.0$, $p < 0.002$, eta2 = 0.71) - Parent thought the program was helpful and would recommend it.	- Highly motivated parents - Child with intellectual disability (IQ < 60) could not complete the neurocognitive measures; others completed only some sessions. - Parents were not blinded (VABS, CBQ) - No bias with TOVA (computerized measures) - Both intervention groups had higher TOVA API at baseline compared to controls (possible ceiling effect)	Moderate (RoB-2)

			contexts (5 weekly sessions after 5 weeks of children and parent training)	regulation skills (5 weekly 1-hour sessions parallel to children's sessions) - Children + Parents: Behaviour analog therapy (BAT): Children and parents apply the FAR methodology in everyday contexts (5 weekly sessions after 5 weeks of children and parent training					

					)					
Kable et al. (2016) (17) **RCT**	- Inclusion: Children with PAE with significant levels of alcohol-related physical features or with a clinical diagnosis of FAS/pFAS - Parents needed to attend a group workshop on the impact of PAE on neurodevelopmental functioning before enrolment - Age: 5–10 years - Recruited: n = 30			FACELAND: re-initiation after 8 months due to family crisis: n = 1	GoFAR with 2 components: - Children: Children learn metacognitive control strategies (FAR methodology) through computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitate the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to children's sessions)	FACELAND with 2 components - Children: Children learn to identify emotions through a computer game (5 weekly sessions) - Parents: Parents learn about the neurodevelopmental/ behavioural impacts of PAE and how to facilitat	Control: no intervention	- Impact of parental engagement in the learning program on child's self-regulation skills - Disruptive behaviour	Impact of parental engagement in the learning program on child's self-regulation skills: - Child's ability to regulate attention was significantly related to therapist's ratings of achievement of therapy goals ($r = -0.70$, $p < 0.001$) - Trend: Child's ability to regulate attention was correlated with parental completion of homework ($r = -0.44$, $p = 0.059$) - Trend between therapist's ratings of parent's achievement of therapy goals and reduction in children's destructive behaviour ($r = 0.39$, $p = 0.10$) Disruptive behaviour: - No significant multivariate group effect, $F(12, 42) = 1.58$, $p = 0.134$, $\eta 2 = 0.311$ - Trend for a specific univariate effect on change in sustained mental effort, $F(2, 25) = 2.77$, $p = 0.08$, $\eta 2 = 0.181$ - GoFAR had a significant reduction in frustration level relative to individuals in FACELAND and Controls, $p = 0.05$, and a trend was found for those in GoFAR making more improvement in sustained mental effort, $p = 0.09$. Contrasts between those in FACELAND and Controls were not significant. - GoFAR demonstrated greater reductions on disruptive behavioural outcomes than FACELAND on change in sustained mental effort $F(1, 17) = 5.85$, $p = 0.027$, $\eta 2 = 0.26$ (but not a significant multivariate group effect).	- Highly motivated parents - Parents were not blinded (parents questionnaire for disruptive behaviour)	Moderate (RoB-2)
	GoFAR - Assigned: n = 10 - Completed: n = 9 - Analysed: n = 9	FACELAND - Assigned: n = 10 - Completed: n = 9 - Analysed: n = 10	Control - Assigned: n = 10 - Completed: n = 9 - Analysed: n = 9							

						e the child's behavioural regulation skills (5 weekly 1-hour sessions parallel to childre n's sessions)					
Petrenko et al. (2017) (18) **RCT**	- Inclusion: FASD diagnosis or confirmed PAE; 4-8 years old; living within a reasonable distance of two New York study sites; expected to remain in their current placement for the study duration (~18 months, including 9-month intervention and follow-up time points) - Exclusion: moderate to severe intellectual disabilities (IQ < 55); lacked sufficient English proficiency; severe physical or mental conditions - Age: 4–8 years FoT: - Assigned: n = 19 - Accepted: n = 16 - Completed: n = 15 - Analysed: n = 15 Control: - Assigned: n = 11 - Accepted: n = 10 - Completed: n = 9 - Analysed: n = 12 (3 declining treatment were included in analysis)			FoT: 3 families declining treatment (logistical difficulties)	FoT: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to caregivers) FoT including 2 empirically-validated programs: - The	Control: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to	- Satisfaction with FoT - Child's emotional and behavioural functioning - Child's impairment - Child's self-perception and environment - Child's behavioural problems - Parental knowledge and	Satisfaction with FoT: - CSQ: high satisfaction - PEI-FOT: high level of enjoyment; felt that they could apply what they learned; good relationship with their FMF Specialist; felt the Specialist understood their feelings and problems; children generally looked forward to coming to group; and learned new skills; children had relatively more difficulty applying what they learned Child's emotional and behavioural regulation: ERC: - Emotion regulation: significant group difference: parents reported a change in child emotion regulation (ERC d_{ppc} = 1.18). This effect reflected a medium to large improvement in emotion regulation for the intervention group and medium-sized decrement for the comparison group. - Negative affect: main effect of time Child's impairment: IRS: medium to large group effect size for parent-reported self-esteem was found (IRS self-esteem d_{ppc} = 0.77), which was not statistically different between groups. (significant effect of time p = 0.046); main	- Families were not precluded from participating in other intervention programs. - Fidelity was monitored in weekly individual/group supervision - Attempts were made for blinding research assistant to intervention condition at assessment points - Small sample size => powered to detect only large effects - Effect sizes are resistant to sample size influence and give a truer measure of the magnitude of effects. - 3 families declined	Modeate (RoB-2)

				preschool/ kindergarten Promoting Alternative Thinking Strategies (PATHS) curriculum (Domitrovich et al., 2005): Program in small groups including children with and without PAE and aiming at preventing violence, aggression, and other behavioural problems by promoting social competence and developing emotional skills. Children learn self-control, emotional understanding, positive self-esteem, peer relationships, and interpersonal problem solving skills - The Families Moving	caregivers)	advocacy - Families' needs met - Parenting strategies and parental attributions for child misbehaviour - Efficacy in parenting role and satisfaction with parenting role: - Perceives support from family, friends, significant others, and involved professionals - Change in self-care - Stress in parent-child system	effect of time for global impairment Child's self-perception and environment: BPI: medium to large group effect was found for child-reported anxiety symptoms (BPI Overanxious d_{ppc} = 0.75), which did not reach statistical significance. FoT had a higher level of anxiety symptoms at pre-intervention with improvement over time (d within = 0.80) Controls had a minimal change in self-reported anxiety. Main effect of time for child report of prosocial skills and conduct problems Child's behavioural problems: ECBI: Main effect of time for parental report of child disruptive behaviour Parental knowledge and advocacy: K&A: statistically significant between-group difference: large effect size for knowledge and advocacy with FoT improving (K&A d_{ppc} = 1.02) Families' needs met: FNM: significant between group difference: large effect with FoT improving (d_{ppc} = 0.72) No statistical significance: - Parenting strategies and parental attributions for child misbehaviour - Efficacy in parenting role and satisfaction with parenting role - Perceives support from family, friends, significant others, and involved professionals - Change in self-care - Stress in parent-child system	intervention for logistical reasons and were combined with control group in analyses - All caregivers completed one individualized session; 12 completed 2 individualized sessions; 11 completed the school consultation - Children in both groups declined in their self-esteem. FoT may have buffered this decline. - Highly motivated families - Some families had logistical reasons not to participate in intervention - Lack of objective data (parental reports) - Findings could be due to the more intensive care with FoT compared to controls	

				Forward (FMF) Program (Bertrand, 2009): Core sessions for parents in groups aiming at creating a stable home to reduce violence by targeting family-level risk and protective factors					
Petrenko et al. (2019) (19) **RCT**	- Inclusion: FASD diagnosis or confirmed PAE; 4-8 years old; living within a reasonable distance of two New York study sites; expected to remain in their current placement for the study duration (~18 months, including 9-month intervention and follow-up time points) - Exclusion: moderate to severe intellectual disabilities (IQ < 55); lacked sufficient English proficiency; severe physical or mental conditions - Age: 4–8 years FoT: Initial trial: - Assigned: n = 19 - Accepted: n = 16 - Completed: n	Control: Initial trial: - Assigned: n = 11 - Accepted: n = 10 - Completed: n = 9 - Analysed: n = 12 (3 declining	Follow-up: n = 3 (change in child placement (n = 1); loss of contact (n = 1); declining to participate due to time demands of other services (n = 1))	FoT: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to caregivers) FoT including 2 empirically-validated programs: - The	Control: Children received a neuropsychological and diagnostic evaluation to promote the protective factor of early diagnosis and to identify the child's neuropsychological profile (Personalized feedback to	6 months sustainability of: - Child's emotional and behavioural functioning - Child's impairment - Child's self-perception and environment - Child's behavioural problems - Parental knowledge	Child's emotional and behavioural regulation: ERC: - Emotion regulation: FoT had medium-large improvements during intervention and declined in follow-up (remained above baseline-levels) (d within = -0.56); controls had a moderate worsening during the study and improved in follow-up (slightly below baseline-levels) (d within = 0.38). Significant group*time effect: changes in emotion regulation over time differed significantly by treatment group ($F(2, 44) = 8.032$, $p = 0.001$) - Negative affect: FoT had a small-medium improvement during intervention and an additional minimal-small improvement in follow-up (d within = 0.15); controls had a minimal improvement during study and a small improvement in follow-up (d within = 0.24), both groups had a similar magnitude of change. Significant time effect: significantly higher levels of negative affect at baseline than at 6-month follow-up ($F(2, 44) = 4.68$, $p = 0.014$), no significant group or group*time effect Child's impairment: IRS: FoT remained stable during intervention and had a moderate decrease in follow-up (d within = -0.41);	- Families were not precluded from participating in other intervention programs. - Fidelity was monitored in weekly individual/group supervision - Attempts were made for blinding research assistant to intervention condition at assessment points - Small sample size => powered to detect only large effects - Effect sizes are resistant to sample size influence and give a truer measure of the magnitude of effects. - 3 families declined	Moderate (RoB-2)

