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Autism spectrum disorders in childhood, adolescence and adulthood

Part 1: Diagnostics

Interdisciplinary S3 guideline of the DGKJP and the DGPPN

as well as the participating professional societies, professional associations and patient organisations

Long version; consensus conference on 24/25.04.2015

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Chair of the steering group

Prof. Dr. Christine M. Freitag, DGKJP e.V.

Prof. Dr. Dr. Kai Vogeley, DGPPN e.V.

Guideline coordination and project management

Prof. Dr. Christine M. Freitag, Dr. Eftichia Duketis (until 12/2012), Catrin Schalk (until 07/2013), Pia Mehler (until 12/2012), Krystyna Ufniarz (until 11/2013), Stephanie Hoss (until 05/2014), Marie Landenberger (until 06/2014), Leonora Vllasaliu (since 01/2014), Marianne Menze (since 05/2014), Magdalena Schütz (since 06/2014).

Clinic for Psychiatry, Psychosomatics and Psychotherapy of Childhood and Adolescence

University Hospital Frankfurt am Main, Goethe University

Steering committee

Dr. Uwe Büsching, Prof. Dr. Matthias Dose, Prof. Dr. Christine M. Freitag, Dr. Ulrich Hagenah, Dr. Helmut Hollmann, Prof. Dr. Inge Kamp-Becker, Claus Lechmann, Dr. Tobias Leppert, Rudi Merod, Friedrich Nolte, Prof. em. Dr. Fritz Poustka, Prof. Dr. Luise Poustka, Prof. Dr. Ludger Tebartz van Elst, Prof. Dr. Judith Sinzig, PD Dr. Ingo Spitczok von Brisinski, Leonora Vllasaliu, Prof. Dr. Dr. Kai Vogeley, Diana Will and two representatives of Aspies e.V. (for assignment to scientific societies and self-help organizations see Method Report)

Methodological consulting and meta-analyses

Dr. Katrin Jensen (Institute of Medical Biometry, University Hospital Heidelberg)

Moderation of the consensus process

Dr. Cathleen Muche-Borowski (AWMF e.V.)

Contact address

Prof. Dr. med. Dipl.-Theol. Christine M. Freitag

Director, Clinic for Psychiatry, Psychosomatics and Psychotherapy of Childhood and Adolescence & Frankfurt Autism Therapy and Research Centre

University Hospital Frankfurt am Main, Goethe University

Deutschordenstraße 50, 60528 Frankfurt am Main, Germany

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Introduction

Christine M. Freitag, Leonora Vllasaliu,

1 Why is a guideline on autism spectrum disorders important for Germany?

2. what is the primary objective of this guideline? [1]

The initiative to develop a German S3 guideline on the diagnosis and treatment of autism spectrum disorders came from the two professional societies German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy. (DGKJP) and the German Society for Psychiatry and Psychotherapy, Psychosomatics and Neurology (DGPPN). (DGPPN). The current background includes the constantly growing prevalence figures of autism spectrum disorders (Elsabbagh et al. 2012), but also the fact that numerous diagnostic and screening instruments as well as new versions of already proven instruments have been developed and are in circulation. In addition to research on diagnostics, numerous studies have been conducted in recent years in the area of therapy (both psychotherapeutic-exercise procedures and medication-based procedures). The results of studies are currently available mainly to people who have access to the original English-language literature and who often also work scientifically. On the other hand, many groups of people who mainly work clinically with patients[2] with autism spectrum disorders (physicians, psychologists, pedagogues, occupational therapists, speech therapists, etc.) are not familiar with the current state of research on the diagnosis and therapy of autism spectrum disorders.

A central aim of the guidelines is therefore to develop the evidence-based basis for scientifically justified diagnostic and therapeutic recommendations and to achieve broad consensus on the corresponding recommendations.

Currently, there is no German S3 guideline on the diagnosis and treatment of autism spectrum disorders (ASD). In contrast to numerous reviews published in German, an S3 guideline aims to first define clinically relevant key questions, then, on the basis of an extensive systematic literature search, to first aggregate the corresponding database (if possible within the framework of a meta-analysis) and, based on the level of evidence thus scientifically proven, to provide

[1] Information on the selection of key questions can be found in the methods report.
[2] For reasons of better readability, the present guideline primarily uses the generic masculine; this is intended to include female and male persons equally. If differences between the genders exist or are assumed to exist in the scientific literature or from experience within clinical practice, this is explicitly stated.

broadly consensual recommendations on appropriate diagnostics and therapy in the German health care system for children, adolescents and adults with autism spectrum disorders. The intention is thus to improve the care of patients with autism spectrum disorders and their relatives by applying empirically tested procedures in diagnostics and therapy.

Although there are some methodologically excellent English-language guidelines (e.g.SIGN 2007; NICE 2011, 2012, 2013), due to the very practice-oriented approach and the health care systems that vary greatly from nation to nation, the recommendations for action are not easily transferable to Germany. In addition, many of the English-language studies and guidelines on the diagnosis and evidence-based therapy of autism spectrum disorders are not at all or not sufficiently known to many people in Germany who work with affected patients, and conversely, some German studies have not been included in the aforementioned British and Scottish guidelines. An important goal is therefore to fill these gaps by answering the clinically centrally relevant key questions formulated by the steering group based on the current state of studies. A broadly consensual, evidence-based (S3) guideline adapted to the German health care system is therefore required.

Despite numerous research papers, there are not enough studies of appropriate quality for some key questions, so that an evidence-based foundation for some recommendations is hardly possible. In such cases, a clinical consensus decision is therefore made for the guideline. For this purpose, it is important to involve a multidisciplinary team of experts in the guideline development. This was attempted in the best possible way by asking all German professional societies, associations and organizations important for the guideline for their support and cooperation. [3]

[3] A detailed list can be found in the method report.

In summary, the primary goals of this autism spectrum disorder guideline are thus:

- Bringing together scientific evidence and broad clinical experience to produce "best practice" recommendations, formulated as far as possible in an evidence-based manner, and widely disseminating and promoting the implementation of the relevant recommendations.
- Creating transparency about clinical decision-making
- Provide evidence- or consensus-based recommendations for the diagnosis of autism spectrum disorders.
- Provide evidence- or consensus-based recommendations for the effective treatment of autism spectrum disorders.
- Provide evidence- or consensus-based recommendations for psychosocial support services and school and labour market integration measures.
- Improve communication between the relevant professionals, patients and their parents or guardians.
- Identification of focal points for future research
- Promoting the implementation of evidence- and consensus-based recommendations by adapting them to the German health care system

This S3 guideline is published with the following components:

Part 1: Diagnostics

Part 2: Therapy (including sociotherapy and integration measures)

A long version and a method report for each long version will be published. An abridged version, which mainly contains the recommendations, will also be produced.

A.1 History

Judith Sinzig

The term "autism" (from the Greek autos = self) has undergone a diverse development throughout history. In 1908, Theodor Heller, pedagogue and director of the Educational Institution for Mentally Abnormal and Nervous Children in Vienna, described children who, after an inconspicuous development in the first three to four years of life, show a loss especially of language, but also of other already acquired skills with the development of a severe reduction in intelligence. The disorder, also called "dementia infantilis" or "Heller's dementia", is very similar to descriptions of autism.

The Swiss psychiatrist Eugen Bleuler introduced the term "autism" in 1911 as a basic symptom of schizophrenia. He used it to describe the marked loss of communication in people with schizophrenia and the accompanying withdrawal into a world of their own thoughts. In the course of history, the psychoanalyst Sigmund Freud equated the terms "autism" and "autistic" with the terms "narcissism" and "narcissistic" and used these as counter terms to "social". However, today's version of the content of the disorder "autism" and "autism spectrum disorder" differs significantly from the ideas of Bleuler or Freud, both of which must be considered historical and are no longer used in this way.

Until the 1970s, schizophrenia and autism were considered disorders with the same nosology and etiology; autism was considered an early form of schizophrenia. In the ICD-9 (World Health Organization 1986) or DSM-III (American Psychiatric Association 1984), early childhood autism was assigned as category 299.0 to diagnosis group 299, "typical psychoses of childhood". In particular, epidemiological studies such as those by Rutter (1970; 1972) are largely responsible for the fact that the two disorders are now understood to be separate.

In 1943, the Austrian child psychiatrist Leo Kanner first applied the term "autism" to children who do not actively withdraw into their fantasy world but who have deficits in establishing social interactions from birth, thus deviating from the literal sense of Bleuler's definition of "autism", whose definition presupposes an originally intact interactional behavior. His psychopathological descriptions remain a major basis of the definition of autism and autism spectrum disorders today. Under the title "Autistic Disorders of Affective Contact", Kan ner described eleven children whose common features he described as follows: "[...] the outstanding fundamental pathognomonic disorder is the inability, existing from birth, to relate in a normal way to persons or situations. Parents [...] describe [these children] as 'self-sufficient', 'living as if in

a shell', 'happiest when left alone', 'acting as if no one were present', 'taking no notice of their surroundings', 'giving the impression of quiet wisdom, unable' to muster the social measure of social flair', 'acting as if hypnotized'. ' [....] For the time being, we may find in these children congenital disorders of affective contact in pure form." The term "early childhood autism" was then introduced as a medical term by Kanner in 1944. Other historical terms for early childhood autism therefore include Kanner syndrome, Kanner autism, or infantile autism.

In 1944, the Viennese pediatrician Hans Asperger, without knowing the writings of Leo Kanner, simultaneously described four patients between the ages of 6 and 11 who also showed deficits in social interactions, but no language development disorder or qualitative intellectual abnormalities. Hans Asperger himself named the syndrome he described "autistic psychopathy" and, like Kanner, assumed it was a congenital disorder passed on from father to son. However, he assumed that the behavior he observed was the extreme variant of a personality trait and that the disorder could not be recognized before the age of 3. Since Asperger published in German and his publications were not translated into English for decades, he was initially little known internationally. Asperger's work only became internationally known through the English summary by the English psychologist Lorna Wing (1981) under the term "Asperger's syndrome". Uta Frith 1991 finally translated Asperger's original work into English. However, to this day it is not certain whether Asperger's description is actually a first description, since as early as 1926 Grunja Jefimowna Sucharewa described children with very similar symptomatology, albeit using the term "schizoid psychopathy", in the "Monatszeitschrift für Psychiatrie und Neurologie".

For decades, psychosocial assumptions prevailed regarding the etiology of autism spectrum disorder. For example, Leo Kanner himself considered it possible that autistic symptomatology was due to a lack of maternal warmth. Bruno Bettelheim, in particular, formulated the thesis that early educational errors on the part of mothers were mainly responsible for the psychoge nesis of autism, and in his book "Birth of the Self" (1967) coined the term "refrigerator mother", which was used until the 1970s. Although Leon Eisenberg described the characteristics of fathers of children with autism in great detail as early as 1957, it was not until the 1980s that it was suspected, on the basis of the familial accumulation of autistic behaviour or on the basis of twin studies, that it was a hereditary, genetically determined disorder (Folstein and Rutter 1977; Rutter 1977; Rutter and Sandberg 1985; Spence 1976).Today, there is consensus that early childhood autism or autism spectrum disorders must be based on neurobiological causes.

A.2 Presentations, symptoms and classification ICD-10/DSM-IV-TR/DSM-5

Kai Vogeley, Judith Sinzig, Christine M. Freitag

3. what is understood by the term autism spectrum disorders?
(13) Are there other "accessory" criteria (e.g. Gillberg criteria) worthy of attention in addition to the leading diagnostic symptoms (ICD-10, DSM-IV TR, DSM-5)?
14 Should autism spectrum disorders be understood as categorical disorders or as a dimensional cluster of traits?
19. are there (syndromal) reliably definable subgroups of autism spectrum disorders (e.g. early childhood, high-functioning, atypical autism, Asperger syndrome; e.g. severity levels of autism spectrum disorders, etc.)?

A.2.1 Clinical presentation and leading symptoms of autism spectrum disorders

The core symptoms of autism spectrum disorders include age-independent deficits in social interaction and communication as well as restricted, repetitive behaviour patterns, interests or activities. Interaction disorders refer to the initiation, maintenance and shaping of interpersonal relationships in the context of family, friendship, partnership as well as peers in kindergarten, school and work. Communication disorders relate on the one hand to language development, and on the other hand in particular to non-verbal communication including gestures, facial expressions or gaze behaviour. In addition, in cognitively well gifted affected persons, there are also paraverbal performances such as the understanding of transferred meaning in proverbs and humour or irony. Restricted, repetitive behaviors, interests, or activities include special interests, ritualized daily routines, and a strong aversion to change in one's circumstances. These phenomena must exist from early childhood and remain present throughout life.

The clinical presentation changes significantly over the lifespan from infancy through school age and puberty to (independent) adult life. All phases of life hold different demands on social interaction and communication skills. The changing nature and expression of the aforementioned core symptoms over the course of a person's life poses the essential question, particularly for diagnostics, of which symptom constellations are predominant at which age. In the case of persons with autism spectrum disorders who are not additionally affected by a reduction in intelligence, there are also individually developed compensatory strategies that can mask autistic symptoms and thus complicate the diagnosis.

A.2.2 Classification of Autism Spectrum Disorders

Autism spectrum disorders are classified comparably in the ICD-10 (World Health Organization 1992) and DSM-IV-TR (American Psychiatric Association 2000) in the group of "profound developmental disorders" (ICD-10: F84; DSM-IV-TR: 299). Differentiations are made into the diagnostic subgroups of "early childhood autism" (ICD-10: F84.0; DSM-IV-TR: 299.00), "atypical autism" (ICD-10: F84.1) and "Asperger syndrome" (ICD-10: F84.5; DSM-IV-TR: 299.80) as well as, in the sense of a residual category, the "other" or "unspecified" "pervasive developmental disorders, not otherwise specified": PDD-NOS; ICD-10: F84.8 and F84.9; DSM-IV-TR: 299.80). Intellectual/mental disability is [4]present in about half of all individuals with autism spectrum disorders (IQ < 70; Baird et al. 2006; Brugha et al. 2011).

In the case of early childhood autism according to the ICD-10 currently valid in Germany (2015), all three diagnostic criteria (social interaction, communication, stereotypic and repetitive behavior) must be met. A developmental or language disorder is present before the age of three. An Asperger syndrome requires autism-specific abnormalities of social interaction and in the area of stereotypic and repetitive behavior, including special interests. Linguistic and cognitive development are inconspicuous. Atypical autism is diagnosed when either only one or two of the three diagnostic criteria can be demonstrated and a developmental disorder is present before the age of three or evidence of the autistic core symptomatology can only be provided after the age of three. Unspecified profound developmental disorders are available as a residual category in cases in which no clear assignment to autistic disorders according to ICD-10 is possible, but evidence of developmental disorders with autistic symptoms and clinical impairment can nevertheless be demonstrated.

In 2013, the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was introduced in the USA, and the German translation has been available since 2015 (Falkai and Döpfner 2015). The DSM-5 includes the following changes (Freitag 2014): i) the transfer of all autism spectrum disorders into a single diagnostic category of autism spectrum disorder (A.2.3), ii) the change of the diagnostic criteria itself with the grouping of social interaction and communication into one symptom domain and of stereotypic and repetitive behavior into a second one; in addition, a somewhat modified assignment of symptoms to the two defining domains (A.2.4), iii) the additional classification in terms of clinical severity (A.2.4), iv) the detailed presentation of autism spectrum disorders across the lifespan with possible later onset of

[4] In the following, the term "intellectual disability", which is common in German, is used for persons with IQ < 70 and the associated everyday and learning difficulties. Internationally, the term "intellectual disability" is also frequently used.

the abnormal behaviour after the age of three years, and v) the possibility of diagnosing other mental disorders in parallel. Initial empirical studies suggest that especially in the "low-functioning" (unspecified pervasive developmental disorder, PDD-NOS) as well as in the "high-functioning" borderline range of the spectrum, the diagnosis of autism spectrum disorders under DSM-5 will be more restrictive (A.2.3). A recent meta-analysis (Kulage et al. 2014), which reviewed 418 studies and included 14 trials, demonstrates that prevalence rates of autistic disorders will be significantly reduced under DSM-5, with decreases in diagnosis rates ranging from 7.3% to 68.4% across individual studies.

It should be emphasised here that in Germany, diagnosis is currently (2015) carried out according to ICD-10. The ICD-11, which is to be harmonised with the DSM-5, is not expected until 2017 at the earliest. Other classifications have been proposed but have not gained international acceptance. These include the Gillberg & Gillberg classification, which is very closely based on Hans Asperger's criteria (Gillberg and Gillberg 1989).

For a comparison of the diagnostic criteria of ICD-10, DSM-IV-TR as well as DSM-5 see the two following tables 1 & 2.

Table 1: Comparison ICD-10 - DSM-IV-TR - DSM-5 - criteria for early childhood autism - autistic disorder - autism spectrum disorder (adapted from Freitag 2014).

	ICD-10	DSM-IV TR	DSM-5
Number and type of diagnoses of "profound developmental disabilities". (ICD-10/DSM-IV TR) respectively Autism Spectrum Disorder (DSM-5)	F84.0 Early childhood autism F84.1 Atypical autism F84.2 Rett syndrome F84.3 Other childhood disinte-grative - disorder F84.4 Overactive disorder with reduced intelligence and movement stereotypies F84.5 Asperger syndrome F84.8 Other profound developmental disorders F84.9 Profound developmental disorder, unspecified	299.00 Autistic disorder 299.10 Disintegrative disorder of childhood 299.80 Rett syndrome 299.80 Asperger syndrome 299.80 Profound developmental disorder, unspecified (PDD-NOS) Additional: 307.3 Stereotypic movement disorder (for F84.4)	299.00 Autism spectrum disorder (includes 299.00, 299.10, 299.80 or F84.0, F84.1, F84.3, F84.5) Additional: 315.39 Social (pragmatic) communication disorder (for 299.90/F84.1 without stereotyped and repetitive behaviours) 307.3 Stereotypic movement disorder (for F84.4)
Criteria for Early Childhood Autism/Autistic Disorder/Autism Spectrum Disorder			
	ICD-10	**DSM-IV TR**	**DSM-5**
Number of domains	3	3	2 (A, B)
Number Criteria	12	12	7
Minimum number of criteria fulfilled	5	6	5
Social interaction	≥1/3	≥2/4	3/3 (A)
Communication	≥2/4	≥2/4	
Stereotypical behaviour and special interests	≥2/5	≥1/4	≥2/4 (B) New: Hyper- and hypo-reactivity regarding sensory aspects
Start (Domain C in DSM-5)	Before the age of 3 ≥1/3	Before the age of 3	Symptoms must be present in early childhood, but may not fully manifest until social demands are appropriately high.

Table 2: Other aspects of the classification of autism spectrum disorder according to DSM-5 compared to ICD-10 and DSM-IV-TR (adapted from Freitag 2014).

	ICD-10	DSM-IV TR	DSM-5
Severity classification	Indirectly via different classification (F84.1, F84.5, F84.8, F84.9)	Indirectly via different classification (299.00, 299.80)	Table 2: 3 severity levels each for A: Social communication and interaction and B: Restrictive, repetitive behaviours and interests
Rett Syndrome	Independent psychiatric diagnosis	Independent psychiatric diagnosis	Falls out, is coded as existing genetic risk factor if necessary
Additional coding DSM-5 Cognitive skills	Five axes WHO Axis 3: Intelligence level	Five axes DSM-IV Axis II: Intellectual - disability	With/without mental - disability
Additional coding DSM-5 Language	Five axes WHO axis 2: Partial impairment	Five axes DSM-IV Language not coded	With/without speech disorder
Additional coding DSM-5 Medical/genetic/environmental risk factor	Five axes WHO Axis 4: Physical diseases including genetic findings Axis 5: Psychosocial environmental risk factors No coding of non-genetic biological environmental risk factors	Five axes DSM-IV Axis III: General medical condition, acute medical condition, - physical illness. Axis IV: Psychosocial and environmental risk factors	Associated with medical/genetic/environmental risk factor Additional coding of the medical or genetic condition
Additional coding DSM-5 Additional psychiatric comorbidity or developmental disability	Five axes WHO Axis 1: mental disorder Axis 2: Partial performance disorder However: Other exclusion criteria - than DSM-5 (e.g. ADHD)	Five axes DSM-IV Axis I: Mental disorder Axis II: Personality disorder and intellectual disability However: other exclusion criteria than DSM-5 (e.g. ADHD)	The respective disease is additionally coded with the corresponding DSM-5 number.
Additional coding DSM-5 Catatonia	Will not be coded	Will not be coded	F293.89

A.2.3 Autism Spectrum Disorders as a Dimensional Disorder

Empirical studies over the last two decades or so have clearly shown that at none of the levels examined (e.g. clinical, neurobiological, cognitive) within the autistic spectrum, reliable distinctions cannot be made between the subgroups of early childhood autism, Asperger syndrome and PDD-NOS as defined by ICD-10 and DSM-IV-TR (Cederlund et al. 2008; Kamp-Becker et al. 2010a; Klin and Volkmar 2003; Leekam et al. 2000; Lord 2012; Miller and Ozonoff 2000). This is also the basis of the current DSM-5 classification (Falkai and Döpfner 2015). Recent work that has addressed the question of dimensionality or categoricality has most recently been able to show that while it is possible to differentiate between autism spectrum disorders and non-autistic disorders in terms of categorical differentiation, it is not possible to distinguish between different subgroups within the autistic spectrum (Coghill and Sonuga-Barke 2012; Frazier et al. 2010; Frazier et al. 2012; McPartland et al. 2012). The authors (Frazier et al. 2010; Frazier et al. 2012) have therefore proposed a hybrid model that makes a categorical distinction between autism spectrum disorders and non-autism spectrum disorders while assuming a dimensional trait distribution within these two groups.

[1]	**Consensus statement** *Key questions 3, 13, 14, 19*
KKP	Autism spectrum disorders are characterised by disturbances in social interaction, disturbances in communication and repetitive, stereotyped behaviours and special interests. Relevant for diagnosis in Germany is the ICD-10. The DSM-5, which aims to harmonize the ICD-11, foresees changes including i) the transfer of all autistic disorders into a single diagnostic category of autism spectrum disorder, ii) the modification of the diagnostic criteria themselves, iii) the additional classification in terms of clinical severity. Empirical evidence shows that subgroups as proposed in ICD-10 cannot be reliably delineated.
	Strong consensus (13 out of 13)

A.3 Descriptive epidemiology

9. are prevalence rates for ASD and comorbid conditions available and what are they?

63. is there an increased rate of delinquency in individuals with ASD?

A.3.1 Incidence and prevalence of autism spectrum disorders

Luise Poustka, Ulrich Hagenah, Christine M. Freitag
Literature research and selection: Stephanie Hoss, Marie Landenberger

While prevalence describes the frequency of a disease in the population (usually expressed as a percentage), the incidence rate is understood as the number of new cases per 100,000 persons in the population. Prevalence rates are further differentiated according to cut-off date or point prevalence, a range prevalence or period prevalence (e.g. 1-year prevalence) and a lifetime prevalence.

One problem in comparing prevalence and incidence rates over time is that during the development of the DSM and ICD classification systems, the criteria for diagnosing autism spectrum disorders and thus the case definitions have changed. This makes direct comparison of the available studies difficult, for example, when asking whether prevalence and incidence rates of autism spectrum disorders have changed over the past four decades. Early epidemiological studies of autism concerned almost exclusively the severe courses as defined by Kanner (1943). It was not until the increasingly expanded criteria of Rutter (1970), ICD-9 (1986), DSM-III (1984), and DSM-III-R (1987) that the less severe forms (high-functioning autism, pervasive developmental disorder, atypical autism, Asperger syndrome) were also included. Despite many similarities between the DSM-IV-TR used until 2013 and the current ICD-10, some differences between the classification systems are significant with regard to epidemiology of autism spectrum disorders. In particular, atypical autism (ICD-10: F 84.1), for example, cannot be equated with pervasive developmental disorder, not otherwise classified (PDD-NOS) in DSM-IV-TR, which is sometimes simplistically referred to as atypical autism. This necessitates careful interpretation of studies that refer to atypical autism.

In selecting the population to be studied for the collection of prevalence or incidence rates, different case identification strategies are used. Some studies are based exclusively on data from utilisation populations or case registers, e.g. from the health care system or school system, thus capturing only those cases that have already made use of this system, while persons who have not yet had contact with these institutions up to the time of the survey remain undetected. The

data collected in such studies lead to an underestimation of the prevalence of autism spectrum disorders, while the extent of the "dark figure", i.e. the undetected cases, remains unclear. Population-based and so-called population-representative studies often use a multistage approach, i.e., first screening out potentially affected individuals in the relevant cohort using a screening procedure in the form of a questionnaire and then screening them for the presence of an autism spectrum disorder in a more detailed examination. Screening for autism spectrum disorders is often done through doctors' offices, kindergartens, or schools using a wide variety of procedures. The sensitivity of such screening procedures must currently still be assessed as insufficient overall (see Chapter B.3), so that it remains unclear how many individuals who are actually affected are not detected by the screening. This problem cannot be sufficiently narrowed down by examining a random sample of negatively screened individuals, since due to the low prevalence rates of autism spectrum disorders, such a group would have to be very large on the one hand (in order to detect 10 individuals with autism spectrum disorder at the prevalence of 1%, correspondingly about 1000 individuals would have to be examined in detail). Estimates would accordingly cause both very high costs and again lead to inaccurate results.

The comparison of prevalence and incidence rates for autism spectrum disorders found in epidemiological studies is complicated by the different methodologies used to confirm the diagnosis, i.e. the final case identification. Various diagnostic instruments are used for this purpose, ranging from unspecified "investigations by professionals" to surveys using standardized measurement instruments by specially trained research staff. In studies of very large populations, direct examinations of subjects are often not conducted; case identification here is accomplished through a combination of population-based screening procedures, evaluation using systematic reviews and standardized scoring systems, and, if necessary in the case of unclear cases, with the involvement of clinical experts (e.g., Centers for Disease Control and Prevention's (CDC's) Metropolitan Atlanta Developmental Disabilities Surveillance Program, MADDSP; Rice et al. 2007; Van Naarden Braun et al. 2007). An initial validation study of this methodology (Avchen et al. 2011) did identify a high specificity (0.96) and a relatively high positive (0.79) and negative (0.91) predictive value. However, the sensitivity was significantly lower at 0.6, suggesting that data obtained using this method are likely to underestimate the true prevalence of autism spectrum disorders.

Prevalence

Epidemiological studies have reported increasingly higher prevalence rates for autism spectrum disorders since around the mid-1980s. A systematic review of 48 studies (including 13 studies

from the UK, six from the US and six from Japan) published between 1966 and 2009 (Fombonne et al. 2011) found prevalence rates for autism ranging from 0.7/10,000 to 72.6/10,000 with a median of 12.9/10,000. Sample sizes examined varied from 826 - 4.95 million participants with a wide age range of 3-15 years (median 8.5 years). Sample size and prevalence rates were significantly negatively correlated (Spearman's r: -0.71; $p<.001$), studies with smaller populations accordingly found higher prevalence rates. A significant positive correlation was also found between the respective prevalence rates and the year of publication (Spearman's r: 0.69; $p<.001$), indicating higher prevalence rates in more recent studies.

Research published since 2000 actually suggests a dramatically higher prevalence of autism and associated disorders. A comprehensive review of the global prevalence of autism spectrum disorders (Elsabbagh et al. 2012) included a total of 36 studies (16 from Europe, seven from the USA, 13 from Asia) regarding the prevalence estimate of autism, resulting in a rate between 2.8-94/10,000 and a median of 17/10,000. Studies on the broader autism spectrum (n = 33) showed a rate between 1-189/10,000 with a median of 62/10,000. For Europe alone (n = 16 studies), the rate ranged from 30/10,00 -116/10,000 with a median of 61.9/10,000. The sample sizes analysed here on the spectrum of profound developmental disorders ranged from 2536 - 134 661 participants. Variability in study designs, instruments used, case identification and sensitivity of screening contribute to the high variability in prevalence rates found (Posserud et al. 2010). Registry studies are usually associated with lower case identification sensitivity, such as Magnusson & Saemundsen (2001), who found prevalence rates ranging from 3.8-8.6/10,000 in an Icelandic population. Studies in which case identification techniques are based on multiple screenings of participants at multiple time points involving multiple sources of information thereby maximise the sensitivity of case identifications and often arrive at significantly different results, such as the study by Baird et al. (2006) from the UK with a rate of 38/10.000 for early childhood autism, 77.2/10,000 for other pervasive developmental disorders, and a prevalence estimate for the entire autism spectrum of 116.1/10,000. Two recent studies from Korea (Kim et al. 2011) and Japan (Kawamura et al. 2008), also based on multilevel screening and diagnostic processes, report as high as 189/10,000 and 181.1/10,000, respectively, for the entire autism spectrum. Furthermore, Kim et al. (2011) even assumed a probability estimate of 264/10,000.

Overall, there is a trend, especially in recent studies, to use multiple, standardized screening procedures in total populations or birth cohorts, with the consequence that comparatively fewer cases remain undetected than was the case in older studies with preselected samples. Second, the continuing expansion of the diagnostic concept of the disorder has contributed to the increasing recognition of milder or subclinical courses in children with average intelligence. Both the

increasingly inclusive design of official autism diagnostics according to ICD and DSM and the growing sensitivity of experts to these diagnostic concepts contribute to this expansion. Based on Kanner's (1943) and Asperger's (1944) descriptions of the disorder, a psychiatric classification of autism spectrum disorders has emerged in the ICD-10 (World Health Organization 1992) and especially in the DSM-5, newly published in 2013 (Falkai and Döpfner 2015), which leaves sufficient diagnostic scope for diagnosing milder forms relatively frequently.

In summary, based on most studies since 2000 in different geographic regions, a median of approximately 62/10,000 can be assumed for all profound developmental disorders. This meant that at least one in 160 children is currently affected by an autism spectrum disorder. In addition, as noted above, some population-based, well-controlled studies report prevalence rates approximately two to three times higher (Baird et al. 2006; Kawamura et al. 2008; Kim et al. 2011), so that currently an **overall prevalence of 0.9-1.1%** is assumed for **autism spectrum disorders** (Fombonne et al. 2011).

This estimate represents an average number, and studies are difficult to compare with each other due to substantial heterogeneity and large methodological differences. However, estimates of narrower "core" autism since 2000 in the United States, Asia, and Europe are not statistically significantly different ($p = 0.3$), suggesting no ethnic differences for autism spectrum disorders. Significantly fewer studies have been conducted on the broad autism spectrum or pervasive developmental disorders, again the numbers found in Europe and the US are quite comparable (Elsabbagh et al. 2012). In some countries, such as Africa, prevalence rates are not yet available or can only be evaluated provisionally.

Moreover, epidemiological studies have been conducted only in very circumscribed regions, such as primarily Northern Europe (Baird et al. 2006; Brugha et al. 2011; Chakrabarti 2001; Chakrabarti and Fombonne 2005; Latif and Williams 2007; Magnússon and Saemundsen 2001; Williams et al. 2008a, et al.), Japan (Honda et al. 2005; Kawamura et al. 2008), China (Chen et al. 2007; Wong, V. C. N. and Hui, S. L. H. 2007, among others), or the United States and Canada (Barbaresi et al. 2005; Bertrand et al. 2001; Center for Disease Control 2007b, 2007a, 2009; Croen et al. 2002; Fombonne et al. 2006; Kogan et al. 2009; Yeargin-Allsopp et al. 2003). With the exception of China, studies come mainly from high-income countries, while few prevalence rates are available from low-income regions. In addition to a low availability of appropriate regional health institutions and experts to enable case identification, economic factors also play a role in supporting scientific studies. Few studies to date have included the influence of geographical, economic, social and cultural factors. For example, two recent studies from

the United States (Center for Disease Control 2009; Palmer et al. 2010) suggest lower rates of autism spectrum disorders among children of Hispanic origin. Palmer et al. (2005) also reported a significantly higher utilization prevalence of autism spectrum disorders among children from high-income versus low-income families. Again, the availability of appropriate points of contact in the health sector may have contributed to the observed differences, as prevalence rates increased uniformly across ethnic or/and cognitive subtypes. Elsabbagh et al (2012) therefore emphasised that the current estimate for the prevalence of autism spectrum disorders, with a median of 62/10,000, should not be considered a 'global' prevalence rate, but a best estimate based on currently existing evidence from different regions.

Incidence

Currently, few studies are available on the incidence of autism spectrum disorders that document an overall upward trend. In one of the most comprehensive studies to date, with a total of 1410 participants, Smeeth et al. (2004) reported a 10-fold increase in the incidence of initial diagnoses of profound developmental disorders between 1988-1992 to 2000-2001 in a population from the United Kingdom. The increase was more evident in the wider spectrum of profound developmental disorders compared with the narrower 'core' autism, but again an increase in incidence rates was observable. In addition, data are available from Australia (2005, incidence rates 4.3-5.5/10,000), the United Kingdom (2000, incidence rates of 8.3/10,000), Denmark (Lauritsen et al. 2004, 8.6/10,000), and China (Wong, V. C. N. and Hui, S. L. H. 2007, 5.4/10,000). The current highest incidence rates were found in a Japanese population (27.2/10,000, Honda et al. 2005), and the lowest rates in Israel (0.65-0.84/10,000, Davidovitch et al. 2013). Barbaresi et al. (2005) found an incidence of 4.5/10,000 in a US population (age up to 21 years) as part of a retrospective, population-based study between 1976 and 1997. The research group then examined the incidence of autism spectrum disorders by clinically based diagnoses versus diagnoses by research criteria in the same population (Barbaresi et al. 2009). They found an incidence for clinically diagnosed autism spectrum disorders of 0.15/10,000 (0.0-0.37) between 1980-1983 and of 3.31 (2.28-4.33) between 1995-1997, corresponding to a 22-fold increase. In contrast, according to research-based criteria, the incidence increased from 0.55 (0.14-0.95)/10,000 to 4.49 (3.29-5.69)/10,000 during the same period, corresponding to an 8.2-fold increase. Furthermore, only 46.8% of cases identified by research criteria received a clinical diagnosis of autism spectrum disorder. Thus, case identification according to purely clinical criteria would have yielded, on the one hand, a significantly lower incidence during the

observation period, but at the same time a much steeper increase in incidence rates. These results demonstrate how misleading results of epidemiological studies can be interpreted if no research-based criteria are used for case identification. Whether the rising prevalence rates are due to an actual increase in the incidence of autistic disorders cannot be conclusively clarified due to the methodological prerequisites of individual incidence studies (Fombonne 2009).