	= 15 - Analysed: n = 15 Follow-up: - Completed: n = 14 - Analysed: n = 14	treatment were included in analysis) Follow-up: - Completed: n = 10 - Analysed: n = 10		preschool/ kindergarten Promoting Alternative Thinking Strategies (PATHS) curriculum (Domitrovich et al., 2005): Program in small groups including children with and without PAE and aiming at preventing violence, aggression, and other behavioural problems by promoting social competence and developing emotional skills. Children learn self-control, emotional understanding, positive self-esteem, peer relationships, and interpersonal problem solving skills - The Families Moving	caregivers)	and advocacy - Families' needs met - Parenting strategies and parental attributions for child misbehaviour - Efficacy in parenting role and satisfaction with parenting role: - Perceives support from family, friends, significant others, and involved professionals - Change in self-care - Stress in parent-child system	controls had a medium-large decline during study and a minimal decline in follow-up (d within = -0.10). Significant time effect: F(2, 38) = 10.07, p = 0.018), no significant group or group*time effect. Both groups had a decline in self-esteem Child's behavioural problems: ECBI: FoT group moderately decrease in behavioural intensity during the course of the intervention and maintained this change over the 6-month follow-up interval (d within = 0). Children in the comparison group, who had a small decrease in behavioural intensity during the intervention time, had an additional small decrease in intensity of behaviour problems during last 6 months (d within = -0.25). When considering overall change from baseline to follow-up, effect size analysis showed negligible group difference (d_{ppc} = 0.03). Significant time effect, with the most intense behaviours at baseline, significantly less intense behaviours at post-intervention, and significantly less intense behaviours at 6-month follow-up (F(2, 44) = 16.77, p < 0.001) on average across groups. No significant main effect for group and no significant group*time interaction. Parental knowledge and advocacy: K&A: FoT had large gains during intervention and maintained them in follow-up; controls had approximately the same level across all time points. Significant main effect of time; no group effect; significant group*time effect (F(2, 40) = 3.241, p < 0.050), with families in the intervention group reporting significantly less knowledge at baseline (M = 26.50) compared to post-intervention (M = 31.00) and 6-month follow-up (M = 31.21)) Families' needs met: FNM: FoT had a large increase in needs met during intervention and had a large decline (d within = -1.03) in the follow-up (remained above baseline-level and reflected an overall medium level improvement (d within = 0.55)); controls had a small-medium increase during study and a large decline (d within = -1.03) in follow-up (below baseline-level (d within = -0.60)). The overall group effect across the length of the study was	intervention for logistical reasons and were combined with control group in analyses - All caregivers completed one individualized session; 12 completed 2 individualized sessions; 11 completed the school consultation - Children in both groups declined in their self-esteem. FoT may have buffered this decline. - Highly motivated families - Some families had logistical reasons not to participate in intervention Follow-up: - Lack of objective data (parental reports) - 3 participants completed the follow-up measures at home - The decline in families' needs met could be due to an increase in needs as children progress in early school years - Data collection at different time points: baseline (summer),	

				Forward (FMF) Program (Bertrand, 2009): Core sessions for parents in groups aiming at creating a stable home to reduce violence by targeting family-level risk and protective factors			large (d_{ppc} = 1.07), and favoured the intervention group (M = 3.2) as compared to the comparison group (M = 2.8; F(1, 20) = 4.682, p = 0.043). Main effect for time: scores for FNM were significantly higher for both groups immediately post-intervention (M = 3.37) than they were at baseline (M = 2.84) or follow-up (M = 2.79; F(2, 40) = 6.78, p = 0.003). Significant group*time interaction (F(2, 40) = 2.90, p = 0.067) with FoT reporting that their needs were better met post-intervention (M = 3.62) compared to baseline (M = 2.81), and the comparison group reporting their needs were better met post-intervention (M = 3.13) compared follow-up (M = 2.41). Efficacy in parenting role and satisfaction with parenting role - PSOC: Parenting self-efficacy: FoT had a small-medium improvement during study and an additional small-medium improvement (d within = 0.34) in follow-up; controls had a minimal change during study and a small-medium worsening (d within = -0.39) in follow-up. large group effect in follow-up (d_{ppc} = 1.14 => large effect size), favouring FoT . Changes in efficacy over time significantly differed by treatment group (F(2, 44) = 3.51, p = 0.038) - Parenting satisfaction: FoT had a medium improvement during intervention and a small-medium worsening (d within = -0.37) in follow-up (remaining above baseline); controls had a minimal change during study and a moderate improvement (d within = 0.52) in follow-up (similar level to FoT post-intervention). Significant group*time interaction, with parenting satisfaction in the comparison group significantly higher at follow-up (M = 38.3) than at baseline (M = 34.6) or post-intervention (M = 34.3; F(2, 44) = 3.48, p = 0.039). Small-moderate group difference favouring the comparison group (d_{ppc} = -0.38) Stress in parent-child system PSI: both groups had minimal-small changes in distress across each time point; FoT had minimal-small improvements (d within = -0.11) in follow-up; controls had minimal-small worsening (d within = 0.13) in	post-test (summer), follow-up (winter) - No intent-to-treat analyses => results could overestimate the treatment effect	

							follow-up. Small group effect at follow-up compared to baseline (d_{ppc} = 0.21), no significant time effect, no significant group or group*time effect Outcomes meeting statistical significance (treatment x group: $p < 0.05$) or practical significance (d_{ppc} = 0.41): - Parents' outcomes: self-efficacy (p = 0.039; dpcc = 1.14), family needs met (p = 0.067; dpcc = 0.67), FASD knowledge (p = 0.050; dpcc = 0.60), parenting satisfaction (p = 0.038; dpcc = -0.38). - Children's outcomes: emotion regulation (p = 0.001; dpcc = 0.30), self-esteem (p = 0.294; dpcc = 0.56).		
O'Connor et al. (2016) (20) **RCT**	- Inclusion: Composite IQ ≥ 70; English speaking; living with at least 1 custodial parent/guardian; history of PAE - Exclusion: diagnosis of intellectual disability; psychotic disorder, pervasive developmental disorder - Age: 13–18 years - Recruited: n = 83 - Eligible after screening: n = 56 - Analysed: n = 54 Project Step up (SUI): - Assigned: n = 28 - Analysed: n = 26 - Abstinent/infrequent drinkers: n = 15 - Light/moderate drinkers: b = 11	Control: - Assigned: n = 28 - Analysed: n = 28 - Abstinent/infrequent drinkers: n = 21 - Light/moderate drinkers: b = 7	SUI: Drop-out: n = 2 (conflicting obligation)	SUI with 2 components (parallel; each b = 6; weekly 1-hour sessions in small groups): - Adolescents: Modified version of an empirically validated procedure. The used strategies are focussed on modelling, coaching, behavioural rehearsal, and performance feedback; intervention incorporated motivational enhancement techniques, normative feedback, education, risk	Control: Adolescents and caregivers got written materials on alcohol misuse and stress reduction.	- Prevention and reduction of alcohol-related negative outcomes - Determination of possible increase in alcohol risk in abstinent youths - Satisfaction of SUI	Prevention and reduction of alcohol-related negative outcomes: - Light/moderate drinkers (post-intervention): significant treatment effects, with SUI having significantly lower levels of alcohol risk and fewer negative behaviours than controls: AUDIT (F(1, 15) = 5.43, p = 0.03, d = 1.08) and RAPI (F(1, 15) = 8.60, p = 0.01, d = 0.99). No significant differences in CRAFFT. - Light/moderate drinkers (Follow-up): Gains in RAPI sustained (F(1, 15) = 4.53, p = 0.05, d = 0.83). Gains in AUDIT reached a nonsignificant large effect size (d = 0.76) Determination of possible increase in alcohol risk in abstinent youths: No group differences at baseline; no differences or change in outcome variables at post-test or at 3 months follow-up Satisfaction of SUI: - Adolescents: 96 % reported to be confident at avoiding risky situations based upon what they have learned; 92 % reported the program to be helpful - Caregivers: 96 % stated that they believe the program help the teens to make better choices regarding alcohol; 96 % reported to be satisfied	- Trained and qualified group leaders, standardized manuals, ongoing weekly supervision, live monitoring of sessions.; fidelity rating ≥ 95 % - No detailed definition of drinker-type; no heavy drinker-type classification - No significant differences in CRAFFT might be due to low occurrence of behaviours measured in CRAFFT - Motivated caregivers who actively seeked help - Impact of caregivers has not been assessed - Impact of age has not been analysed (large age range)	Moderate (RoB-2)

				assessment, coping and alcohol refusal skills training. Participants got a Workbook. - Caregivers: Adapted from the NIAAA protocol "Make a Difference: Talk to Your Child About Alcohol". The aim was to empower them in assisting their teens to resist alcohol use. Caregivers got a workbook, as well.					
Jirikowic et al. (2016) (21) **CCT (not randomized)**	- Inclusion: confirmed PAE; diagnosis of FASD (FAS, SE-AE or ARND); a previously identified sensorimotor impairment based on clinical diagnostic assessment results. - Exclusion: IQ < 60; a severe, co-occurring neuromotor condition that impaired ambulation/independent standing for at least 2 minutes; a history of serious head injury/seizures; a visual acuity impairment not corrected by glasses; report of any lower limb or back injury within the previous 6 months; current living in an unstable home placement. - Age: 8–15 years		STABLE home: 3 children received equipment but never started; 2 started but did not finished due to frustration or dizziness; 1 finished but did not complete post-intervention assessments	STABEL: Virtual reality game (STABEL) that facilitates task-specific balance practice under altered sensory conditions (visual, vestibular, somatosensory) by moving on a pliable standing surface. Training consisted of 3 6-	Control: No intervention	- Effectiveness of STABEL on balance and motor performance - Feasibility in laboratory and home setting	Motor skills MABC-2: - Balance standard score: no significant interaction, but significant differences by session (p = 0.02) and group (p = 0.04); home group had significant improvements compared to controls (p = 0.01); home and lab group (together) had significant improvements from pre-test to 1 week (p = 0.004), but no significant improvements from pre-test (p = 0.09) or 1 week (p = 0.11) to 1 month - Total Motor standard score: significant interaction (p = 0.05); significant differences by session; home and lab group (together) had significant improvements from pre-test to 1 week, and pre-test to 1 month, but not from 1 week to 1 month Dynamic balance:	- P-CTSIB-2 only suitable for children aged 6-12 years - Small dose of STABEL - No randomization - No control for fidelity in home group and for other parallel interventions - Possible ceiling effect might explain no detected changes in dynamic balance - Pre- and 1-week-test differences were beyond the error of the MABC-2 test, at a	High (ROBINS-I)

				minute blocks that progressed in difficulty by altering stability and complexity of the VR visual display. Total of 5 30–35 minute sessions over 1 month.				DGI: no significant differences across time or between groups Static balance: P-CTSIB-2: Total Sensory Score: significant interactions (p = 0.02) and significant improvements for home STABEL compared to controls (p = 0.01); trends show higher post-intervention scores for lab and home groups	level that also suggests potential clinical significance - Lab group did not show significant improvements in any test compared to controls - Home group had overall milder CNS dysfunction based on their FASD diagnosis; lab group had more muscular weakness and - 1/3 who agreed to the home intervention did not complete training protocol due to unknown reasons, frustration or dizziness	
	University laboratory (STABEL lab): - Enrolled: n = 6 - Completed: n = 6 - Analysed: n = 6	Home (STABEL home): - Enrolled: n = 15 - Completed: n = 9 - Analysed: n = 9	Control: - Enrolled: n = 8 - Completed: n = 8 - Analysed: n = 8		STABEL lab: Participants used STABEL in an university laboratory	STABEL home: Participants used STABEL at home				

McCoy et al. (2015) (22) **Uncontrolled intervention study**	- Children with FASD: Inclusion criteria: 8-16 years; confirmed PAE; FASD diagnosis; previously identified sensorimotor impairment based on clinical diagnostic assessment results - Exclusion: IQ < 60; severe co-occurring neuromotor condition that impaired ambulation or independent standing for ≥ 2 minutes; history of serious head injury/seizures; visual acuity impairment not corrected by glasses; report of any lower limb or back injury within the previous 6 months; currently living in an	- Typically developed children (TD): - Inclusion: 8-16 years - Exclusion: identified sensory/motor impairment; current/past special education services; history of serious head injury/seizures; PAE (> 3 reported drinks by mother for the duration of pregnancy); visual acuity impairment not corrected by glasses; report of any lower limb or back injury within the previous 6 months - Age: 8–16 years Received: n = 11 - Completed: n = 11 - Analysed: n = 11	NA	STABEL: Virtual reality game (STABEL) that facilitates task-specific balance practice under altered sensory conditions (visual, vestibular, somatosensory) by moving on a pliable standing surface. Training consisted of 3 6-minute blocks that progressed in difficulty by altering stability and complexity of the VR visual display for a total of 30 minutes.	NA	- Feasibility of STABEL - Immediate effect on sensory attention and postural control	Feasibility: all participants interacted with STABEL and completed all training blocks For FASD children: 1. block: - fun: 82 % had fun, 18 % felt ok, 0 % had no fun - dizziness: 0 % felt dizzy, 18 % felt a little dizzy, 82 % had no dizziness 2. block: - fun: 100 % had fun - dizziness: 9 % felt dizzy, 9 % felt a little dizzy, 82 % had no dizziness 3. block: - fun: 55 % had fun, 18 % felt ok, 27 % had no fun - dizziness: 18 % felt dizzy, 0 % felt a little dizzy, 82 % had no dizziness For all children: Postural control: - No significant interactions for ellipse area of body sway or velocity outcomes - Significantly higher medial-lateral and anterior-posterior RMS velocities in post STABEL in most conditions in both groups (p = < 0.01 to 0.05) - No significant differences in ellipse area of body sway pre- compared to post-testing or FASD compared to TD. Sensory attention: - Entrainment gain: LLM = visual screen gain and tilt board gain increased significantly from pre- to post-testing only in TD (p = 0.08); LLL (p = 0.06) and LLH (p = 0.09) = significantly higher touch pole entrainment gain in both groups in post-testing; LLH = significantly higher visual screen gain in both groups in post-testing (p = 0.02); HHL = significantly lower touch pole gain in post-testing (p = 0.02) - SAF: No significant interaction or pre/post differences	- Dizziness did not persist - Different exclusion criteria for FASD and TD children (TD children might have other diagnoses) - Examiner was not blinded for FASD or TD - α = 0,1 - Decreased postural stability could be due to fatigue (long testing sessions of 2.5h) - One-time practice with STABEL might be not enough to change sensory attention fractions - Body sway without any extra sensory stimulation has not been measured - Measures of balance and functional motor performance have not been included to complement kinematic measures of sensory attention and postural control	Low (ROBINS-I modified)

	unstable home placement - Age: 8–16 years - Received: n = 11 - Completed: n = 11 - Analysed: n = 11								
Zarnegar et al. (2016) (23) **Uncontrolled intervention study**	- Inclusion: age of ≤5 years, in the care of their adopted families for 6 months, diagnosis of FASD by a medical provider, history of maltreatment or loss, adoptive caregiver(s) who could fully engage in the intervention process during the study time period and who could complete measures in English - Exclusion: taking of psychotropic medications, additional genetic syndrome, active grand-mal epileptic seizures, history of serious head injury, profound intellectual disability - Age: 10–53 months - Agreed to participate: n = 38 - Assigned: n = 15		NA	The Neurosequential Model of Therapeutics (NMT) Metrics were used to estimate the child's functional capacity. Based on that individual somatosensory interventions were suggested for each child.	NA	- Children's developmental skills - Children's functional capacity - Parental skills - Parental stress	Baseline: all children had clinically significant deficits in all 4 functional domains in the CMR; all parents had clinically significant parenting stress Children's developmental skill: BBDI-2 Total Score: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 0.205 [0.148, 0.261]; Post-mean and 95 % CI: 0.518 [0.394, 0.641]; Standard error: 9.80; Standardized test statistic: 2.81; r (rank-biserial correlation): 0.63; p: 0.005*) Children's functional capacity: - NMT Total Score: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 23.40 [18.56, 28.24); Post-mean and 95 % CI: 45.20 [40.88, 49.52]; Standard error: 9.79; Standardized test statistic: 2.81; r (rank-biserial correlation): 0.64; p: 0.005*)	- Therapists were under the supervision of a licensed paediatric psychologist who was trained in CPP, Mindful Parenting, and NMT - Significant amount of families did not complete intervention (unknown reasons) - Improvements observed by multiple reporters: clinicians, parents - Possible effect of	NI (ROBINS-I modified)

	- Excluded before treatment: n = 5 (missed appointments: 3; movement: 2) - Excluded after treatment: n = 3 (movement: 1; other familial reasons: 2) - Completed for at least 6 months: n = 10 - Analysed: N = 10 children and 20 adoptive parents		Additionally to somatosensory interventions: - Child-Parent Psychotherapy (CPP): evidence-based, relationship-focused, reflective, and developmentally oriented model of psychotherapy that uses caregivers as the agents of change. Weekly for 6 months. - Mindful Parenting Education (MPE): Parents received psychoeducation regarding FASD, their child's self-regulation and on how to work through their own feelings and emotions while dealing with them. Twice per week for 6 months.			- NMT Cortical Modulation Ratio: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 0.205 [0.148, 0.261]; Post-mean and 95 % CI: 0.518 [0.394, 0.641]; Standard error: 9.80; Standardized test statistic: 2.81; r (rank-biserial correlation): 0.63; p 0.005*) Parental skills: Satisfaction survey: 18 reported an improvement in different areas of parental skills. Parental stress: PSI-SF Total Score: Statistically significant improvements from pre-intervention to post-intervention (Pre-mean and 95 % CI: 23.40 [18.56, 28.24; Post-mean and 95 % CI:] 45.20 [40.88, 49.52]; Standard error: 9.79; Standardized test statistic −2.81; r (rank-biserial correlation): −0.63; p: 0.005*)	time - Different somatosensory interventions for each child - Unknown impact of CPP, MPE and NMT alone - Very short evaluation window (unknown long-term effects)	

Regehr (2015) (24) **CCT (not randomized)**	- Inclusion: PAE or FASD, 4–10 years old - Exclusion: significant neurological or medical condition that would prevent them from benefiting from the interventions (e.g. autism) - Age: 4–10 years - Enrolled: n = 29		NA	SSIS-IG: - Individual program that focusses on instruction, modelling, rehearsal, and performance feedback on social skills difficulties and in problem behaviours. - One-on-one instruction - 30 min. sessions, 1–2 times a week over 5–7 weeks (total of 5 hours)	MILE: - Individualized program that is based on specific math deficits and learning needs. - One-on-one-instruction - 30 min. sessions, 1–2 times a week over 5–7 weeks (total of 5 hours)	- Social skills and competing problem behaviours - Social, emotional and behavioural problem areas	Social skills and competing problem behaviours SSIS-RS: - No significant impact of SSIS-IG on the SSIS-RS composite scores social skills F(1, 26) = 0.016, p = 0.90; problem behaviours F(1, 26) = 2.81, p = 0.12 relative MILE. - Analysing differences between participants pre- and post-test SSIS-RS scores separately within each intervention (paired-sample t tests): SSIS-IG improved significantly on problem behaviour scale (decrease by 8.6 standard points; t(13)= 2.52, p = 0.03) compared to MILE (decrease by 1.7; t(13) = 0.76, p = 0.46). Social, emotional and behavioural problem areas CBCL: Social composite approached significance F(1, 21) = 3.4, p= 0.08; however it did not approach significance for the social problems subtest F(1, 21)= 0.54, p= 0.47.	- Inclusion of children with ADHD or ODD - Groups not randomized but matched by age, diagnosis, IQ and gender - Group assignment after pre-tests - Families with two children in the study were allowed to have both children in the same group (sibling pairs N = 2). - Post-tests by a blinded research assistant - SSIS-IG: normally in group setting - Caregivers who are able to have their child participate in a study may also be more likely to connect their children with various social activities. - Possible impact of individualized attention from researchers on problem behaviour (both groups) - Unknown long-term effects - Possible impact of MILE on social skills - Possible mismatch between the degree of each type of deficit targeted	Low (ROBINS-I)
	The Social Skills Improvement System Intervention Guide (SSIS-IG): - Assigned: n = 14 - Completed: n = 14 - Analysed: n = 14	MILE: - Assigned: n = 15 - Completed: n = 15 - Analysed: n = 14							

									within SSIS and children's social skills impairments - Baseline: all children in the clinical range and significantly different than the normative mean on social skills, the Externalizing Problem scale and Total Problems scale - Improvements of SSIS-IG on problem behaviour cannot be exclusively attributed to the intervention - CBCL social scales were only available for participants ≥ 5 (N for each group = 12).	
O'Connor et al. (2012) (25) **CCT (not randomized)**	- Families were required to complete 2 intake sessions with a Child and Family Guidance Centre clinician (assessment and treatment planning session) - Inclusion criteria for children: 6-12 years of age; IQ ≥ 70; English speaking; living with at least 1 custodial parent or guardian; with/without PAE - Inclusion criteria for parents: English or Spanish speaking - Exclusion criteria for children: major sensory or motor deficits; past diagnosis of intellectual disability, psychotic disorder, pervasive developmental disorder - Age: 6–12 years - Recruited: 85 children (with PAE =		CFT n = 9 Reasons for not receiving intervention: child illness, family circumstances, child unsafe, unknown	SOC: n = 9 Reasons for not receiving intervention: child illness, family circumstances, child unsafe, unknown	Modified CFT with 2 components: - Children training in group setting to emphasize the child's friendship skills. It is tailored to the neurodevelopmental needs of children with FASD. Social skills were taught using	SOC: - Children training in group sessions that were process-oriented and behaviourally based, involving group discussion and cooperati	- Knowledge of social skills - Child self-concept - Overall social skills - Behaviour problems (parent-report) - Comparison between children with and without FASD	Knowledge of social skills: TSSK: Significant condition effect, with CFT showing significantly improved knowledge of appropriate social skills compared to SOC, $F(1, 62) = 21.34$, $p < 0.0001$, $d = 1.22$ (95 % CI (0.69, 1.73)); $F^2 = 0.34$ (95 % CI (0.09, 0.90)). No other significant main or interaction effects. Child self-concept: Piers Harris 2: Significant condition effect, with CFT showing significantly improved overall self-concept, $F(1, 62) = 4.21$, $p < 0.05$, especially on individual domains of self-concept, children reported improved behavioural adjustment $F(1, 62) = 5.69$, $p < 0.02$, $d = 0.58$ (95 % CI (0.09, 1.07)), $F^2 = 0.09$ (95 % CI (0.004, 0.36)); intellectual ⁄ school status, $F(1, 62) = 6.01$, $p < 0.02$, $d = 0.39$ (95 % CI (-0.10, 0.87)), $F^2 = 0.10$ (95 % CI (0.006, 0.34)); and freedom from anxiety, $F(1, 62) = 7.63$, $p < 0.01$,$d = 0.70$ (95 % CI (0.21, 1.19)), $F^2 = 0.12$ (95 % CI (0.008, 0.42)), compared to SOC. No	- Possible impact of involvement of parents in the program on subjective outcome measures. - Children reported changes themselves - No independent evaluation of children's behaviour in a naturalistic setting - No child with FAS - Only families included of parents who actively seek help for their children and who	Moderate (ROBINS-I)