A.3.2 Sex distribution and sex differences

A clear preponderance of males in autism spectrum disorders is a consistent finding of epidemiological studies. Previous studies show a male:female sex ratio of approximately 4:1, with the ratio becoming lower in the area of intellectual disability (Yeargin-Allsopp et al. 2003). Results from a meta-analysis of 40 prevalence studies that accounted for sex differences (Fombonne et al. 2011) showed male:female ratios ranging from 1.33:1-16:1 (average 4.4:1). Furthermore, a significant correlation was found between the proportion of participants with intelligence in the normal range and the male-to-female ratio (Spearman's rho: 0.53). This result is consistent with the known association between gender and intelligence in autistic disorders. Over time, the relationship between study publication year and the male/female participant quotient becomes progressively smaller (Spearman's r: 0.36). **Recent findings suggest a ratio of approximately 2-3:1 in favour of males, probably independent of cognitive performance** (Idring et al. 2012; Mattila et al. 2010; Baird et al. 2006). Some studies suggest that females are more likely to go undiagnosed (Baron-Cohen et al. 2011) and, especially in the high-functioning range, to be diagnosed later than males (Giarelli et al. 2010). Girls with autism spectrum disorders, moreover, appear to have to show more accompanying behavioral and cognitive problems to receive a clinical diagnosis for the same autism-specific symptom severity (Wiggins et al. 2014), which may indicate a diagnostic bias in favor of boys based on the known behavioral criteria or, alternatively, better adaptive skills and compensatory mechanisms in affected girls. There is a high rate of concomitant psychiatric disorders in both sexes. However, it is unclear whether female patients, for example, are particularly likely to first receive other diagnoses before an autism spectrum disorder is recognised in them.

In addition to hormonal and endocrinological causes (Baron-Cohen et al. 2011; Lai et al. 2015), protective factors in the female sex (FPE = female protective effect) are also discussed as causal factors for the gender differences. Results from analyses of the two largest twin cohort studies worldwide (Robinson et al. 2013) convincingly suggest that female sufferers must have a higher

familial and environmental burden in order to reach the diagnostic thresholds and that, in addition, relatives of female sufferers carry a higher risk for the disorder than relatives of male sufferers (see also Werling and Geschwind 2015).

A.3.3 Comorbid mental disorders and somatic diseases

Inge Kamp-Becker, Leonora Vllasaliu, Christine M. Freitag
Systematic literature search: Stephanie Hoss, Marie Landenberger
Literature selection and data extraction: Magdalena Schütz, Marianne Menze and Leonora Vllasaliu

9. are prevalence rates for autism spectrum disorders and comorbid conditions available and what are they?

A.3.3.1 Summary from the source guidelines

The NICE guideline for children included a total of 38 studies, all of which involved an uncontrolled observational design and were judged to be of low quality (Allik et al. 2006; Baghdadli et al. 2003a; Baghdadli et al. 2003b; Bertrand et al. 2001; Black 2002; Canitano et al. 2005; Canitano and Vivanti 2007; de Bruin, Esther I. et al. 2007; Depienne et al. 2009; Fombonne et al. 1997; Gadow and DeVincent 2005; Gail Williams et al. 2004; Goldstein and Schwebach 2004; Green et al. 2009; Hartley et al. 2008; Herring et al. 1999; Kamio 2002; Kielinen et al. 2004; Kim et al. 2000; Levy et al. 2010; Leyfer et al. 2006; Matson et al. 2009; Mattila et al. 2010; Mazefsky et al. 2010; Miano et al. 2007; Montiel-Nava and Pena 2008; Moore et al. 1998; Oliveira et al. 2005; Oslejsková et al. 2008; Page and Boucher 1998; Pondé et al. 2010; Ringman and Jankovic 2000; Shen et al. 2010; Simonoff et al. 2008; Ünal et al. 2009; Valicenti-McDermott et al. 2008; Weisbrot et al. 2005; Yasuhara 2010; Yeargin-Allsopp et al. 2003).

Pooled prevalence for comorbid disorders across studies is reported for early childhood autism and autism spectrum disorders.

From the NICE children's source guideline (diagnosis), the following prevalence figures were obtained for **autism** (95% confidence interval):

- mental and behavioural disorders
  - 62% Fear (not specified)
  - 49% self-injurious behaviour (not specified)
  - 41% Attention deficit hyperactivity disorder (ADHD) (21 - 63)
  - 37% Obsessive-compulsive disorder (not specified)
  - 13% Depression (not specified)

  - 7% oppositional behaviour disorder (not specified)
- Neuronal developmental disorders
  - 76% Intelligence impairment (61 - 89)
- medical-neurological disorders
  - 37% Sleep problems (11 - 68)
  - 24% Epilepsy (8 - 46)
  - 18% Seizures (not specified)
  - 13% motor problems (not specified)
  - 7% Visual impairment (0 - 26)
  - 5% cerebral palsy (4 - 6)
  - 3% Hearing impairment (0 - 9)
  - 3% gastrointestinal problems (not specified)

From the NICE children (diagnosis) source guideline, the following prevalence figures (95% confidence interval) were obtained for **autism spectrum disorders:**

- mental and behavioural disorders
  - 45% Attention deficit hyperactivity disorder (ADHD) (24 - 67)
  - 27% Anxiety (10 - 49)
  - 23% oppositional behavior disorder (6 - 47)
  - 19% Tic disorders (2 - 47)
  - 12% Tourette syndrome (2 - 28)
  - 8% Obsessive-compulsive disorder (2 - 17)
  - 9% Depression (3 - 19)
  - 3% Social behaviour disorder (0 - 9)
- Neuronal developmental disorders
  - 65% Intelligence impairment (38 - 87)
- medical-neurological disorders
  - 62% gastrointestinal problems (not specified)
  - 61% Sleep problems (31 - 88)
  - 25% motor problems (0 - 75)
  - 15% Epilepsy (7 - 26)
  - 8% Hearing impairment (1- 20)
  - 6% Visual impairment (0 - 21)

– 5% Seizures (2 - 69)

– 5% cerebral palsy (1 - 13)

In contrast to the NICE children's guidelines (diagnosis), the SIGN guidelines emphasise a case-control study (Black 2002), according to which children with autism do not suffer more frequently from gastrointestinal disorders before diagnosis than children without autism. However, after diagnosis, parents are more likely to report such symptoms (particularly vomiting and constipation). Parents are also more likely to report selective eating behaviors (Valicenti-McDermott et al. 2006). In addition, both guidelines indicate that children with autism spectrum disorder show no differences from children without autism spectrum disorder in attachment behaviors. However, a meta-analysis indicates that they are more likely to exhibit insecurely attached behaviors (Rutgers et al. 2004).

A.3.3.2 Update: Mental and somatic disorders

With regard to the update, a separate systematic search was carried out. To ensure a high representativeness of the figures, only data from population-based studies were considered. Accordingly, the included studies are all level 1 studies according to the CEBM classification. The results of these population-based studies, some of which have already been included in the NICE guidelines, are summarised in Tables 3-6 below. For financial and time reasons, no meta-analysis of the different studies was calculated. In addition to the population-based studies (N>50), other meta-analyses, review and original papers were considered for the comorbid mental disorders (see Baird et al. 2006; Centers for Disease Control and Prevention 2012; Centers for Disease Control Prevention 2014; Charman et al. 2011; Green et al. 2009; von Gontard et al. 2015b; Krakowiak et al. 2008; Levy et al. 2010; McDermott et al. 2005; Melville et al. 2008; Noterdaeme and Wriedt 2010; Schieve et al. 2010; Sharp et al. 2013; Simonoff et al. 2008; Sullivan et al. 2013; Totsika et al. 2011; Yeargin-Allsopp et al. 2003). For adulthood, other studies have also been added (see Buck et al. 2014; Hofvander et al. 2009; Joshi et al. 2013; Lugnegård et al. 2011; Melville et al. 2008; Stahlberg et al. 2004; Stoppelbein et al. 2006; Strunz et al. 2014a; Vannucchi et al. 2014). Additional studies were also included on the prevalence of somatic conditions. As the studies mentioned in the NICE guidelines predominantly refer to children and adolescents or were not differentiated in this respect, the prevalence data from the NICE children's guideline are also listed.

Table 3: Prevalence of comorbid developmental disorders in children and adolescents with autism spectrum disorder.

Developmental Disabilities	N/100 (=%) KiJu total spectrum	N	Reference	Prevalence Total population
Language development disorder	63.4* (n/a)	2568	Levy et al. 2010	5 – 8%
Reduced intelligence IQ< 70	76 (61 - 89) Autism 65 (38 - 87) ASS		NICE 2011	3%
	52 (42 - 62)*	89	Totsika et al. 2011	
	18.3* (n/a)	2568	Levy et al. 2010	
	55 % (53 – 73%)	158	Baird et al. 2006	
	68%	987	Yeargin-Allsopp et al. 2003	
	31% (18 – 37%)	3604	Centers for Disease Control Prevention 2014	
	38% (13 -54%)	3820	Centers for Disease Control and Prevention 2012	
	43% (n/a)	1129	Schieve et al. 2010	
Below average intelligence (IQ70 - 84)	16.6 (9.9 – 26.6)*	100	Charman et al. 2011	
	14 (n.d.)	601	Noterdaeme and Wriedt 2010	
	24% (n/a)	1129	Schieve et al. 2010	
Mild intelligence impairment (IQ 50-69)	39.4 (26.0–54.7)*	100	Charman et al. 2011	
	30 (n.d.)	601	Noterdaeme and Wriedt 2010	
Moderate intelligence impairment (IQ 35-49)	8.4 (3.6 – 18.4)*	100	Charman et al. 2011	
	20 (n/a)	601	Noterdaeme and Wriedt 2010	
Severe intelligence impairment (IQ<35)	7.4 (3.0 –1 7.1)*	100	Charman et al. 2011	
	10 (n.d.)	601	Noterdaeme and Wriedt 2010	

Continued Table 3: Prevalence of comorbid developmental disorders in children and adolescents with autism spectrum disorder.

Developmental Disabilities	N/100 (=%) KiJu total spectrum	N	Reference	Prevalence Total population
Motor development disorders	13 Autism 25 (0 - 75) ASS		NICE 2011	
	79.2 Autism	101	Green et al. 2009 [5]	
	9.1 Autism (mild) 3.2 Autism (moderate) 1.1 Autism (severe)	187	Kielinen et al. 2004 [6]	
	3.3 Autism 8.7 AS	3023	Williams et al. 2008a [7]	

[5] This study focuses on motor deficits and uses Henderson and Sugden's (1992) *Movement Assessment Battery for Children (M-ABC)* for assessment.
[6] The authors recorded walking difficulties spiecifically:
Mild = walks with support from one hand
Moderate = crawls, uses two walking sticks or a wheelchair.
Severe = bedridden (see p. 54)
[7] Authors called it "*specific motor function disorder and mixed developmental disorder.*"

Table 4: Prevalence of comorbid mental disorders in children and adolescents with autism spectrum disorder

Mental disorder	N/100 (95% confidence interval) KiJu total spectrum	N	Reference	Prevalence Total population
infancy and childhood				
Total comorbid mental disorders	70.8 (58.2 - 83.4)**	112	Simonoff et al. 2008	
ADHD	41 (21 - 63) Autism 15 (24 - 67) ASS		NICE 2011	5,0 (4,3–5,7) [1]
	28.2 (13.3 - 43.0)**	112	Simonoff et al. 2008	
	21.3* (n/a)	2568	Levy et al. 2010	
Anxiety Disorders	62 Autism 27 (10 - 49) ACE		NICE 2011	10,0 (8,7–11,6) [2]
	41.9 (26.8 - 57.0) **	112	Simonoff et al. 2008	
	3.4* (n/a)	2568	Levy et al. 2010	
Generalized anxiety disorder	13.4 (0 - 27.4)**	112	Simonoff et al. 2008#	0.653
Social anxiety disorder	29.2 (13.2 - 45.1)**	112	Simonoff et al. 2008	0.323
Panic Disorder	10.1 (0 - 24.8)**	112	Simonoff et al. 2008	
Anxiety Disorders				
Agoraphobia	7.9 (3.0 - 12.9)**	112	Simonoff et al. 2008	
Specific phobia	8.5 (2.8 - 14.1)**	112	Simonoff et al. 2008	1.[173]
Separation anxiety	0.5 (0 - 1.6)**	112	Simonoff et al. 2008	1.[173]
Emotional disorders (include anxiety and depressive disorders)	44.4 (30 - 59)**	112	Simonoff et al. 2008	
social disorders	3 (0 - 9) ASS		NICE 2011	7.6 (6,5–8,7) [2]
	0.2* (n/a)	2568	Levy et al. 2010	
	3.2** (0 – 7.1)	112	Simonoff et al. 2008	
Oppositional behaviour	7 (n/a) Autism 23 (6 - 47) ACE		NICE 2011	2.313
	28.1 (13.9 - 42.2)**	112	Simonoff et al. 2008	
	4* (n/a)	2568	Levy et al. 2010	

Continued Table 4: Prevalence of comorbid mental disorders in children and adolescents with autism spectrum disorder.

Mental disorder	N/100 (95% confidence interval) KiJu entire spectrum	N	Reference	Prevalence Total population
infancy and childhood				
Affective disorder in general	2.3* (n/a)	2568	Levy et al. 2010	
Depression	13 (n/a) Autism 9 (3 - 19) ASS		NICE 2011	
	1.1* (n/a)	2568	Levy et al. 2010	5,4 (4,3–6,6) [2]
	1.4 (0 - 3.0)**	112	Simonoff et al. 2008	
major depression	0.9 (0 -2.3)**	112	Simonoff et al. 2008	0.683
Dysthymia	0.5 (0 - 1.4)**	112	Simonoff et al. 2008	
Bipolar disorder	0.7* (n/a)	2568	Levy et al. 2010	1.5 (1.1-2.0) [4]
Tic disorder	19 (2 - 47) ACE		NICE 2011	
	9 (3.3 -14.6)**	112	Simonoff et al. 2008	0.073
	0.5*	2568	Levy et al. 2010	
Tourette's syndrome	12 (2 - 28) ACE		NICE 2011	
	4.8 (0.1 - 9.5)**	112	Simonoff et al. 2008	
Some form of incontinence	10.8 Normal population	718	von Gontard et al. 2015a	
Enuresis	11 (4 - 18)**	112	Simonoff et al. 2008	
Nightly	30.0 (n.a.) ASS 58.3 (n/a) Autism 26.7 (n.s.) Atypical 7.7 (n/a) Asperger's	25	von Gontard et al. 2015b	
	8.2 Normal population	718	von Gontard et al. 2015a	
Incontinence during the day	25.0 (n.s.) ASS 25.0 (n/a) Autism 40.0 (n/a) Atypical 7.7 (n/a) Asperger's		von Gontard et al. 2015b	
	1.5 Normal population	718	von Gontard et al. 2015a	
Encopresis	6.6 (2 - 11)**	112	Simonoff et al. 2008	
	12.5 (n/a) ASS 16.7 (n/a) Autism 20.0 (n/a) Atypical	25	Gontard et al. 2015b	
	1.1 Normal population	718	von Gontard et al. 2015a	

Continued Table 4: Prevalence of comorbid mental disorders in children and adolescents with autism spectrum disorder.

Mental disorder	N/100 (95% confidence interval)	N	Reference	Prevalence Total population
infancy and childhood				
Reactive Attachment Disorder	0.3* (n/a)	2568	Levy et al. 2010	
Mutism	0.5* (n/a)	2568	Levy et al. 2010	
Obsessive Compulsive Disorder	37 (n/a) Autism 8 (2 - 17) ASS		NICE 2011	
	2* (n/a)	2568	Levy et al. 2010	0.253
	8.2 (3.2 -13.1)**	112	Simonoff et al. 2008	
Trichotillomania	3.9 (0 - 10.3)**	112	Simonoff et al. 2008	
Self-injurious behaviour	49 (n/a) Autism		NICE 2011	
Psychoses	0.3* (n/a)	2568	Levy et al. 2010	
	2.8 (1.07 - 7.34)	5359	Sullivan et al. 2013	
Schizophrenia	0.1* (n/a)	2568	Levy et al. 2010	
	1.43	2393778	Kohane et al. 2012	

k. A. = not specified; #: already included in NICE guidelines
◦ Data are not based on clinical diagnoses, but only on records, school reports, etc.
* Point prevalence; ** 3-month prevalence; *** Lifetime
Autism = data for diagnosis of early childhood autism; ASD = data for diagnosis of autism spectrum disorder or all disorders of the spectrum.
For studies outside of the NICE children (diagnosis) guidelines, all prevalence data refer to the full autism spectrum.
[1](Schlack et al. 2014); [2](Ravens-Sieberer et al. 2007); [3](FORD et al. 2003); [4](Jacobi et al. 2014).

Table 5: Prevalence of comorbid mental disorders in adults with autism spectrum disorder.

Mental disorder	N/100 (95% confidence interval) Total Autism Spectrum	N	Reference	Prevalence Total population
Adults				
Anxiety Disorders	35.9* (n/a) 52.7*** (n/a)	129	Buck et al. 2014	15.3 (14.2-16.6) [3]
Depression	13***(n/a)	129	Buck et al. 2014	6.0 (5.2-6.8) [3]
Psychoses	5* (n/a) 13*** (n/a)	129	Buck et al. 2014	2.6 (2.1-3.2) [3]
Schizophrenia	8.8 (n/a)	2.393.778	Kohane et al. 2012	
Obsessive Compulsive Disorder	36*** (n/a)	129	Buck et al. 2014	3.6 (3.1-4.4) [4]
Adults with intelligence impairment				
Problem behaviour1	37.7/0 [2*] (n/a)	77	Melville et al. 2008	
ADHD	3.4/0 [2*] (n/a)	77	Melville et al. 2008	
Anxiety disorder without specific phobias	3.9/2.6 [2*] (n.a.)	77	Melville et al. 2008	
Affective disorder in general	5.2/3.9 [2*] (n/a)	77	Melville et al. 2008	
Depression	5.9*	51	McDermott et al. 2005	
Alcohol/substance abuse	0/0 [2*] (n/a)	77	Melville et al. 2008	
Personality Disorders	0/0 [2*] (n/a)	77	Melville et al. 2008	
Obsessive Compulsive Disorder	0/0 [2*] (n/a)	77	Melville et al. 2008	
Psychoses	1.3/0 [2*] (n/a)	77	Melville et al. 2008	
Eating disorder (without pica)	0/0 [2*] (n/a)	77	Melville et al. 2008	
Pica	5.2/1.3 [2*] (n/a)	77	Melville et al. 2008	

Continued Table 5: Prevalence of comorbid mental disorders in adults with autism spectrum disorder.

Mental disorder	N/100 (95% confidence interval) Total Autism Spectrum	N	Reference	Prevalence Total population
Adults without intelligence impairment				
Personality Disorders	62*** (n/a)	117	Hofvander et al. 2009	4.[44]
	Men: 65* (n.a.) Women: 32* (n.a.)	54	Lugnegård et al. 2012	Men: 5.4%, Women: 3.4%4
	Men: 56* (n.a.) Women: 36* (n.a.)	58	Strunz et al. 2014a	
Antisocial personality disorder	5* (n/a) 10*** (n/a)	63	Joshi et al. 2013	
Affective disorder	53*** (n/a)	122	(Hofvander et al. 2009)	9.3 (8.3 – 10.3) [3]
Depressive Episode	16 * (n. a.)	58	Strunz et al. 2014a	6.0 (5.2-6.8) [3]
	31* (n.a.) 77*** (n/a)	63	Joshi et al. 2013	
Dysthymia	9* (n/a)	58	Strunz et al. 2014a	2.0 (1.6-2.4) [3]
Bipolar disorder	10* (6 - 21.4)		Vannucchi et al. 2014	1.5 (1.1-2.0) [3]
	7* (n/a)	129	Stahlberg et al. 2004	
	6* (n/a) 25*** (n/a)	63	Joshi et al. 2013	
Anxiety Disorder	50*** (n/a)	119	Hofvander et al. 2009	15.3 (14.2-16.6) [3]
	38* (n/a) 59*** (n/a)	63	Joshi et al. 2013	
Social phobia	14* (n/a)	58	Strunz et al. 2014a	2.7 (2.2-3.4) [3]
	40* (n/a) 56*** (n/a)	63	Joshi et al. 2013	
Obsessive Compulsive Disorder	24*** (n/a)	122	Hofvander et al. 2009	3.6 (3.1-4.4) [3]
	2* (n/a)	58	Strunz et al. 2014a	
Tic Disorder	20*** (n/a)	122	Hofvander et al. 2009	
	6* (n/a) 11*** (n/a)	63	Joshi et al. 2013	
Tourette's	5* (n/a) 5*** (n/a)	63	Joshi et al. 2013	
Substance Abuse	16*** (n/a)	122	Hofvander et al. 2009	
	11* (n/a) 33*** (n/a)	63	Joshi et al. 2013	

Continued Table 5: Prevalence of comorbid mental disorders in adults with autism spectrum disorder.

Mental disorder	N/100 (95% confidence interval) Total Autism Spectrum	N	Reference	Prevalence Total population
Adults without intelligence impairment				
Psychotic disorder	12*** (n/a)	122	Hofvander et al. 2009	
	7.8 * (n/a)	129	Stahlberg et al. 2004	2.6 (2.1-3.2) [3]
	8* (n/a) 13*** (n/a)	63	Joshi et al. 2013	
Catatonia symptoms	17* (n/a)	Review	Stoppelbein et al. 2006	
Impulse Control Disorder	9*** (n/a)	122	Hofvander et al. 2009	
post-traumatic stress disorder	7* (n/a)	58	Strunz et al. 2014a	2.3 (1.8-2.8) [3]
	5* (n/a) 11*** (n/a)	63	Joshi et al. 2013	
Somatoform disorder	5*** (n/a)	119	Hofvander et al. 2009	3.5 (2.9-4.1) [3]
Eating Disorder	5*** (n/a)	119	Hofvander et al. 2009	0.9 (0.7-1.3) [3]

k. A. = not specified; #: already included in NICE guidelines ;
* Point prevalence; ** 3-month prevalence; *** Lifetime
[1] Problem behavior in this study includes verbally and also physically aggressive behavior; destructive behavior; self-injurious behavior; sexually inappropriate behavior; oppositional behavior; overly demanding behavior; agitated and other problem behavior.
[2] The first figure represents prevalence by clinical diagnosis and the second by ICD-10 diagnosis.
[3](Jacobi et al. 2014); [4](Coid 2006).

Table 6: Prevalence of comorbid somatic disorders in individuals with autism spectrum disorder.

Somatic disease	N/100 (95% confidence interval)	N	Reference	Prevalence Overall.
Epilepsy	24 (8 - 46) Autism 15 (7 - 26) ACE		NICE 2012	
	15.5 (n/a)	2568	Levy et al. 2010	
	38%* (n/a)	108	Danielsson et al. 2005	
	24.6%*	118	Mouridsen et al. 2011a	
	22.5%**	89	Mouridsen et al. 2011b	
	3.9% *** (n/a)	4130	Mouridsen et al. 2013b	
	19.4 (n/a) 19.2 (age 0 - 17) 21.4 (age 18 - 34)	2393778	Kohane et al. 2012	
	18.2* (n/a)	187	Kielinen et al. 2004	
	16.7* (n/a) 8.7 *** (n.a.)	30 23	Williams et al. 2008a	
	OR for autism spectrum disorder in adults with epilepsy 7.4 (1.5 -35.5)	7403	Rai et al. 2012a	1.2% (1.0-1.5).
	5% of the examined children with epilepsy show ASS	555	Berg et al. 2011	
infantile spasms	OR for ASA in early onset epilepsy: 5.53 (1.25 - 23.06).	95	Saemundsen et al. 2008	
Seizures in the first year of life (without infantile spasms)	7.1 % of the examined children had ASD	102	Saemundsen et al. 2007	
Continuous Spikes and Waves during slow Sleep (CSWS)	ASD was present in 8% of individuals with CSWS	25	Margari et al. 2012	
Sleep problems	37 (11 - 89) Autism 61 (31 - 88) ACE		NICE 2012	
	53.3 (n. d.)*	303	Krakowiak et al. 2008	
	1.25	2393778	Kohane et al. 2012	
Trouble falling asleep	24.4 (n/a)*	303	Krakowiak et al. 2008	
Often awake	33.8 (n/a)*	303	Krakowiak et al. 2008	
Waking up screaming	5.2 (n. d.)*	303	Krakowiak et al. 2008	
Nightmares	3.8 (n. d.)*	303	Krakowiak et al. 2008	

Continued Table 6: Prevalence of comorbid somatic disorders in individuals with autism spectrum disorders.

Somatic Disease	N/100 (95% confidence interval)	N	Reference	Prevalence total population
Cerebral Palsy	8 (4 - 6) Autism 5 (1 - 13) ACE		NICE 2012	3.3 (3.1-3.7) per 1000
	1.7 (n/a)	2568	Levy et al. 2010	
	4.3* (n/a)	187	Kielinen et al. 2004	
	5.0 (n/a)	617	Schendel et al. 2009	
	4.3 *** (n.a.)	23	Williams et al. 2008a	
	8% ASA in children with cerebral palsy	142.338	Kirby et al. 2011	
Neurofibromatosis	26% ASA in children with neurofibromatosis	82	Plasschaert et al. 2015	
Congenital deformities	6.7*,** (n.a.)	30; 15	Williams et al. 2008a	
Encephalopathy	5.9 (n/a)	2568	Levy et al. 2010	
	2.7* (n/a)	187	Kielinen et al. 2004	
Blindness / visual impairment / visual impairment	7 (0 - 26) Autism 6 (0 - 21) ASS		NICE 2012	
Blindness / visual impairment / visual impairment	19.3* (mild) (n.s.) 3.7 (blind) (n/a)	187	Kielinen et al. 2004	
	1.0 (n/a)	2568	Levy et al. 2010	
	11.7% ASD in blind children	257	Mukaddes et al. 2007	
Numbness	3 (0 - 9) Autism 8 (1 - 20) ASS		NICE 2012	
	7.0 *(mild) (n.s.) 1.6* (significant) (n.a.)	187	Kielinen et al. 2004	
	1.7 (n/a)	2568	Levy et al. 2010	
	6.7 ** (n.a.)	15	Williams et al. 2008a	
	1.5 (n/a)	617	Schendel et al. 2009	
Birth defect	6.4 (4.7 - 8.7) 5.0 (2.6 - 8.5) * 7.4 (5.0 - 10.6) (Autism & Intelligence Reduction)	617	Schendel et al. 2009	
Mitochondrial disease	7.2 (n/a)	69	Oliveira et al. 2005	
	5.0% (3.2 - 6.9%)	536	Rossignol and Frye 2011	

Continued Table 6: Prevalence of comorbid somatic disorders in individuals with autism spectrum disorder.

Somatic Disease	N/100 (95% confidence interval)	N	Reference	Prevalence Overall.
Gastrointestinal Malfunctions	3 Autism 62 ASS		NICE 2012	
	7.2 (n/a)	487	Maenner et al. 2012	
	Risk ratio 1.21* (0.93 - 1.57)	121	Ibrahim et al. 2009	
Constipation	Risk ratio 1.97* (1.25 - 3.10)		Ibrahim et al. 2009	
Dietary peculiarities/selective eating behaviour	Risk ratio 1.95* (1.18 - 3.24)		Ibrahim et al. 2009	
Hydrocephalus	3.2* (n/a)	187	Kielinen et al. 2004	
Microdeletion syndrome 22q11	0.9 (n/a)	2568	Levy et al. 2010#	
Down's syndrome	0.5 (n/a)	2568	Levy et al. 2010	
	3.7* (n/a)	187	Kielinen et al. 2004	
	0.9 (n/a)	2.393.778	Kohane et al. 2012	
	38.9% V.a. ASD in persons with Down syndrome (screening)	293	Ji et al. 2011	
	6.4* (2.6 - 11.6) 18.2 (9.7 - 26.8) V.a. ASD in children with Down syndrome (screening)	123	Di Guiseppi et al. 2010	
Fragile X Syndrome	0.3 (n/a)	2568	Levy et al. 2010	
	2.1* (n/a)	187	Kielinen et al. 2004	
	2.1* (n/a)	187	Kielinen et al. 2004	
	0.5 (n/a)	2.393.778	Kohane et al. 2012	
Klinefelter syndrome	37% V.a. ASS in persons with Klinefelter syndrome (screening)	51	Bruining et al. 2009	
Suspected genetic disorder	3.2* (n/a)	187	Kielinen et al. 2004	

Continued Table 6: Prevalence of comorbid somatic disorders in individuals with autism spectrum disorder.

Somatic Disease	N/100 (95% confidence interval)	N	Reference	Prevalence Overall.
Numerical chromosomal aberrations (predominantly sex chromosomes)	2.0* (n/a)	187	Kielinen et al. 2004	
Tuberous sclerosis	0.2 (n/a)	2568	Levy et al. 2010	
	0.8 (n/a)	2393778	Kohane et al. 2012	
Muscular dystrophy	0.47 (n/a)	2393778	Kohane et al. 2012	
Fetal Alcohol Syndrome	1.1* (n/a)	187	Kielinen et al. 2004	

k. A. = not specified
V.a. = Suspicion of
#: already included in NICE guidelines
*= Study population: individuals with early childhood autism.
**= Studied population: persons with atypical autism
***= Investigated population: persons with Asperger syndrome
Autism = data for diagnosis of early childhood autism
ASS= Indications for diagnosis of Autism Spectrum Disorder
[1]Steinsbekk et al. 2013

[2]	**Consensus statement** *Key question 9 - Mental and developmental disorders, somatic diseases*
KKP	Overall, developmental disorders related to language, motor skills and cognitive development (mental retardation) are the most common comorbid disorders and are present in more than half of those affected. Sleep disorders are significantly more common in young children diagnosed with autism spectrum disorder than in the general population. Hyperactivity is the most common comorbid symptom, with slightly less than one-third of children and adolescents with autism spectrum disorder meeting diagnostic criteria for simple activity and attention disorder or isolated attention deficit disorder. Emotional problems and anxiety disorders, as well as oppositional behavior, are the most common comorbid disorders in children and adolescents with autism spectrum disorders. In affected adults, the comorbid symptoms differ greatly depending on the presence of intelligence impairment. Here, a variety of behavioural disorders are reported, but usually no additional diagnosis is made. In adults without intelligence impairment, the prevalence rate of personality disorders is very high, but also affective disorders, anxiety disorders, ADHD, tic disorders, psychotic and other disorders are often comorbid. Among the physical diseases of all age groups, epilepsies are the most common, this is especially true for affected persons with a reduction in intelligence. But genetic syndromes and sensory impairments may also be present.
	Strong consensus (13 out of 13)

A.3.3 Delinquency

Inge Kamp-Becker, Leonora Vllasaliu
Literature research and selection as well as data extraction: Magdalena Schütz, Marianne Menze and Leonora Vllasaliu

63. is there an increased rate of delinquency in individuals with autism spectrum disorder?

An association between autism spectrum disorders and delinquency has been discussed in the media at times. The question of whether an increased rate of delinquency is found in individuals with autism spectrum disorders was therefore investigated. A systematic search on this topic revealed only a small amount of literature of sufficient quality. The present studies deal with the question of whether autism spectrum disorders or neuropsychiatric disorders are more frequent in certain delinquent groups.

A recent review (King and Murphy 2014) considered a total of 22 studies (1994 - 2012) that investigated whether the prevalence rate of autism spectrum disorders is increased among offenders (7 studies) and whether the rate of delinquent behavior is increased among individuals with autism spectrum disorder (6 studies). The authors emphasize the methodological shortcomings (small samples, different diagnostic systems, unclear diagnostic methods, information source bias, lack of control groups, and others) of the available studies. A prevalence rate for autism spectrum disorders of more than 1% was found in the studies, although the variance in the data was considerable (3 to 27%), which is explained by the different methods and data sources. The highest rate of delinquent behavior was found in individuals with Asperger syndrome, again with considerable variance in the data (2.74 to 26%). All studies that included a control group concluded that delinquent behavior was equal to or lower in the entire autism spectrum disorder group than in the control group without autism spectrum disorder. Lower rates of traffic and drug offenses were found in two studies. With regard to arson, the results were inconclusive, with some studies finding an increased rate with autism spectrum disorder. The question of whether delinquent individuals with autism spectrum disorder have increased rates of comorbid disorders was also inconclusive. Overall, the authors conclude that individuals with autism spectrum disorders are not disproportionately overrepresented in the justice system, although they may exhibit a range of delinquent behaviors. Two studies included in this review, each of which examined a control group, will be discussed in some detail by way of example.