	32; without PAE = 53)				instruction on simple rules of social behaviour, modelling, behavioural rehearsal, and performance feedback through coaching during treatment sessions. 12 90-minute sessions over the course of 12 weeks. - Parents training in separate concurrent sessions in group setting to learn the key skills being taught to their children. They were taught how to facilitate social competence in their children by arranging play dates, facilitating completion of weekly homework assignments,	ve projects. Training involved discussion and practice of rules of social behaviour typically thought important by adults, but not necessarily empirically demonstrated to be predictive of peer acceptance nor often practiced by socially skilled children in naturalistic settings. 12 90-minute sessions over the course of		significant improvement in physical appearance, $F(1, 62) = 0.12$, $p = 0.73$, popularity, $F(1, 62) = 0.51$, $p = 0.48$, or happiness and satisfaction, $F(1, 62) = 1.85$, $p = 0.18$. No other significant main or interaction effects. Overall social skills: SSRS-P: No significant condition effect in improvement of overall social skills, $F(1, 62) = 2.37$, $p = 0.12$ because the 2 groups differed on their pre-treatment social skills scores. Some children in the SOC group started out scoring higher than the children in the CFT group and actually demonstrated a significant decline in social skills according to parent report. The CFT group, while showing a significant 18 point improvement compared to the improvement of 4 points in the SOC group, did not differ from the SOC group after controlling for pre-treatment levels. Analyses of individual index scores revealed statistically significant condition effects for assertion, $F(1, 62) = 4.04$, $p < 0.05$, $d = 0.18$ (95 % CI (-0.31, 0.66)), $F^2 = 0.07$ (95 % CI (0.0009, 0.28)); and responsibility, $F(1, 62) = 4.53$, $p < 0.04$, $d = 0.16$ (95 % CI (-0.32, 0.64)), $F^2 = 0.07$ (95 % CI (0.001, 0.31)); in favour of the the CFT condition over the SOC condition. Analyses of cooperation, $F(1, 62) = 0.30$, $p = 0.59$, and self-control, $F(1, 62) = 0.75$, $p = 0.39$, did not yield statistically significant effects. No other significant main or interaction effects. Parent satisfaction questionnaire: - 90.7 % in CFT and 68.6 % in SOC reported confidence in their children's ability to get along better with other children because of treatment ($p < 0.04$). - 87.5 % in the CFT and 57 % in SOC reported that they were confident that they were better able to help their children make and keep friends because of the treatment ($p < 0.007$). - Groups were comparable in their overall satisfaction with ($p < 0.68$). Overall, 93.7 % in CFT and 88.6 % in SOC reported being very satisfied or highly satisfied with the treatment. Therapist satisfaction questionnaire: In CFT, 84 % agreed that the treatment was helpful, 100 % agreed that their clients enjoyed treatment, 92	were highly motivated to participate - 2 children were asked to leave the program because of significant disruptive behaviour (CFT and SOC) - Therapists in the SOC condition were provided weekly supervision by their supervisors	
	Children's Friendship Training (CFT): - Assigned: n = 41 - Received: n = 32 - Analysed posttreatment: n = 32 - Analysed using multiple imputations: n = 41	Standard of care (SOC): - Assigned: n = 44 - Received: n = 35 - Analysed posttreatment: n = 35 - Analysed using multiple imputations: n = 44								

					and providing in vivo social coaching. Handouts outlining the skills being taught to children are distributed to parents. 12 90-minute sessions over the course of 12 weeks.	12 weeks. - No parent training		% agreed that they would like to see the program adopted permanently at Child and Family Guidance Centre and would continue to use it. Concerns: program was hard to integrate into busy schedules, more time needed Treatment is equally effective for children with and without PAE		
Leenaars et al. (2012) (26) **Retrospective cohort study**	- Inclusion: closed case files of families for which at least one post needs or goals measure was available; families with ≥ child with FASD (confirmed FASD diagnosis; children possibly having FASD, but - maternal drinking was not confirmed, children being suspected of having FASD, but had not yet been assessed) - Age: 1–23 years - Analysed: n = 186 families		NA		Coaching Families Program (CF) is a family goal-based mentoring program on an individual level. Mentors educate families about FASD, help them access resources, and engage them in successful advocacy.	NA	- Individual needs - Goal attainment - Caregiver stress - Satisfaction	Individual needs and goal attainment: - Length of time in the program was significantly related to both needs ($r = -0.27$, $P < 0.001$) and goals ($r = 0.22$, $P < 0.001$) indicating that the longer families spent in the program, the greater their reduction in needs and achievement of goals. - Individual needs significantly decreased from pre- to post-program: $F(1, 187) = 152.69$, $P < 0.001$, $\eta p2 = 0.45$ - Significant increase in goal achievement from pre- to post-program: $F(1, 165) = 317.46$, $P < 0.001$, $\eta p2 = 0.66$ Caregiver stress: Significant decrease in overall levels of caregiver stress from pre- to post-program: $F(1, 72) = 39.409$, $P < 0.001$, $\eta p2 = 0.354$ No gender or age effect. Satisfaction:	- Self-referred recruitment - No control for quality of mentorship, participation in other services, family variables, or comorbid disorders. - Many files were not included in the analyses as there were no post needs or goals measure available (possible bias)	Moderate (ROBINS-I modified)

						- High satisfaction with the program (98 %) and willingness to participate again (99 %); 32.1 % of caregivers reported parenting and handling their child better, 28.2 % reported understanding their child and/or FASD better, and 14.5 % reported feeling less stressed, having increased patience, and being more positive. 65.6 % reported that they had not experienced any problems with the program - Reported challenges: feeling that mentor did not understand what it was like to live with a child with FASD, difficulties collaborating with other services, and a need for longer-term support. 38.8 % reported that there was no need for improvement or were unsure.		
Graham et al. (2016) (27) **Intervention study**	- Inclusion: English as primary language, 8-12 years - Exclusion: other known causes of mental deficiency, adopted from abroad after age of 5, head injury involving loss of consciousness, physical or psychiatric conditions that prevented involvement - Exclusion for analyses: accuracy < 80 % in Flanker task; being an extreme outlier (at least 3 SD from group mean) across RT and accuracy in Flanker task - Age: 8–12 years	NA	Modified flanker task including reward (positive reinforcement) and response cost (negative punishment): 4 blocks of 96 trials (total of 25 minutes) were presented varying by	NA	Influence of extrinsic motivation on response time (RT) and accuracy as measures of interference control (ability to suppress competing distracters	Significant between-group differences on FSIQ (Wechsler Intelligence Scale for Children-4th Edition): AE < ADHD < CON Inhibitory control performance: - Accuracy: AE was significantly slower than ADHD ($p = 0.038$) and CON ($p < 0.001$) and significantly slower in incongruent trials compared to congruent trials ($p < 0.001$) - RT: AE had significantly poorer accuracy in incongruent trials than CON ($p = 0.001$) and significantly poorer accuracy in incongruent trials compared to congruent trials ($p < 0.001$). Age significantly interacted with condition [F (1.235,	- Study was part of a larger project at Centre for Behavioural Teratology at San Diego State University. Flanker task was the third out of four computerized attention tasks that lasted about 1 h and 45 minutes in total and required a long	Moderate (ROBINS-I)

	Alcohol-exposed (AE): - Inclusion: heavy PAE - exclusion: other known causes of mental deficiency, adopted from abroad after age of 5, head injury involving loss of consciousness, physical or psychiatric conditions that prevented involvement - Analysed: n = 34	idiopathic ADHD (ADHD): - inclusion criteria: ADHD - exclusion: greater than minimal PAE (average exposure < 1 drink per week and no more than 2 drinks per occasion) - Analysed: n = 23	Controls (CON): - exclusion: indicators of ADHD; subclinical symptoms of ADHD on the C-DISC-4.0 - Analysed: n = 31		flanker type: - Congruent - Incongruent - Neutral - Single and reinforcement condition: - No Reward or Response Cost (NR) - Reward Only (REW) - Reward + Occasional Response Cost (ROR) - Equal Probability of Reward and Response Cost (EQ) Points were earned or lost based on speed and accuracy and were shown on screen (feedback and extrinsic motivation). Prize corresponding to the points at the end.		to carry out a target response)	103.725) = 7.74, p = 0.004, ηp2 = 0.084] and flanker type [F (2.144, 180.130) = 4.24, p = 0.014, ηp2 = 0.048]. Response to rewards: - In all conditions, AE was significantly slower than CON (p < 0.001) and slower than ADHD (p = 0.046; except for REW, p = 0.051) - For all groups, RT in the NR condition was significantly slower than in the other conditions (p = 0.002) - For AE (p > 0.39) and ADHD (p > 0.19), RT was similar for all 3 reinforcement conditions - For CON, ROR improved RT compared to REW (p = 0.03) - All groups improved with reinforcement in RT, but CON showed the most improvement in RT when response cost was applied. For AE and ADHD, type of reinforcement was not critical. - For RT, main effect of group [F (1, 84) = 10.69, p < 0.001, ηp2 = 0.203] with AE being slower than CON and ADHD p < 0.017) - For RT, main effect of flanker type [F (2.144, 180.130) = 11.70, p < 0.001, ηp2 = 0.122]. RTs were significantly slower without reinforcement (p < 0.001) - For congruent trials, accuracy was better in the NR condition compared to REW (p = 0.03) and ROR (p = 0.01) - For incongruent trials (p < 0.001) and neutral trials (p < 0.029), accuracy was better in the NR condition compared to all other conditions - Accuracy was poorer for incongruent trials compared to all other trials (p < 0.001) - For ROR, accuracy was significantly poorer for neutral trials compared to congruent trials (p = 0.019) - For EQ, accuracy was poorer for neutral trials compared to congruent (p = 0.005) or single trials (p = 0.03) - For accuracy, main effect of flaker type [F (1.530, 130.049) = 118.06, p < 0.001, ηp2 =.581] and condition [F (2.309, 196.230) = 37.01, p < 0.001, ηp2	duration of attention (possible impact on outcome) - Children were asked to abstain from medication use the day of testing. However, 7 AE and 2 ADHD took medication - AE showed greater difficulties with executive control - Regarding RT, AE and ADHD benefited similarly from both types of extrinsic reinforcement - Regarding accuracy, all groups showed better performance without reinforcement for all conditions except for single targets - Study utilized primary and secondary reinforcement - Oppositional defiant disorder and conduct disorder have not been assessed - No child with ADHD symptoms had the hyperactive/impulsive type; all of them had the inattentive or combined type - Analyses were repeated without the 5 AE without ADHD => same	