- One study examined the question of how many youth with autism spectrum disorder (N = 609) came into contact with law enforcement. The type of crime as well as the outcome of law enforcement was compared to a group of 99 charged youth without autism spectrum disorder (Cheely et al. 2012). It was found that of the 609 youth, 5.24% (N = 32) had ever received a criminal charge. Their offending was characterised by significantly higher rates of violence directed at individuals in the course of altercations and also more public order offences and offences in the school context compared to the control group without autism spectrum disorder. Offenses in the school context were summarized as the following: Carrying a weapon while attending school, assault, battery, or threat to life against school employees or teachers. In contrast, significantly fewer property crimes and probation violations were found among youth with autism spectrum disorder. Furthermore, this study found that individuals with autism spectrum disorder were significantly more likely to have charges dismissed and more likely to have resocialization efforts initiated. The mean number of offenses per person was 3.3 in the group of youth with autism spectrum disorder, while it was 5.7 in the control group.

- In a Danish study (Mouridsen et al. 2008), 313 former patients diagnosed with autism spectrum disorder from two child and adolescent psychiatric units from 1960 to 1984 were followed up approximately 25 years later. The frequency of criminal behavior was compared with a matched control group from a Danish registry of the total population. Criminal behaviour was present in 29 individuals with autism spectrum disorder (9%), compared with 168 individuals in the matched control group (18%). Thus, a significantly reduced number of criminal acts (29/313 vs. 168/933, p = .0002) were found in individuals with autism spectrum disorder. However, comparisons between the "atypical autism" and "Asperger syndrome" groups and their respective control groups were not significantly lower. Traffic violations were found significantly more often in the control groups (p = .003), whereas no group differences were otherwise found in the atypical autism group. The rate of arson was increased in the group with Asperger syndrome (p = .0009). Although other areas (e.g., robbery, possession of weapons, sexual offenses, theft, vandalism, fraud, assault on property) showed somewhat increased prevalence rates, no significant difference was found when compared with the control group.

Below are a few more studies that were not included in the aforementioned reviews.

- A Swedish study examining the prevalence of autism spectrum disorders in a group of convicted offenders and juveniles in institutions/homes showed that among the juvenile offenders

there were a total of 17% with an autism spectrum disorder (5% with early childhood autism, 5% with Asperger syndrome, 7% with PDD-NOS) (Ståhlberg et al. 2010). In addition, 11 adolescents had comorbid ADHD.

- Among sex offenders diagnosed with autism spectrum disorder (N = 27), there was an increased rate of depression, past abuse, and neglect compared to the group of offenders without autism spectrum disorder (Bleil Walters et al. 2013). The risk of sexual offending was significantly increased among individuals with autism spectrum disorder if they had been physically abused (Mandell et al. 2005).

When interpreting the results presented, it must be borne in mind that persons within these institutions - forensic psychiatry, prisons or juvenile institutions - generally have a higher incidence of mental illness. Therefore, studies conducted in these institutions should be viewed with caution. It should also be noted that the majority of individuals with autism spectrum disorder have been diagnosed with PDD-NOS or atypical autism, the differentiation of which from other disorders is questionable (Mandy et al. 2011; Walker et al. 2004). Therefore, it remains unclear whether the prevalence data are as high according to the new DSM-5 criteria, which improve the specificity of the diagnosis. Overall, the existing studies indicate that individuals with autism spectrum disorder are overrepresented among offenders in conflict with the legal system (Woodbury-Smith and Dein 2014). However, existing studies are subject to many biases, and there are no population-based studies to date. Co-morbid disorders appear to potentially increase the risk of delinquency, but again the evidence is inconclusive. Also, only studies conducted in other countries are currently available, and it remains unclear whether these data can also be transferred to the German health care system. It seems central that the diagnosis of an autism spectrum disorder is also considered for persons who come into contact with the justice system, so that these persons can be treated in a disorder-specific manner. In order to prevent stigmatization, the results listed here should be handled with care.

[3]	**Consensus statement** *Bowl question 63 on delinquency*
KKP	Population-based studies on the question of increased delinquency in people with autism spectrum disorders are currently not available for Germany.
	Strong consensus (12 of 13, 1 abstention)

Table 7: Prevalence of Autism Spectrum Disorders in the Presence of Delinquency

Sample studied; age; country	N = ASS group	% Proportion of ASD persons with delinquency	Control sample	% KG*	Authors
Review work					
6 studies: 2053 persons in forensic psychiatry or special institutions for delinquent juveniles; Sweden	129	2.3 – 18% ~ 13% 10% atypical autism			Anckarsäter et al. 2008
6 studies: 9813 offenders from Sweden, England, Japan		3% to 27% ASA; 2.74 to 26% Asperger's syndrome; prevalence of ASD in criminal justice system > 1%.			King and Murphy 2014
100 juvenile offenders; 12 - 19 years; Sweden	5 autism, 5 AS, 7 PDD-NOS; 11 comorbid ADHD	17%	99		Ståhlberg et al. 2010
Former inpatients of child and adolescent psychiatry with a diagnosis of ASD; control group from total population; age at follow-up: 25-59 years; Denmark.	313 with ASS	9% for all ASS	933 matched controls from the total population	18% of the control group	Mouridsen et al. 2008
	113 autism	0.9%			
	86 atypical autism	8.1%	252	14.7	
	114 AS	18.4	342	19.6	
Young people who have been in contact with the justice system	609	5.24%	99		Cheely et al. 2012
43 juvenile sex offenders who participated in a treatment program; 15-20 years; U.S.	27 (elevated levels of depressive symptoms in self-report; elevated rates of abuse and neglect).		19		Bleil Walters et al. 2013

Notes: Autism = early childhood autism; ASD = autism spectrum disorder; AS = Asperger syndrome. *Percentage of control subjects with delinquency.

A.4 Course and prognosis

Ingo Spitczok von Brisinski, Luise Poustka, Ludger Tebartz van Elst, Christine M. Freitag
Systematic literature search: Leonora Vllasaliu

A.4.1 Introduction

This chapter presents an overview of how stable the diagnosis of an autism spectrum disorder is in terms of time into adulthood. A meta-analysis on the course and stability of early diagnosis before the age of two years and at preschool age between two and six years is presented in Chapter B.4 (Diagnostics) (Key Question 16), where consensus- and evidence-based recommendations on the best age of diagnosis as well as on follow-up examinations (see also B. 7) are also given. For this chapter, a systematic literature search was conducted to answer the key questions; however, due to time and financial constraints, the studies were not systematically evaluated or summarized in a meta-analysis.

32. how stable is the diagnosis of ASD over time?

57. what is the long-term course from childhood through adolescence into adulthood?

58. what factors (e.g. intelligence, severity, timing of diagnosis) determine psychosocial functioning levels during the course?

How often does a genuine deterioration of the clinical course (regression) occur?

A.4.2 Summary of information from source guidelines

NICE Children 2011

This guideline provides the following information on course and prognosis:

NICE children's chapter 5.17: Overview of evidence: stability of ICD-10 and DSM-IV-TR criteria

Available studies were grouped by age at initial diagnosis: 24 months or younger, 25-36 months, 37-48 months, and 49-60 months. Data were reported, when available, for autism, autism spectrum disorder, and no autism spectrum disorder, as these were the three options for children screened for autism spectrum disorder.

Thirteen studies were included in the systematic review. These studies were conducted in Canada, the Netherlands, the United Kingdom and the United States. All studies were uncontrolled observational studies and were judged to be of low quality.

In four studies, children received their first diagnosis at 24 months or earlier, and in nine studies between 25-36 months. No studies examined diagnoses between 37-48 or 49-60 months. DSM-IV-TR were used in nine studies to examine stability, while ICD-10 were examined in 5 studies.

NICE children's chapter 5.19 Evidence statement: stability of ICD-10 and DSM-IV-TR criteria.

Children under 24 months of age at initial assessment based on ICD-10/DSM-IV-TR.

All children, except for a single case (1%), diagnosed with an **autism diagnosis** according to ICD-10/DSM-IV-TR retained the initial diagnosis at the second assessment 12 months later. All children diagnosed with **another autism spectrum disorder** according to ICD-10/DSM-IV-TR retained this initial diagnosis at the second assessment 12 months later. However, 41% of children under 24 months of age with developmental disabilities who did not receive an autism spectrum diagnosis at initial assessment were diagnosed with an autism spectrum disorder at the second assessment 12 months later.

Children between 25 and 36 months at initial assessment according to ICD-10/DSM-IV-TR

The majority of children (95%) with an autism **diagnosis** according to ICD-10/DSM-IV-TR retained this initial diagnosis at second assessment 12 months later. The majority of children (84%) with an autism **spectrum diagnosis** according to ICD-10/DSM-IV-TR retained this initial diagnosis at second assessment at least 12 months later. No child without an autism spectrum diagnosis was diagnosed with an autism spectrum disorder at second assessment ≥12 months later.

Children between 37 and 48 months at initial assessment according to ICD-10/DSM-IV-TR

No studies were identified for this analysis.

Children between 49 and 60 months at initial assessment according to ICD-10/DSM-IV-TR

No studies were identified for this analysis.

NICE adults 2012

The guideline did not include information on course and prognosis.

SIGN Clinical Guideline "children and young people with autism spectrum disorders" 2007

The guideline did not include information on course and prognosis.

A.4.2.1 Comparison of recommendations/synopsis

No evidence-based statements about progression are made in the source guidelines.

A.4.2.2 Justification of deviations/modifications based on evidence

Since the present English-language guidelines do not list follow-up data up to adulthood and the included literature only comprises studies up to 2010, the studies were updated in the following (for preschool age see Chapter B.4) and studies on the long-term course up to adulthood were added.

A.4.3 Updating the evidence

Autism spectrum disorders are heterogeneous in terms of aetiology and phenotype, so that the stability of the symptoms and the long-term course can vary. Nevertheless, there are now a number of meaningful long-term studies of higher quality that allow empirically proven statements about the course and individual predictors of the course.

A.4.3.1 Childhood and adolescence

In children with autism spectrum disorders, a lack of social and play interest in particular can sometimes be observed as early as the first year of life. In the majority of affected children, however, the symptoms appear after the first year of life (2b, Maestro et al. 2005). Approximately one third of all children with autism spectrum disorder experience a loss of previously acquired language, social, and/or other skills in the second year of life (1a, Barger et al. 2013).

Of children diagnosed with autism spectrum disorder at age 2 in the United States or Canada, 5 to 37.5% no longer met diagnostic criteria for autism spectrum disorder by age 4 (1b, Kleinman et al. 2008; 2b, Turner and Stone 2007). However, the stability of diagnosis does not appear to be the same across all autism spectrum subtypes (see Section B.4.6.3 - Meta-analysis and Outcome). Factors that appear to contribute to instability of diagnosis are weaker symptoms at diagnosis, particularly in terms of social interaction, and higher intellectual ability (Turner and Stone 2007). Similar factors are described as predictors of improvements in symptomatology over time in two-year-old children with autism spectrum disorders (Charman et al. 2003; Lord 1995). In children for whom the diagnosis of autism spectrum disorder cannot be maintained over the course, other persistent developmental delays are often found.

Within early childhood autism, there is considerable variability in the development of communicative and social skills. For example, Fountain et al. (2b, 2012) describe 6 different developmental curves for communication, social interaction, and repetitive behavior for children aged 3 to 14 years, modeled from the data of 6,975 children born between 1992 and 2001 with a diagnosis of early childhood autism who had been examined at least four times at intervals of one year. Of these, five developmental trajectories regarding communication and social interaction, beginning at different levels of impairment, proceeded more or less in parallel towards improvement. With regard to long-term development, there was a clear heterogeneity. Cognitively more developed children at initial diagnosis showed a faster and more marked improvement compared to children who additionally showed a marked developmental delay. An exception was a subgroup of children (so-called "Bloomers") who started at a very low level of functioning, especially in social interaction and communication, and then showed a steep increase in improvement up to the age of 12 years into the range of high functioning, only to decline again somewhat by the age of 14 years. Children from the group of "Bloomers" with particularly steep developmental trajectories in terms of improvement in social interaction and communication were distinguished from the other groups by good cognitive abilities and a higher level of education of their mothers. In addition, one subgroup showed a significant deterioration in their repetitive behaviour.

In a study comparing the course of Asperger's syndrome and high-functioning autism (i.e., a diagnosis of early childhood autism with IQ > 70), children aged 4-6 years at baseline (1b, Starr et al. 2003) showed after 2 years that children with Asperger's syndrome had fewer symptoms of social interaction and stereotypic and repetitive behaviors in both examinations. However, communication improved only in children with high-functioning autism and social interaction deteriorated equally in children with autism and Asperger's syndrome. There was no improvement in repetitive activities in either diagnostic group. This study indicates a very similar course of Asperger's syndrome and high-functioning autism, which has also been found in long-term follow-up studies into adulthood (Howlin 2003; Howlin et al. 2000; Mawhood et al. 2000).

In their systematic review, Woolfenden et al. (1a, 2012) describe 23 cohort follow-up studies with a total of 1,466 participants with diagnoses of early childhood autism, Asperger syndrome, atypical autism, or pervasive developmental disorder, respectively. Diagnosis was required to have been established by a standardized diagnostic instrument or diagnostic criteria including DSM III/IV/IV TR or ICD-9/10 at both baseline and follow-up. The interval between examinations had to be at least 12 months. In this study, depending on the exact age as well as follow-

up period, 53% [95%-CI 38-67] to 100% [95%-CI 82-100] of children with an initial diagnosis of early childhood autism aged 0-3 years still met criteria for early childhood autism at the follow-up examination after an average of 3.7 years. Up to 30% of children were assigned to another form of autism spectrum disorder, with the remainder no longer receiving an autism spectrum diagnosis. Diagnoses from the age of 3 (with a further slight increase from the age of 5) already showed a significantly higher stability. The stability of diagnoses from the spectrum was significantly lower than the stability of an early childhood autism diagnosis (highest quality studies: 88-89% for stability of an autism diagnosis). For early childhood autism, it was particularly children with cognitive impairment who were diagnosed with early childhood autism in preschool and not later. In addition, a total of 5 of the included studies had used early interventions that the children studied had received during the observation period as possible predictors of diagnosis stability and found no difference in this respect for children with and without a stable diagnosis.

Fein et al. (2013) describe in a case series 34 individuals aged 8 to 21 years who had a history of autism spectrum disorder with language developmental delay in the sense of early childhood autism in the high-functioning range diagnosed by experienced professionals, but at the time of the review according to DSM-IV-TR criteria no differences were found between them and children and adolescents without autism spectrum disorder. In this study, however, it must be mentioned that it is a highly selective sample, in which the diagnosis at the time of the initial examination was not standardized, which is why no further conclusions can currently be drawn from the study.

Whether the improvements in symptomatology observed in some of the children in the long-term course are due to maturation, interventions and/or other factors cannot be decided on the basis of the current data situation. Kanner (1973) reported a relatively favorable course in about 10% of the children he diagnosed with "autism" despite a largely lack of specific interventions. Similarly, Darrou et al. (2b, 2010) found no association between course and amount of intervention in hours per week in 208 children diagnosed with profound developmental disorder according to ICD-10 (early childhood autism, atypical autism, and Asperger syndrome) at a follow-up 3 years later. The type of intervention was nonspecific but had to have been delivered by experienced therapists for longer than 3 months. However, the influence of the type of intervention was not investigated.

With regard to gender, comorbid disorders, socioeconomic status, educational level of parents or guardians or other demographic data, no clear statement can be made on the influence on the

course based on previous studies, whereby many of these factors have not yet been sufficiently investigated. However, it is clear that children with early childhood autism and existing intelligence impairment show a rather stable symptom pattern in the short-term course and can hardly live independently even in the long-term course into adulthood, but usually live in appropriate institutions for the disabled or with parents/relatives in Western countries and have a clear need for support (Howlin et al. 2000; Howlin et al. 2004; Mordre et al. 2012). In contrast, children with better cognitive skills at initial diagnosis have a much more favourable, but still variable, prognosis (2004; Lord and Bailey 2002).

A.4.3.2 Adulthood

There are some studies on the long-term course of early childhood autism and Asperger syndrome into adulthood. Studies on atypical autism according to ICD-9/10 or profound developmental disorders (PDD-NOS according to DSM-IV TR/DSM-IIIR) are not available. Results from systematic reviews and cohort studies are summarized in Table 8 (next page). Overall, a homogeneous picture emerges. The symptomatology in the sense of an autism spectrum disorder is qualitatively present from the time of initial examination over 5 years in a relatively stable manner until old adulthood. In Asperger's syndrome, the general prognosis is often better than in early childhood autism. The quantitative extent of the symptoms depends on successful adaptation strategies as well as centrally on the cognitive skills, especially the non-verbal IQ. Even with occupational success, most affected individuals are dependent on social support from families or institutions. Studies on the long-term course of patients who were first diagnosed in adulthood are not yet available. In this group, there are significantly more patients with average or even above-average IQ and often successful compensatory strategies and resources.

Table 8: Follow-up studies into adulthood

Quote	Subject	Sample	Target figure	Main result
Schonauer et al. 2001	Review, - presumably - systematic (methodology of the search is not described, however)	1,020 adults with predominantly early childhood autism and Asperger syndrome or high-functioning autism. Average age at initial diagnosis 6.2 years, average age at follow-up 24 years.	Long-term course with regard to core symptomatology, living and working situation, IQ, language competence, social competence, partnership, maladaptive behaviour, sexual behaviour, mortality	Qualitative stability of core autistic symptomatology. Gains in competence and autonomy more in work life than in the home. Asperger's syndrome has a slightly better course than autism. Cumulative death rates from catamnesis studies suggest increased mortality in individuals with autism spectrum disorder.
Rumsey et al. 1985	Retrospective cohort study	14 adults (18-39 years) with early childhood autism. N = 9 with IQ 82 - 126 and good language skills ("high functioning subgroup"). N = 2 with IQ 48 - 77 "lower functioning group; N = 3 with IQ 88 - 129 with language disorders.	Long-term outcome of autistic symptoms and other psychiatric diagnoses	All subjects had social impairments as well as other behavioral problems. Stereotypic movements and concrete thinking occurred - particularly frequently. None of the subjects showed positive schizophrenic symptoms or other DSM-III diagnoses of adulthood.
Howlin et al. 2004	Cohort study	Follow-up included 68 adults (mean age 29 years, range 21-48 years) who met criteria for autism in childhood (mean age 7 years, range 3-15 years) and had a nonverbal IQ > 50.	Standardised IQ, language and literacy tests as well as Autism Diagnostic Interview-revised (ADI-R)	The majority continued to rely on support systems. Only a few lived alone, had close friends or permanent work. Communication continued to be generally impaired. Reading skills low. Stereotypical behaviors or interests often persisted. 10 subjects had developed epilepsy. IQ >70 (45 of 68) in childhood was correlated with significantly better outcome. Within the group with average IQ, the course was highly variable.

Continued Table 8: Follow-up studies into adulthood

Quote	Subject	Sample	Target figure	Main result
Howlin et al. 2000	Non-systematic review	>350 "more able individuals within the autistic spectrum" (children and adults)	Long-term course of cognitive, language, academic and adaptive functioning, educational and occupational career, independence and social relationships, behavioural and psychiatric problems, variables correlating with course.	Even professionally successful people often relied considerably on their families to find work and housing. Social contacts often centered around special interests and skills. Close spontaneous friendships hardly developed. Subjectively, there was a constant pressure to adapt to the demands of society, which was experienced as stress and anxiety-producing and sometimes also led to a psychiatric crisis.
Howlin 1997	Non-systematic review	N > 100. long-term course of children and -adolescents with ASD into adulthood.	Composite rating Long term	There is little evidence for any "cure" for autism, but appropriate support programmes in early life can significantly help to improve functioning in later life.
Danielsson et al. 2005	Population-based cohort study	108 (77 male, 31 female, mean age 25.5 years, range 17-40 years) of initially 120 adults with autism spectrum disorders diagnosed in childhood -(N = 78 autism, N = 42 autistic-like condition) were followed up (follow-up after 13-22 years), 43 of them with epilepsy.	IQ, adaptive functions, epilepsy type	119 of 120 subjects (N = 92 autism, N = 15 autistic-like condition) still met DSM-III-R criteria for autism or autistic-like condition (4 or more criteria for autism). 71% had an IQ <50, only 4% had an IQ >69. 38% had epilepsy at some time (55% of them focal with or without secondary generalization).
Billstedt et al. 2007	Longitudinal, prospective, community-based follow-up cohort study	105 adults diagnosed with early childhood or atypical autism in childhood. Follow-up was 13-22 years later (mean 17.8 +/- 3.6 years). The mean age at follow-up was 25.5 +/- 6.4 years, range 17-40 years).	Diagnostic Interview for Social and Communication disorders (DISCO), IQ, occurrence of -communicative language before the age of 5 years.	Problems in social interaction persisted in most cases, but behavioural problems varied greatly in extent. Perceptual problems were reported to persist in almost all of them. Language before age 5, IQ, gender, somatic disease, and occurrence of epilepsy before age 5 correlated with autistic symptomatology.

A.5 Risk factors

Kai Vogeley, Helmut Hollmann, Ulrich Hagenah, Judith Sinzig, Christine M. Freitag
Literature research: Stephanie Hoss and Marie Landenberger

10. what are the scientifically justifiable causes of autism spectrum disorders and their psychiatric and neurological comorbidities?

11. what are the risk factors?

Key question 10 was only answered summarily based on a hand search by the authors involved, as no presentation of the current state of science regarding the possible causes of autism spectrum disorders can be made within the framework of clinical guidelines. The selection of studies to answer key question 11 was based on the search strategy conducted for the risk factors (see Methods Report); it yielded 81 studies. All literature reviews were carefully screened and then included in this review if an odds ratio (OR) outcome could be reported and if the OR was at least 1.25 and the lower limit of the confidence interval (CI) was at least 1.0. After applying these criteria, 32 studies could be included. However, due to time and financial constraints, the studies were not systematically evaluated or combined in a meta-analysis. Since a standardized search for population-based studies was performed here and the data were extracted and presented, a synopsis of the source guidelines was not performed.

A.5.1 Scientifically justifiable causes of autism spectrum disorders

It must be stated at the outset that research into autistic disorders is still far from being able to identify with certainty a single cause or a bundle of causes that produce autistic disorders. Well scientifically proven causes are **genetic risk factors as** well as **early acting environmental risk factors, especially in the context of pregnancy**. These are elaborated below. The exact neurobiological mechanisms of the increase in risk have not yet been researched, but it has been demonstrated in numerous studies that neuronal development and especially neuronal differentiation are altered in autism spectrum disorders. This is also the probable basis of the linguistic, cognitive and perceptual peculiarities in autism spectrum disorders, for which reference is made to further literature (Freitag 2008; Remschmidt and Kamp-Becker 2006; Sinzig 2011; Vogeley 2012; Tebartz van Elst 2013).

[4]	Consensus statement
KKP	Autism spectrum disorders have not yet been conclusively researched causally. However, it can be safely assumed that early biologically effective risk factors influence the development of the nervous system and thus lead to the autism-specific behaviors and neuro-cognitive skills. Psychosocial factors are particularly relevant with regard to the promotion and management of autism-specific behaviours and may have an influence on the course of the disorder.
	Strong consensus (12 out of 12)

A.5.2 Genetic risk factors

Numerous different genetic risk factors have been found in autism spectrum disorders, some of which were inherited from the parents and some of which arose newly through germline mutation. The heritability of autism spectrum disorders is approximately 40-80% based on recent twin and family studies (Frazier et al. 2014; Freitag 2011; Hallmayer et al. 2011; Lichtenstein et al. 2010; Ronald and Hoekstra 2011; Sandin et al. 2014). European studies show increased heritability compared to US studies, which can probably be attributed to different diagnostic criteria (Hansen et al. 2015) as well as different environmental exposures in the respective populations (Kim and Leventhal 2015). With regard to the genetic risk factors for autism spectrum disorders, we speak of so-called genetic heterogeneity, i.e. there are numerous different genetic risk factors that can lead to autism spectrum disorders.

The **global recurrence risk** for parents of a child with autism spectrum disorder to have another child with autism spectrum disorder is between 10-20% (Ozonoff et al. 2011a; Sandin et al. 2014). If two children already have the diagnosis, the risk of recurrence is > 30% . There is ample evidence that this knowledge has since spread to Western countries, resulting in families who already have a child with an autism spectrum disorder not having any more children (Hoffmann et al. 2014; Wood et al. 2015). This global risk of recurrence must be distinguished from the **specific risk of recurrence**, which can be calculated once the underlying genetic risk factor has been elucidated in a child with autism spectrum disorder. Thus, the specific recurrence risk may be significantly lower than the global recurrence risk, e.g., if the affected child carries a dominant-effective new mutation (e.g., TSC1/TSC2; see below) or a de novo microdeletion or duplication (approximately 1%), or significantly higher if, for example, an inherited fragile X syndrome has been detected (50% in boys).

The following genetic risk factors for autism spectrum disorders are described in the literature: inherited or newly emerged mutations in single genes (so-called "monogenic" forms) or also in several genes simultaneously, inherited or newly emerged microdeletions or microduplications of single or several genes, mostly newly emerged chromosomal aberrations and predominantly inherited common variants. These forms have different significance for understanding heritability as well as for clinical diagnosis. Common **variants** explain a large part of the heritability as well as the global recurrence risk (Gaugler et al. 2014), but are currently not applicable for diagnostics. This is due to the small increase in risk caused by the single variant, the population-specific distribution of allele frequencies, and the genetic heterogeneity of the disease. It can be assumed that in different populations a different combination of common variants increases the risk for autism spectrum disorder. If none of the risk factors mentioned below were found in a human genetic examination and a high-functioning autism spectrum disorder is present, it is likely that, in addition to possible pregnancy-associated environmental risk factors, these common variants in particular are causative for the disorder.

Monogenic disorders, micro-deletions and -duplications as well as chromosomal alterations, on the other hand, are risk factors, the presence of which should be taken into account for possible symptoms of an autism spectrum disorder in order to initiate early diagnosis and therapy. Similarly, the findings are relevant for genetic counseling of families. In the case of some genetic diagnoses, the need for further examinations also follows, such as, for example, in the case of Prader-Willi syndrome, the examination of growth hormone administration (Deal et al. 2013) or in the case of Klinefelter syndrome, therapy with testosterone (Nieschlag 2013).

Population-based studies on the rate of genetic syndromes in children with autism spectrum disorder or on the rate of autism spectrum disorders in children with a specific genetic syndrome have been scarce. However, based on clinical samples, an association of certain monogenic disorders and microdeletion as well as duplication syndromes with autism spectrum disorders can be hypothesized (Persico and Napolioni 2013). Depending on whether these were inherited from the birth parents or are new to the affected individual, the risk of recurrence varies greatly, which is relevant for genetic counseling. Current and future sequencing studies will describe numerous other monogenic disorders that are possible causes of autism spectrum disorders in the near future. Since the findings are still very heterogeneous, these new findings are not listed here. The following summary table (Table 9) draws information from the following recently published review articles (Brandler and Sebat 2015; Carter and Scherer 2013; Geschwind 2011; Murdoch and State 2013; Persico and Napolioni 2013) to list the well-documented monogenic

forms as well as relevant microdeletion and duplication syndromes associated with increased rates of autism spectrum disorders. The following criteria were chosen: The prevalence of the genetic finding must be either 1% in autism spectrum disorder or, in the case of rare genetic disorders, at least 50-fold more common in autism spectrum disorder than in the general population, and the carriers of the genetic finding must also show autism spectrum disorder in at least 5% of cases.

Table 9: Common monogenetic and chromosomal findings in autism spectrum disorder

	Name of the genetic disease	Gene/s	Prevalence in ASA	Prevalence of ASA among carriers
Monogen	Fragile X Syndrome	FMR1	approx. 2-5%	approx. 30-60%
	Tuberous brain sclerosis	TSC1/TSC2	approx. 1-4% with epilepsy: 8-14%	approx. 25-60%
	Rett syndrome (girl)	MECP2	approx. 1%	approx. 80 -100
	Adenylosuccinate lyase deficiency	ADSL	< 1%	approx. 80 - 100%
	Cornelia de Lange Syndrome	Unknown	< 1%	approx. 45 -70%
	Smith-Lemli-Opitz Syndrome	DHCR7	< 1%	approx. 50%
	untreated phenylketonuria	PAH	very rare.	approx. 6%
	Cohen's syndrome	Unknown	< 1%	approx. 50%
	Lujan-Fryns Syndrome	UPF3B, MED12	< 1%	approx. 63%
Micro-deletions	2q37.3	HDAC4 and others	< 1%	approx. 35%
	Angelman syndrome maternal 15q11.2-3	UBE3A and others	< 1%	approx. 50 - 80%
	Prader-Willi syndrome paternal 15q11-q13	SNRPN, GABRB3, CYFIP1 and others	< 1%	ca.20 - 40%
	Hypomelanosis Ito Mosaic deletion 15q11-q13	SNRPN, GABRB3, CYFIP1 and others	< 1%	approx. 10%
	16p11.2	MAPK3, MVP, KCTD13 and others	< 1%	approx. 30-50%
	Smith Magenis Syndrome 17p11.2		< 1%	approx. 90%
	Velocardiofacial syndrome 22q11.2	COMT, unknown	< 1%	approx. 20-50%
	Phelan-McDermid syndrome 22q13.3	SHANK3	< 1%	approx. 50 - 70%
Micro-duplications	7q11.23		< 1%	approx. 40 - 90%
	15q11.2-13.1 (duplication and triplication possible)	SNRPN, GABRB3, and others	approx.1%	approx. 10%
	15q13.2-13.3	CHRNA7 and others	< 1%	ca.10-20%
Chromosomen-aberration	Klinefelter syndrome (XXY) XYY		approx. 1%	approx. 5-10% approx. 20%

A.5.3 Demographic risk factors

Several studies examine the **age of the parents at the time of birth** as a risk factor. Most studies differentiate between the age of the mother and the age of the father. A total of four studies could be found that identify the age of the mother as a risk factor. An overarching presentation is difficult because the authors stratified differently. In any case, the risk increases with increasing age of the mother from 30 to 34 years up to the highest risk in mothers with an age of more than 40 years. The mediating factor is probably spontaneous mutations and epigenetic changes. A single paper also describes comparatively young maternal age, younger than 25, as a risk. Also uniquely mentioned is the age of the maternal grandmother at the time of birth of the mother of the child affected by autism spectrum disorder (OR: 1.66; CI: 1.16 - 2.37; Golding et al. 2010).

Table 10: Risk factor age of mother

Age of mother (reference value)	OR	AI	Reference
< 25 (25 - 29)	1,40	1,10 - 1,90	Maimburg and Vaeth 2006
30 - 34 (25 - 29)	1,30	1,10 - 1,70	Maimburg and Vaeth 2006
≥ 35 (< 35)	1,80	1,30 - 1,60	Williams et al. 2008b
> 35 (25 - 29)	1,60	1,10 - 2,00	Maimburg and Vaeth 2006
> 40 (15 - 29)	9,68	3,51 - 26,67	Reichenberg et al. 2006
> 40 (25 - 29)	2,60	1,20 - 5,50	Haglund. and Kallen 2011

Similarly, the age of the father at birth is identified as a risk factor, here again differentiated by age groups and stratified differently in different studies. Here, too, it becomes clear that the risk for children with autism spectrum disorders increases with the age of the father up to an approximately tenfold increased risk for fathers older than 50 years compared to fathers younger than 25 years. It can be assumed that with higher age the rate of spontaneous mutations and chromosomal changes increases significantly and the repair mechanisms become less; this seems to be even more pronounced in fathers than in mothers.

Table 11: Risk factor age of father

Age of the father	OR	AI	Reference
26 - 30 (≤ 25)	1,40	1,10 - 1,70	Daniels et al. 2008
30 - 34 (25 - 29)	1,30	1,10 - 1,70	Maimburg and Vaeth 2006
30 - 39 (15 - 29)	1,64	1,08 - 2,50	Reichenberg et al. 2006
31 - 35 (≤ 25)	1,70	1,30 - 2,10	Daniels et al. 2008
> 35 (25 - 29)	1,30	1,00 - 1,80	Maimburg and Vaeth 2006
36 - 40 (≤ 25)	1,80	1,40 - 2,40	Daniels et al. 2008
40 - 49 (15 - 29)	5,65	2,98 - 10,71	Reichenberg et al. 2006
41 - 50 (≤ 25)	1,90	1,40 - 2,50	Daniels et al. 2008
> 41 (no reference values)	1,46	1,00 - 2,12	(Eriksson et al. 2012)
> 50 (≤ 25)	2,70	1,50 - 4,80	Daniels et al. 2008
> 50 (15 - 29)	9,39	1,28 - 68,94	Reichenberg et al. 2006

Another interesting influencing factor seems to be the **immigration history of** the parents. It turns out that the immigration of parents who give birth to their child in a country that is not their own home country can also increase the risk for autism spectrum disorders. The significance of this finding or the risk factors (biological and psychosocial) that may directly mediate it have not been further elucidated.