	- Analysed with ADHD symptoms: n = 29							= 0.303] - For accuracy, no main effect of group	results - IQ was significantly correlated with accuracy in AE and CON, and with RT in ADHD	
Kable et al. (2012) (28) **RCT**	- Recruited from a multidisciplinary FAS diagnostic clinic - Inclusion for children: clinical diagnosis of FAS or pFAS (IOM Criteria) or significant levels of alcohol-related dysmorphology (standard pediatric dysmoprhia checklist) - Inclusion for adults: parents or caregivers of children - Mean age of participating children: 6–7 years			n = 23	Workshop group: - 2 days workshop in-person (each 2h)	Internet group: - Web-based workshops - Education about FASD, infor	Standard Information group: - Paper form - Information packets regarding the diagnosis, neurodev	- Satisfaction - Knowledge about FASD - Behavioral changes in children	Satisfaction (Likert scale response and open-ended questions): - All groups: high satisfaction - Workshop group: higher ratings on usefulness, understandability, amount, overall satisfaction, and willingness to recommend than Standard Information group - Workshop group: higher ratings on amount of information and overall satisfaction than Internet group Knowledge (Caregiver advocacy knowledge	- Gender differences between the groups as a potential reason for the Internet group not showing sign. Improvements - Significantly more participants with a higher dysmorphia score dropped out of the Internet group. This trend was also seen in the Standard	Moderate (ROB-2)

	Workshop group: - Recruited: n = 29 - Analysed: n = 23	Standard Information group: - Recruited: n = 24 - Analysed: n = 18	Internet group: - Recruited: n = 29 - Analysed: n = 18		- Education about FASD, information on effective behaviour management strategies, and advocacy tools	mation on effective behaviour management strategies, and advocacy tools	elopmental consequences and access to community services and information on sources		questionnaire (CA) and Behavioral regulation knowledge questionnaire (BR)): - Standard Information group: significant gains in knowledge on behavioral regulation (BR: $t(17) = -2.7$, $p < 0.01$, $\eta p^2 = 0.305$); only trend for improvement on the caregiver advocacy knowledge (CA: $t(17) = -1.9$, $p < 0.08$, $\eta p^2 = 0.170$) - Workshop group: significant gains in both areas of knowledge: Caregiver advocacy (CA: $t(21) = -3.9$, $p < 0.001$, $\eta p^2 = 0.422$; BR: $(t(11) = -6.7$, $p < 0.0001$, $\eta p^2 = 0.668$) - Internet group: significant gains in both areas of knowledge (CA: $t(11) = -2.8$, $p < 0.02$, $\eta p^2 = 0.412$; BR: $(t(11) = -3{,}4$, $p < 0.005$, $\eta p^2 = 0.526$) - Significant time effect and group effect - No significant group*time effect, but a trend was found on the BR data ($F(2, 50) = 2.0$, $p < 0.152$, $\eta p^2 = 0.073$) for the Internet group gaining more knowledge than the Standard Information group. - Strongest relationship between caregiver educational level and knowledge gains was in the Standard Information group (CA: $r = -0.36$, $p < 0.16$ and BR: $r = 0.44$, $p < 0.08$) as compared to the Workshop (CA: $r = -0.15$, $p < 0.52$ and BR: $r = 0.25$, $p < 0.26$) and Internet (CA: $r = -0.03$, $p < 0.93$ and BR: $r = 0.18$, $p < 0.57$) groups. Child behavioral changes (Children behavior checklist): - Standard Information group: trend in improving total problem behavior ($t(1, 17) = 1.8$, $p < 0.09$, $\eta p^2 = 0.164$) and externalizing problem behavior ($t(1, 17) = 2.0$, $p < 0.06$, $\eta p^2 = 0.192$) - Workshop group: For total problem behaviors, a significant effect was found ($t(1, 21) = 2.7$, $p < 0.014$, $\eta p^2 = 0.254$) - Internet group: no changes in total problem behaviour - On the total problems scale, a significant treatment by group effect was found ($F(2, 50) = 3.2$, $p < 0.048$, $\eta p^2 = 0.115$) with improvements in behavioral ratings only in the Standard Information and Workshop groups.	Information group, but not in the Workshop group. - Initiation of the Internet group was the biggest hurdle (once logged in the method was effective). - Caregiver educational level had the strongest relationship with knowledge gains in the Standard Information group (not significant). - Only 50 % of the children showed improvements, only 25 % showed significant improvements => only effective for some families - Content differences between Standard Information group and Workshop group/Internet group	

									- On the externalizing scale, a significant general treatment effect by gender ($F (1, 50) = 5.3$, $p < 0.026$, $\eta p^2 = 0.096$) was found with males showing greater improvements than females and a trend was found for a time by group effect ($F (2, 50) = 2.9$, $p <0.064$, $\eta p^2 = 0.104$) with those in the Standard Information and Workshop groups showing improved behavior but those in the Internet group not. For the internalizing scale, there was a trend for a general treatment effect ($F (1, 50) = 2.2$, $p < 0.14$, $\eta p^2 = 0.043$) with post-test scores being lower than those at pretest. - Examination of the pattern of change scores found on the externalizing and total problem scores suggested that the treatment effects were skewed (Externalizing = 1.175 and Total = 1.492) such that about 50 % of participants made positive gains with half of these making what could be termed clinically significant changes (> 1/2 of standard deviation).		

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Systematische Reviews

Reference	Last search	Country	Included articles (N)	Types of included articles	Programs or Intervention types	Population (age in years)	Population (characteristics)	Outcomes reported	Results	Comments	Critical appraisal modified after AMSTAR
Flannigan et al. (2020) (1)	01.04.2020	Canada	33	Inclusion: original and peer-reviewed, contributed empirical data (quantitative, qualitative, or mixed), and included the following: (i) interventions for individuals of any age with PAE or FASD, (ii) with quantitatively or qualitatively reported outcomes related to mental health and/or substance use, and (iii) published in English, from	Any intervention to improve mental health (emotional, psychological, spiritual, behavioural, and social well-being) and substance use outcomes	All age groups	Any individuals with PAE and FASD	Mental health (emotional, psychological, spiritual, behavioural, and social well-being) and substance use outcomes	- Supporting Attachment and Family Wellness: All interventions included caregiver components; Interventions were original and specifically designed for the PAE/FASD child–caregiver dyad and may be particularly (although not necessarily exclusively) impactful in early childhood. They had positive impacts on attachment and child adjustment, including improved relationships, enhanced caregiving experiences, and increased family functioning. They support a preventative model in which better bonding may aid the developmental process in the child and diminish the risk of adversity. - Building Skills and Strategies (Self-regulation, Behavioural Skills, Social Skills, Mental Health Literacy): Nearly half of the interventions involved caregiver/teacher training. They were often conducted in middle childhood. Self-regulation and social skills strategies have the strongest evidence for use in children with PAE/FASD, and there is promising evidence for interventions to support the development of positive behavioral skills and strategies. Skill-building was not exclusive to the individual with PAE/FASD; in many cases, interventions also incorporated external support through facilitators, caregivers, teachers, or mentors. Importantly, these interventions led to improved indicators of mental health, suggesting that the acquisition of skills and strategies is one viable mechanism for individuals with FASD (and their families), to cope, interact, and feel better. - Responding to Risk and Reducing Harm (Substance Use, Justice Involvement): In later adolescence and adulthood, as needs may become more complex, interventions shifted to a more responsive approach to mitigate risk and reduce harm.	Most studies were RCTs (n = 12) and controlled clinical trials (CCTs; n = 8); 4 were case studies, 3 were case series, 3 were cohort (before and after) studies, one was a file review, one was an implementation study, and one was an exploratory study.	1. PICO: Yes (no comparator needed) 2. Protocol: Yes 3. Study selection: No 4. Search strategy: Yes 5. Selection in duplicate: Yes 6. Extraction in duplicate: Yes 7. Excluded studies: No 8. Included studies: Partial Yes 9. RoB: Yes; Yes 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in dicussion: Yes 14. Heterogeneity: Yes 15. Publication bias: NA 16. Conflicts: Yes

				the year 2000 onward. Exclusion: animal studies; dietary or pharmalogical interventions					=> Importance of caregivers and their active and intensive participation => Combined, these approaches may reflect the components critical to integrated and interdependent care planning for individuals with PAE/FASD across the life course.		Low RoB
Mela et al. (2018) (2)	04.02.2017	Canada	25	Only peer-reviewed journal articles will be sourced or identified. No gray literature searches. Articles will be restricted to English or transcribed English, no timeline restrictions, only human studies to be included, no restrictions to study design	All literature evaluating pharmacological interventions for children and adults living with FASD	All age groups	Adults and children either diagnosed with FASD or who are at risk of having FASD	benefits and risks of psychotropic medications on patients (adults and children) diagnosed with FASD	- Hyperactivity and inattention: Inattention was found to respond better to Dextroamphetamine than Methylphenidate, but a high adverse event profile induced discontinuation. Atomoxitine may be useful in the inattention domain of FASD due to its noradrenergic stimulation effect. - Social skills: Stimulants were found to be less efficacious compared to second-generation neuroleptics, specifically in the domain of social skills. Stimulants showed comparatively poor response both as monotherapy and in combination with neuroleptics. Greater improvement was found with neuroleptics compared to those not prescribed neuroleptics (with and without combination with stimulants) - Seizure disorders: Second-generation antipsychotics are used to treat complications of seizure disorders, as adjunct therapy for Conduct Disorder, for disruptive behaviour in children with low IQ, and for secondary disabilities associated with FASD. - Short-term aggressiveness: Risperidone has demonstrated strong benefits in the treatment of short-term aggressiveness in some research => but too low evidence - Appetite: Risperidone has the tendency to increase appetite - Adverse effects: There is concern for long-term use of Risperidone because of the metabolic risk associated with most second-generation antipsychotics as well as having the potential for extrapyramidal symptoms and altering the dopaminergic system. - Depression: Antidepressants such as SSRI, SNRIs, NRIs, and TCAs are a class of medication prescribed for those diagnosed with FASD in the context of depression. - ADHD symptoms: SSRIs were reported as effective in treating ADHD symptoms when those coexist with behaviour problems such as outbursts, aggression, and compulsive behaviours in children with FASD. Atomoxetine appears to be less effective than Methylphenidate in children with an IQ below 85. ADHD symptoms	Very poor studies included: animal studies, not only patients with FASD, study with 4 participants, placebo group with 1 child, no medication at all => critical! A standardized critical appraisal of the studies was done, but the risk of bias or level of evidence is not recorded for the studies included Not all included studies are reported in the discussion No real results/conclus	1. PICO: Yes (no comparator needed) 2. Protocol: Yes 3. Study selection: No 4. Search strategy: Yes 5. Selection in duplicate: Yes 6. Extraction in duplicate: Yes 7. Excluded studies: No 8. Included studies: Partial No 9. RoB: Yes; No information (RoB is not documented!!) 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in discussion: No 14. Heterogeneity: No 15. Publication bias: NA

									can be treated with a stimulant such as Adderall or Dexedrine. - In paediatric patients living with FASD, a lot of medications used are "off label". - The choice of medication should be based on the most relevant diagnosis causing functional impairment or targeting two co-existing diagnoses.	ion	16. Conflicts: Yes Critical RoB because of the studies included
Reid et al. (2015) (3)	NI	Australia	32	No restrictions on the types of study designs Inclusion: Non-pharmacologial intervention studies that aim to improve an aspect of functioning Exclusion: Studies that evaluate diagnostic services	non-pharmalogical interventions	all age groups	Any individuals with FASD	Improvements in functioning for people with a FASD e.g. adaptive, cognitive, self-regulation, social skills, behaviour	- Developmental outcomes in infants: Mixed results: 1 study showed that following their intensive home visiting service, children with PAE scored in the average range on developmental tests. 1 study with a considerably stronger design found no effect of the home visiting service on the same measures of developmental outcome, with children scoring significantly below age-expected norms. - Self-regulation and attentional control (early to middle childhood): ALERT showed to be effective in improving executive functioning and showed changes in grey matter volume in critical regions for self-regulations. A computerised progressive attention program (CPAP) showed significant decrease in reaction times and distractibility, and significant improvement in auditory sustained attention. Activities from the pay attention training protocol with additional visual search tasks showed significant improvements in nonverbal reasoning, auditory and visual sustained attention and a trend for improved performance on alternating attention. A small study on cognitive control therapy (learning metacognitive skills) showed no gains in cognitive functioning. => Promising results, but limited follow-up - Specific skills: MILE showed to be effective in improving math knowledge, parent reported problem behaviour, improved nonverbal reasoning, reading comprehension, and mathematics reasoning. CPAP showed improvements in math and reading fluency. A virtual reality game of fire/street safety showed significantly better knowledge of fire/street safety immediately and at follow-up (1 week) and most children (72%) were able to generalize the information within a behavioural setting. Classroom-based literacy training showed improvements in specific language and literacy skills, but not in general scholastic skills. Experimental group rehearsal training showed increase in digit span scores. A cover, copy and compare spelling procedure showed an increase in	No study had a strong quality for selection bias, or blinding. 19 had a strong study design (RCTs and controlled clinical trials) 27 used reliable and valid measures 17 had a strong for withdrawal/dropouts	1. PICO: Yes 2. Protocol: Yes 3. Study selection: No 4. Search strategy: partial yes 5. Selection in duplicate: Yes 6. Extraction in duplicate: No information 7. Excluded studies: No 8. Included studies: Yes 9. RoB: Yes 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in discussion: Yes 14. Heterogeneity: Yes 15. Publication bias: NA 16. Conflicts: Yes Low RoB

									number of words spelt correctly. A motor skill training (FAST) could not affect cortisol levels. - Social skills in 3-12 year olds: Child Friendship Training (CFT) showed improvements in social skills and a decrease in hostile attribution (maintained at follow-up). Children with PAE can be treated in community settings if interventions are suitable. A community-based social skills group showed gains in parent-rated social skills. => Strong evidence for structured programs that include children and parents in helping to improve social skills. - Parenting skills: Families moving forward program showed improvement in parental self-efficacy, parent needs and parent self-care, and a reduction in child behaviour problems. A child interaction therapy and a parent-only parenting support and management program were both effective to reduce child behavioural problems and parent stress. A group workshop, an internet program and a standardized written information are effective to increase parental knowledge. The workshop and the written information are effective in improving child behaviour. => parents show improved well-being from support in managing their children's behaviour. - Support, education and advocacy: Coaching Families (CF) was effective in decreasing familiy's needs and caregiver stress and in increasing goals. Specialized FASD training for workers and foster caregivers showed significant decline in number of placement changes. Workshops for teachers showed improved classroom behaviour. Key worker and parent support program that provides support, education and liaison to existing intervention services showed a better understanding of FASD and increased emotional and practical support, but only a trend to improve caregiver stress, parenting-self-confidence and child's behaviour.		
Ordenewitz et al. (2021) (4)	Sep 19	Germany	25	Intervention studies, randomized controlled trials (RCTs) for children and adolescents with FASD Language: English, German,	Any intervention	<18 years	Children and adolescents (<18 years), diagnosed with FASD (FAS, pFAS, ARND)	Effects on the affected CNS domain according to the German guideline for the	Language/speech: Language and literacy training (LLT): FASD-children and healthy control group improved. FASD-Children in the LLT group did catch up to their peers in some subtests regarding their skills in written letters, reading, and spelling of words and nonwords. There was a statistically significant improvement with respect to phonological and literacy skills in the FASD- LLT group compared to the FASD-control group. Learning/memory skills:	No quality analysis of included studies. But quality of studies is very high.	1. PICO: Yes 2. Protocol: No 3. Study selection: No 4. Search strategy: partial yes 5. Selection in duplicate: No 6. Extraction in duplicate: No information 7. Excluded

				French Date of publication: Since 01/01/2000				diagnosis of FASD	- Choline supplementation: no evidence for an effect on memory, executive function, and attention deficits. No effects of on neurocognitive development. But younger participants (<4 years) improved in behavioural imitation tasks more than older participants (4-5 years). Follow-up: statistically significant effect of choline on non-verbal visual-spatial reasoning and non-verbal working memory compared to the placebo group. - Verbal rehearsal: no statistically significant differences between the experimental and the control group regarding memory of numbers Executive functions: - ALERT with parents: ALERT-group displayed statistically significant improvements in executive functioning and emotional functioning compared to the control group. - ALERT without parents: treatment effect on inhibition tasks in children and on parent-reported behavioural regulation. There was a positive treatment effects on emotional control and performance in an inhibition task after intervention. Arithmetic skills: - MILE with parents: increase in parents' knowledge of FASD, caregiver advocacy and behavioural regulation. Significantly less problematic behaviour in their children were reported after the study. MILE-group showed greater gains in math performance than those in the control group. Follow-up: further betterment in mathematical skills in the MILE-group compared to control. An extension of the program to 15 weeks did not lead to a more distinct treatment effect (math skills) compared to the 6-weeks-program. - MILE without parents: Evidence for the effectiveness of the MILE intervention without parent training. Attention: Sustained attention training: clear evidence for improvements in the intervention group compared to the controls in several domains of attention on direct child measures. But, both groups showed improvements in the teacher-rated domains in attention and executive functioning. Social skills and behaviour:		studies: No 8. Included studies: Yes 9. RoB: No 10. Funding: No 11. Meta-analysis method: NA 12. Meta-analysis RoB: NA 13. RoB in discussion: Yes 14. Heterogeneity: Yes 15. Publication bias: NA 16. Conflicts: Yes Low RoB

									- Workshop/community/online: workshop- and community-groups showed gains in overall behavioural functioning of their children. All groups improved knowledge of parents. - Step Up Intervention (SUI): A positive treatment effect for light/moderate drinkers in reducing alcohol consumption compared to controls was observed. For abstinent/infrequent drinkers, no changes in alcohol consumption were reported. - Families on Track (FoT) Program: Intervention increased caregivers' knowledge about FASD and their advocacy. Perceived needs of families decreased in both groups, with an observable trend for a larger decrease in the intervention group compared to the controls. A positive effect of FoT on parent-rated emotional regulation of the child was observable. - FAR strategy trough GoFAR game: Training of the FAR technique has benefits for the child. Parent training alone did not prove to be sufficient for behavioural changes of the child. Results indicated that parent engagement in the child's treatment is an integral part of behavioural improvements in children with FASD (less parent-reported disruptive behaviour of the children). GoFAR group showed greater improvements in behaviour than children in the FACELAND group. Positive treatment effects of the GoFAR program in attention and adaptive functioning. - Parent assisted Children's Friendship Training (CFT): Results pointed towards enhancement in appropriate social skills (direct child measure) after the treatment that remained stable over a 3-month period. Parent-rated social skills and problematic behavioural patterns of their child enhanced notably after treatment. Decline in hostile attributions in peer group entry scenarios, which were maintained at a 3-months follow-up. Higher levels of self-regulation were associated with greater improvements in social skills after CFT. Treatment effects of the CFT program were further enhanced by neuroleptic medication, whereas stimulant medication or no medication at all did not ameliorate the outcomes. CFT-group benefitted from stronger increments in knowledge of appropriate social behaviours and in self-concept compared to children in the SOC group. Children with FASD demonstrated improvement in social skills and could be successfully integrated in social skills groups with children without PAE in a community mental health setting. No differences in parent reports of social skills between the CFT and SOC group occurred. However, there was an observable trend that some children in SOC		

									became worse in parent-reported social skills, while children in CFT generally displayed advances after treatment.		

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A. 17 Eingeschlossene Studien der systematischen Literaturrecherche zu Interventionen bei FASD

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A. 18 Übersicht zu Interessenkonflikten der Leitlinienmitglieder

Im Folgenden sind die Interessenserklärungen als tabellarische Zusammenfassung dargestellt sowie die Ergebnisse der Interessenkonfliktbewertung und Maßnahmen, die nach Diskussion der Sachverhalte von der LL-Gruppe beschlossen und im Rahmen der Konsensuskonferenz umgesetzt wurden.