Table 12: Migration background of parents

Migration background Comparison: without migration background	OR	AI	Reference
Mother	3,00	1,70 - 5,20	Hultman et al. 2011
Mother	2,70	2,00 - 3,70	Haglund and Kallen 2011
Mother	1,70	1,30 - 2,50	Maimburg and Vaeth 2006
Mother	1,86	1,15 - 2,29	Hultman et al. 2011
Mother	1,50	1,10 - 2,10	Williams et al. 2008b
Father	1,89	1,54 - 2,31	Hultman et al. 2011
Parents	1,50	1,30 - 1,70	Magnusson et al. 2012

In addition, the **socio-economic status of** parents or guardians also appears to increase the risk for autism spectrum disorders. This was demonstrated in two studies that showed an increased risk in children of comparatively less educated fathers who had experienced less than 9 years of schooling (OR: 1.34; CI: 1.02-1.75; Hultman et al. 2011) and in children of families with poor socio-economic status (OR: 1.40; CI: 1.30 - 1.60; Rai et al. 2012b).

A.5.4 Previous illnesses of the parents as risk factors

The parents' previous illnesses also play a role, with somatic and psychiatric illnesses predominantly affecting the mother.

Table 13: Somatic previous illnesses of the parents

Illness of the parents	OR	AI	Reference
Allergies (Mother)	1,50	1,10 - 1,90	Croen et al. 2005
Asthma (mother)	1,60	1,20 - 2,10	Croen et al. 2005
Type I diabetes (mother)	2,90	1,00 - 8,80	Croen et al. 2005
Psoriasis (mother)	2,90	1,40 - 6,10	Croen et al. 2005
Autoimmune diseases (mother)	1,60	1,10 - 2,20	Keil et al. 2010
Metabolic Erkrg (Mother)	1,61	1,10 - 2,37	Krakowiak et al. 2012
Type I diabetes (father)	4,90	1,40 - 17,90	Mouridsen et al. 2007
Autoimmune diseases (father)	1,40	1,00 - 2,00	Keil et al. 2010

In one study, the DR4 allele of the Human Leucocyte Antigen (HLA) was found to be significantly elevated in families from a specific geographic region (Tennessee) in which a male relative was affected by an autism spectrum disorder, in contrast to affected families from a wider area and unaffected families (OR: 5.54; CI: 1.74 - 18.67; Lee et al. 2006). This may indicate that the interaction of the immune systems of mother and child within a geographically defined environment may also influence brain development.

Of course, neurological or psychiatric pre-existing conditions of the parents, again especially of the mother, including the corresponding medication, play a special role.

Table 14: Neurological or psychiatric previous illnesses of parents

Illness of the parents	OR	AI	Reference
Focal epilepsy of the mother	4,77	1,42 - 15,94	(Bromley et al. 2013)
Psychiatric condition of one of the parents	1,70	1,50 - 2,00	Daniels et al. 2008
Psychiatric disorders of both parents	2,00	1,20 - 3,10	Daniels et al. 2008
Depression mother	1,70	1,00 - 2,60	Daniels et al. 2008
Depression mother	1,61	1,17 - 2,23	Rai et al. 2013
Other non-psychotic illness of the mother	1,70	1,30 - 2,20	Daniels et al. 2008
Psychiatric stay mother	2,11	1,70 - 2,63	Hultman et al. 2011
Psychiatric stay father	1,58	1,27 - 1,98	Hultman et al. 2011
Critical life events mother (until the child is 3 years old)	1,56	1,10 - 2,20	Rai et al. 2012b

A.5.5 Pregnancy-associated risk factors

It is known from longitudinal studies that rubella infections during pregnancy are associated with an increased rate of autism spectrum disorders (Chess 1971, 1977; Chess et al. 1978). In

addition, the use of antiepileptic drugs in particular (most notably including valproate) increase the risk of autism spectrum disorder in the child. Diabetes mellitus in the mother before and during pregnancy was also described as a risk factor in a meta-analysis (Xu et al. 2014).

Table 15: Use of medication by the mother during pregnancy

	OR	AI	Reference
Antidepressants mother	3,69	1,68 - 8,10	Rai et al. 2013
Antidepressants mother	2,10	1,20 - 3,60	Croen 2011
SSRI mother	4,50	2,19 - 9,05	Eriksson et al. 2012
SSRI mother	2,70	1,40 - 5,40	Croen 2011
Valproate monotherapy	7,16	1,65 - 24,53	Bromley et al. 2013
Valproate (with other medications)	9,26	1,82 - 49,40	Bromley et al. 2013
Antiepileptic drugs mother (not valproate, carbamazepine, lamotrigine)	8,75	1,09 - 49,40	Bromley et al. 2013
Other psychoactive substances	1,60	1,10 - 2,50	Maimburg and Vaeth 2006
Other psychoactive substances	4,40	2,50 - 8,00	Eriksson et al. 2012
Other drugs	1,50	1,10 - 2,10	Eriksson et al. 2012

In addition, studies have recently been conducted on particulate matter exposure of the mother during pregnancy. The risk of autism spectrum disorder in the child increased if the mother lived in the third trimester (OR: 2.22; CI: 1.16 - 4.42; Volk et al. 2011) or close to a highway at the time of birth (OR: 1.86; CI: 1.04 - 3.45; Volk et al. 2011). A more detailed analysis showed that particles smaller than 2.5 m (OR: 2.14; CI: 1.48 - 3.09; Volk et al. 2013), particles smaller than 10 m (OR: 2.14; CI: 1.47 - 3.10; Volk et al. 2013) and nitrogen dioxide (OR: 2.06; CI: 1.39 - 3.06; Volk et al. 2013) were possibly responsible for this.

A.5.6 Birth-associated risk factors

One particular group concerns risk factors related to birth itself and birth complications. However, the increase in risk due to these factors tends to be small, and it often does not persist when appropriately corrected for other coexisting influencing factors, as was shown in a recent article on the question of whether an increased risk of autism is associated with birth by caesarean section. Here, uncorrected, cesarean section was associated with increased autism risk; corrected for significant other influencing factors, cesarean section was no longer found to increase risk (Curran et al. 2015). Also, an underlying genetic condition in the fetus is often associated with pregnancy complications secondary to the consequences of the genetic risk factor in the child. For this reason, the risk factors listed in Table 16with the exception of preterm birth, should not be evaluated as stand-alone, but should always be viewed in the context of other risk factors. Moreover, many of the risk factors listed in Table 16are also poorly defined

(such as pregnancy complications or birth trauma), so that no further conclusions can be drawn from them.

Table 16: Birth-associated risk factors

Complication	OR	AI	Reference
Multiple pregnancies	2,00	1,00 - 4,10	Williams et al. 2008b
Multiple pregnancies	1,51	1,19 - 1,92	Hultman et al. 2011
Smoking mother	1,40	1,10 - 1,80	Hultman et al. 2002
Pregnancy complication	4,70	1,30 - 17,60	Badawi et al. 2006
Pregnancy complication	2,41	1,56 - 3,73	Glasson et al. 2004
Pregnancy complication	1,40	1,00 - 2,00	Haglund and Kallen 2011
Birth trauma	2,40	1,30 - 4,20	Maimburg and Vaeth 2006
Birth trauma	11,20	3,10 - 39,80	Badawi et al. 2006
Postpartum hemorrhage	2,33	1,11 - 4,89	Glasson et al. 2004
Sectio caesarea (elective)	2,05	1,49 - 2,82	Glasson et al. 2004
Epidural anesthesia	1,68	1,12 - 2,51	Glasson et al. 2004
Sectio caesarea (emergency)	1,57	1,11 - 2,22	Glasson et al. 2004
Sectio caesarea (elective)	2,40	1,30 - 4,60	Haglund and Kallen 2011
caesarean section	1,50	1,12 - 2,13	Eriksson et al. 2012
caesarean section	1,60	1,10 - 2,30	Hultman et al. 2002
caesarean section	1,50	1,10 - 1,90	Maimburg and Vaeth 2006
Birth weight < 1500 g	2,52	1,51 - 4,23	Hultman et al. 2011
Birth weight < 1500 g	3,10	1,40 - 6,50	Lampi et al. 2012
Birth weight 1500 - 2500 g	1,78	1,36 - 2,35	Hultman et al. 2011
Birth weight < 2500 g	1,57	1,05 - 2,30	Lampi et al. 2012
Birth weight < 2500 g	2,00	1,20 - 3,50	Haglund and Kallen 2011
Birth weight < 2500 g	2,50	1,70 - 3,50	Maimburg and Vaeth 2006
Relative birth underweight	2,10	1,10 - 3,90	Hultman et al. 2002
Relative birth underweight	2,52	1,93 - 3,29	Hultman et al. 2011
Relative birth underweight	1,80	1,10 - 3,10	Haglund and Kallen 2011
Relative birth underweight	1,72	1,10 - 2,60	Lampi et al. 2012
Relative birth underweight	1,50	1,10-2,20	Maimburg and Vaeth 2006
Relative birth excess weight	1,42	1,02-1,97	Hultman et al. 2011
Premature birth < 32.W	2,51	1,30 - 5,00	Lampi et al. 2012
Prematurity < 37 W.	2,30	1,50 - 3,70	Williams et al. 2008b
Premature birth	2,05	1,26 - 3,34	Buchmayer et al. 2009

Continued Table 16: Birth-associated risk factors

Complication	OR	AI	Reference
Gender male	3,70	2,50 - 5,50	Haglund and Kallen 2011
Gender male	8,34	2,83 - 24,59	Palma et al. 2012
Gender male	4,80	3,20 - 7,20	Williams et al. 2008b
Apgar Index at 1 min < 5	1,70	1,10 - 2,70	Williams et al. 2008b
Apgar Index at 1 min < 7	1,64	1,10 - 2,43	Glasson et al. 2004
Apgar Index at 5 min < 7	3,20	1,20 - 8,20	Hultman et al. 2002
Apgar Index at 5 min < 8	1,80	1,10 - 2,80	Maimburg and Vaeth 2006
Respiration after 1 min.	1,42	1,05 - 1,93	Glasson et al. 2004
Intensive care after birth	2,10	1,50 - 2,90	Maimburg and Vaeth 2006
Neurological abnormalities	4,00	1,50 - 10,70	Maimburg et al. 2008

Neonatal seizures	9,00	1,10 - 71,10	Maimburg et al. 2008
Foetal distress	1,76	1,26 - 2,45	Hultman et al. 2011
Foetal distress	1,50	1,20 - 1,90	Maimburg and Vaeth 2006
Foetal distress	1,59	1,20 - 2,11	Glasson et al. 2004
Abnormal serum glucose	1,50	1,10 - 2,20	Maimburg et al. 2008

A.5.7 Excluded risk factors

Numerous risk factors for autism spectrum disorders, which have been widely discussed in the public, could be clearly excluded:

1. Vaccinations, especially the triple vaccine against measles, mumps and rubella, but also other vaccinations are not associated with an increased risk of autism; mercury, which was partly used to preserve the vaccinations, is also not associated with an increase in risk (Taylor et al. 2014).
2. Gastrointestinal disorders (including food intolerances) of the child (Buie et al. 2010).
3. Maternal alcohol use during pregnancy (this is associated with significant cognitive impairment, numerous organic malformations, and other behavioral abnormalities in the child; but not autism spectrum disorders) (Eliasen et al. 2010).

[5]	**Consensus statement**
KKP	The following risk factors for autism spectrum disorders are well established and have been replicated many times: • Genetics: e.g. (spontaneous) mutations, microdeletions and duplications, chromosomal disorders, common genetic variants. Common genetic mechanisms are also likely to underlie other risk factors, such as some parental mental and somatic disorders and some pregnancy and birth complications. • Higher age of mother and father (mediating mechanism probably genetic or epigenetic) • Drug exposure during pregnancy (valproate, antiepileptic drugs, selective serotonin reuptake inhibitors, possibly also other psychoactive substances) • Rubella infection of the mother during pregnancy • Migration status of parents
	Strong consensus (11 out of 11)

B.1 Introduction to the Diagnostics Part

Christine M. Freitag, Ulrich Hagenah

B.1.1 Overview of the diagnostics chapter

In this chapter, the entire path from the (early) recognition of autistic symptoms to the diagnosis of an autism spectrum disorder is presented, as well as the necessary diagnosis of comorbid diseases, differential diagnosis and recommended follow-up diagnosis. This diagnosis is the basis for therapy, which is presented in a differentiated manner in the second part of the guideline. The recommendations for (early) detection and diagnostics are made in relation to the German health care system. In Germany, some aspects differ significantly from the source guidelines used by[8] NICE ("*Autism: recognition, referral, and diagnosis of children and young people on the autism spectrum*" from 2011 and "*Autism: recognition, referral, diagnosis and management of adults on the autism spectrum" from* 2012) and SIGN ("*Assessment, diagnosis and clinical intervention for children and young people with autism spectrum disorders*" from 2007). In the United Kingdom (UK), where all source guidelines originate from, the entire health and social system is organized differently than in Germany. The qualifications, competences and tasks of identically designated professional groups differ considerably between the countries. In Great Britain, there is a much greater separation between general practitioners/pediatricians and special institutions. There, referrals to special institutions must always be made officially; parents or guardians or patients themselves cannot go there directly. This is different in Germany: parents or guardians and patients have a free choice of doctor and can, for example, go directly to special child and adolescent psychiatric consultations without a special referral. In Germany, many different professions currently offer screening or diagnostic services for autism spectrum disorders. In the individual subchapters, therefore, a recommendation is made in relation to the specific situation in Germany as to which persons with which qualifications should generally carry out the corresponding examination, and recommendations are made for improving the organisation and implementation of diagnostics.

[8] Hereinafter for Part B summarily referred to as the "Source Guidelines".

B.1.2 Process and professional responsibilities for (early) detection, referral and diagnosis

There are no empirical studies on the care situation for affected persons or relatives with suspected autism spectrum disorder in Germany. The - sometimes tortuous - paths to a correct diagnosis have also not been empirically investigated. However, it can be assumed that the path to diagnosis still takes a relatively long time - especially for individuals with more mild autism spectrum disorders and good cognitive skills, some of whom are not diagnosed until adolescence or adulthood - and is marked by numerous other psychiatric (mis)diagnoses until the correct diagnosis is made (Koelkebeck et al. 2014). This is supported by clinical studies of the median age of diagnosis in Germany (Noterdaeme and Hutzelmeyer-Nickels 2010), which is higher than in many other Western countries (Daniels and Mandell 2014), as well as epidemiological studies from the UK in children, adolescents and adults with autism spectrum disorders, which described a proportion of approximately 20% (children) to 100% (adults) of previously undiagnosed individuals with autism spectrum disorder (Brugha et al.In the United States in 2010, the median time to diagnosis for autism spectrum disorder ranged from 46 to 61 months (Baio J. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators 2014), with a median time to diagnosis for autism at 48 months, for pervasive developmental disorder (PDD-NOS according to DSM-IV TR) at 50 months, and Asperger syndrome at 74 months. Numerous factors were associated with delayed diagnosis in these studies (Daniels and Mandell 2014):

- lower symptom expression,
- low socioeconomic status,
- Minority Status,
- lower sensitivity for autism-specific early signs among parents or guardians,
- lack of resources in the environment,
- greater number of bodies consulted before a diagnosis is made.

In Germany, in an uptake population, the average age at the time of first diagnosis for autism was 76 months, for Asperger syndrome 110 months (Noterdaeme and Hutzelmeyer-Nickels 2010).

On the other hand, autism spectrum disorders are currently suspected more frequently in children, adolescents and adults than was the case a few years ago, which is reflected in a significantly higher utilization of corresponding special consultation hours. Studies that have evaluated populations of these specialty consultations show a rate with a wide spread of 30-70% of actual

autism spectrum diagnoses following referral to such a specialty consultation (Kamp-Becker et al. 2013). This is comparable to other special consultations in the child/adolescent and adult psychiatric fields.

[6]	**Consensus statement**
KKP	There is an urgent need for improvement regarding the early, timely and correct diagnosis of autism spectrum disorders in Germany.
	Strong consensus (12 out of 12)

In the source guidelines from the UK, a distinction is made between two stages of diagnostic investigation in each case: An initial investigation is carried out when autism spectrum disorder is suspected, based on (early) symptoms. In this - hereinafter referred to as "primary care" - screening instruments should be used and the suspicion confirmed or ruled out. If the suspicion persists, a detailed diagnosis should be carried out at a specialist centre. The authors of the present German guideline propose the same procedure for the German health care situation:

[7]	**Consensus-based recommendation**
KKP	To improve care and with the aim of facilitating timely and accurate diagnosis, a staged approach should be adopted: (1) If an autism spectrum disorder is suspected, the first step should be a prompt, orienting assessment using valid, age-specific screening instruments and conducting an orienting clinical evaluation. (2) If the suspicion is confirmed, the person should be referred to a centre specialising in autism spectrum disorders, which can guarantee a full diagnosis and differential diagnosis....
	Strong consensus (14 out of 14)

The content of the diagnosis and the necessary qualifications of the professional groups working in a centre specialising in autism diagnosis and/or therapy, or in a closely linked local network of colleagues, are dealt with in detail in Part B.4.

B.1.3 Basic objectives of the screening and diagnostic process

Any clarification with regard to the diagnosis of an autism spectrum disorder as well as the comorbid illness should be carried out with a view to the necessary therapy for the affected person (medicinal, psychotherapeutic-exercising) as well as accompanying measures (support of the parents or guardians, support/support of the affected person with regard to kindergarten, school, training and occupation, housing, further living environment). Therefore, diagnostics also include an assessment of the specific competencies, behaviours and difficulties of the respective patient in everyday life (B.4). It goes without saying that the results must be explained in detail to the patients and their guardians and - after an appropriate release from the obligation of confidentiality has been granted - passed on to the referring doctors as well as therapeutic and social institutions (B.6) and concrete, individualised therapy recommendations (see Part 2) must be made.

B.1.4 Recommendation for research

No epidemiological data on autism spectrum disorders exist for Germany. In the area of care, only an analysis of health insurance data regarding drug therapy for children and adolescents with autism spectrum disorders has been published (Bachmann et al. 2013). It seems necessary to establish targeted health care research for the area of diagnostics with the aim of improving early and correct diagnostics: Documentation of the process up to diagnosis, survey of the actual need for care in the area of diagnosis, based on this, formulation of improved models with subsequent empirically based investigation including the costs as well as the advantages and disadvantages for the individual patient and the health and social system.

B.2 Recognition of autistic symptoms

Ulrich Hagenah, Claus Lechmann, Christine M. Freitag
Collaboration (literature research and selection): Stephanie Hoss

12. what are the leading symptoms of autism spectrum disorder?

15) What are the early symptoms of early childhood autism, and what are the early symptoms of Asperger's syndrome?

B.2.1 Introduction

Identifying children with symptoms of autism spectrum disorder as early as possible and securing the diagnosis continues to be a major challenge, especially in preschool age. Core symptoms of the disorders are typically present in early childhood, but are not always apparent before the child enters kindergarten or school, for example. Reliable biological markers for autism spectrum disorders do not yet exist. The diagnosis is confirmed on the basis of behavioural observations. In accordance with the current classification systems (ICD-10, Falkai and Döpfner 2015), the leading symptoms of autism spectrum disorders can be assigned to the domain of *reciprocal social communication and interaction on the one* hand, and to the domain of *unusual or restricted interests and/or rigid, stereotyped and repetitive behaviors on* the other. With regard to reciprocal social interaction and communication, the abnormalities can be subdivided into:

- the spoken language
- the reaction to other people,
- interaction with other people,
- Eye contact, pointing, gestures,
- Ideas and imagination.

The leading symptoms described change in the course of development, but usually lead to lifelong impairment in the areas described.

The current diagnostic standards are largely based on the observation of children and adolescents of school age. It is particularly difficult to detect precursors of the symptomatology in infancy and toddlerhood, in which a particularly high variance in the achievement of age-typical developmental tasks, e.g. linguistic and motor development, makes a reliable differentiation between normal and abnormal development difficult. First indications of an autism spectrum disorder cannot be detected at birth, but usually show up in late infancy and early toddlerhood

in the form of delayed, reduced or atypical development of social interaction and communication skills as well as conspicuous play behaviour and stereotypic behaviour. The first perception of abnormalities in development that indicate an autism spectrum disorder often occurs through the parents, sometimes as early as the first year of life (Howlin and Asgharian 1999).

Prospective studies of siblings of a child with autism spectrum disorder who are at increased risk of also developing autism spectrum disorder showed the following differences in the children studied who later received an autism spectrum diagnosis compared to those who did not:

For infants between six and twelve months of age with later autism spectrum diagnoses, evidence of attentional system disorders has been described in the form of difficulty disengaging attention from an object (Ibanez et al. 2008; Zwaigenbaum et al. 2005), or in the form of reduced attention to faces or other social stimuli toward objects (Chawarska et al. 2013). Abnormal motor movement patterns in this age group are probably not specific to autism spectrum disorders, but can also be observed in infants with other developmental abnormalities. Studies on eye contact abnormalities do not show consistent results in infants (Ozonoff et al. 2010; Rozga et al. 2011; Bedford et al. 2012).

From around the beginning of the second year of life, some abnormalities seem to be more consistently associated with the later diagnosis of an autism spectrum disorder. In particular, these include a weaker response to calling the child by his or her own name (Nadig et al. 2007), difficulties in joint attention ("Joint Attention"; Landa et al. 2007) and eye contact (Ozonoff et al. 2010). However, studies on the sensitivity and specificity with regard to the prediction of later autism spectrum disorders are only available for a few of these characteristics.

With regard to diagnosis, it must be taken into account that about 20-25% of infants and toddlers in whom an autism spectrum disorder could later be confirmed initially show no abnormalities with regard to social interaction and communication between the ages of 6 and 24 months (Ozonoff et al. 2011b). On the other hand, some high-risk children showed autism-associated abnormalities at 12 months of age without a later (at age 3) confirmed diagnosis of autism spectrum disorder (Georgiades et al. 2013). This illustrates the difficulties of early diagnostic confirmation with the risks of both a false positive diagnosis with the corresponding consequences on the one hand and the false negative exclusion of an autism spectrum disorder in children who initially develop inconspicuously.

B.2.2 Summary from the source guidelines

Nice children (diagnostics)

The corresponding question to both key questions (SF 12, SF 15) in the NICE children's guidelines is:

What are the signs and symptoms that should lead to autism being considered from a professional perspective?

Based on a systematic literature review with predefined criteria for assessing the sensitivity and specificity of various features, the authors of the British guideline[9] identified for the preschool age group (0-5 years) only a combination of several features (*protodeclarative pointing, tracking gaze*, and *"as-if" play*) that provided a sufficiently empirically validated prediction. For the group of primary school-aged children (6-11 years), only the items "*no social play*" and "*does not maintain conversations/conversations with others*" met the predefined criteria. For older children and adolescents (12-17 years), no symptoms or warning signs could be identified. For the overall group of school-aged children and young people (6-17 years), only one item ('*repetitive talking about a topic*') met the predefined criteria. No studies were found for children and young people with an intellectual disability. For all age groups, the quality of the included studies was rated as *very* low.

For the different age groups, three tables list warning signs and symptoms for which evidence could be identified. In addition, some of the less clear signs for which evidence was available have been transformed by the guideline group into terms that can be more easily understood by non-experts. The use of these tables is intended to help professionals identify warning signs in a child or young person who is suspected of having an autism spectrum disorder.

Recommendations of the guideline group are divided into three categories, graded from *"must"* or "must *not"* (strongest recommendation level) to *"should"* or *"should not"* and corresponding formulations (*"refer ...."*, *offer..."*) to *"consider..."* (weakest level of recommendation). It is recommended that the presence of an autism spectrum disorder should be considered if there are concerns about the child's development or behavioural problems (*strong recommendation*). The concerns of parents or other carers, or affected older children themselves, should be taken seriously, even if they are not shared by others (*strong recommendation).* The presence of an autism spectrum disorder should not be ruled out because good eye contact, smiles, and affective reactions toward family members may be observed (*strong recommendation*). In addition,

[9] http://www.nice.org.uk/guidance/cg128/evidence/cg128-autism-in-children-and-young-people-full-guideline2

children who show regression in language development or social skills under the age of three should be referred to an agency specializing in the diagnosis of autism spectrum disorders (*strong recommendation*).

An update to the NICE children's guideline in April 2013 found no relevant new data to require a change in recommendations.

NICE Adult [10]

The corresponding question to the key questions here is:

In contact with an adult who may have an autism spectrum disorder, what signs or symptoms should prompt consideration of diagnostic workup?

The guideline group emphasizes a major challenge and complexity of detection and screening, especially in adults who have not been diagnosed with autism spectrum disorder in childhood. Seeking professional help is often because of other medical or mental health problems. According to the authors of the guidelines, comorbid psychiatric disorders, e.g. depression and schizophrenia, but also autism-specific difficulties, e.g. in social interaction with the environment, often complicate the diagnostic clarification in practice.

Due to the lack of good quality evidence, the recommendation of the guideline group is based exclusively on the consideration of the two classification systems DSM-IV and ICD-10 as well as the expert knowledge of the guideline group. The primary criteria for the development of the recommendation were ease of application in practice even without expert knowledge of the disorder, transferability into an easy-to-use algorithm with regard to further decision-making, and also a high degree of comprehensibility for the people affected or their relatives. It is recommended to consider further diagnostic steps if one of the following three key symptoms is present:

- persistent difficulties in social interaction
- persistent difficulties in social communication
- stereotyped (rigid and repetitive) behaviours, resistance to change, (e.g. in diet, routines, environment) or restricted interests.

Given the association between autism spectrum disorders and various biographical factors, additional consideration should be given:

[10] NICE, guidance.nice.org.uk/cg142

- Problems entering or maintaining employment or training
- Difficulties in initiating or maintaining social relationships
- previous or current contacts with psychiatric institutions or other support systems for people with disabilities.

There are no new statements or changes to the relevant key questions in the May 2014 update of the guidance.

***SIGN*[11]**

The corresponding question in the Scottish guidelines is:

- *SF 1: What methods, parental concerns, and developmental abnormalities are relevant to an investigation regarding the presence of autism spectrum disorder?*

The guideline group recommends that professionals involved in the diagnosis of children and young people with autism spectrum disorders use either ICD-10 or DSM-IV classification. Autism spectrum disorder as a differential diagnosis should be considered in screening programs for preschool children who show abnormalities in the domains of social interaction, play, language development, and behavior (recommendation grade D; weakest level of recommendations, corresponding to an evidence level of 3 or 4). Because typical features of autism spectrum disorders may not be apparent in children less than two years of age, the absence of appropriate features should not be used to rule out the possibility of a diagnosis. Parental concerns about the child's development should be considered as significant as the presence of clinically prominent features.

Similar to NICE, the Scottish recommendations include tables of warning signs for autism spectrum disorders for the appropriate age groups (pre-school children, school-age children, adolescence). These are drawn for pre-school age from the New York Department of Health[12] clinical practice recommendations , and for school age from recommendations in the UK National Autism Plan for Children (Le Couteur 2003). The warning signs for adolescence were compiled by the Scottish guideline authors with reference to the group members' knowledge of the evidence base and their clinical experience.

The evidence regarding the earliest possible time of diagnosis is considered to be unclear, however, assessing the data available at the time the Scottish guidelines were written, it would seem

[11] http://www.sign.ac.uk/guidelines/fulltext/98/, last checked on 07.09.2015
[12] https://www.health.ny.gov/community/infants_children/early_intervention/disorders/autism/, last checked on 07.09.2015

that the diagnosis of autism, regardless of age, is more reliable and stable than the diagnosis of other autism spectrum disorders and can be reliably made by experienced examiners between the ages of two and three years.

Autism-specific screening should be considered for any age group as new information becomes available, regardless of the results of previous screening (*good practice point).*

B.2.3 Comparison of recommendations/synopsis

While the UK guidelines for adults (NICE adults) are very closely aligned with the descriptions in the two classification systems (DSM-IV, ICD-10) with regard to the leading symptoms, there are very strong efforts in both the Scottish and the UK guidelines for children and adolescents to identify age- and developmentally-typical features of autism spectrum disorders. Empirical support for the recommendations is weak given the predominantly low quality of the studies available at the time the guidelines were written. There are no fundamental differences in terms of the symptoms listed for children and young people, and in some cases these are identical. Both the UK and Scottish Children's Guidelines recommend that the threshold for referral for detailed investigation at a specialist institution should be set low, but also highlight the risk of a false positive diagnosis for affected individuals and their families. The authors of the Scottish guidelines consider the diagnosis of autism to be reliably assessable by experienced examiners at between two and three years of age. All three guidelines emphasise that, in principle, a diagnosis of autism spectrum disorder should be considered at any stage of life when new information becomes apparent, even if the diagnosis has once been ruled out in the past history.

B.2.4 Justification of deviations/modifications based on evidence

The search for biological markers has intensified significantly in recent years (Walsh et al. 2011; Mizejewski et al. 2013; Voineagu and Yoo 2013). However, no marker has yet reached maturity for clinical application.

After Kanner (1943) had already noticed a larger head circumference in some of the children of his group with early childhood autism, an accelerated growth of the head circumference (macrocephalus) compared to the age norms has meanwhile been determined several times in utilization populations, especially in the first year of life in children with a later confirmed diagnosis from the autism spectrum (Chawarska et al. 2011; Fukumoto et al. 2011), which then seems to slow down at a later time (Dawson et al. 2010). The assumption that accelerated

growth of the head circumference can be seen as an early marker of a different neural development of the brain in these children is supported by a review of MRI studies of the brain at different ages from infancy or toddlerhood to middle adulthood. Here, accelerated brain growth was shown in the first 3-4 years of life, followed by a marked slowing of brain growth compared to subjects not affected by autism spectrum disorder (Courchesne et al. 2011). However, neither sensitivity nor specificity were calculated in this study. Furthermore, the abnormalities of head growth could not be replicated in representative samples (Barnard-Brak et al. 2011). A possible explanation for this could be secular effects with regard to brain growth, which lead to the fact that norms (percentile curves) used for comparison in the studies were already outdated at that time and thus the growth of the brain of the children studied was systematically overestimated (overview in: Raznahan et al. 2013). Since it cannot be ruled out that differences found in clinical samples are due to the fact that the children examined there showed more serious abnormalities at an early age and were therefore more likely to be diagnosed (i.e. epidemiological studies may have recorded more children who are "false negatives" for an autism spectrum disorder), the absence of macrocephalus in children in this age group should not prompt us to rule out the diagnosis. If macrocephalus is present, especially if growth is accelerated "out of percentiles" and other developmental abnormalities are present at the same time, autism spectrum disorders should also be considered for differential diagnosis.

B.2.5 Update: What are the leading and early symptoms of autism spectrum disorder?

All studies since 1980, including those included in NICE Children (Diagnostics), that met the following criteria were included: At least one control group, sensitivity or specificity data available or can be calculated, age of children up to 3 years, appropriate diagnostic criteria (DSM-III-R, DSM-IV, DSM-IV-TR, ICD-9, ICD-10), minimum case number of n = 10 children with autism spectrum disorders, and control group for each trait studied.

The (early) detection of autism spectrum disorders is based on the observation of specific behavioural peculiarities. For early childhood autism, such early identification signs could be identified at least for the second year of life; in the following, those symptoms are mentioned first that discriminate best. There are no corresponding studies for the early detection of atypical autism; Asperger syndrome is discussed separately below.

B.2.5.1 Age group under 12 months

In the search for characteristic warning signs in the first year of life, sometimes contradictory results have been obtained so far, e.g., no significant differences were found in eye contact of infants aged 6-7 months (Ozonoff et al. 2010; Rozga et al. 2011; Bedford et al. 2012). Similarly, in a recent eye-tracking study (Jones and Klin 2013), 2-month-old infants who were later diagnosed with autism spectrum disorder did not differ from other infants, but there was a significant decrease in eye-part preference later in life.

The majority of prospective studies and retrospective analyses of video recordings suggest that affected children still differ little from other children in their behaviour in the first year of life, but that striking peculiarities only become noticeable in the second year of life, particularly in social communication (Elsabbagh et al. 2013b; Landa and Garrett-Mayer 2006; Zwaigenbaum et al. 2013; Lemcke et al. 2013). The following abnormalities have been described, although they have not been replicated to date. Information on the sensitivity and specificity of the characteristics examined in the studies for predicting a later diagnosis from the autism spectrum is listed in Table 17

Asymmetric movements

In a retrospective study (Esposito et al. 2009), video recordings of 5-month-old infants were evaluated and often showed an asymmetric movement pattern in infants later diagnosed as autistic.

Less anticipatory opening of the mouth when being fed.

Another retrospective study (Brisson et al. 2012) used family video to show that children who were later diagnosed as autistic were much less likely to open their mouths at the appropriate moment when fed at 4-6 months of age than the control group.

Lack of head posture

In a prospective study (Flanagan et al. 2012), 9 out of 10 children who were later diagnosed with autism spectrum disorder showed difficulty holding their head when pulled into the seat.

Fewer sounds

Children with later autism spectrum diagnoses showed significantly less babbling with repetition of syllables ("Dadada...") on video recordings (Patten et al. 2014) at 9-12 months of age than children without developmental disabilities.

regression in communication and lack of vocal imitation

In a prospective study (Rowberry et al. 2015), parents of children later diagnosed on the autism spectrum described losses in communicative and play behaviors or missed imitating sounds.