Erster Teil des Leitlinienprojektes (2011)

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik des Fetalen Alkoholsyndroms** **Registernr: 022-025**								
		Dr. med. Dipl.-Psych. Mirjam Landgraf	Prof. Dr. med. Florian Heinen	Dr. med. Juliane Spiegler	Prof. Dr. med. Franz Kainer	Prof. Dr. med. Rolf F. Maier	Dr. med. Ulrike Horacek	Priv. Doz. Dr. med. Anne Hilgendorff
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	+	-	-	+	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	+	-	+	+	-	+
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	+	-	-	+	-	+
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	+	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-	-	-
6	Persönliche Beziehungen zu einem	-	-	-	-	-	-	-

	Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft							
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	+	+	+	+	+	+
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	-	-	-	-	+

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik des Fetalen Alkoholsyndroms** **Registernr: 022-025**								
		Carla Pertl	Veerle Moubax	Andreas Rößlein	Dr. med. Beate Erbas	Dr. med. Wendelina Wendenburg	Dipl.-Psych. Penelope Thomas	Dr. med. Monika Reincke
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	-	-	-	+	-	-
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	+	-	-
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	-	-	-	-	+	-	+
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	-	-	-	-	-

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik des Fetalen Alkoholsyndroms** **Registernr: 022-025**								
		Regine Gresens	Dr. med. Martin Sobanski	Priv. Doz. Dr. med. Gerhard Reymann	Dr. med. Regina Rasenack	Gisela Michalowski	Dr. Eva Rehfueß	Prof. Dr. rer. medic. Rainhild Schäfers
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	+	+	+	-	-	+
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	+	-	-	-	-

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik des Fetalen Alkoholsyndroms** **Registernr: 022-025**								
		Dr. med. Gabriele Trost-Brinkhues	Prof. Dr. phil. Dipl.-Psych. Tanja Hoff	Dipl.-Psych. Jessica Christine Wagner	Dipl.-Psych. Gela Becker	Dr. Dr. med. Nikolaus Weissenrieder	Gila Schindler	Prof. Dr. med. Hans-Ludwig Spohr
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	+	-	+	-	-	-
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	+	+	+	+	-	-
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	+	-	-	+	-

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik des Fetalen Alkoholsyndroms** **Registernr: 022-025**						
		Prof. Dr. med. Frank Häßler	Dipl.-Psych. Laszlo Pota	Dr. med. Heike Hoff-Emden	Prof. Dr. med. Andreas Schulze	Dr. phil. Dipl.-Psych. Reinhold Feldmann
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	-	-	-	+
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	-	-	+	+
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	+	-	+	-
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	-	-	-

Zweiter Teil des Leitlinienprojektes (2015/2016)

Leitlinienkoordinator*innen Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik der Fetalen Alkoholspektrumstörungen** **Registernr: 022-025**								
		Dr. med. Heike Hoff-Emden	Heike Wolter	Dipl.-Psych. Laszlo Pota	Jule Friedrich	Dr. med. Wendelina Wendenburg	Dipl.-Psych. Gela Becker	Prof. Dr. rer. medic. Rainhild Schäfers
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	-	-	-	+	-	-
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-	-	-
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	-	+	+	-	-	+
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	-	-	-	-	-

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik der Fetalen Alkoholspektrumstörungen** **Registernr: 022-025**								
		Prof. Dr. med. Frank Häßler	Dr. phil. Dipl.-Psych. Reinhold Feldmann	Dr. med. Matthias Brockstedt	Gila Schindler	Dr. med. Antje Erencin	Dr. med. Gabriele Trost-Brinkhues	Prof. Dr. phil. Dipl.-Psych. Tanja Hoff
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	-	+	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	+	-	-	-	-	-
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	+	+	-	-	-	-	-
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	+	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	-	+	-	-	+	+
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	-	-	-	-	-

Leitlinienkoordinator*innen: Dr. med. Dipl.-Psych. Mirjam Landgraf, Prof. Dr. med. Florian Heinen **Leitlinie: Diagnostik der Fetalen Alkoholspektrumstörungen** **Registernr: 022-025**						
		Gisela Michalowski	Dr. med. Martin Sobanski	Priv. Doz. Dr. med. Gerhard Reymann	Dr. med. Anette Stiegler	Dipl.-Psych. Jessica Christine Wagner
1	Berater- bzw. Gutachtertätigkeit oder bezahlte Mitarbeit in einem wissenschaftlichen Beirat eines Unternehmens der Gesundheitswirtschaft (z. B. Arzneimittelindustrie, Medizinproduktindustrie), eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-
2	Honorare für Vortrags- und Schulungstätigkeiten oder bezahlte Autoren- oder Co-Autorenschaften im Auftrag eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	+	-	-	-
3	Finanzielle Zuwendungen (Drittmittel) für Forschungsvorhaben oder direkte Finanzierung von Mitarbeitern der Einrichtung von Seiten eines Unternehmens der Gesundheitswirtschaft, eines kommerziell orientierten Auftragsinstituts oder einer Versicherung	-	-	-	-	-
4	Eigentümerinteresse an Arzneimitteln/Medizinprodukten (z. B. Patent, Urheberrecht, Verkaufslizenz)	-	-	-	-	-
5	Besitz von Geschäftsanteilen, Aktien, Fonds mit Beteiligung von Unternehmen der Gesundheitswirtschaft	-	-	-	-	-
6	Persönliche Beziehungen zu einem Vertretungsberechtigten eines Unternehmens Gesundheitswirtschaft	-	-	-	-	-
7	Mitglied von in Zusammenhang mit der Leitlinienentwicklung relevanten Fachgesellschaften/Berufsverbänden, Mandatsträger im Rahmen der Leitlinienentwicklung	+	+	+	+	+
8	Politische, akademische (z. B. Zugehörigkeit zu bestimmten „Schulen“), wissenschaftliche oder persönliche Interessen, die mögliche Konflikte begründen könnten	-	-	-	-	-

Dritter Teil des Leitlinienprojektes (2022/2023)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
Dipl.-Psych. Gela Becker	Nein	Nein	Ja[2]	Nein	Nein	Nein	Wiss. Schwerpunkte: FASD in verschiedenen Hilfefeldern Weiterbildung zur FASD-Fachkraft	Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dr. Reinhold Feldmann	Nein	Nein	FH-Münster	Nein	Diverse UKM-Münster	Nein	Wiss. Schwerpunkte: FASD Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten: FH-Münster	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dr. med. Heike Hoff-Emden	Nein	Nein	Ja[2]	Nein	Nein	Nein	Klinische Tätigkeiten: FASD Fachzentrum, SPZ Diagnostik und Beratung entwicklungsgestörter und behinderter Kinder	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
Dr. med. Anna Hutzelmeyer-Nickels	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: Marburger Bund, DGKJP Klinische Tätigkeiten: Autismusspektrumsstörungen, Entwicklungsstörungen, Mutismus	(Keine Interessenkonflikte, keine Konsequenzen)
Dr. med. Kristina Kölzsch	Nein	Nein	Nein	Nein	Nein	Nein	Nein	(Keine Interessenkonflikte, keine Konsequenzen)
Dr. med. Björn Kruse	Amtsgericht Lichtenberg	Nein	Forum für medizinische Fortbildung FASD-Deutschland	Nein	Nein	Nein	Mitgliedschaften: Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde; Deutsche Gesellschaft für Neurologie; Deutsche Gesellschaft für Epileptologie; Deutsche Gesellschaft für Medizin für Menschen mit geistiger oder mehrfacher Behinderung Wiss. Schwerpunkte: FASD bei Erwachsenen, Demenz bei Intelligenzminderung Klinische Tätigkeiten: Diagnostik + Begleitung von Erwachsenen mit FASD, Behandlung Erwachsener mit Intelligenzminderung, Schwerpunkte psychische Erkrankungen, Autismus, FASD, emotionale Entwicklung	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Gila Schindler	Nein	Nein	Nein	Nein	Nein	Nein	Nein	(Keine Interessenkonflikte, keine Konsequenzen)
Lina Schwerg, M. Sc.	Nein	University of British Columbia	Ja[2]	Nein	Universität Potsdam/Ev. V. Sonnenhof e. V.	Nein	Wiss. Schwerpunkte und klinische Tätigkeiten: FASD Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten[2]	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Interventionen (geringer

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
								Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Hans-Ludwig Spohr	Nein	Nein	FASD-Vorträge[2]	Ja	Nein	Nein	Wiss. Schwerpunkte: Vorträge zu FASD-Themen Klinische Tätigkeiten: FAS-Sprechstunde	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dr. med. Dorothee Veer	Nein	Nein	Vituswerk Meppen	Nein	Nein	Nein	Mitgliedschaften: DGSM; DGKJ; DGSPJ; FASD Deutschland (ohne Funktion) Klinische Tätigkeiten: Entwicklungsstörungen; FASD Diagnostik; ADHS; Autismus	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dipl.-Psych. Jessica Christine Wagner, M. A.	KEH	Nein	Nein	KEH	Nein	Nein	Wiss. Schwerpunkte: FASD; Gesundheitspsychologie Klinische Tätigkeiten: FASD-Sprechstunde	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
								Stimmrechts)
Heike Wolter	Nein	Nein	Bundesakademie für Kinder und Diakonie Stiftung zum Wohle des Pflegekindes	Nein	Nein	Nein	Wiss. Schwerpunkte: FASD; ADHS Klinische Tätigkeiten: Diagnostik und Behandlung Patienten mit FASD; gesamtes Spektrum der Erwachsenen in der Kinder- und Jugendpsychiatrie; Konsiltätigkeit in der Neuropädiatrie	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Markus Backmund	Nein	Assist	Nein	Nein	Nein	Nein	Mitgliedschaften: DGS e. V. (1. Vorsitzender) Schwerpunkte: Suchtmedizin, Infektologie Klinische Tätigkeiten: Häusärztliche Versorgung; Suchtmedizin, Infektologie; Psychiatrie; Psychotherapie	Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dr. med. Annegret Brauer	Nein	Nein	Nein	Nein	Nein	Nein	Schwerpunkte: Humangenetik; Ursachenforschung/Therapie bei Kindern mit Intelligenzminderung Klinische Tätigkeiten: Ambulante Kinderpsychiatrie und Psychotherapie, allg. Versorgung Therapie und Beratung für Kinder mit Intelligenzminderung	Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dr. med. Matthias Brockstedt	bvkj e. V.	Nein	Nein	Ja[2]	Nein	Nein	Mitgliedschaften: Fortbildungsausschuss der Ärztekammer Berlin (Vorsitzender) Wiss. Schwerpunkte: Herausgeber des Lehrbuchs „Vergiftungen im	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)Interventionen