[8]	**Consensus-based recommendation Age < 12 months**
KKP	For infancy, there are no empirically validated characteristics for the prediction of a later autism spectrum disorder. For children who show developmental abnormalities between the 10th and 12th month of life (at the U6 disease screening examination), an additional examination should be performed between 16 and 18 months of age to check whether the abnormalities have become more pronounced or have receded at this time. This is also recommended for children whose parents express concerns about their child's development at this time (U6).
	Strong consensus (14 out of 14)

Table 17: Warning signs under 12 months

Symptoms	Source	Study design	Age	ASS N =	Sens.	Draft Verz. N =	Spec.	Type. Entw. N =	Spec.
Asymmetric movement	Esposito et al. 2009	Retrospective Video analysis	12 - 21 Wo.	18	0,4	12	1,0	18	1,0
Lack of anticipatory movements during feeding	Brisson et al. 2012	Retrospective Video analysis	4 - 6 Mon.	13	0,6			14	0,8
Poor head posture	Flanagan et al. 2012	Prospective study	6 months	10	0,9	13	0,4	17	0,6
Rarer sounds	Patten et al. 2014	Retrospective Video analysis	9 - 12 Mon.	23	0,8			14	0,6
Regression in communication and no vocal imitation	Rowberry et al. 2015	Prospective questionnaire study	12 months	16	0,6	36	0,9*	44	0,9*

* Results for typically developed and delayed developed children were not reported separately.

B.2.5.2 Age group 12-18 months

The results of the studies on age 12 months and older are listed in Table 18

No pointing to share interest

Typically developed children have learned by the beginning of the second year of life to follow another person's gaze or to point to things in order, for example, to draw their parents' attention to things they find interesting (Mundy and Newell 2007). This "joint attention" is considered a crucial skill for language development and learning in a social context. In young children with early childhood autism, this pointing gesture to share interest does not develop or is very delayed. The differentiation from inconspicuously developed children was very good, but there is a lack of research for this age group to determine whether otherwise developmentally disabled children do not also show deficits in this area. This also applies to the other behaviours at this age listed below (Barbaro and Dissanayake 2013).

No wave goodbye gesture

Most children mimic the wave-wave gesture when the adult waves as they walk away. Children with early childhood autism usually do not do this (Barbaro and Dissanayake 2013).

Lack of response to naming

If a child at 1 year of age generally does not turn around when his or her name is called, this is an indication of a possible developmental disorder, particularly autism (Nadig et al. 2007; Barbaro and Dissanayake 2013).

Lack of imitation

Lack of imitation can be another marker. If one gets the attention of one-year-olds and then demonstrates how to comb one's hair, children with a later diagnosis from the autism spectrum usually do not imitate this. However, even typically developed children do not always follow this request at this age (Barbaro and Dissanayake 2013).

Table 18: Warning signs from 12 months

Symptoms	Source	Study design	Age	ASS N =	Sens.	Draft Verz. N =	Spec.	Type.design. N =	Spec.
No pointing to share interest	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	0,8			13	0,9
No wave goodbye gesture	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	0,7			13	0,9
Lack of response to being called by name	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	1,0			13	0,5
Lack of imitation	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	0,8			13	0,6
Lack of eye contact	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	0,4			13	1,0
Unusual exploration of objects	Ozonoff et al. 2008	Prospective study	12 Mon.	9	0,7			47	0,7
No following the pointing gesture	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	0,6			16	0,7
Rare social smile	Barbaro and Dissanayake 2013	Prospective, population-based sample	12 Mon.	9	0,5			16	0,8
Slowed flexibility in visual adaptation	Elsabbagh et al. 2013a	Prospective study	14 Mon.	17	1,0	12	1,0	68	1,0
Preference for geometric figures	Pierce et al. 2011	Prospective, population-based sample	14-42 Mon.	37	0,4	22	0,9	51	0,9

Lack of eye contact

Children with early childhood autism are less likely to make spontaneous eye contact with adults. However, this does not apply to all, while in the aforementioned study all typically developed children did so (Barbaro and Dissanayake 2013).

Unusual exploration of objects:

Another clue may be the unusual exploration of objects. For example, another prospective study (Ozonoff et al. 2008) shows that children who were later diagnosed with autistic disorder differed at 1 year in how they handled various objects. For example, they more often spun a plastic ring or tried to make it spin or explored it visually in a striking way.

No following the pointing gesture

If one gets the child's attention and then tries to show him something ("wow, look at that"), two-thirds of children with a subsequent autism spectrum diagnosis do not direct their gaze in the appropriate direction, whereas most children without this diagnosis do (Barbaro and Dissanayake 2013).

Rare social smile

Children with early childhood autism rarely show spontaneous smiling at or even smiling back in contact with an adult (Barbaro and Dissanayake 2013).

Slowed flexibility in visual adaptation

While 7-month-old children who were later diagnosed with autism spectrum disorder responded visually as quickly to a new visual stimulus, by 14 months of age they were clearly distinguishable from other children and responded more slowly (Elsabbagh et al. 2013b).

Preference for geometric figures

In a study of 14-month-old children (Pierce et al. 2011), it was shown that for those children who direct their gaze to geometric figures rather than pictured children, an autism spectrum disorder can be predicted very confidently.

However, if children do not show any abnormalities in these early identification signs, it does not mean that an autism spectrum disorder can be ruled out.

[9]	**Consensus-based recommendation Age 12 - 18 months**
KKP	Infants who are reported by parents or observed on examination to have one or more of the following characteristics: - lack of or reduced tracking of another person's line of sight, - lack or absence of eye contact, - infrequent or lack of finger pointing to draw another person's attention to something, - weakened or absent reaction to being called by one's own name, - Regression or loss of previously acquired skills in language or social interaction, or - where parents express increasing concerns about their child's development at this time the differential diagnosis of an autism spectrum disorder should be considered and checked using an appropriate screening instrument. If the suspicion is confirmed, the child should be referred immediately to an autism spectrum disorder diagnostic specialist.
	Strong consensus (14 out of 14)

B.2.5.3 Age group 18 -24 months

The results of the studies on age 18 months and older are shown in Table 19

No pointing to share interest

Hardly any child with early childhood autism pointed at things to share interest at this age, however, in a study (Baron-Cohen et al. 1996) other, especially developmentally delayed children were also conspicuous here, while in a more recent study (Barbaro and Dissanayake 2013) the lack of pointing gestures also best distinguished children with other developmental disorders in comparison. However, if the survey is based exclusively on interviews with parents, the sensitivity also drops considerably (Stenberg et al. 2014).

Lack of eye contact

Eye contact abnormalities are also highly specific for this age group, with excellent sensitivity for early childhood autism but only moderate sensitivity for spectrum disorder (Barbaro and Dissanayake 2013; worse measures in Baron-Cohen et al. 1996).

Lack of bringing to show

Children with a later autism spectrum diagnosis usually lack the social side of communication: when they do draw the attention of those around them to something, it tends to be to things they want, but not to show them to others. This feature demarcates very well from other disorders and is found in all children studied with early childhood autism, but only a proportion of children with an autism spectrum diagnosis (Barbaro and Dissanayake 2013).

Lack of "do-as-you-go" gameplay.

From about 14 months, children develop the ability (Bretherton 1984) to pretend that an object (e.g. wooden block) symbolises something else (e.g. mobile phone) and play with it accordingly. Children with early childhood autism usually do not develop this ability or develop it much later. However, it is not uncommon for other developmentally delayed children to show a delay here as well (Baron-Cohen et al. 1996; Barbaro and Dissanayake 2013).

No or little reaction to the distress of other people

For example, when a teammate pretends to be hurt, children with autism spectrum disorder are less likely to look up and not show compassion (Charman et al. 1997).

The risk markers 'Lack of imitation' and 'No wave goodbye gesture' mentioned for younger children are no longer included here as they do not discriminate well against other developmentally disabled children.

Table 19: Warning signs from 18 months

Symptoms	Source	Study design	Age	ASS N =	Sens.	Draft Verz. N =	Spec.	Type. de-sign. N =	Spec.
No pointing to share interest	Barbaro and Dissanayake 2013	Prospective, popula-tion-based sample	18 Mon.	30	0,9	7	1,0	12	0,9
	Baron-Cohen et al. 1996	Prospective, popula-tion-based sample	18 Mon.	10	1,0	17	0,0	23	0,6
Lack of eye contact	Barbaro and Dis-sanayake 2013	Prospective, popula-tion-based sample	18 Mon.	30	0,8	7	1,0	12	1,0
Lack of pursuit of the gaze	Baron-Cohen et al. 1996	Prospective, popula-tion-based sample	18 Mon.	10	1,0	17	0,6	23	1,0
Missing bring to show	Barbaro and Dis-sanayake 2013	Prospective, popula-tion-based sample	18 Mon.	30	0,8	7	1,0	12	1,0
Lack of "do-as-you-go" gameplay.	Baron-Cohen et al. 1996	Prospective, popula-tion-based sample	18 Mon.	10	1,0	17	0,5	23	1,0
	Barbaro and Dissanayake 2013	Prospective, popula-tion-based sample	18 Mon.	30	0,9	7	0,4	12	1,0
No mimic reaction or no eye contact in distress of others	Charman et al. 1997	Prospective, popula-tion-based sample	20 Mon.	10 10	1,0 0,6	9 9	0,4 1,0	19 19	0,6 1,0

[10]	**Consensus-based recommendation Age 18 - 24 months**
KKP	Infants who are reported by parents or observed at the screening examination (U7) to have any of the following characteristics: - lack of or reduced tracking of another person's line of sight, - little or no "as-if" play the suspicion should be checked using an appropriate screening instrument (B.3). In addition, the following symptoms can also be considered for diagnostic clarification: - lack or absence of eye contact, - lack of bringing to show objects, - infrequent or lack of finger pointing to draw another person's attention to something, - weakened or absent reaction to being called by one's own name, - lack of facial reaction or eye contact to other people's expressions of pain, - Regression or loss of previously acquired skills in language or social interaction, - where parents express increasing concerns about their child's development at this time. If the suspicion is confirmed, the child should be referred immediately to a centre specialising in the diagnosis of autism spectrum disorders.
	Strong consensus (14 out of 14)

B.2.5.4 Age group 24 months and over

The results of the studies on age 24 months and older are shown in Table 19

No pointing to share interest

All children diagnosed with early childhood autism continued to show here, whereas in children with autism spectrum disorder half have begun to show. Almost all delayed or typically developed children pointed to a teddy at this developmental age (Barbaro and Dissanayake 2013).

Lack of eye contact

Also for this age group, abnormalities in eye contact are very salient for autistic children with early childhood autism, somewhat less so for children with other autism spectrum disorder; they discriminate very well against typically developed children, but only moderately against delayed-developed children (Barbaro and Dissanayake 2013).

Missing bring to show

Even at this age, this feature demarcates very well from other disorders and is found in all children studied with early autism, but only a proportion of children with an autism spectrum diagnosis (Barbaro and Dissanayake 2013).

Lack of "do-as-you-go" gameplay.

A proportion of children with an autism spectrum diagnosis (40%) have learned to pretend at this age, e.g., drinking from a toy cup, but specificity remains excellent, i.e., (almost) all other children are proficient at "so-doing-as-if" (Barbaro and Dissanayake 2013).

In addition, at this developmental age, any regression or loss of already acquired language and social skills should be clarified.

Table 20: Early symptoms from 2 years onwards

Symptoms	Source	Study design	Age	ASS N =	Sens.	Draft Verz. N =	Spec.	Type. de-sign. N =	Spec.
No pointing to share interest	Barbaro and Dis-sanayake 2013	Prospective, popula-tion-based sample	24 Mon.	50	0,7	12	0,9	11	1,0
Lack of eye contact	Barbaro and Dis-sanayake 2013	Prospective, popula-tion-based sample	24 Mon.	50	0,9	12	0,7	11	1,0
Missing bring to show	Barbaro and Dis-sanayake 2013	Prospective, popula-tion-based sample	24 Mon.	50	0,7	12	0,9	11	1,0
Lack of "do-as-you-go" gameplay.	Barbaro and Dis-sanayake 2013	Prospective, popula-tion-based sample	24 Mon.	50	0,6	12	0,9	11	1,0

[11]	**Consensus-based recommendation for ages 24 months and older:**
KKP	Young children and preschoolers who are reported by parents or observed in one of the disease screening examinations (U7-U9) to have one or more of the following characteristics: - lack or absence of eye contact, - lack of bringing something to show for it, - little or no "as-if" play - no pointing gesture to show interest - Regression or loss of previously acquired skills in language or social interaction, In addition, the following symptom can also be considered for diagnostic clarification: - where parents express increasing concerns about their child's development at this time If the suspicion is confirmed, the child should be referred immediately to ~~a~~ centre specialising in the diagnosis of autism spectrum disorders.
	Strong consensus (14 out of 14)

B.2.6 Early symptoms of Asperger syndrome

There is a lack of meaningful, prospective studies for Asperger syndrome. Looking back (i.e. retrospectively), half of the parents state (Kamp-Becker et al. 2010b) that they had already been worried before the age of three. However, the specifics given are less specific than for early childhood autism and concern the following aspects:

- No, little or inadequate contact
- stereotypic behaviour
- Fear of change
- sensory abnormalities
- Striking reaction to approach of other children
- Limited fantasy game
- Makes few offers to share anything (food, toys, etc.)
- Rarely uses the pointing gesture with *accompanying* eye contact

- Rarely speaks just to be friendly or sociable, but mostly to communicate needs or give information.
- Stereotypical use of language
- Compulsive and ritualized behaviors

B.2.6.1 Current situation in Germany

An important role in identifying warning signs of a possible autism spectrum disorder in very young children in Germany is played by the early detection examinations ("U" examinations) carried out by paediatricians and adolescent doctors, general practitioners and general practitioners.

Another possibility is now offered by local and regional support systems within the framework of "early help" for parents and children (from pregnancy and in the first three years of life), which have been legally anchored in the Federal Child Protection Act since 2012. Knowledge transfer or training of the professional groups involved here seems to be significant, since behavioural conspicuities occurring in the context of autism spectrum disorders are not infrequently misinterpreted at first, e.g. as pronounced defiance of a young child, and in the course of time can provoke dysfunctional pedagogical reactions by the caregivers.

The school entry examination, which is carried out on all children aged 5-6 years, offers a further opportunity to identify abnormalities or symptoms that may indicate an autism spectrum disorder and should be referred for specific diagnosis at an appropriate centre.

B.3 Screening procedure

Text: Leonora Vllasaliu, Christine M. Freitag
Systematic literature search, data extraction: Marianne Menze, Magdalena Schütz, Stephanie Hoss, Marie Landenberger and Leonora Vllasaliu
Meta-Analyses: Katrin Jensen

B.3.1 Introduction

According to the three-stage system (1. symptoms/2. screening/3. diagnostics), a quick screening for autism spectrum disorder should be carried out if symptoms are present (B.2), in order to - if suspicion is confirmed - initiate adequate diagnostics or - if suspicion is not confirmed - either to have the person clarified with regard to other psychiatric and/or neurological differential diagnoses or to continue close monitoring with regard to the development of the symptoms.

With regard to this screening process, a great many questionnaires as well as individual observation instruments have been developed internationally and also systematically studied, only some of which are available in German translation. Since the present guideline refers exclusively to the German health care system, evidence-based recommendations are only made in this chapter for screening instruments that are available in Germany and in German. These include some non-systematic questionnaires, mainly translated from English, which are mostly accessible via the Internet. If the steering group became aware of these non-validated instruments during the systematic search process, the instruments are mentioned in this chapter and an evidence-based recommendation is made that these instruments should not be used according to the current state of knowledge. Such an evidence-based recommendation seems necessary because there are now numerous internet forums for "self" screening for autistic disorders, especially for adults, and the results of this "self-diagnosis" are often discussed by those affected with professional staff from the health and social care system.

Should all individuals be screened for autism and/or are there certain risk groups that should be screened in any case?

18) When should a child, adolescent, or adult be referred to a medical facility specializing in ASD diagnosis?

29. what screening tools are available (taking into account age, intelligence, stage of development)?

B.3.1.1 Procedure for the literature search

As part of the systematic search for screening instruments and evidence for the use of screening instruments, two systematic searches were first conducted for (1) internationally existing screening instruments and (2) for screening instruments available in German. A systematic search for validity studies was then conducted only for the instruments that remained based on the second search. In addition, a search for reliability studies was conducted. The results of this search are summarized in the method report. All instruments have at least a satisfactory reliability.

Inclusion criteria

As a certain quality of studies was considered essential, only studies were included,

- in which the reference diagnosis was based on ICD-9/ICD-10 or DMS-IIIR/DSM-IV(-TR) criteria, or was based on ADOS and/or ADI-R.
- There had to be a control group.
- The autism spectrum group and the control group should be at least N = 10 persons.
- Validity information (sensitivity/specificity) had to be provided so that four-field tables could be calculated and values compared where appropriate.

(The same inclusion criteria were also applied to the diagnostic studies [see Chap. B.4.]).

Depending on the specifics of the respective instrument, further exclusion criteria were discussed and applied. These are explicitly mentioned in the description of the results.

B.3.1.2 Use and relevance of screening instruments

Early detection and the associated possibility of early, professional support is important in autism spectrum disorders and can be crucial for the further development of the child (e.g. Kitzerow et al. 2014; Rogers and Vismara 2008). Screening tools can, on the one hand, help to improve precisely this early detection, but at the same time, conversely, avoid overburdening agencies specializing in the diagnosis of autism spectrum disorders. This is particularly relevant because the diagnostic process for autism spectrum disorders takes a lot of time. Screening instruments, on the other hand, are more economical; they are often questionnaires that pediatricians and adolescents, for example, can have parents fill out.

Different levels are distinguished for the use of screening procedures. One can either screen only at-risk groups ("level 2") (e.g. siblings of autism spectrum patients, children with developmental abnormalities, children with certain genetic syndromes) or the entire population is

screened ("level 1"), which can be done e.g. in U-examinations or school entry examinations. An important question that is also answered in this guideline is for which of these populations screening makes sense and which instruments should best be used at which level.

To classify the test quality of the screening instruments investigated below (as well as the diagnostic instruments, section B.4), the following guideline values for sensitivity and specificity were taken from the NICE adult guideline:

> 0.9	Excellent
0.8 – 0.9	Good
0.5 – 0.7	Moderate
0.3 – 0.4	Low
< 0.3	Bad

B.3.2 In which individuals is screening for autism spectrum disorders appropriate?

B.3.2.1 Summary from the source guidelines

NICE children (diagnostics)

In this source guideline, the use of screening instruments is only thematically addressed in cases of already existing suspicion due to first symptoms. The possibility of level 1 screening is not mentioned, and no risk groups are named in which screening should be routinely performed. However, several risk factors are considered, as these are considered by the guideline development group to be at least as important as a positive screening result in the decision to refer to a specialist service. The group concludes that the relevant professional should act primarily when autism-specific symptoms are concurrent with known risk factors, but not when a risk factor is singularly observable.

NICE Adult

No specific groups of people for whom screening would be appropriate are identified.

It is recommended that the following constellation of symptoms be evaluated for autism spectrum disorder:

1. **At least 1 out of 3:**

- Persistent difficulties in social interaction

- Persistent difficulties in social communication
- Stereotypical behaviors, resistance to change, or limited interests.

AND

2. **At least 1 of the following factors (often associated with autism):**

- Difficulties in obtaining or maintaining employment/training
- Difficulties in establishing or maintaining social relationships
- Early/current use of mental health services.
- (Neuro)psychiatric history

In adults with intelligence impairment, a clarification is recommended if the following aspects apply:

- Difficulties in reciprocal social interaction
- Lack of responsiveness to others
- Little to no change in behavior occurred as a function of different social situations.
- Hardly any signs of compassion
- Inflexible routines and resistance to change
- Striking repetitive actions

SIGN

The Scottish guideline explicitly recommends that population-based screening should *not be* performed, as no robust instrument for such level 1 screening exists. The decision as to whether there is a need for diagnostic clarification at a specialist centre should primarily be based on clinical assessment (for this purpose, SIGN refers to warning signs/symptoms; see also Chapter B.2 in the present guideline). Screening instruments could at most be used here in a supportive manner as a kind of structured guide to information gathering; although only two of them are mentioned at all in the guideline: the CHAT and the M-CHAT. However, it is stressed that these tools should only be used to gather information about clinical signs suggestive of increased risk, but *not to* rule out an autism spectrum diagnosis. Furthermore, SIGN points out that not all individuals with autism spectrum disorders are detected by such tools, so parents should be encouraged to seek clarification again if concerns about child development persist.

With regard to screening in at-risk populations (level 2), the working group recommends that this should be part of routine screening for children and adolescents with developmental delays, emotional and behavioral problems, and the presence of genetic syndromes. In addition, families of autism spectrum patients should be made aware that their siblings are also at increased

risk. In contrast to level 1 screening, the use of screening instruments is considered appropriate here. However, none is mentioned by name or recommended, as these are often only developed for certain age or diagnostic groups.

B.3.2.2 Current situation in Germany, adaptation of the recommendation

In Germany, there is no systematic screening for autism spectrum disorders yet, neither for the general population, as it would be conceivable e.g. in the context of paediatric U-examinations or school enrolment examinations, nor for children, adolescents or adults who represent a risk population, such as siblings of a child with autism spectrum disorder, children with delayed language development, developmental delay/mental disability, after prematurity or in the case of certain underlying genetic diseases. To date, no evidence-based findings or recommendations have been made in this regard.

Based on the evidence below on the validity of screening instruments and the findings of screening studies conducted to date, the following recommendation is made:

[12]	**Evidence-based recommendation** *Bowl Question 17 Part 1*
A [13]	Screening of the entire population of children, adolescents or adults for the presence of autism spectrum disorders should not be carried out, as the rate of false positive and false negative results is high for all screening instruments available in German. Screening individuals without further risk factors or symptoms, followed by a detailed diagnosis of the (false) positive screened individuals, overloads the specialized services and leads to a sharp increase in waiting time for individuals who have further pioneering risk factors (see below), making the diagnosis more likely.
Evidence level: 2 - 4	Strong consensus (14 out of 14)

[13]	**Consensus-based recommendation** *Bowl Question 17 Part 2*
KKP	In the presence of one of the following risk factors and at least one additional symptom indicating an autism spectrum disorder, screening should be considered: - genetic findings in which an increased rate of autism spectrum disorders has been described (e.g. mutation, microdeletion or microduplication, chromosomal aberration) - Drug exposure during pregnancy - Viral infections during pregnancy - Birth weight < 1500g and/or birth < 32 weeks - Neonatal seizures - Sibling with autism spectrum disorder
	Strong consensus (14 out of 14)

[13] Explanations of the grades of recommendation and levels of evidence can be found in the methods report.

B.3.3 Who should carry out the screening?

B.3.3.1 Summary from the source guidelines

NICE children (diagnostics)

It is not clear by whom and at which institution the screening should be carried out. It only mentions "*professionals*" who can use the structured information to make a decision on whether to refer the person to a specialist service. Indirectly, it is implied that the person should be able to refer to the correct service, as the symptoms of the initial suspicion may also be present in a range of other conditions. The role of the professional is therefore to gather information that will support correct referral to the appropriate diagnostic work-up. The NICE paediatric diagnostic guideline identifies three key sources that professionals can use to do this: Screening tools, knowledge about the presence of risk factors and whether these indicate an increased likelihood of autism spectrum disorders, and other information such as information about the child's behaviour in different contexts (home, nursery, school) or, if available, information from other agencies.

NICE adults:

It is anticipated that recognising signs or symptoms of autism spectrum disorder will be necessary across a wide range of health and social care settings. This could be nurses, doctors or social care workers.

SIGN

It is not specifically stated in the text who should carry out the screening, but rather that the first presentation could be made to a wide range of institutions, including the health and education system as well as social services. However, the text emphasizes the importance of child *health surveillance for* early detection and treatment of autism spectrum disorders. General examinations of child development should therefore be followed by an examination for autism spectrum disorders. All professionals working with children and adolescents should be familiar with autism spectrum disorders so that they can be considered as a possible explanation for norm deviant behavior. Individuals who wish to screen should be well versed in the core symptoms, but at the same time be aware of how multifaceted this disorder can be. In particular, the different levels of ability in terms of language and intelligence should be taken into account, as well as previous family support, personality and gender of the individual.

B.3.3.2 Current situation in Germany, adaptation of the recommendation

In Germany, there are currently no studies or recommendations on this topic. The guideline group makes the following consensus-based recommendation, taking into account the ideas from the source guidelines and the special circumstances of the German health and social care system:

[14]	**Consensus-based recommendation**
KKP	Screening examinations should only be conducted by health care professionals who are knowledgeable and skilled in mental and developmental disorders and the screening instruments used and their evaluation and interpretation.
	Strong consensus (14 out of 14)

B.3.4 What screening instruments are available and what is their validity?

B.3.4.1 Summary from the source guidelines

NICE children (diagnostics)

Validity data were found on the following instruments in the Child and Adolescent Guidelines: *Social Communication Questionnaire* (SCQ); *Modified Checklist for Autism in Toddlers* (M-CHAT); *Autism Behavior Checklist* (ABC); *Developmental Behavior Checklist - Early Screen* (DBC-ES); and the *Autism Spectrum Screening Questionnaire* (ASSQ).

The data are based on a total of 9 studies, 5 of which refer to the SCQ alone. For none of the instruments are the quality standards for predictive accuracy met, which were defined in advance by the NICE working group as follows: at least 80% sensitivity and specificity, whereby the lower value of the 95% confidence interval (95% CI) should not be less than 70%.

This also applies to the subdivision according to age and IQ groups, insofar as this was possible on the basis of the studies. In addition, the study quality of all studies was assessed as very low, so that the working group ultimately does not recommend *any* of the instruments and does not assess them as essential for decision-making. Although they could support the decision as to whether and where the person concerned should be referred further, further information is essential for this. If one of these instruments is used to collect information in a structured way and

if, after considering all the information, there is still a suspicion of an autism spectrum disorder, it is recommended that the information collected be forwarded as well, as the working group expects this to save time.

The following instruments did not meet the inclusion criteria of NICE children, so evidence was not sought here either: *Autism - Tics, ADHD and other coexisting conditions (ATAC), Baby and Infant Screen for Children with Autism Traits* (BISCUIT), *Brief Infant-Toddler Social and Emotional Assessment (*BITSEA), *Childhood Asperger Syndrome Test (*CAST), *Children's Communication Checklist* (CCC), *Infant/Toddler Checklist of Communication and Language Development* (CHECKLIST), *Child Symptom Inventory - 4 (*CSI-4), *Early Childhood Inventory - 4* (ECI-4), *Early Screening of Autistic Traits (*ESAT) questionnaire, *Early Social Communication Scale* (ESCS), *Gilliam Asperger's Disorder Scale* (GADS), *Infant/Toddlers Checklist* (ITC), *Krug Asperger's Disorder Index* (KADI), *MacArthur Communicative Development Inventories (*MCDI), *Parental Concerns Questionnaire* (PCQ), *Scale of Pervasive Developmental Disorder in Mentally Retarded Persons (*PDD-MRS), *Pervasive Developmental Disorder Rating Scale* (PDDRS), Pervasive *Developmental Disorder Screening Test* (PDDST), *Repetitive Behavior Scale* (RBS), *Screen for Social Intervention* (SSI), *Strengths and Difficulties Questionnaire (*SDQ), *Social Responsiveness Scale* (SRS), *Screening Tool for Autism in Two-year-olds* (STAT), *Young Autism and other developmental disorders Checkup Tool* (YACHT-18).

NICE Adult

The following instruments met the inclusion criteria: AQ, SCQ, Autism Behaviour Checklist (ABC) and the PDD-MRS. However, only the AQ included more than one study. Overall, none of the instruments meets the previously stated requirements for a good and very compact level 2 screening, so *none* is *generally recommended.* For people with normal intelligence, NICE adults suggests the AQ-10 (UK version), as the test performance of the different versions is considered similar and therefore a time-saving version is preferred. For people with reduced intelligence, none of the instruments studied are recommended.

SIGN

No particular instrument is recommended. The only ones mentioned at all as a possibility for level 1 screening are the CHAT and the M-CHAT, but their use in a level 1 screening is explicitly discouraged.

B.3.4.2 Current situation in Germany

Of the numerous screening instruments mentioned above, many are also translated into German and accessible through very different distribution channels. Partly they can be filled out directly on the internet, partly they can be downloaded from various internet sites and partly they are sold by companies that distribute psychodiagnostic tests. In each case, there are often different instructions, different cut-off values, etc., so that the interpretation of the results of a screening is often very difficult. Within the framework of this guideline, a search was first made for the screening instruments available in Germany. Only for these instruments a systematic search and meta-analysis was then followed.

B.3.4.3 Evidence based on current studies

The systematic search for screening instruments available in German resulted in a total of ten instruments, which are listed in Table 21Among these, no studies could be found for the following instruments that would have fulfilled the inclusion criteria, so that *no validation of the following instruments is* available: AQ-10, AQ-20, PDD-MRS (= SEAS-M/PDD-inventory), EQ-children and EQ-adults. Their use is therefore not recommended. Additionally, in 2015, after the consensus conference, the DiBAS-R and ASL for screening adults with intellectual disabilities were published, which will be discussed in more detail in the next revision of this guideline (Sappok et al. 2015).

For other instruments, either only a single study is available, or very few non-comparable studies are available, so that no meta-analysis could be calculated. Validity data for these are reported only descriptively in Table 22AQ-adults (Woodbury-Smith et al. 2005; Baron-Cohen et al. 2001), AQ-short (Freitag et al. 2007), AQ-children (Auyeung et al. 2008), AQ-adolescents (Baron-Cohen et al. 2006), ASAS (Melfsen, 2005), CAST (Matson et al. 2008a), CHAT (Oosterling et al. 2009; Baird et al. 2000; Scambler et al. 2001), MBAS (Kamp-Becker et al. 2005), and SRS-A (Bölte et al. 2011).

In the meta-analyses for Chapters B.3 Screening Procedures and B.4 DiagnosticProcedures, the investigated patient group (early childhood autism, Asperger syndrome, atypical autism/PDD-NOS or full spectrum with all three diagnoses) as well as the investigated control group (clinical utilization without or with spectrum, healthy subjects) and the cut-offs were examined in detail in each case. Only if all three characteristics matched could a study be included in a meta-analysis.

Table 21: Screening instruments included

Screening tool	Age groups	Format	number of items	Processing time	Information and material	Original publication	German language publication/translation
Diagnostic interview for autism, short version **(ADI-R short version)**	> 2 years	Structured interview	8	20 - 30 min.	See Hoffmann et al., 2013	Hoffmann et al. 2013	Hoffmann et al. 2013
Autism Spectrum Quotient, Adult Version **(AQ-Adult)**	Adulthood (≥ 16 years)	Questionnaire (patient)	50	10 min.	autismresearch-centre.com	Woodbury-Smith et al. 2005	Friday et al. 2007
Autism Spectrum-Quotient, short version **(AQ-k)**	Adulthood (≥ 16 years)	Questionnaire (patient)	33	< 10 min.	autismresearch-centre.com	Friday et al. 2007	Friday et al. 2007
Autism Spectrum-Quotient, child version **(AQ Child)**	4-11 years	Questionnaire (parents)	50	10 min.	autismresearch-centre.com	Auyeung et al. 2008	Gundelfinger (a) or Michel (b)
Autism Spectrum-Quotient, child version **(AQ-Adolescent)**	< 16 years	Questionnaire (parents)	50	10 min.	autismresearch-centre.com	Baron-Cohen et al. 2006	German translation only as self rating instead of external rating
The Australian Scale of Asperger`s Syndrome **(ASAS)**	Primary school age	Questionnaire (parents)	24	5 - 10 min.	www.aspergersyndrome.org	Garnett and Attwood 1995	Melfsen et al. 2005
Childhood Autism Spectrum Test **(CAST)**	4-11 years	Questionnaire (parents)	37	< 10 min.	autismresearch-centre.com	Scott et al. 2002	Prothmann (a) and Bölte (2005) (b) respectively.
Checklist for Autism in Toddlers (CHAT)	18-30 months	mixture of questionnaire (parents) and behavioural observation	14	15 min.	autismresearch-centre.com www.autismus-koeln.de/CHATFORMULAR.html	Baird et al. 2000; Scambler et al. 2001	Friday (a) and Prothmann14(b) 15respectively.