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
							Kindesalter“ 3. Auflage 2011, Thieme Verlag Stuttgart Klinische Tätigkeiten: Ärztlicher Leiter KJGD Berlin – Mitte-Kindesmisshandlung Ehrenamtlicher Leiter der Fortbildungsakademie der Ärztekammer Berlin für 33.000 ÄrztInnen seit 1996	(geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Christine Freitag	Servier	Autismus Deutschland e. V.	Nein	Ja[2]	Neue Drittmittel DFG, EU	Nein	Mitgliedschaften: DGKJP e. V. (Vorstand); DGPPN; WGAS Wiss. Schwerpunkte: Autismusspektrum, ADHS; Störungen des SV Klinische Tätigkeiten: Kinder- und Jugendpsychiatrie und -psychotherapie	Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Frank Häßler	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: DGKJP; DGPPN Wiss. Schwerpunkte: Intelligenzminderung Klinische Tätigkeiten: KJPP	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Prof. h. c. Florian Heinen	Nein	Nein	Nein	Nein	Ja[2]	Nein	Mitgliedschaften: DGKJ; BVKJ; DGKN; DGN; DGSPJ Vorstand: EPNS; GNP; DMG Wiss. Schwerpunkte: Epilepsie; FASD Klinische Tätigkeit: Neuropädiatrie Federführende Beteiligung an Fortbilduingen/ Ausbildungsinstituten: GNP Jahrestagungen – scientific committee; EPNS biannual Gongress – scientific committtee; GNP Neurowoche 2022, Kongresspräsident; RehaKind Fokus Cerebrainparese, 2022, Vertreter GNP; EPNS Glasgow	Versorgung, Therapie (geringer Interessenkonflikt, zusätzliche/r Leitlinienkoordinator*In ohne Themenbezug, keine Einschränkung des Stimmrechts)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
							2022, Sektionsverantwortlicher Haedache; EPNS Masterclass 2022 Cambridge, Head & Organisation mit Rob Forsyth, Newcastle	
Prof. Dr. Tanja Hoff	Nein	Nein	Nein	Ja	Nein	Nein	Mitgliedschaften: VSFJ; VHBC; PTK NRW; dgps; Forschungsgruppe Psychologie der Mensch-Tier-Beziehung am Institut für Psychologie der Rheinischen Friedrich-Wilhelms-Universität Bonn; Deutsche Gesellschaft für Suchtpsychologie Wiss. Schwerpunkt: klinische Psychologie; Suchtpsychologie; Beratungspsychologie	Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Franz Kainer	Nein	P&G Health Germany	Nein	Nein	Nein	Nein	Mitgliedschaften: DGGG; DGPM; DEGUM Wiss. Schwerpunkte: Pränatalmedizin Klinische Tätigkeiten: Geburtshilfe	Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Dipl.-Psych. Mirjam N. Landgraf	Nein	Nein	Ja[2]	Ja[2]	Ja[2]	Nein	Mitgliedschaften: GNP; DGKJ; DGKN; Hauner Verein; Marburger Bund; Deutscher Hochschulverband; FASD Beauftragte der GNP (Mitglied des erweiterten Vorstands) Wiss. Schwerpunkte: FASD Klinische Tätigkeiten: FASD; Kinderschutz Federführende Beteiligung an Fortbildungen/ Ausbildungsinstituten: EUFASD conference, Mitglied des Scientific Committee; FASD Fachtagung	Diagnostik (geringer Interessenkonflikt, zusätzliche/r Leitlinienkoordinator*In ohne Themenbezug, keine Einschränkung des Stimmrechts) Interventionen (geringer Interessenkonflikt, zusätzliche/r Leitlinienkoordinator*In ohne Themenbezug, keine Einschränkung des Stimmrechts)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
Prof. Dr. med. Bernd Lenz	Nein	Nein	DG-Sucht	Ja[2]	Deutsche Forschungsgemeinschaft STAEDTER Stiftung Forschungsstiftung Medizin, Universitätsklinikum Erlangen	Nein	Mitgliedschaften: AGNP; DG-Sucht; DGNTF; DGPPN; ESBRA; Marburger Bund; Deutscher Hochschulverband Wiss. Schwerpunkte: Suchtforschung; FASD im Erwachsenenalter; Bedeutung intrauteriner Einflussfaktoren für die psychische Gesundheit im späteren Leben; Forschung zu psychischer Gesundheit Klinische Tätigkeiten: Abhängigkeitserkrankungen; weitere psychische Erkrankungen; FASD im Erwachsenenalter	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Interventionen (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Silvia Lobmaier	Nein	Nein	Wissenschaftlicher Art	Wissenschaftlicher Art	Nein	Nein	Wiss. Schwerpunkte: Fetale Wachstumsrestriktion; fetale kardiale Funktion; pränataler Stress; Fetalchirurgie Klinische Tätigkeiten: Geburtsmedizin/Pränataldiagnostik	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Rolf Felix Maier	GKV-SV	IQTIG Bundesärztekammer	Ja[2]	Ja[2]	EU	Nein	Wiss. Schwerpunkte: Neonatologie	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. med. Eva Möhler	Nein	Nein	Nein	Nein	Nein	Nein	Wiss. Schwerpunkte: Early Life Stress, Trauma, Prenatal Stress, Kindesmisshandlung Klinische Tätigkeiten: Allgemeine Kinder-Jugendpsychiatrie, Stressresilienztraining, Traumatherapie	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Intervention (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
								Stimmrechts)
Prof. Dr. med. Ulrich Preuss	Nein	Nein	Janssen (Johonson&Johonson)	Nein	Nein	Nein	Mitgliedschaften: Deutsche Gesellschaft Suchtmedizin (stellv. Vorsitzender); Deutsche Gesellschaft Suchtforschung und Suchttherapie; DGPPN; ESBRA; RSA; EPA Wiss. Schwerpunkte: Substanzkonsumstörung (inkl. Alkohol); Cannabis Psychiatrie und Psychotherapie allg. Klinische Tätigkeiten: Akutversorgung stationäre Psychiatrie und Psychotherapie	(Keine Interessenkonflikte, keine Konsequenzen)
Andrea Ramsell	Nein	Nein	Nein	Nein	Nein	Nein	Nein	(Keine Interessenkonflikte, keine Konsequenzen)
PD Dr. med. Dietmar Schlembach	Nein	ROCHE	Ja[2]	Nein	DFG: PETN-Studie	Nein	Mitgliedschaften: DGGG, DGPGM, DGPM, DEGUM, EFCNI, Qualitätsverbund Babylotse	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dipl.-Psych. Ralph Schliewenz	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: Berufsverband Deutscher Psychologinnen und Psychologen e. V. / berufspolitische Interessensvertretung, Klinische Kinder- und Jugendlichenpsychologie (Leiter); Klinische Psychologie (Vorstand); Delegiertenkonferenz (Vorstand); Präsidium für Kindeswohl und Kinderrechte (Beauftragter); AWMF-Leitlinienprojekte/Kinderschutz (Mandatsträger), Borderline-Persönlichkeitsstörung; Behandlung depressiver Störungen bei Kindern und Jugendlichen Klinische Tätigkeiten: Kinder- und jugendpsychiatrische /-psychotherapeutische Versorgung => Institutsambulanz	(Keine Interessenkonflikte, keine Konsequenzen)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
Prof. Dr. med. Juliane Spiegler	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: DGKJ; GNP; EACD; BVKJ; DGfE; DGKN Klinische Tätigkeiten: Neuro- und Sozialpädiatrie Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten: Train-the Trainer für die Epilepsieschulung Flip&Flap für Kinder-Jugendliche und ihre Eltern	Betreuung (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dr. rer. nat. Johanna Thünker	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: Verband Psychologischer Psychotherapeutinnen und Psychotherapeuten im BDP e. V. (Vorsitzende)	(Keine Interessenkonflikte, keine Konsequenzen)
Dr. med. Gabriele Trost-Brinkhues	Nein	Nein	AWO Potsdam	Nein	Nein	Nein	Wiss. Schwerpunkte: Kinder und Jugendgesundheit insgesamt; Prävention und Gesundheitsforschung; Nachrangige Versorgungssicherheit durch ÖGD (ohne Bezug zur Leitlinie)	(Keine Interessenkonflikte, keine Konsequenzen)
Dr. sc. hum. Christine Schmucker, Dipl. Ing.	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: Arzneimittelkommission (Außerordentliches Mitglied)	(Keine Interessenkonflikte, keine Konsequenzen)
Sonja Strieker, M. Sc.	Nein	Nein	Nein	Nein	S3-Leitlinie FASD	Nein	Wiss. Schwerpunkte: S3-Leitlinie FASD	(Keine Interessenkonflikte, keine Konsequenzen)
Annika Ziegler, MPH	Nein	Nein	Nein	Nein	Nein	Nein	Wiss. Schwerpunkte: Arbeitsschutz- Erholungsforschung; Pandemic management / Pandemic preparedness	(Keine Interessenkonflikte, keine Konsequenzen)
Sandra Kramme	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: FASD Deutschland e. V. (Kassenwart)	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des

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								Stimmrechts) Intervention (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts))
Katrin Lepke	Nein	Nein	Ja[2]	Nein	Nein	Nein	Stellvertr. Vorsitzende FASD Deutschland e. V., Patientenvertretung	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts) Intervention (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Dipl.-Soz.päd. Gisela Michalowski	Nein	Nein	Nein	Nein	Nein	Nein	Mitgliedschaften: FASD Deutschland e. V.	Diagnostik (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)Intervention (geringer Interessenkonflikt, keine Leitungsfunktion, keine Einschränkung des Stimmrechts)
Prof. Dr. Ina Kopp	Nein	Nein	Nein	Nein	Nein	Nein	Nein	(Keine Interessenkonflikte, keine Konsequenzen) (als Moderatorin nicht stimmberechtigt)

	Tätigkeit als Berater*in und/oder Gutachter*in	Mitarbeit in einem Wissenschaftlichen Beirat (advisory board)	Bezahlte Vortrags-/oder Schulungstätigkeit	Bezahlte Autor*innen-/oder Coautor*innenschaft	Forschungs-vorhaben/ Durchführung klinischer Studien	Eigentümer*innen-interessen (Patent, Urheber*innen-recht, Aktienbesitz)	Indirekte Interessen	Von COI betroffene Themen der Leitlinie[1], Einstufung bzgl. der Relevanz, Konsequenz
Dr. Monika Nothacker	Nein	Nein	Berlin School of Public Health	Nein	Ja[2]	Nein	Mitgliedschaften: German Network Evidence Based Medicine; German Cancer Society; Guidelines International Network/GRADE Working Group Federführende Beteiligung an Fortbildungen/Ausbildungsinstituten: Guideline seminars within Curriculum for guideline developers in Germany	(Keine Interessenkonflikte, keine Konsequenzen) (als Moderatorin nicht stimmberechtigt)

[1] In die tabellarische Zusammenfassung wurden hier nur die Angaben übertragen, für die nach Diskussion und Bewertung der vollständig entsprechend Formblatt der AWMF offengelegten Sachverhalte in der Leitliniengruppe ein thematischer Bezug zur Leitlinie festgestellt wurde. Die vollständigen Erklärungen sind im Leitliniensekretariat hinterlegt.

[2] Alternativ kann auch nur ein „Ja“ eingetragen werden und auf die Nennung der Unternehmen verzichtet werden

Versionsnummer: **3.1**

Erstveröffentlichung: **10/2012**

Überarbeitung von: **05/2024**

Nächste Überprüfung geplant: **05/2025**