[14] Autism Research Centre, Section of Developmental Psychiatry, University of Cambridge, Douglas House, 18b Trumpington Road, CAMBRIDGE, CB2 2AH, England.

http://www.autismresearchcentre.com

[15] https://www.kgu.de/kliniken-institute-zentren/einrichtungen-des-klinikums/kliniken/psychiatrie-psychosomatik-und-psychotherapie/linksdownloads/downloads.html

Modified Checklist for Autism in Toddlers **(M-CHAT)**	16-30 months	Questionnaire (parents)	23	< 10 min.	www.m-chat.org	Robins et al. 2001	Bölte and Poustka 2005

Continued Table 21: Included screening instruments

Screening tool	Age groups	Format	number of items	Processing time	Information and material	Original publication	German language publication/translation
Social Communication Questionnaire **(FSK)** [formerly: Questionnaire on Behaviour and - Social Communication (VSK); English: **SCQ**].	From 4 years and mental age min. 2	Questionnaire (parents)	40	< 10 min.	Purchasable	Rutter et al. 2003	Bölte et al. 2006
Marburg Assessment Scale for Asperger Syndrome **(MBAS)**	6 - 24 years	Questionnaire (parents)	65	20 - 30 min.	Available online at Springer	Kamp-Becker et al. 2005	Is German developed
Social and Communication Disorder Checklist **(SCDC)**		Questionnaire (parents)	12	5 min.	Appendix Skuse et al., 2005	Skuse et al. 1997	Bölte et al. 2011
Social Responsiveness Scale **(SRS)**	2.5 to 18 years	Questionnaire (parents or teachers)	65	15-20 min	Purchasable	Constantino and Gruber 2005a	Bölte and Poustka 2008a
Social Responsiveness Scale for Adults **(SRS-A)**	Adults	Questionnaire external assessment	65	15-20 min	Purchasable	Constantino and Todd 2005b	Bölte et al. 2011

Table 22: Descriptive validity data

Disease	Control group	Age group	N	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Study	Additional notes
AQ adults										
AS	Healthy KG	16 - 60 years	232	32	0.79	0.67 - 0.89	0.98	0.94 - 0.99	Baron-Cohen et al. 2001	
AS	AI without ASS	18 - 69 years	100	32	0.77	0.65 - 0.86	0.74	0.54 - 0.89	Woodbury-Smith et al. 2005	Authors recommend cut-off of 26
Special subgroups: Gender										
AS ♂	Healthy KG ♂	16 - 60 years	121	32	0.76	0.60 - 0.87	0.96	0.89 - 0.99	Baron-Cohen et al. 2001	
AS ♀	Healthy KG ♀	16 - 60 years	111	32	0.92	0.64 - 1.00	0.99	0.94 - 1.00	see above	
AQ-Short										
AS/HFA	Healthy KG + forensically examined Pbn	Childhood to adulthood	341	17	0.89	0.65 - 0.99	0.92	0.88 - 0.94	Friday et al. 2007	
AQ Kids										
AUT + AS/HFA	Healthy KG	4 - 9 years	1765	76	0.95	0.93 - 0.97	0.95	0.94 - 0.96	Auyeung et al. 2008	
AUT	Healthy KG	4 - 9 years	1417	76	0.95	0.91 - 0.97	0.96	0.94 - 0.97	see above	
AS/HFA	Healthy KG	4 - 9 years	1573	76	0.95	0.92 - 0.97	0.96	0.94 - 0.97	see above	
AQ Youth										
AUT + AS/HFA	Healthy KG	9.8 - 16.5 years	181	30	0.89	0.83 - 0.94	1.00	0.93 - 1.00	Baron-Cohen et al. 2006	
AS/HFA	Healthy KG	10.3 - 16.5 years	102	30	0.90	0.79 - 0.97	1.00	0.93 - 1.00	see above	
AUT	Healthy KG	9.8 - 16.5 years	129	30	0.89	0.79 - 0.95	1.00	0.93 - 1.00	see above	
ASAS										
AS	AI without ASS	6 - 19 years	51	13	0.78	0.52 - 0.94	0.55	0.36 - 0.72	Melfsen et al. 2005	
CAST										
AS	Healthy KG	2 - 16 years	29	15	0.71	0.42 - 0.92	0.47	0.21 - 0.73	Matson et al. 2008a	

Continued Table 22: Descriptive validity data

Disease	Control group	Age group	N	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Study	Additional notes
CAST										
AS	Healthy KG	2 - 16 years	29	15	0.71	0.42 - 0.92	0.47	0.21 - 0.73	Matson et al. 2008a	
CHAT										
AUT	Healthy KG + PDD	16 - 20 months	16235	5	0.20	0.10 - 0.34	1.00	1.00 - 1.00	Baird et al. 2000	Cut-off 5: High risk;
AUT	Healthy KG + PDD	16 - 20 months	16235	2	0.38	0.25 - 0.53	0.98	0.97 - .098	see above	Cut-off 2: Medium and high risk
AUT	Other developmental disorders	2 - 3 years	44	5	0.46	0.27 - 0.67	1.00	0.81 - 1.00	Scambler et al. 2001	
AUT	Other developmental disorders	2 - 3 years	44	2	0.65	0.44 - 0.83	1.00	0.81 - 1.00	see above	
SCDC										
ASS	AI without ASS + Healthy KG	2.5 - 18 years	402	9	0.89	0.84 - 0.93	0.69	0.62 - 0.75	Skuse et al. 2005	
ASS	Healthy KG	4 - 18 years	225	9	0.87	[0.81, 0.92]	0.82	0.71 - 0.90	Bölte et al. 2011	
MBAS										
AS/HFA	AI without ASS	*(MW 11.89, SD 3.59)*	91	104	0.95	0.85 - 0.99	0.96	0.85 - 0.99	Kamp-Becker et al. 2005	
SRS-A										
HF ASS	AI without ASS + Healthy KG	18 - 79 years	265	67	0.85	0.62 - 0.97	0.82	0.76 - 0.86	Bölte et al. 2011	

Continued Table 22: Descriptive validity data

Disease	Control group	Age group	N	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Study	Additional notes
SRS										
ASS	AI without ASS	4 - 15 years	48	60	0.83	0.66 - 0.93	0.38	0.14 - 0.68	Aldridge et al. 2012	Teacher version
ASS	AI without ASS	4 - 17 years	316	75	0.66	0.60 - 0.72	0.32	0.20 - 0.47	Warren et al. 2012	Parent version
ASS	Healthy KG	4 - 24 years	3207	60	0.95	0.94 - 0.96	0.96	0.95 - 0.97	Schanding et al. 2012	Parent version
ASS	Healthy KG	4 - 19 years	1365	60	0.69	0.66 - 0.73	0.95	0.93 - 0.97	Schanding et al. 2012	Teacher version
ASS	AI without ASS	4 - 18 years	442	60	0.75	0.69 - 0.80	0.96	0.92 - 0.98	Constantino et al. 2007	Parent AND teacher version [16]
ASS	Healthy KG	4 - 18 years	225	75	0.80	0.72 - 0.86	1.00	0.95 - 1.00	Bölte et al. 2011	Parent version
ASS	AI without ASS	11 - 13years	119	60	0.79	0.67 - 0.87	0.67	0.52 - 0.80	Charman et al. 2007	Parent version
For differential diagnosis examined										
ASS	Selective mutism (SM)	6 - 18 years	103	75	0.83	0.71 - 0.92	0.74	0.59 - 0.86	Cholemkery et al. 2014b	
ASS	Social phobia (SP)	6 - 18 years	98	78	0.80	0.68 - 0.89	0.84	0.69 - 0.94	see above	
ASS	SM + SP	6 - 18 years	141	75	0.83	0.71 - 0.92	0.77	0.66 - 0.85	see above	
ASS	Disruptive behavioural disorders	6 - 18 years	110	80	0.76	0.63 - 0.87	0.82	0.69 - 0.91	Cholemkery et al. 2014a	
ASS	ADHD	4 - 18 years	246	75	0.80	0.72 - 0.86	0.78	0.68 - 0.85	Bölte et al. 2011	
ASS	Anxiety Disorders	4 - 18 years	189	75	0.81	0.74 - 0.87	0.73	0.57- 0.86	see above	

[16] Consideration of the lower of two total scores (1st total score = parent rating/2nd total score = teacher rating).

Continued Table 22: Descriptive validity data

Disease	Control group	Age group	N	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Study	Additional notes
SRS (continued) Broken down by sex										
ASS ♀	Healthy KG ♀	6 - 18 years	35	64	1.00	0.80 - 1.00	1.00	0.81 - 1.00	Cholemkery et al. 2014b	
ASS ♂	Healthy KG ♂	6 - 18 years	67	43	0.98	0.88 - 1.00	0.96	0.79 - 1.00	see above	
ASS ♀	Selective mutism ♀	6 - 18 years	34	88	0.82	0.57 - 0.96	0.82	0.57 - 0.96	see above	
ASS ♂	Selective mutism ♂	6 - 18 years	69	75	0.79	0.64 - 0.90	0.81	0.61 - 0.93	see above	
ASS ♀	Social phobia ♀	6 - 18 years	34	71	1.00	0.80 - 1.00	0.71	0.44 - 0.90	see above	
ASS ♂	Social phobia ♂	6 - 18 years	63	80	0.74	0.59 - 0.86	0.90	0.68 - 0.99	see above	
ASS ♀	SM + SP	6 - 18 years	52	71	1.00	0.80 - 1.00	0.69	0.51 - 0.83	see above	
ASS ♂	SM + SP	6 - 18 years	89	75	0.79	0.64 - 0.90	0.83	0.69 - 0.92	see above	
ADI-R short version										
ASS	AI without ASS	2 - 24 years	309	5	0.93	0.88 - 0.96	0.47	0.39 - 0.55	Hoffmann et al. in press	
ASS	AI without ASS	Until 11 years	159	5	0.96	0.87 - 0.99	0.45	0.34 - 0.55	see above	
Separated by IQ										
ASS	AI without ASS	2 - 24 years		5	0.93	0.81 - 0.99	0.53	0.34 - 0.72	see above	**IQ < 85**
ASS	AI without ASS	2 - 24 years		5	0.93	0.86 - 0.97	0.46	0.35 - 0.57	see above	**IQ 85-114**
ASS	AI without ASS	2 - 24 years		5	0.96	0.78 - 1.00	0.46	0.30 - 0.63	see above	**>114**

Continued Table 22: Descriptive validity data

Disease	Control group	Age group	N	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Study	Additional notes
ADI-R short version										
ASS	AI without ASS	2 - 24 years		6	0.70	0.54 - 0.83	0.83	0.65 - 0.94	see above	**IQ < 85**
ASS	AI without ASS	2 - 24 years		6	0.63	0.52 - 0.73	0.69	0.58 - 0.78	see above	**IQ 85-114**
ASS	AI without ASS	2 - 24 years		6	0.70	0.47 - 0.87	0.77	0.61 - 0.89	see above	**>114**
Separated by gender										
ASS ♂	AI without ASS ♂	2 - 24 years		5	0.93	0.87 - 0.97	0.46	0.37 - 0.54	see above	
ASS ♂	AI without ASS ♂	2 - 24 years		6	0.65	0.56 - 0.73	0.72	0.64 - 0.79	see above	
ASS ♀	AI without ASS ♀	2 - 24 years		5	0.91	0.71 - 0.99	0.57	0.29 - 0.82	see above	
ASS ♀	AI without ASS ♀	2 - 24 years		6	0.68	0.45 - 0.86	0.86	0.57 - 0.98	see above	
For differential diagnosis										
AS	ADHD	(MW: 10.65 SD: 3.19)	105	6	0.82	0.70 - 0.91	0.93	0.81 - 0.99	Hoffmann et al. 2013	
AS	ADHD	Until 11 years	55	6	0.92	0.74 - 0.99	0.90	0.73 - 0.98	Hoffmann 2013	
SCQ/FSK										
ASS	AI without ASS	24-92 months	590	15	0.71	0.67 - 0.75	0.71	0.63 - 0.78	Corsello et al. 2007	
ASS without AUT	AI without ASS	Toddler/Pre-school	25	15	0.43	0.10 - 0.82	0.89	0.65 - 0.99	Wiggins et al. 2007	
ASS	Healthy KG	School Age	658	15	0.82	0.48 - 0.98	0.97	0.95 - 0.98	Chandler et al. 2007	
AUT	AI without ASS	Toddler/Pre-school	157	11	0.92	0.85 - 0.97	0.26	0.16 - 0.39	Oosterling et al. 2010a	
ASS*	AI without ASS	School Age	173	22	0.64	0.31 - 0.89	0.96	0.91 - 0.98	Johnson et al. 2010	

Continued Table 22: Descriptive validity data

Disease	Control group	Age group	N	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Study	Additional notes

SCQ as teacher sheet									
ASS	Healthy KG	4 - 21 years	927	15	0.60	0.56 - 0.64	0.95	0.92 - 0.97	Schanding et al. 2012
ASS	Healthy KG	4 - 21 years	927	12	0.74	0.70 - 0.78	0.88	0.84 - 0.91	see above
SCQ for differential diagnosis									
ASA without ADHD	ADHD	Children and teenagers	122	15	0.60	0.39 - 0.79	0.95	0.87- 0.99	Schwenck and Friday 2014
ASA with ADHD	ADHD	Children and teenagers	97	15	0.91	0.77- 0.98	0.95	0.87- 0.99	see above
ASS with ID	ID	Adults	69	15	0.71	0.48 - 0.89	0.77	0.63 - 0.88	Brooks and Benson 2013

Notes: AI = Clinical Utilization Population, ASD = Full Autism Spectrum, AUT = Early Childhood Autism, AS = Asperger's; HFA = High Functioning Autism, ID = Intellectual Disabilities. *9 of the 11 ASD subjects have Early Childhood Autism and the other two PDD-NOS; the authors therefore still tested the autism cut-off suggested in the literature in this population, but this was not the optimal cut-off determined.

AQ (different versions) - Autism Spectrum Quotient

The AQ was predominantly tested against healthy control subjects, where it has very good sensitivity and specificity. In contrast, sensitivity and specificity are much lower when differentiating clinical populations. Since especially the sensitivity to clinical comparison populations is relatively low and the studies consistently show an evidence level of only 3, no recommendation for the use of the AQ (independent of age) can be made at present.

ASAS - Australian Scale for the Assessment of Asperger Syndrome

A single low-quality study is available. A low specificity was found compared to clinical control subjects. The sensitivity also appears low for a screening instrument, so that its use cannot currently be recommended.

CAST - Childhood Autism Spectrum Test

A single low-quality study is available. A low specificity was found compared to clinical control subjects. The sensitivity also appears low for a screening instrument, so that its use cannot currently be recommended.

CHAT - Checklist for Autism in Toddlers

The CHAT shows a high specificity but a very poor sensitivity. Since sensitivity is more important for screening instruments than for diagnostic instruments (see Aldridge et al. 2012) and the CHAT has meanwhile been replaced by the M-CHAT, this instrument cannot be recommended either.

MBAS - Marburg Assessment Scale for Asperger Syndrome

The MBAS shows excellent validity values in comparison to a clinical utilization population and is therefore a promising instrument for the detection of high-functioning autism spectrum disorders. Unfortunately, since the only study currently available has an evidence level of only 3, the MBAS cannot be recommended without reservation at this time. An independent replication study with a reference standard independent of the instrument should be conducted.

SRS-A - Scale for the Assessment of Social Responsiveness for Adults

The SRS-A has so far only been tested against a mixed clinical and healthy control group. The study has an evidence level of 3. Therefore, the SRS-A cannot be recommended without reservation at the moment. An independent replication study with a reference standard independent of the instrument should be conducted.

Only for 5 instruments were enough comparable studies found so that meta-analyses could be calculated. The results of these calculations are shown in Table 23

ADI-R short version - collected in interview with parents

The meta-analysis was calculated on the basis of a published study and a study that is currently in print. Both studies show a low quality with a high risk of bias, because the ADI-R was used to establish the diagnosis and at the same time the short version was calculated based on the ADI-R (evidence level 4). Compared with the clinical utilisation population, the studies showed good sensitivity in primary school children. An independent replication study should be conducted with a reference standard independent of the instrument, as well as conducting the ADI-R short version in the interview alone (without the remaining questions of the ADI-R). Only then can a statement be made about the use of the instrument. Currently, the instrument cannot be recommended.

FSK (= SCQ) - Questionnaire on social communication

The FSK is one of the best-studied screening instruments. The officially published cut-off for the FSK is 15 and has already been investigated in numerous studies. In addition, two other cut-offs have been proposed, one of which is said to lead to better scores in young children as well as in high-functioning patients with autism spectrum disorders (Kröger et al. 2011) (cut-off 11) and the other has been suggested as a separation between early childhood autism and the spectrum (cut-off 22). In addition, it is discussed whether the cut-off of 15 is not too high overall, especially for the range of high-functioning autism spectrum disorders, so that it should be lowered to improve sensitivity (see Schwenck and Freitag 2014).

The meta-analysis calculated for this guideline shows that at the published cut-off of 15, the FSK has a good sensitivity > 80% with respect to detecting the full autism spectrum only for primary school age compared to a clinical utilization population. At preschool age, the sensitivity for a screening instrument is significantly too low, with a sensitivity < 70% for autism and autism spectrum. The alternative cut-off value of 11 leads to a significantly better sensitivity > 80% for the autism spectrum at this age, although the specificity is significantly reduced.

Using the cut-off of 22 to separate Early Childhood Autism versus Spectrum and Clinical Utilization, meta-analysis shows a deterioration in sensitivity from 78% to 68%, but an improvement in specificity from 58% to 85%.

Overall, the study quality is almost consistently very low (see Appendix: QUADAS II tables). In particular, patient selection, but also the possible lack of blinding of the index test or the fact that in 3 studies new cut-offs were generated within the same sample in the first place, may have led to distortions of the data here. Whether blinding was present for the reference standard is unclear for most studies. Most studies were assessed with an evidence level of 3, a few with an evidence level of 2.

M-CHAT - Modified checklist for autism in young children

The M-CHAT has been studied primarily as a level 1 screener. Most of these population-based studies did not meet the inclusion criteria for the guidelines. Five studies were eligible for inclusion in the meta-analysis, of which two (Snow and Lecavalier 2008; Eaves 2006) examine the M-CHAT as a single-stage procedure and three (Robins et al. 2014, Wiggins et al. 2014, Canal-Bedia et al. 2011) examine the M-CHAT as a 2-stage procedure with follow-up telephone or on-site interview. In the 2-stage procedure, the interviewer revisits the items with the parent/caregiver and also asks for everyday examples. Only the symptoms confirmed in the second examination are then considered in the evaluation. For the meta-analysis of the two-stage instruments, the stated sensitivity and specificity values of the respective studies were not adopted, which for this purpose included all negatively screened persons without diagnostic testing in the healthy control group; instead, only the persons actually evaluated with regard to a correct diagnosis were used. As a result, the control groups are very small.

The two-step procedure showed an excellent sensitivity of 92% but a low specificity of 46%. For this two-stage procedure, a double cut-off was used in the studies, which had previously only been used as separate cut-off options in the single-stage M-CHAT. In the M-CHAT with follow-up, a child is classified as being at risk for an autism spectrum disorder after the second interview if either 3 of the total of 23 items were rated as present or if 2 of 6 of the so-called "*key items*", which are intended to separate particularly well, are fulfilled.

For the one-step procedure, the M-CHAT with the cut-off of 2/6 *key items* shows a similar sensitivity (91%), but a slightly worse specificity (30%). For the cut-off 3 out of 23, however, it is worse for both values than for the two-step interview.

The study quality of the individual studies varied greatly and the respective evidence level was between 2 - 4.

SCDC- Social and Communication Disorders Checklist

Compared to healthy individuals, sensitivity and specificity are relatively high; when clinical comparison groups were included, specificity was significantly lower. The available studies have an evidence level of 3. The instrument cannot be recommended at present.

SRS - Scale for the assessment of social responsiveness

The SRS exists as a parent and a teacher version, but it has only been studied well enough with regard to the parent version, so that a meta-analytical calculation was only possible for this version. The results of these calculations show that the SRS has moderate to good sensitivities (0.70 - 0.89) in differentiating individuals with autism spectrum disorders from those who showed other clinical abnormalities, but only low to good (0.43 - 0.84) specificities. Different cut-offs have been used for SRS in the scientific literature and have also been consistently reported in different studies. In the present study, the cut-off of 75 shows the best values. The study quality is very low (see Method Report/Appendix QUADAS-II), and the evidence level of the studies is 2 - 3, with significantly more studies showing an evidence level of 3.

Table 23: Results of meta-analyses for screening procedures

Disease	Control group	Age group	Number of studies	N persons	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Notes
SCQ (Corsello et al. 2007; Oosterling et al. 2009; Oosterling et al. 2010a; Wiggins et al. 2007; Allen et al. 2007; Eaves 2006; Eaves et al. 2006a; Snow and Lecavalier 2008; Chandler et al. 2007; Charman et al. 2007; Johnson et al. 2010; Schwenck and Freitag 2014; Warren et al. 2012; Schanding et al. 2012; Kröger et al. 2011).										
AUT	Non-AUT	2 - 16 years	2	747	15	0.78	0.73 - 0.82	0.58	0.52 - 0.63	
AUT	AI without ASS	Toddler/ Preschool	2	187	15	0.67	0.42 - 0.92	0.75	0.48 - 1.02	
AUT	AI without ASS	2 - 16 years	2	463	15	0.68	0.41 - 0.95	0.79	0.61 - 0.97	
ASS	AI without ASS	Toddler/ Preschool	8	1075	15	0.67	0.60 - 0.73	0.66	0.56 - 0.74	
ASS	AI without ASS	School Age	6	1306	15	0.80	0.72 - 0.86	0.77	0.58 - 0.89	
ASS	ADHD without ASD	Children and teenagers	2	193	11	0.85	0.77 - 0.93	0.78	0.67 - 0.89	
ASS	AI without ASS + Healthy KG	School Age	2	1129	15	0.84	0.75 - 0.93	0.95	0.91 - 1.00	
ASS	Healthy KG	4 - 28 years	2	2470	15	0.75	0.72 - 0.79	0.98	0.95 - 1.02	
ASS	AI without ASS	Toddler/ Preschool	6	916	11	0.84	0.79 - 0.88	0.53	0.32 - 0.73	
AUT	Non-AUT	2 - 16 years	2	845	22	0.68	0.23 - 1.12	0.85	0.81 - 0.89	

Continued Table 23: Results of meta-analyses for screening procedures

Disease	Control group	Age group	Number of studies	N persons	Cut-Off	Sensitivity	95% CI	Specificity	95% CI	Notes
M-CHAT (Eaves 2006; Snow and Lecavalier 2008).										
ASS	AI without ASS	Toddler/ Preschool	2	138	2 out of 6	0.74	0.65 - 0.83	0.42	0.27 - 0.57	
ASS	AI without ASS	Toddler/ Preschool	2	138	3 from 23	0.91	0.85 - 0.97	0.30	0.16 - 0.44	
M-CHAT with follow-up interview (Canal-Bedia et al. 2011; Robins et al. 2014; Wiggins et al. 2014).										
ASS	AI without ASS + Healthy KG	Toddler/ Preschool	3	401	2 out of 6 or 3 out of 23	0.92	0.81 - 1.03	0.46	0.00 - 1.00	
ADI-R short version (Hoffmann et al. 2013; Hoffmann et al. in press)										
ASS	AI without ASS	2 - 24 years	2	414	6	0.74	0.57 - 0.90	0.83	0.64 - 1.00	In Hoffmann 2013, only Pbn with ADHD are in the KG.
ASS	AI without ASS	Until 11 years	2	214	6	0.83	0.66 - 1.00	0.81	0.64 - 0.98	
SCDC (Bölte et al. 2011; Skuse et al. 2005)										
ASS	AI without ASS	2.5 - 18 years	2	687	9	0.88	0.83 - 0.93	0.38	0.32 - 0.44	
SRS (Aldridge et al. 2012; Charman et al. 2007; Warren et al. 2012; Bölte et al. 2011; Schanding et al. 2012; Bölte and Poustka 2008a).										
ASS	AI without ASS	4 - 17 years	3	528	60	0.89	0.79 - 0.98	0.43	0.11 - 0.75	Parent version
ASS	AI without ASS	4 - 24 years	2	3608	75	0.80	0.78 - 0.82	0.84	0.54 - 1.15	Parent version
ASS	Healthy KG	4 - 18 years	2	897	85	0.76	0.70 - 0.82	0.79	0.74 - 0.84	Parent version

Notes: AI = Clinical Utilization Population, ASD = Full Autism Spectrum, AUT = Early Childhood Autism, AS = Asperger's.

B.3.5 For which individuals (age, IQ, special risk factors, special differential diagnostic considerations, etc.) should which screening instrument be used?

B.3.5.1 Summary from the source guidelines

NICE children (diagnostics)

No specific instrument is recommended. Although the data of the included 9 studies were also subdivided and considered according to age groups and IQ, none of the instruments is recommended, not even for special groups, due to the poor validity results and study quality.

NICE Adult

Autism: For the identification of possible autism in a broad spectrum of intellectual, social and personal abilities, the FSK (= ASQ/SCQ) and the ABC are recommended. Both tests showed good sensitivities and specificities as well as relatively good internal consistency. Competitive validity was sufficient for the ABC and good for the ASQ/SCQ. However, a high risk of bias in the corresponding validation studies should be considered for both instruments. In addition, the clinical utility of the FSK (= ASQ/SCQ) is questionable, as it is not freely available and can only be used with the permission of the developers.

High-Functioning Autism: Only the AQ (all versions) is recommended for identifying possible autism at IQ > 70. The 50-item AQ shows good sensitivity and excellent specificity at a cutoff of 32, good to excellent sensitivity at a cutoff of 26, but only low to moderate specificity. The 20-item AQ showed moderate sensitivity and specificity, and the 21-item AQ showed excellent sensitivity and good specificity. The 10-item AQ showed moderate sensitivity and excellent specificity in the Japanese version and good sensitivity and excellent specificity in the British version. Internal consistency and discriminant validity were good for all AQ versions, while retest reliability was good for the 50-item AQ but unacceptable for the 21-item AQ and the 10-item AQ. The 50-item AQ also showed good interrater reliability. In general, a high risk of bias in the corresponding validation studies and concerns about applicability should be considered. Overall, the clinical utility of the AQ is rated as good, as it can be performed quickly and is available online free of charge.

Intelligence impairment: Only the PDD-MRS is recommended for the identification of profound developmental disorders in persons with intelligence impairment. It shows good sensitivity and specificity, interrater reliability, retest reliability and internal consistency. However, a

high risk of bias as well as concerns about the applicability in the corresponding validation studies should be taken into account.

For the identification of autism in individuals with intelligence impairment, the recording of specific autistic behaviors, independent of formal diagnostic instruments, has also been reported. Here, the presence of at least 2 out of 5 autistic features (minimal language; low social interaction; lack of empathy; inflexible routine actions; stereotyped behaviors) is associated with the best sensitivity and specificity.

Women: No instrument exists that is specific to this population. However, it is suggested that autism spectrum disorders may be underdiagnosed in females compared to males. Possible reasons cited include better social, language, and communication skills, fewer inappropriate specific interests, and less aggressive and hyperactive behavior in girls, as well as a tendency for girls who appear socially withdrawn to be more likely to be assessed as "shy." A possible interaction with other mental impairments should be noted.

Older persons: No instrument exists that is specific to this population. However, it is noted that autism spectrum disorders may be under-diagnosed in the elderly, particularly in light of the initial introduction of autism disorder in the DSM-III in 1980. Other behavioral or medical problems may present additional barriers to identification.

Ethnic minorities: No instrument exists that is tailored to specific ethnic groups. However, various studies indicate underdiagnosis in various ethnic minorities compared to white patients. This is true for dark-skinned children, Asian and Hispanic children (especially those with intelligence impairment), and Moroccan and Turkish children.

Transgender persons: No instrument exists that is specific to this population. However, it is noted that autism spectrum disorders may be underdiagnosed in female-to-male transsexuals. In addition, there may be an increased prevalence of autism spectrum disorders of 6% in young people with gender dysphoria.

SIGN

There is no allocation of instruments to specific groups; rather, no specific instrument is recommended, precisely because these are often aimed at specific age or diagnostic groups (e.g. specifically for Asperger's syndrome), so that the choice is based on this and none can be recommended in general.

B.3.5.2 Evidence based on current studies

For all of the results that follow, it should be noted at the outset that apart from the age groups, the data can again only be reported descriptively, as there are not enough studies that look at other subgroups at all, or do so similarly enough for them to be summarised.

SRS: The results of the calculated meta-analysis only refer to a broad spectrum of childhood and adolescence; no data are available here for special subgroups or only for the very small, middle age range of 11 - 13 years, from which no recommendation for a specific age group can be derived. The SRS has also been further investigated with regard to its ability to differentiate between autism spectrum disorders and anxiety disorders - specifically social phobia and selective mutism (Cholemkery et al. 2014b, Bölte et al. 2011). Compared to the separation of healthy subjects, the values are, as expected, significantly worse, but the sensitivity is still in the good and specificity in the moderate to good range. If one still separates here according to gender, the values for women and girls are better, but for boys and men somewhat worse. The differentiation of autism spectrum disorders and ADHD (Bölte 2010) as well as disruptive behaviour disorders (Cholemkery et al. 2014a) also shows moderate to good values.

SCDC: The SCDC is intended for children and adolescents and has only been studied for this broad age range. Therefore, no validity data are available for specific age subgroups. Distinctions according to IQ are not available. However, it was tested in comparison to both the ADHD and anxiety disorder control groups. With ADHD as the comparison group, there was a very good sensitivity of 90% but an extremely poor specificity of 29% for cut-off 8 and a good sensitivity of 85% and slightly better but still lower specificity of 43% for cut-off 9. In the case of anxiety disorders, the situation is quite similar: for a cut-off of 8, the sensitivity is 90% and the specificity 34%, and for cut-off 9, the values for sensitivity are 87% and for specificity 44%.

ADI-R Short Version: In differentiating autism spectrum disorders from ADHD, the ADI-R Short Version shows excellent sensitivity and specificity scores. The cut-off of 5 also shows excellent sensitivity scores in all three IQ subgroups (<85, 85 - 114, > 114), but only low to moderate specificity scores. It was also examined separately by gender. Both the cut-off of 5 and that of 6 again show excellent sensitivity values in girls and women, but only low to moderate specificities. For the male gender all values are rather moderate. Furthermore, the instrument was meta-analytically examined for the age range of 2 - 11 years. Here it showed good sensitivity and specificity values.

FSK = SCQ: The FSK has been studied mainly in preschool and school age, where it shows good values especially for school age. In toddler/preschool age, the proposed lower cut-off of

11 led to an improvement in sensitivity from 67% to 84%, but specificity decreases from 66% to 53%. For adults without intelligence impairment, studies in this regard are still lacking, so that no statement can be made about the suitability of the FSK.

However, the FSK has been studied in adults with intelligence impairment (Brooks and Benson 2013). In this population, it has only moderate sensitivity and specificity. In contrast, when separating autism spectrum disorders from ADHD, it usually shows good to excellent sensitivities and specificities.

Johnson and colleagues (2010) have also investigated the question of how the validity of the FSK turns out in the risk population of premature infants. They found a good sensitivity of 82% and an equally good specificity of 88%.

The FSK was also examined in comparison to ADHD (Kröger et al. 2011; Schwenck and Freitag 2014). Both studies showed that this comparison yields quite good results, but that a lower cut-off is better suited for this differentiation. With a cut-off of 11, Kröger and colleagues (2011) found a sensitivity of 87% and a specificity of 83% for examinees with an IQ ≥ 70, whereas in the study by Schwenck et al. (2014) only a sensitivity of 80% and a specificity of 69% for the same comparison. Schwenck et al. (2014) therefore even recommend to choose a cut-off of only 10 (sensitivity: 84%, specificity: 65%). The risk of bias is high due to the poor study quality.

M-CHAT: The M-CHAT has only been studied for very young children. For results see chapter 3.4.

For High Functioning Autism and Asperger's, specific instruments such as the MBAS and the ASAS have been developed. The MBAS shows good scores, but replication studies are lacking. The studies on the ASAS are insufficient (see above).

With regard to the age groups, the age-specific AQs show very good values, but only in comparison to healthy persons. The clinically relevant question of validity in relation to a clinical utilisation population was hardly investigated.

[15]	**Evidence-based recommendation** *Bowl question 29*

0	Due to the insufficient study quality, none of the existing instruments can be recommended as mandatory for screening. A diagnosis can neither be made nor ruled out on the basis of screening instruments alone. For **toddlers** from the age of two, the 2-step M-CHAT (Modified Checklist for Autism in Toddlers) can be used to confirm a suspicion regarding an autism spectrum disorder. However, the specificity is very low, so the results must be interpreted very cautiously. Several cut-off values exist for the FSK (Social Communication Questionnaire). It can be used with **preschool and elementary school children** regarding all autism spectrum disorders with a cut-off value of 11 (higher sensitivity, lower specificity), especially when it comes to the differential diagnosis of ADHD. The cut-off value of 15 shows a somewhat more balanced sensitivity and specificity in **school children and adolescents**, but can be judged as moderate overall. The MBAS (Marburg Assessment Scale for Asperger's Syndrome) can be used from **primary school age up to adolescence for** the questioning of a **high-functioning autism spectrum disorder.** The SRS (Social Responsiveness Scale) can be used from **preschool to adolescence.** The cut-off value of 60 shows a high sensitivity but a low specificity. The cut-off value of 75 leads to a more balanced sensitivity and specificity (both ≥ 80) and also separates high-functioning autism spectrum disorders relatively well against **ADHD, social behaviour disorders, social phobia and selective mutism.** The SRS-A (Social Responsiveness Scale for Adults) and the AQ (Autism Spectrum Quotient) can be used in **adulthood in** individuals without intelligence impairment, but the specificity is very low, so the results must be interpreted very cautiously. The FSK (Social Competence Questionnaire) can be used with **adults with intelligence impairment.**

	The SEAS-M (Scale for the Assessment of Autism Spectrum Disorders in the Less Abled) can be used with **children, adolescents, and adults with intelligence impairment.**
	
	In addition, the following recommendation is taken from NICE adults:
	
	In adults with intelligence impairment, the following behaviors should prompt diagnostic workup:
	
	• Poor reciprocal social interaction; this includes
	  ○ Limited interaction with others (e.g., distant, disinterested, or unusual behavior)
	  ○ Only interactions from which a benefit is derived
	  ○ Naive or unusual social approach
	• Lack of responsibility towards others and/or one-sided interactions
	• Behaviour changes little or not at all in response to different social situations
	• No or little social demonstration of empathy
	• Rigid routines and resistance to change
	• Noticeable repetitive activity (e.g., finger mannerisms) especially in stressful situations or when emotions are expressed.
	If two or more of these behaviors are present, the individual should be referred to a service specializing in autism spectrum disorder.
	
	Other screening instruments should not currently be used due to poor study quality.

Evidence: **2 – 4**	Strong consensus (14 out of 14)

B.3.6 What conclusions should be drawn in case of positive as well as negative screening results?

B.3.6.1 Summary from the source guidelines

NICE children (diagnostics)

A positive result could support the decision to refer the individual to a specialist service, but may also be an indication of the presence of another condition and therefore not sufficient in itself to make that decision. A negative result does not rule out the presence of autism spectrum disorder.

NICE Adult

If the AQ-10 score is greater than 6, or if there is a strong clinical suspicion of autism spectrum disorders, the individual should be referred to a specialized agency for diagnosis.

In individuals with intelligence impairment, the following behaviors should lead to diagnostic clarification:

- Poor reciprocal social interaction; this includes
  - Limited interaction with others (e.g., distant, disinterested, or unusual behavior)
  - Only interactions from which a benefit is derived
  - Naive or unusual social approach
- Lack of responsibility towards others and/or one-sided interactions
- Behaviour changes little or not at all in response to different social situations
- No or little social demonstration of empathy
- Rigid routines and resistance to change
- Noticeable repetitive activity (e.g., finger mannerisms) especially in stressful situations or when emotions are expressed.

If two or more of these behaviors are present, the individual should be referred to a service specializing in autism spectrum disorder.

SIGN

If the screening result is positive, the affected person should be referred to a specialized agency for diagnostic clarification. If the result is negative, it should not be assumed that the child does

not have an autism spectrum disorder. The parents or guardians should therefore be encouraged to return if their concerns about the child's development remain.

B.3.6.2 Current situation in Germany, adaptation of the recommendation

In Germany, there is currently no standardised use of screening instruments; the handling of a positive or negative result also varies greatly. Relatively often, a negative screening result seems to lead to the exclusion of the diagnosis, although false negatives can occur with any instrument. In the FSK, the cut-off value of 16 is often used, which leads to a high number of false negatives.

[16]	**Consensus-based recommendation** *Bowl question 18*
KKP	In case of clinical suspicion and a positive screening result, the affected person should be referred to an agency specializing in the diagnosis of autism spectrum disorders. In the case of a negative screening result, a different approach should be taken. 1. If an autism spectrum disorder also seems clinically unlikely and parents/caregivers/affected person report no other specific symptoms, an autism spectrum disorder can thus be ruled out. The relevant psychiatric, somatic and/or genetic differential diagnoses should be clarified if there are clinical indications in this regard. 2. If clinically an autism spectrum disorder seems likely and/or parents/caregivers/affected person also report corresponding symptoms, either a prompt re-presentation or - after clinical assessment - a referral to a centre specialising in autism spectrum disorder diagnostics should be made.
	Strong consensus (14 out of 14)

B.4 Diagnostic procedures

Christine M. Friday
Collaboration: Ms. Vllasaliu, Ms. Menze, Ms. Schütz: Systematic literature search, data extraction diagnostic studies
Data extraction of history studies in preschool age: Ulrich Hagenah
Meta-analysis: Katrin Jensen

B.4.1 Introduction

After a positive screening result (see B.3), a detailed diagnostic clarification of the suspected autism spectrum disorder must take place. This diagnostic clarification also includes differential diagnostic considerations and additional clarification of internal neurological and psychiatric comorbid diseases (see B.5) as well as clarification of findings (see B.6) and recommendations for therapy (Part 2). In addition to the key questions mentioned below, the suggestion was taken from the source guidelines to add an introductory section on the qualifications of the professional groups that perform autism-specific diagnostics as well as on correspondingly meaningful care structures.

The following key questions are answered and recommended in the text:

16. at what earliest can ASD be reliably diagnosed?
20. what information should be used to make a diagnosis (self-history, external history, behavioural observation, psychological performance diagnostics), and what should the procedure be?
21) How should the different information be integrated to arrive at a diagnostic assessment?
What are the minimum requirements for the diagnostic process? What diagnostic information must be provided to physicians, psychologists, parents or guardians, and potential victims?
23. which standardized diagnostic procedures exist and how are they to be scientifically evaluated in relation to the clinical diagnosis (e.g. ADI-R, ADOS)?
24. how high is the agreement for an ASD diagnosis across different diagnostic instruments?
25. how to deal with contradictory results?
26. what is the significance of the internal neurological examination in the context of diagnostics?
27 What is the significance of a human genetic examination in the context of diagnostics?
What is the significance of instrumental diagnostics?

B.4.2 Care structures and diagnostic teams

B.4.2.1 Summary from the source guidelines

The NICE child/adult guidelines and the SIGN guideline recommend, based on clinical consensus, that the diagnosis of autism spectrum disorders should be made by specialist autism

diagnostic services and as part of a team. Appropriate training in the recommended diagnostic tools and in autism spectrum disorders in general and the relevant differential diagnoses and comorbid conditions is expected in all source guidelines. The team should include the following persons:

NICE children (diagnostics)

Paediatrician and/or child and adolescent psychiatrist, speech therapist, clinical and/or educational psychologist. If necessary, in addition or within easy reach: Child neurologist, occupational therapist, special needs teacher/teacher, social worker, outreach health service, if paediatrician or child and adolescent psychiatrist not on the central team, then also within easy reach/close cooperation. A case coordinator should be appointed who is the contact person for the parents or guardians and the patient and coordinates the diagnostic examinations.

NICE Adult

No statements on specific professions, only a general statement that each investigation should be team-based and that different professions with the appropriate skills for a comprehensive investigation should be part of the team.

SIGN

No statements on specific professions, just general statement that different professions should be involved to ensure accurate diagnosis.

B.4.2.2 Current situation in Germany, adaptation of the recommendation

De facto, the diagnosis of an autism spectrum disorder is usually carried out in specialized facilities in Germany as well. However, very different professional groups with very different qualifications are represented in the facilities, and there is not always a doctor present in the facilities. The latter, in particular, appears to be necessary because of the complex (differential) diagnostic constellations, which include not only mental disorders but also neurological and internistic clinical pictures. The improved diagnostic performance of appropriately trained teams compared to examinations by individual diagnosticians from different disciplines has rarely been empirically investigated. A recently published small study from Sweden showed that team-based examination resulted in significantly more accurate and better estimates of the diagnosis of autism spectrum disorder in preschool children than examination by a single individual (. A further study is included in the NICE children's guidelines which showed relatively low agreement (Kappa = 55-56%) between individual examiners and the results of a diagnostic

team, which has also been used to justify the recommended diagnosis in specialist teams (Mahoney et al 1998).

[17]	**Consensus-based recommendation** *Key question 20 (procedure, structural requirements)*
KKP	The comprehensive diagnosis of suspected autism spectrum disorders should be carried out in a specialised centre. An appropriate number of such centres should be available nationwide. With regard to the diagnosis of **children and adolescents, the** following competence should be present in this position: - Skills in the use of specific diagnostic tools - Differential diagnostic skills regarding all psychiatric and somatic comorbidities - Skills in performing an internal medicine-neurology examination and correctly interpreting the results. - Skills in the test psychological investigation of language development and cognitive development - Skills in professional counselling with regard to therapeutic, educational and social issues The diagnosis should be made in consultation with a specialist in child and adolescent psychiatry and psychotherapy or a specialist in child and adolescent medicine who is specially qualified for this purpose. With regard to the diagnosis of **adults, the** following competence should be present in this post: - Clinical diagnostic skills - Differential diagnostic skills with regard to all psychiatric/psychological and somatic comorbidities - Skills in performing an internal medicine-neurology examination - Skills in the test psychological examination of cognitive performance abilities

	- Skills in professional counselling with regard to therapeutic, occupational and social issues as well as the application of the ICF The diagnosis should be made with the involvement of a specialist in psychiatry and psychotherapy or a specialist in neurology and psychiatry or neurology.
	Strong consensus (14 out of 14)

B.4.3 With whom should the diagnostics be performed?

B.4.3.1 Summary from the source guidelines

In addition to history taking (if possible) and examination of the patient, including direct behavioral observation, all three source guidelines recommend that others in the patient's close environment be consulted to obtain good information regarding early development.

NICE children (diagnostics)

Not explicitly mentioned, but implicitly assuming the presence and involvement of parents or guardians in the diagnostic process.

NICE Adult

A family member or other respondent who knows the patient's personal history and early development should be involved. If this is not possible, at least other documents, such as reports from school, should be consulted.

SIGN

Not explicitly mentioned, but implicitly assuming the presence and involvement of parents or guardians in the diagnostic process.

B.4.3.2 Current situation in Germany, adaptation of the recommendation

In the field of diagnostics in children and adolescents, the guardians must always be included in the diagnostic process alongside the patient, if only for legal reasons, but especially because of their role as (usually) parents or guardians and as necessary informants in the context of the case history. In the field of diagnostics in adults, the case history should ideally be taken with the patient and other relatives who, in the best case, can provide information about the patient's

early childhood development (parents or guardians, older siblings). Friends and relatives can also provide information at least on the current daily routine and lifestyle.

[18]	**Consensus-based recommendation** *Key question 20 (Information base)*
KKP	In addition to the person suspected of having autism spectrum disorder, at least one close person who has known the person with suspected autism spectrum disorder since childhood should be included in the diagnostic process. In addition, other documents from childhood and biography such as reports from kindergarten, school reports or doctor's letters/test results etc. should be consulted in order to obtain as objective a picture as possible regarding early development, behaviour and skills in childhood. The absence of external medical history and documents from childhood does not necessarily prevent the diagnosis in adults.
	Strong consensus (13 out of 13)

B.4.4 Necessary and variable components of diagnostics

B.4.4.1 Summary from the source guidelines

The source guidelines concur in recommending, to varying degrees of differentiation, the following components in the diagnostic process (see guideline synopsis on history): Current concerns/questions of the affected child/adolescent/adult and caregivers/guardians, current and early autism-specific symptomatology, developmental history including pregnancy and birth history, family history, examination of comorbid mental and physical illnesses, current strengths and weaknesses, necessary support and treatment needs, education of the affected individual and their family/caregivers/guardians. Further genetic and instrumental examinations are recommended depending on corresponding clinical symptoms.

In addition, a physical examination is recommended in the NICE Children (Diagnostics) guideline and the SIGN guideline.

Only in SIGN is there an evidence-based recommendation to use structured interviews with parents or guardians and standardised behavioural observation.

Standardized assessment of language and cognitive development is not recommended in any of the source guidelines.

The performance of laboratory or instrumental examinations is recommended in all source guidelines based on the anamnestic findings and the results of the physical examination as not mandatory, but only indicated accordingly.

In detail, NICE Children (Diagnostics) recommends the following diagnostic approach:

1. Questions from parents or guardians, questions from the child/adolescent
2. Child's/young person's experience at home, at school and in terms of social support
3. Developmental history with focus on autism-specific symptoms according to ICD-10 or DSM-IV, if necessary with the help of an autism-specific diagnostic instrument.
4. Direct behavioural observation of interaction with other persons, observation of social and communicative skills as well as stereotypic behaviours according to ICD-10 or DSM-IV, if necessary with the help of an autism-specific diagnostic instrument.
5. Medical history including pregnancy, birth and family history, longitudinal and cross-sectional physical diseases
6. Physical examination
7. Differential diagnostic considerations
8. Systematic investigation of possible disorders commonly found in autism spectrum disorders.
9. Description of a profile that formulates strengths, skills and weaknesses as well as support needs, which includes direct references to educational-therapeutic interventions that take into account the family and school context.
10. Informing the child/adolescent and the parents or guardians about the results of the examination.

In detail, NICE adults recommends the following approach:

Central symptoms of autism spectrum disorder cross-sectionally and longitudinally

1. Early history of development
2. Additional current behavioral and psychological problems
3. Influence of symptoms on current level of functioning in terms of personal well-being, social skills, education and occupation.
4. Organic and mental disorders cross-sectionally and longitudinally; demand for untreated complaints

5. Additional developmental neurological abnormalities
6. Recording of necessary individual support measures, e.g. with regard to personal and social life organisation, training/occupation and housing options
7. Assessment of suicidality, aggression potential and challenging behaviours
8. Recording of necessary support measures for family, siblings, carers and partners
9. Comprehensive disclosure of the outcome of the diagnostic assessment. This should include a comprehensive and informative profile of individual strengths and weaknesses, suicidality, potential for aggression, and challenging behaviors, as well as a physician's letter. The physician's letter should include: autistic symptomatology and its expression; comorbid mental or physical illness; behavioral problems; current speech, language, and communication skills; skills in personal, social, occupational, and school settings; risk to self and others; patient's influence on family, partners, caregivers, and their needs; influence of social and material environmental factors.

In detail, SIGN recommends the following procedure:

1. Medical history collection including a parent interview to assess autism-specific symptoms, e.g. ADI-R (2+), 3di (2+), DISCO (3).
2. Direct behavioural observation of the child/adolescent with regard to autism-specific symptoms, e.g. ADOS (evidence level 2+)
3. Contextual and functional information about daily living skills outside the clinical situation from as many different sources as possible to create an individual profile of strengths and weaknesses
4. Comprehensive examination of speech, language and communication skills as well as language comprehension; formulation of related support needs
5. Examination of cognitive, neuropsychological and adaptive skills can be performed
6. Ergotherapeutic or physiotherapeutic examination can be carried out clinically indicated in addition.
7. Internistic-neurological examination (special focus on neurological abnormalities and signs of dysmorphia)
8. Clinically indicated: Karyotyping, fragile X syndrome, other genetic causes.
9. EEG in linguistic regression after the age of three years
10. Clinically indicated: Hearing test
11. Clinically indicated: additional diagnosis of comorbid behavioral, psychological, and physical disorders.

B.4.4.2 Current situation in Germany, adoption of the recommendations from the source guidelines

There is no empirical study on the current standard of diagnosis of autism spectrum disorders in Germany. In principle, the guideline group therefore recommends that the recommendations stated in the source guidelines be predominantly adopted and formulates a general recommendation here, based on the information in the source guidelines. Since it is common practice in Germany to assess cognitive and language development using standardised tests, and this is also very well justified in terms of content (see B.4.8 below), a more specific recommendation is made in this regard than in the source guidelines. The general recommendations formulated here are elaborated in more detail in the following subsections of this chapter, which are predominantly evidence-based.

[19]	**Consensus-based recommendation** *Key question 20 (information, process), Key question 21 (minimum requirement)*
KKP	The diagnostic workup for suspected autism spectrum disorder should include at least the following elements at all ages (children, adolescents, adults) 1. Cross-sectional and longitudinal symptom recording based on ICD-10 criteria for F84.0, F84.1 and F84.5 2. Anamnesis with detailed recording of ICD-10 symptoms in pre-school and school age (own and external anamnesis) as well as current symptoms; general developmental anamnesis, medical and psychiatric anamnesis, documentation of possible risk factors. 3. Direct observation of behaviour 4. For children and adolescents: Standardized developmental diagnostics or multidimensional cognitive testing, as far as feasible. 5. If a language development disorder is suspected: standardised recording of language development 6. Recording of the current level of functioning with regard to personal-family, school and professional aspects 7. Internistic-neurological examination 8. Clinically indicated laboratory and instrumental examinations 9. Clarification of existing internal-neurological and psychiatric comorbid diseases 10. Clarification of the result of the diagnostics (see B.7)

	11. Formulation of a targeted therapy recommendation regarding autism spectrum disorder as well as comorbid conditions.
	Strong consensus (14 out of 14)

B.4.5 Content of the anamnesis survey

B.4.5.1 Summary from the source guidelines

For general contents, see above B.4.4.

Regarding the use of standardized procedures for taking medical histories, the source guidelines recommend the following:

NICE children (diagnostics)

The following instruments, in which a standardized interview is conducted with parents or caregivers, were included in the systematic review: Autism Diagnostic Interview, original version and revised version (ADI/ADI-R); Developmental, Dimensional and Diagnostic Interview (3di); Gilliam Autism Rating Scale (GARS); Development and Well-Being Assessmen (DAWBA); Parent Interview for Autism (PIA); Diagnostic Interview for Social and Communication Disorders (DISCO). Only the studies on the ADI(-R), and one study on the GARS and the 3di were eligible for inclusion in the systematic review. The quality of all included studies was rated as very low. The guidelines also aimed to investigate the diagnostic validity of the corresponding instruments in four different groups, (1) preschool age (0-5 years), (2) primary school age (6-11 years), (3) secondary school (12-19 years); in addition, one (4) subgroup of children and adolescents with intelligence impairment was also investigated. The following recommendations are made: For the diagnosis of early childhood autism (ICD-10: F84.0) and a general diagnosis from the spectrum (autism, Asperger syndrome (F84.5), or atypical autism (F84.1)), the ADI-R (in combination with the ADOS) can be used in preschool children and across age groups, as well as in mentally retarded children; the 3di can be used for the diagnosis of a disorder from the spectrum (without differentiation of subdiagnoses) across age groups. However, sensitivities and specificities were often below 80% (with the exception of the 3di). Overall, the assessment in the NICE children's guidelines is as follows: The guideline group notes that the clinical utility for using these tools is uncertain (even in combination). Only a general recommendation is made to use a combination of a structured interview with direct behavioural observation. Furthermore, it is warned against uncritically using the results of the

standardized instruments with regard to the corresponding achieved values for the diagnosis, since false positive and false negative results are possible with all instruments.

NICE Adult

The following instruments were included in the systematic review, in which a standardized interview (sometimes in combination with questionnaire examination) is conducted with the parents or guardians or the patient himself: Adult Asperger Assessment (AAA) with Autism Spectrum Quotient (AQ) and Empathy Quotient (EQ); Autism Spectrum Disorders-Diagnosis for Intellectually Disabled Adults (ASD-DA); Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI); ADI-R; 3di; DISCO; Ritvo Autism and Asperger's Diagnostic Scale (RAADS); Ritvo Autism and Asperger's Diagnostic Scale - Revised (RAADS-R). At least one diagnostic validity study was available for each of the following: AAA, ADI-R, ASD-DA, ASDI, RAADS, RAADS-R. All instruments were tested for validity exclusively with respect to the diagnosis of early childhood autism, except for the AAA and ASDI, whose studies also included individuals with Asperger syndrome. Inter-rater and re-test reliability data are also available for all of these instruments with the exception of the AAA, RAADS, and RAADS-R. The ASD-DA showed good inter-rater and re-test reliability. Here, the ASD-DA showed very poor scores, while the other interviews showed good to adequate scores. Based on the available evidence, the guideline group did not recommend a specific instrument but indicated that the following interviews with adults of average intelligence could be used: AAA, ADI-R, ASDI, and RAADS-R; for adults with intelligence impairment, only the ADI-R was recommended.

SIGN

Annex 3 lists all questionnaires, diagnostic interviews and direct behavioural observations that were systematically examined. The use of ADI-R and 3di is recommended, with limitations of DISCO, as only reliability but no sufficient validity data were available.

[20]	**Consensus-based recommendation** *Key question 20 on the general content of the case history with the parents or guardians and the (adolescent and adult) patients*
KKP	The medical history should include the following aspects: 1. Current symptoms and reason for presentation. 2. Pregnancy and birth anamnesis with detailed questioning of risk factors 3. Developmental history 4. Care and education situation from infancy to adolescence 5. Educational history 6. Hobbies and friendships 7. Evidence of repetitive, stereotyped behaviours 8. Somatic anamnesis with current physical complaints and substance use 9. Previous pre-treatment and support measures 10. Previous social/youth welfare measures, previous measures for participation in working life 11. Current psychiatric comorbid symptoms (including clarification of suicidality and self-injurious behaviour). 12. Family history
	Strong consensus (14 out of 14)

B.4.5.2 Current situation in Germany, formulation of own recommendations

Generally, in Germany, a detailed history regarding symptom course, development, school and vocational education, psychiatric and medical comorbidity as well as treatment history and family history is taken in the course of a child and adolescent psychiatric as well as adult psychiatric examination. Key points are summarized below in the consensus-based recommendations. In general, the history here is not (semi-)standardized, but free-form. In addition, a (semi-)standardized interview is usually conducted with the caregivers or even with the patient him/herself in order to record autism-specific symptoms. The use of such an interview (beyond the contents of the non-structured general anamnesis) is evaluated in the following evidence-based and with regard to the clinical relevance including the corresponding training effort. For this purpose, a renewed systematic search for literature as well as the performance of a meta-analysis (if possible) was carried out, since the evaluation criteria of the existing source guidelines were very different, the texts within individual source guidelines partly contained contradictory statements

regarding the tables and across the source guidelines the recommendation to perform certain instruments was heterogeneous.

B.4.5.3 Updating the evidence

No study was found regarding the content of the general medical history. For this reason, a recommendation is formulated based on clinical consensus and available data on epidemiology (A.3), course (A.4; B.4.13) and risk factors (A.5).

Regarding diagnostic instruments, a systematic search for internationally used (semi-)structured interviews was conducted. Only instruments published after 1980 were included. Subsequently, studies on the diagnostic validity of these instruments were systematically searched for, the data extracted for a possible meta-analysis, the quality of the validity studies assessed (QUADAS-II) and - in the case of valid instruments - data on reliability systematically supplemented (see method report on this guideline in extra document).

The following (semi-)structured interviews with parents or guardians or the (adult) patient himself were found (the most recent version listed in each case): AAA, ABI, ADI-R, ASD-DA, ASDI, DISCO-11, DCL-TES from DISYPS-II (Diagnostic System for Mental Disorders according to ICD-10 and DSM-IV for Children and Adolescents - II), 3di, 3di short version. Of these, the following are interviews with close caregivers/parents/guardians: ABI, ADI-R, ASD-DA, ASDI, DISCO-11, 3-di, 3di short version. The DCL-TES is a clinical checklist for childhood and adolescence in which, based on the specific but not structured information collected from the history and direct behavioral observation, the symptom criteria for all autism spectrum disorders according to ICD-10 and DSM-IV-TR can be reviewed by the clinical investigators. The AAA is a combination of questionnaire and interviews for adults with V.a. high-functioning autism spectrum disorder. In addition, although it is a self-report questionnaire, the RAADS-R was also included as it is referred to as a 'diagnostic tool' for the adult domain and is also recommended in the NICE adult guideline. As there are hardly any interviews in the adult diagnostic field, this seemed a useful addition.

A meta-analysis could only be calculated for the ADI-R and the new ADI-R infant algorithm (toddler); the results for the other studies are described descriptively.

ADI-R (Autism Diagnostic Interview-revised)

The ADI-R was developed to capture the diagnosis of early childhood autism according to ICD-10 and DSM-IV criteria. There is only one algorithm for autism in the original version, not for other autism spectrum disorders.

In the history of the instrument, it was therefore first investigated whether the diagnosis of early childhood autism can be validly made with the instrument; a mixed group of individuals with a spectrum diagnosis (Asperger's syndrome, atypical autism/PDD-NOS) together with a clinical utilization population often served as a comparison group. In addition, there are studies that included only clinical utilization populations or populations with certain defined clinical characteristics, such as language developmental delay, as a comparison group. Historically later, the diagnostic question changed to whether the ADI-R validly captured spectrum diagnoses. To this end, studies were conducted that examined autism and spectrum diagnoses together as the diagnostic target group, and the clinical comparison group in each case was a clinical utilization population. Individual studies had only spectrum diagnoses without autism as the diagnostic target group. Below are the results of these above comparison groups systematically by age group. Most studies did not differentiate by IQ (intelligence impairment present or absent), and both the autism (spectrum) group and the control group each show a very broad IQ spectrum.

All studies on the ADI-R have a consistently high risk of bias with regard to patient selection, which means that sensitivities and specificities may be overestimated in these studies (see Method Report/Appendix). In some studies, the reference text was unclearly described and the index test was not independent of the reference test, which also lowers the quality of the studies. All studies were positively assessed with regard to applicability in QUADAS-II.

Table 24: ADI-R - toddler and preschool age; research question: diagnosis of early childhood autism; different control groups

Comparison group (1): children on the spectrum without autism and clinical utilisation population.
Comparison group (2): Clinical utilisation population

	Age	Question ADI-R	Number Studies	Sens	95% CI	Spec	95% CI
(1)	Toddler and preschool age	Early childhood autism versus nonautism spectrum and clinical utilization population.	4	0,80	0.75 to 0.84	0,82	0.60 to 0.93
(2)	Toddler and preschool age	Early childhood autism versus clinical utilization population.	4	0,78	0.54 to 0.92	0,91	0.84 to 0.96

Note: Studies included in the analyses were for (1) Gray et al. 2008; Le Couteur et al. 2008; Mazefsky and Oswald 2006; Risi et al. 2006 and for (2) Le Couteur et al. 2008; Mazefsky and Oswald 2006; Wiggins and Robins 2008; Lord et al. 1994.

Table 25: ADI-R - toddler and preschool age; Question: Any diagnosis on the autism spectrum, including autism; comparison group: clinical utilization population.

Age	Question ADI-R	Number Studies	Sens	95% CI	Spec	95% CI
Toddler and preschool age	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	3	0,70	0.37 to 0.91	0,80	0.60 to 0.92

Note: Studies included in the analyses were Wiggins and Robins 2008; Gray et al. 2008; Kim and Lord 2012b.

Table 26: ADI-R - toddler and preschool age; research question: diagnosis from the spectrum without autism; comparison group: clinical utilisation population

Age	Question ADI-R	Number Studies	Sens	95% CI	Spec	95% CI
Toddler and preschool age	Spectrum diagnosis without autism (Asperger's, PDD-NOS) versus clinical utilization population.	1	0,34	0.18 to 0.54	0,92	0.73 to 0.99

Note: Data refer to the study by Le Couteur et al. 2008.

Table 27: ADI-R - Broad age range 2-22 years; research question: diagnosis of early childhood autism; comparison group: ASD without early childhood autism and clinical utilization population.

Age	Question ADI-R	Number Studies	Sens	95% CI	Spec	95% CI
Mixed age group children and youth	Early childhood autism versus nonautism spectrum and clinical utilization population.	5	0,90	0 .88 to 0.92	0,69	0.55 to 0.80

Note: Studies included in the analyses were Corsello et al. 2007; de Bildt et al. 2004; Papanikolaou et al. 2009; Risi et al. 2006; Tsuchiya et al. 2013.

Table 28: Broad age range between 5-20 years; research question: diagnosis from the autism spectrum; comparison group: clinical utilization population

Age	Question ADI-R	Number Studies	Sens	95% CI	Spec	95% CI
Mixed age group children and y-outh	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	1	0,72	0.61 to 0.80	0,79	0.69 to 0.87

Note: Data refer to the study by de Bildt et al. 2004.

In addition, there is a small study that had children and adolescents with early childhood autism (N = 11) as a target group and examined children with a language development disorder (N = 16) as well as partially psychiatric comorbid diagnoses as a comparison group (. The study yielded a high sensitivity of 91% as well as a specificity of 94%, but should be viewed with caution due to the small sample size and the high risk of bias errors.

No study on adults met the inclusion criteria for diagnostic studies in the guidelines.

The studies presented above show that the diagnosis of early childhood autism can be made relatively validly with the published cut-off of the ADI-R at preschool age; however, the spectrum diagnoses of Asperger's syndrome or atypical autism are often not detected with the instrument (low sensitivity). This is due to the original intention of the instrument to validly detect the diagnosis of early childhood autism.

The inter-rater reliability of the ADI-R can be considered good (kappa 70-95%), but only after appropriate training.

Further developments of the ADI-R algorithm (without DSM-5):

In order to also validly collect spectrum diagnoses with the instrument, three studies attempted to define a "spectrum cut-off" for the diagnoses of Asperger's syndrome and atypical autism/PDD-NOS for the ADI-R. The cut-off used was comparable in two studies (Corsello et al. 2007; Risi et al. 2006): A spectrum diagnosis can be assigned if either the autism criteria for "Social Interaction" and "Social Communication" or for "Social Interaction" and for "Social Communication - 2 points" or for "Social Interaction -2 points" and for "Social Communication" or for "Social Interaction -1 point" and for "Social Communication - 1 point" are met. However, the autism spectrum group was defined differently. In the first study, only children and adolescents with a spectrum diagnosis were included. Both sensitivity and specificity were below 80% (Risi et al. 2006); in the other study, autism and spectrum were combined; sensitivity was > 80%, but specificity was not (.

These two studies did not include the domain of stereotypic behaviour in the assessment. This was only done in one study (Le Couteur et al. 2008). Here, the following definition was examined as a possible "spectrum" cut-off: age of onset before 3 years, autism criteria met in two of the three domains (social interaction, communication, stereotypic behavior, and special interests). The sensitivity for autism and spectrum diagnoses was significantly >80% with this cut-off, but the specificity was also significantly lower.

Therefore, both new algorithms for the autism spectrum do not show better validity than the ADI-R.

Another development relates to new ADI-R algorithms for young children under the age of 4. For children under four years of age, the published ADI-R codes items only in terms of current behavior. This algorithm showed low specificity particularly for non-verbal children under 4 years of age, whereas it performed well for verbal children with single words under 4 years of age (sensitivity >80%, specificity >80%), but again showed low sensitivity and specificity for children who were already speaking sentences at this age, in each case compared to a clinical use population (Kim and Lord 2012b, 2012a). Therefore, a new algorithm was developed for each of the different groups under 4 years of age (non-verbal; single words, speech in sentences), which also included only one cut-off value (instead of 4 domain cut-off values in the ADI-R). The values reported below are for the so-called "clinical cut-off", which was chosen to provide balanced sensitivity and specificity. Only data for the "clinical utilization population without healthy children" comparison are shown; when healthy children were included in the comparison group, specificity was higher in each case, as expected (Kim and Lord 2012b, 2012a; Kim et al. 2013).

Table 29: ADI-R - Infant Algorithms 12 - 47 Months

	Age/Properties	Question ADI-R	Number Studies	Sens	95% CI	Spec	95% CI
(1)	Age 12-21 months or non-verbal 21-47 months	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,86	0.82 to 0.89	0,76	0.64 to 0.88
(2)	Age 21-47 months, single words	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,96	0.93 to 0.98	0,77	0.67 to 0.86
(3)	Age 21-47 months, single sets	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,85	0.76 to 0.95	0,77	0.62 to 0.92

Notes: The two studies consulted for these calculations were Kim et al. 2013 and Kim and Lord 2012b.

Summary Assessment ADI-R:

With the currently published autism cut-off, the diagnosis of **early childhood autism** versus autism spectrum and/or clinical utilization population can be made relatively valid in preschool age. In mixed age groups from childhood to adolescence, the instrument also shows very good sensitivity for this question, but the specificity is somewhat lower (comparison group: clinical utilization population). For adulthood, the study situation is not sufficient.

The spectrum diagnoses **Asperger syndrome** and **atypical autism** are not adequately covered by the published autism cut-off by the ADI-R (especially too low sensitivity).

In the age range between 12 - 47 months, the new toddler algorithm with skill-specific items and cut-off values also seems to capture the autism spectrum relatively well. However, independent replication studies should still be conducted here.

In the field of older children and adolescents, published alternative ADI-R cut-off values have so far not shown sufficient diagnostic validity for this question and have also not been replicated.

The above statements on validity refer exclusively to a lege artis completely conducted interview in the corresponding standardized sequence of items.

Data on the diagnostic validity of the ADI-R in combination with behavioral observation instruments are not shown here, but under B.4.7.

A clinical disadvantage of the ADI-R is that it takes a long time to administer (approx. 2-3 hours). As with all autism diagnostic instruments, appropriate training to achieve high inter-rater reliability is initially necessary before implementation, and should also be repeated occasionally to maintain the standard.

AAA (Adult Asperger Assessment)

The instrument is based on results of the AQ and EQ, additionally results of the interview with the adult patient are coded in the three diagnostic domains according to DSM-IVTR/ICD-10. The corresponding publication does not contain sufficient data to calculate diagnostic validity (Baron-Cohen et al. 2005).

ABI (Autistic Behavior Interview)

No validity studies were found for the ABI.

ASD-DA (Autism Spectrum Disorders-Diagnosis for Intellectually Disabled Adults)

The ASD-DA was examined in one study (Matson et al. 2008c). Adults with autism or spectrum diagnosis (PDD-NOS) with intelligence impairment were studied in comparison to a population with mentally retarded patients. Diagnostic validity was inadequate mainly due to low specificity (ROC-AUC 0.74, SE 0.03; sensitivity 0.86, specificity 0.62 at cut-off = 19).

ASDI (Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview)

The ASDI was developed specifically for the diagnosis of high-functioning autism spectrum disorders from primary school age into adulthood. However, the corresponding study does not contain sufficient data on diagnostic validity (Gillberg et al. 2001).

DISCO-11: Diagnostic Interview for Social and Communication Disorders schedule (DISCO), 11th revision

The DISCO-11 is a parent interview for which a study is available (Maljaars et al. 2012). Here, preschool and primary school children with all diagnoses from the entire autism spectrum were compared with a clinically inconspicuous group as well as with a group of mentally handicapped children. Compared to the clinically normal group, the diagnostic validity was excellent (sensitivity 100%, specificity 95%); compared to the group of mentally retarded children, the diagnostic validity was also relatively good (sensitivity 79%, specificity 87%). The quality of the study was good except for a possible risk of bias in patient selection. A replication study is not yet available. Reliability studies on the DISCO-11 are also not available. Various previous versions of the DISCO were not included in the systematic search and meta-analysis.

DCL-TES from DISYPS-II (Döpfner et al. 2008)

To date, no validity or reliability studies are available for this diagnostic checklist.

RAADS-R (Ritvo Autism Asperger Diagnostic Scale-Revised)

This scale is a self-report instrument for adults with autism spectrum disorder from the high-functioning range to be completed with the assistance of the clinician. The scale contains 80 items, each with 4 response options on a Likert scale. With a cut-off of 65 (which was self-determined in the study), it showed a sensitivity of 97% and a specificity of 100% with respect to detecting a diagnosis from across the autism spectrum compared with a mixed psychiatric and healthy comparison group. Test-retest reliability was > 76% in all groups. The quality of the study is reduced due to the establishment of the cut-off in the same population in which

validity was investigated. A replication study from Sweden comparing healthy adults with patients with autism spectrum disorder reached a similar result, but with a higher cut-off of 72 (AUC = 0.96, SE 0.012, 95% CI 0.94 - 0.98); sensitivity 91%, specificity 93%). The study showed a high internal consistency of the total scale (92%) and a 3-6 month re-test reliability score of the total scale of 80%. The quality of the study is also reduced due to the establishment of the cut-off in the same population in which validity was investigated. Studies with purely clinical comparison populations are pending.

3di (Developmental, Dimensional and Diagnostic Interview)

The long version of the 3di was studied in a sample of 6-16 year old children and adolescents with any diagnosis on the autism spectrum compared to a child and adolescent psychiatric utilization population (Skuse et al. 2004). The cut-off of the 3di corresponds to the criteria of the ADI-R: social interaction 10; communication 8, stereotypic behaviour 3. The diagnostic validity was excellent with a sensitivity of 100% and a specificity of 98%. The study shows low quality in the application of the reference standard and there is a risk of bias in patient selection. A replication study has not yet been performed. The inter-rater reliability regarding autism spectrum disorders is good, regarding unaffected controls it is rather low. The instrument and the evaluation software are not freely available and also not commercially available, but are only made available after training with the authors.

3di short version

The short version of the 3di was studied in a sample of children and adolescents with mean age 9.8 years (SD = 3.3) and mean IQ = 89.7 (SD = 21.1) with any diagnosis on the autism spectrum compared to a child and adolescent psychiatric utilization population (Santosh et al. 2009). The cut-off was optimised within the study: social interaction 11.5; communication 8, stereotypic behaviour 5. Diagnostic validity was calculated separately for all three domains and was excellent with sensitivity > 90% and specificity >85% for all domains. The study shows low quality in the application of the reference standard and there is a risk of bias in the patient selection, the index test and the reference standard. A Thai replication study, which defined different cut-offs, showed a low sensitivity (>60%) and specificity (>75%) in all domains (. Reliability data are not available.

The clinical situation in autism diagnostic services/institutions is usually such that only children/adolescents/adults with developmental delay, intellectual disability and/or psychiatric symptomatology are diagnosed in detail and - according to these guidelines - after a positive

screening finding (B.3) or very clear clinical indication symptoms (B.2). Therefore, as a basis for the evidence-based recommendation regarding the use of standardized scales for autism diagnosis, only studies with control groups of children/adolescents/adults with developmental delay and/or intellectual disability or with another mental disorder were included.

[21]	**Evidence based statement** *Key Question 23 Part 1: What standardized diagnostic procedures exist and how are they to be scientifically evaluated in relation to clinical diagnosis (e.g. ADI-R, ADOS)?*
0	As the validity of the different diagnostic instruments was tested against the reference standard "clinical diagnosis by experienced clinicians" in each case, no comparison can be made between the validity of the instruments and the validity of the clinical judgement.
Evidence level No studies available.	Strong consensus (14 out of 14)

[22]	**Evidence-based recommendation** *Key Question 23 Part 2*
B	A standardized instrument (interview with parents or guardians/patients) should be used as part of the diagnostic process for clinically complex questions. **Preschool children - questioning early childhood autism:** ADI-R. **Children of preschool age - questioning Asperger syndrome or atypical autism:** currently no valid German-language instrument available. **Children of primary school and adolescent age (all IQ ranges) - question early childhood autism:** ADI-R. Children of primary school and adolescent age without intelligence impairment - **question autism, Asperger syndrome or atypical autism**: ADI-R. **Adults of all intelligence levels - question of autism, Asperger's syndrome or atypical autism:** currently no instrument recommended. None of the above instruments are recommended as mandatory for the diagnosis of autism spectrum disorders.

Evidence level 2-4	Sources: see evidence tables in the appendix.
	Strong consensus (14 out of 14)

B.4.6 Psychopathological findings and direct observation of behaviour

B.4.6.1 Summary from the source guidelines

For general contents, see above B.4.4.

Regarding the use of standardized procedures for psychopathology and behavioral observation, the source guidelines recommend the following:

NICE children (diagnostics)

Here, only the ADOS (Diagnostic Observation Scale for Autistic Disorders) without and in combination with ADI-R is assessed as diagnostically valid for the following diagnoses in pre-school age as well as in mentally retarded children and adolescents. Study quality is described as very low. The clinical appraisal and recommendation of the NICE children's guidelines is as follows: The guideline group notes that the clinical benefit to using ADOS (even in combination) is uncertain. Only a general recommendation is made to use a combination of a structured interview with direct behavioural observation in the diagnostic process. Furthermore, it warns against uncritically using the results of the standardized instruments with regard to the corresponding achieved values for the diagnosis, since false positive and false negative results are possible with all instruments.

NICE Adult

Module 4 of the ADOS-G and the MASC (Movie for the Assessment of Social Cognition) are discussed here. No diagnostic validity studies are available for the MASC. Module 4 of the ADOS-G is described as sensitive (moderate to excellent) and specific (good to excellent) as well as reliable. The duration of the examination is described as adequate. It is recommended to use the ADOS-G Module 4 especially for complex differential diagnostic considerations.

SIGN

Here the use of the CARS (Childhood Autism Rating Scale) as well as the ADOS is recommended to support the diagnosis.

B.4.6.2 Current situation in Germany, formulation of own recommendations

In Germany, a psychopathological finding is always collected in the course of a child and adolescent psychiatric as well as adult psychiatric examination. There are no statements in the source guidelines on the diagnostic validity of the psychopathological findings with regard to a diagnosis from the field of autism spectrum disorders, nor are there any studies on the nature and validity of a common psychopathological finding. Clinically, it should be noted that both the commonly used psychopathological findings based on the CASCAP-D (Döpfner et al. 1999) in childhood and adolescence and the AMDP system for adults (Arbeitsgemeinschaft für Methodik und Dokumentation in der Psychiatrie (AMDP), 2007) are not suitable for making an autism spectrum diagnosis, as the central aspects of restricted social interaction and communication, the specific stereotypic behaviors and special interests, as well as sensory aspects cannot be adequately captured by these instruments. For this reason, it seems necessary to resort to autism-specific behavioral observation instruments in order to validly capture behavior, self-experience as well as autism-specific diagnostic criteria. In the following, the use of such instruments will be evaluated evidence-based and with regard to clinical relevance including the corresponding training effort. For this purpose, a renewed systematic search for literature as well as the performance of a meta-analysis (if possible) was conducted, since the evaluation criteria of the existing source guidelines were very different, the texts within individual source guidelines contained partially contradictory statements about the tables, and the recommendation for the implementation of certain instruments was heterogeneous across the source guidelines.

B.4.6.3 Updating the evidence

First, a systematic search for internationally used diagnostic observation instruments was conducted. Subsequently, studies on the diagnostic validity of these instruments were systematically searched for, the data extracted for a possible meta-analysis, the quality of the validity studies assessed, and - in the case of valid instruments - data on reliability systematically supplemented (see method report).

The following (semi-)standardized behavioral observation instruments have been published up to and including June 2013: ADOS, ASD-OC, BOS, CARS. A meta-analysis could be calculated for the ADOS and the CARS. The results of the meta-analysis on diagnostic validity are presented below. The additional results on study quality and inter-rater and re-test reliability regarding valid instruments are presented in detail in the Methods Report/Appendix. The study quality of most studies was rather low; most studies showed a high risk of bias.

ADOS (Autism Diagnostic Observation Scale for Autistic Disorders)

The ADOS is a standardized observation instrument that contains four modules that are used depending on the child's/adolescent's/adult's linguistic, cognitive and social-interactive skills. The ADOS-2, which was published in German in 2015, also contains a toddler module; in addition, revised algorithms were developed for modules 1-3. Since the instrument is widely used and both versions are expected to be used in Germany in the future, the results of the meta-analysis for the individual modules (original algorithms and revised ADOS-2 algorithms) are reported separately below. Studies that did not differentiate between the modules were not considered in the meta-analysis.

The ADOS/ADOS-2 generally has the disadvantage that long-term and intensive training is required and that regular training should be conducted to maintain high inter-rater reliability within and between teams.

ADOS MODULE 1

Original algorithm (Lord et al. 2000)

(non or little speaking children)

Table 30ADOS Module 1 pre-lingual - original - target group: early childhood autism; autism cut-off of the ADOS used;- different comparison groups

Comparison Group 1: Clinical Utilization Population Including Spectrum Without Autism
Comparison Group 2: Clinical Utilization Population without Autism Spectrum

	Age/Skills	Question ADOS	Number Studies	Sens	95% CI	Spec	95% CI
(1)	Child, none to single words	Autism versus non-autism spectrum and clinical utilization population.	2	0,85	0.79 to 0.91	0,90	0.85 to 0.96
(2)	Child, none to single words	Autism versus clinical utilization population	2	0,83	0.74 to 0.89	0,95	0.67 to 1.00

Notes: Studies included in the analyses were for (1) Le Couteur et al. 2008; Gray et al. 2008 and for (2) Le Couteur et al. 2008; de Bildt et al. 2009.

Table 31ADOS Module 1 pre-lingual - original - target group: autism spectrum without autism (i.e., Asperger syndrome, atypical autism/PDD-NOS); spectrum cut-off of ADOS used; comparison group clinical utilization population.

Age/Skills	Question ADOS	Number Studies	Sens	95% CI	Spec	95% CI
Child, none to single words	Spectrum without autism vs. clinical utilization population	1	1,00	0.79 to 1.00	0,67	0.49 to 0.81

Notes: Data are based on Le Couteur et al. 2008.

Since children assessed with ADOS Module 1 show very different skills, recent articles have additionally divided this group into two different groups (no speech and single words), for which revised algorithms (ADOS 2) have been developed.

ADOS MODULE 1

(non-speaking children/no words)

Original algorithm (Lord et al. 2000) vs. Revised algorithm or ADOS-2 (Gotham et al. 2007; Poustka et al. 2015).

Table 32: ADOS Module 1 pre-linguistic - Original vs. Revised - Target group: early childhood autism; autism cut-off of the ADOS or the revised ADOS-2 used, different control groups.

Comparison Group 1: Clinical Utilization Population Including Spectrum Without Autism
Comparison Group 2: Clinical Utilization Population without Autism Spectrum

	Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
(1)	pre-language	Autism versus clinical utilization population	4	0,92	0.87 to 0.98	0,83	0.72 to 0.94
	Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
(1)	pre-language	Autism versus non-autism spectrum and clinical utilization population.	1	0,98	0.88 to 1.00	0,82	0.48 to 0.98
(2)	pre-language	Autism versus clinical utilization population	4	0,87	0.79 to 0.93	0,78	0.62 to 0.89

Notes: Studies included in the analyses were for (1) Gotham et al. 2008; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b (Original and Revised Algorithm) and for (2) Gray et al. 2008.

Table 33: Module 1 pre-lingual - Original vs. Revised - Target group: autism spectrum with autism; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without ASD.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
pre-language	Autism and autism spectrum versus clinical utilization population.	2	0,98	0.93 to 1.00	0,42	0.22 to 0.65
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
pre-language	Autism and autism spectrum versus clinical utilization population.	3	0,94	0.89 to 0.97	0,61	0.28 to 0.86

Notes: Data from Molloy et al. 2011; Oosterling et al. 2010b were included in the first comparison for the original algorithm, and data from Molloy et al. 2011; Oosterling et al. 2010b; Gray et al. 2008 were included in the second comparison for the Revised algorithm.

Table 34: ADOS Module 1 pre-linguistic - Original vs. Revised - Target group: autism spectrum without autism; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
pre-language	Spectrum without autism vs. clinical utilization population	3	0,90	0.79 to 0.96	0,53	0.33 to 0.72
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
pre-language	Spectrum without autism vs. clinical utilization population	3	0,85	0.76 to 0.95	0,60	0.27 to 0.92

Notes: Data for both comparisons are based on Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b.

ADOS MODULE 1

(Few words/some words)

Original algorithm vs. revised algorithm or ADOS-2

Table 35: ADOS Module 1 few words - Original vs. Revised - Target group: early childhood autism; autism cut-off of the ADOS or the revised ADOS-2 used; different comparison groups.

Comparison Group 1: Clinical Utilization Population Including Spectrum Without Autism
Comparison Group 2: Clinical Utilization Population without Autism Spectrum

	Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
(1)	Single words	Autism versus clinical utilization population	4	0,75	0.57 to 0.87	0,98	0.63 to 1.00
	Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
(1)	Single words	Autism versus non-autism - spectrum and clinical utilization population.	1	0,89	0.79 to 0.95	0,86	0.76 to 0.94
(2)	Single words	Autism versus clinical utilization population	5	0,90	0.78 to 0.96	0,88	0.68 to 0.96

Notes: Studies included in the analyses were for (1) Original algorithm Gotham et al. 2008; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b; for (1) Revised algorithm only Gray et al. 2008 and for (2) Revised algotithm Gotham et al. 2008; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b; de Bildt et al. 2009.

Table 36: ADOS Module 1 few words - Original vs. Revised - Target group: autism spectrum with autism; spectrum cut-off of the ADOS or the revised ADOS-2 used;Comparison group: clinical utilisation population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Single words	Autism and autism spectrum versus clinical utilization population.	2	0,87	0.45 to 0.98	0,76	0.46 to 0.93
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Single words	Autism and autism spectrum versus clinical utilization population.	3	0,85	0.65 to 0.95	0,48	0.08 to 0.90

Notes: Data from Molloy et al. 2011; Oosterling et al. 2010b were used for both comparisons. For the meta-analysis on the Revised Algotithm, validity data were also extracted from the article by Gray et al. 2008.

Table 37: ADOS Module 1 few words - Original vs. Revised - Target group: autism spectrum without autism; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilisation population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Single words	Spectrum without autism vs. clinical utilization population	5	0,81	0.63 to 0.91	0,76	0.59 to 0.87
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Single words	Spectrum without autism vs. clinical utilization population	5	0,89	0.71 to 0.96	0,73	0.59 to 0.84

Notes: Data from Gotham et al. 2008; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b; de Bildt et al. 2009 were used for the analyses in both cases.

Summary ADOS and ADOS-2, Module 1: Module 1 of the ADOS (original algorithms) has a good diagnostic validity for autism (sensitivity > 80%, specificity > 80%); for the autism spectrum an excellent sensitivity but a non-sufficient specificity < 70% is given. Differentiating the children into "pre-linguistic" and "single words" shows the following result: for the autism question, both the original ADOS and the ADOS-2 have an excellent sensitivity > 90% and specificity > 80% for the "pre-linguistic" children; for the "single words" children, the ADOS-2 is superior to the original algorithm because of the slightly increased sensitivity, showing a sensitivity > 80% and specificity > 80%. With regard to autism spectrum diagnoses (Asperger syndrome, atypical autism), both versions do not show sufficient specificity for the "pre-linguistic" children; in the area of children with single words, both algorithms are comparable (sensitivity > 80%, specificity > 70%).

The inter-rater and re-test reliability for both algorithms is moderate to good after appropriate training (see Appendix, Reliability Tables). The ADOS requires regular inter-rater reliability training.

ADOS MODULE 2

(Children younger than 5 years or children who can speak in two-word sentences but cannot yet hold a conversation).

Original algorithm vs. revised algorithm or ADOS-2

Table 38: Module 2 younger 5 years - Original ADOS vs. Revised - Target group: early childhood autism; autism cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Language in two-word sentences, < 5 years	Autism versus clinical utilization population	4	0,72	0.43 to 0.91	0,96	0.89 to 0.99
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Language in two-word sentences, < 5 years	Autism versus clinical utilization population	4	0,85	0.59 to 0.96	0,90	0.78 to 0.97

Notes: Data from Gotham et al. 2008; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b were used for both analyses.

Table 39: Module 2 younger 5 years - Original ADOS vs. Revised - Target group: early childhood autism and autism spectrum; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Language in two-word sentences, < 5 years	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,66	0.38 to 0.93	0,89	0.74 to 1.00
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Language in two-word sentences, < 5 years	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,69	0.55 to 0.80	0,72	0.51 to 0.87

Notes: Data from Molloy et al. 2011 and Oosterling et al. 2010b were used for the analyses in both cases.

Table 40: Module 2 younger 5 years - Original ADOS vs. Revised - Target group: autism spectrum without autism; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilisation population without autism spectrum

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Language in two-word sentences, <5 years	Spectrum without autism vs. clinical utilization population	4	0,65	0.41 to 0.84	0,88	0.72 to 0.96
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Language in two-word sentences, <5 years	Spectrum without autism vs. clinical utilization population	4	0,71	0.60 to 0.80	0,77	0.61 to 0.88

Notes: Data from Gotham et al. 2008; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b were used for both analyses.

ADOS MODULE 2

(Children older than 5 years or children who can speak in two-word sentences but have not yet mastered conversation).

Original algorithm vs. revised algorithm or ADOS-2

Table 41: ADOS Module 2 older 5 years - Original vs. Revised - Target group: early childhood autism; autism cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Language in two-word sentences, >5 years	Autism versus clinical utilization population	4	0,71	0.32 to 0.93	0,96	0.90 to 0.98
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Language in two-word sentences, >5 years	Autism versus clinical utilization population	4	0,88	0.67 to 0.97	0,81	0.68 to 0.90

Notes: Data from de Bildt et al. 2009; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b were used for the analyses in both cases.

Table 42: ADOS Module 2 older 5 years - original vs. revised - target group: early childhood autism and autism spectrum; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Language in two-word sentences, >5 years	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,67	0.33 to 1.00	0,81	0.56 to 1.00
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Language in two-word sentences, >5 years	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	2	0,78	0.55 to 0.92	0,74	0.51 to 0.89

Notes: Data from Molloy et al. 2011; Oosterling et al. 2010b were used for the analyses in both cases.

Table 43: ADOS Module 2 older 5 years - original vs. revised - target group: autism spectrum without autism; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilisation population without autism spectrum

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Language in two-word sentences, >5 years	Spectrum without autism vs. clinical utilization population	4	0,68	0.49 to 0.83	0,76	0.61 to 0.87
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Language in two-word sentences, >5 years	Spectrum without autism vs. clinical utilization population	4	0,72	0.57 to 0.84	0,73	0.59 to 0.84

Notes: Data from de Bildt et al. 2009; Gotham et al. 2007; Molloy et al. 2011; Oosterling et al. 2010b were used for the analyses in both cases.

Summary ADOS and ADOS-2, Module 2: Module 2 of the ADOS shows a relatively low sensitivity for autism and autism spectrum for the original algorithm. In the range of children < 5 years, the ADOS-2 is preferable regarding the diagnosis of autism (sensitivity > 80%, specificity > 80%). Regarding the diagnosis of autism spectrum disorder, both algorithms are not sufficiently sensitive (< 70%). Regarding children > 5 years, the ADOS-2 algorithm is more sensitive than the original algorithm, showing sensitivity > 80% and specificity> 80% for autism; sensitivity > 70% and specificity > 70% for spectrum disorders. However, the specificity of the ADOS-2 algorithm is slightly lower than the specificity of the original algorithm.

The inter-rater and re-test reliability for both algorithms is moderate to good after appropriate training (see Appendix, Reliability Tables). The ADOS requires regular inter-rater reliability training.

ADOS MODULE 3

(children and adolescents who can converse fluently)

Original algorithm vs. revised algorithm or ADOS-2

Table 44: ADOS Module 3 - Original vs. Revised - Target group: early childhood autism; autism cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Fluent language	Autism versus clinical utilization population	5	0,75	0.69 to 0.80	0,86	0.76 to 0.92
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Fluent language	Autism versus clinical utilization population	5	0,88	0.81 to 0.92	0,76	0.62 to 0.86

Notes: Data from de Bildt et al. 2009; Gotham et al. 2007; Gotham et al. 2008; Kamp-Becker et al. 2013; Molloy et al. 2011 were used for the analyses in both cases.

Table 45: ADOS Module 3 - Original vs. Revised - Target group: early childhood autism and autism spectrum; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilization population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Fluent language	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	1	0,89	0.80 to 0.94	0,48	0.38 to 0.57
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Fluent language	Autism spectrum diagnosis (autism, Asperger's, PDD-NOS) versus clinical utilization population.	1	0,86	0.78 to 0.93	0,34	0.25 to 0.43

Notes: Data based on Molloy et al. 2011.

Table 46: ADOS Module 3 - Original vs. Revised - Target group: autism spectrum without autism; spectrum cut-off of the ADOS or the revised ADOS-2 used; comparison group: clinical utilisation population without autism spectrum.

Age/Skills	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Fluent language	Spectrum without autism vs. clinical utilization population	5	0,92	0.73 to 0.98	0,62	0.41 to 0.79
Age/Skills	**Question ADOS - 2 (Revised algorithm)**	**Number Studies**	**Sens**	**95% CI**	**Spec**	**95% CI**
Fluent language	Spectrum without autism vs. clinical utilization population	5	0,81	0.67 to 0.90	0,64	0.45 to 0.79

Notes: Data from de Bildt et al. 2009; Gotham et al. 2007; Gotham et al. 2008; Kamp-Becker et al. 2013; Molloy et al. 2011 were used for the analyses in both cases.

Summary ADOS and ADOS-2, Module 3: For the diagnosis of autism, the new ADOS-2 algorithm has a slightly higher sensitivity but lower specificity than the original algorithm (original sensitivity > 70%, specificity > 80%, ADOS-2 sensitivity > 80%, specificity > 70%). In the autism spectrum, the specificity of both algorithms is relatively low (< 70%). The inter-rater as well as re-test reliability is moderate to good for both algorithms after appropriate training (see Method Report/Appendix). The ADOS requires regular inter-rater reliability training.

For Module 4, only one study was found that included adults aged 18 - 66 years (Bastiaansen et al. 2011). The research question was autism and autism spectrum versus a mixed group of a clinical population (schizophrenia, psychopathy) and healthy individuals. Different cut-off values were used in the study. For the original algorithm, sensitivity was 61% (95%-CI 43%-75%) and specificity 71% (95%-CI 69%-91%); for the alternative cut-off, sensitivity was slightly higher (at 71%, 95%-CI 54%-85%). The study has not been replicated to date and also shows a high risk of bias. The inter-rater as well as re-test reliability is good after appropriate training (see method report/appendix). The ADOS requires regular inter-rater reliability training.

ADOS Infant Module:

The ADOS Infant Module was developed to validly diagnose children from the age of 12 months. It can be used for children between 12-30 months of age. Two different algorithms exist, one for 12-20 month old children and older non-verbal children, the other for 21-30 month old verbal children. The original study (Luyster et al. 2009) showed very high sensitivities (>88%) and specificities (>90%) for the diagnosis of early childhood autism or spectrum disorders. Study quality was relatively good with little risk of bias. Independent replication is lacking to date. Inter-rater as well as re-test reliability was good (see Methods Report/Appendix).

ASD-OC: Autism Spectrum Disorder Observation for Children (ASD-OC)

Only one study exists on ASD-OC, which did not meet the inclusion criteria.

BOS: Behaviour observation scale

No validity studies were found for the BOS.

CARS: Childhood Autism Rating Scale

The CARS is a behavioral observation scale originally developed for the diagnosis of early childhood autism. It is the oldest instrument that assesses autistic symptoms using a semi-standardized behavioral observation. The CARS can be used from the age of 2 years into adulthood. Recently, a revision (CARS-2) was published that includes new items specifically for patients with high-functioning autism spectrum disorders. No validity data exist on this one yet, so only the data on the CARS could be compiled in the meta-analysis mentioned below. The inter-rater reliability of the CARS is very heterogeneous from moderate to good (see Method Report/Appendix).

Table 47: CARS - Target Group: Early Childhood Autism, Preschool Age; Comparison Group: Autism Spectrum and Clinical Between Utilization Population

Age	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Preschool age	Autism versus non-autism spectrum and clinical utilization population.	3	0,96	0.83 to 1.00	0,89	0.39 to 1.00

Notes: Data from Chlebowski et al. 2010; Perry et al. 2005; Rellini et al. 2004a were used in both analyses.

Table 48: CARS - target group: early childhood autism and autism spectrum disorder, preschool and primary school age; comparison group: clinical utilisation population

Age	Question ADOS (original algorithm)	Number Studies	Sens	95% CI	Spec	95% CI
Pre-school and primary school age	Autism versus non-autism spectrum and clinical utilization population.	4	0,78	0.69 to 0.85	0,88	0.41 to 0.99

Notes: Data from Matson et al. 1998; Russell et al. 2010; Wiggins and Robins 2008; Mayes et al. 2009 were used in both analyses.

[23]	**Consensus-based recommendation** *Key question 20 on the assessment of psychopathological findings: What information should be used to make the diagnosis (self-history, external history, behavioural observation, psychological performance diagnostics) and what should the procedure be?*
KKP	The classic psychopathological findings should be collected and documented during the diagnostic process, as they provide indications of possible comorbid disorders as well as possible differential diagnoses. The interpretation should take into account that peculiarities of autism-specific (verbal and non-verbal) communication and perception can lead to misinterpretation.
	Strong consensus (14 out of 14)

[24]	**Evidence-based recommendation** *Key Question 23: What standardized diagnostic procedures exist and how are they to be scientifically evaluated in relation to clinical diagnosis (e.g. ADI-R, ADOS)?*
B	As part of the diagnostic process, a (semi-)standardized behavioral observation should be conducted, since autism-specific symptomatology is not adequately covered in the classic psychopathological findings. The following instruments can be used for different age groups and questions: **Toddler 12 - 30 months, questioning autism or autism spectrum:** ADOS Toddler Module (part of ADOS-2). **Preschool child 30 - 60 months, autism questionnaire:** CARS, ADOS module 1/2, ADOS-2 module 1/2. **Preschool child 30 - 60 months, questioning autism spectrum:** CARS, ADOS-2 module 1/2. **Preschool and primary school children from 5 years of age, questioning autism:** CARS, ADOS-2 module 2/3. **Preschool and primary school children from 5 years of age, questioning autism spectrum:** CARS, ADOS-2 module 2/3.

	Adolescents Questioning Autism and Autism Spectrum: ADOS Module 3 or 4. **Adult Questioning Autism and Autism Spectrum:** No instrument currently recommended. None of the above instruments are recommended as mandatory for the diagnosis of autism spectrum disorders.
Evidence level 2-4	Sources: see evidence tables in appendix.
	Strong consensus (14 out of 14)

B.4.7 Comparative evaluation of individual diagnostic instruments; combination of instruments, integration, contradictions.

B.4.7.1 Summary from the source guidelines

A comparative assessment of all diagnostic tools was not made in the source guidelines.

B.4.7.2 Updating the evidence, formulating own recommendations

Of the structured interviews presented in B.4.5 as well as B.4.6, none were directly compared, and of the direct behavioral observation instruments, only the ADOS and CARS were directly compared. Both studies had conflicting results. In a study with young children, the ADOS and CARS showed comparable sensitivity for autism and spectrum, while the specificity of the CARS was better In a study with preschoolers, the ADOS showed significantly higher sensitivity than the CARS; specificity was not reported (Reszka et al. 2014). Both studies show a high risk of bias.

In addition, there are few studies on the combination of individual instruments. Here, on the one hand, the combination ADI-R and ADOS, and on the other hand, the combination FSK and ADOS were investigated.

Individual studies show an increased sensitivity and specificity with regard to the combination of ADI-R and ADOS compared to one instrument alone or to the combination of FSK and ADOS in children and adolescents aged 2 to 16 years (Kim and Lord 2012a; Corsello et al. 2007), other studies showed a superiority of the ADOS alone (Oosterling et al. 2010b). Since

the study situation here is rather poor (no replication studies) and also inconsistent, no conclusive statement can be made on the usefulness of the combinations of instruments.

Since no diagnostic instrument and no clinical examination can ever have a sensitivity and a specificity of 100%, there is a risk of false positive and false negative diagnoses with every diagnostic method. Also, different examiners may arrive at different assessments with the same instrument (low inter-rater reliability) or different correctly evaluated and reliable instruments may show different results.

[25]	**Evidence-based recommendation** *Key question 25: How to deal with contradictory results?*
A	The aim is to reach a team-based diagnostic consensus based on a detailed synopsis of all findings and differentiated differential diagnostic considerations. It should be verified that the instruments used were objective and in accordance with the relevant manuals.
(Westman Andersson et al. 2013) II	Strong consensus (14 out of 14)

B.4.8 Test psychological examinations

B.4.8.1 Summary from the source guidelines

NICE children (diagnostics)

Here, it is generally recommended to establish a developmental profile of strengths and weaknesses in order to establish a therapy plan oriented towards personal needs. The use of standardised instruments is not recommended and it is emphasised that there are no studies on this.

NICE Adult

Here, it is also generally recommended to get an impression of the psychosocial functioning level at home, in education or at work. The use of standardized instruments is not addressed.

SIGN

It is recommended to obtain information on psychosocial functioning levels from kindergarten and school and to describe an individual profile of strengths and weaknesses. In addition, it is recommended to consider standardized cognitive, linguistic and neuropsychological testing, including adaptive skills. Particular emphasis is placed on examining language development and speech and communication skills. Annex 3 lists numerous instruments studied for this purpose, although no specific one is recommended.

B.4.8.2 Current situation in Germany, formulation of own recommendations

In Germany, it is common practice in the field of child and adolescent psychiatric diagnostics to carry out a standardised IQ test and, in the case of a suspected language development disorder or partial performance disorder, a standardised language development test and, depending on the suspicion, a standardised reading and spelling test or arithmetic test (see B.5). In the field of adult psychiatric diagnostics, this procedure is not regularly established.

However, it is well documented that many individuals with autism spectrum disorder may have a heterogeneous intelligence profile, which can be particularly evident in multidimensional developmental and IQ tests (Oliveras-Rentas et al. 2012). It is particularly helpful in the area of school and work if the individual profile is known, as this can often explain many strengths and weaknesses in the performance shown. In addition, it is also important to know the cognitive, linguistic and adaptive skills for the assessment of special needs at any age in order to make individualized and as concrete as possible recommendations for therapy.

Often the cognitive skills of children, adolescents and adults with autism spectrum disorder are clinically underestimated, because due to reduced communication or cooperation skills the impression arises that the affected person is not cognitively capable of some requirements. For this reason, standardized cognitive testing is recommended, especially before starting school, but also when deciding on secondary school or training/studies.

Neuropsychological test procedures of any kind, on the other hand, are not useful, since there are no corresponding standardized test procedures and it has not yet been proven that they can validly distinguish between autism spectrum disorders and relevant psychiatric differential diagnoses or intelligence reduction - beyond mere differences in mean values.

[26]	**Consensus-based recommendation** *Key question 22, part 1: What should be the minimum requirements for the diagnostic process (information for physicians, psychologists, parents and possible affected persons)? → on standardised test procedures in connection with diagnostics: cognition, language, adaptive behaviour*
KKP	As part of the diagnosis of an autism spectrum disorder, cognitive abilities and skills should be assessed. In children and adolescents, a developmental or multidimensional intelligence test should be performed if there is sufficient cooperation for this. Currently standardized test procedures are to be used. It is also recommended that standardised language development tests be carried out on children whose language development is conspicuous. Neuropsychological tests of any kind are not necessary for the diagnostic process.
	Strong consensus (14 out of 14)

B.4.9 Profile of strengths and weaknesses

B.4.9.1 Summary from the source guidelines

All source guidelines recommend describing an individual profile of strengths and weaknesses at the end of the diagnostic process in order to be able to make specific support and therapy recommendations based on this. However, no specific procedures are outlined.

B.4.9.2 Current situation in Germany, formulation of own recommendations

In Germany it is currently not common to describe a profile of individual strengths and weaknesses beyond autistic symptomatology, psychiatric and physical comorbidity as well as linguistic and cognitive skills at the end of a diagnostic process. Since the WHO has developed the "International Classification of Functioning, Disability and Health" (ICF; https://www.dimdi.de/static/de/klassi/icf/index.htm), it is theoretically possible to use this to help formulate strengths and weaknesses in the diagnostic process. There are international efforts to extract autism-specific core items from the (very detailed) ICF and to test them for clinical validity. However, this process has not yet been completed, so that the ICF currently appears to be too detailed for the diagnostic process for autism spectrum disorders, since the entire classification mentions many aspects that are not relevant for persons with autism spectrum disorders.

[27]	**Consensus-based recommendation** *Key Question 22, Part 2: What should be the minimum requirements for the diagnostic process (information for physicians, psychologists, parents and possible stakeholders)?→ on the profile of strengths and weaknesses*
KKP	A profile of strengths and weaknesses, based on the results of autism-specific diagnostic testing, clarification of psychiatric/psychiatric and physical comorbid conditions, and the results of developmental and multidimensional intelligence testing and, if applicable, a language development test, should be formulated, at least qualitatively, at the end of a diagnostic process.
	Strong consensus (14 out of 14)

B.4.10 Physical examination

B.4.10.1 Summary from the source guidelines

NICE children (diagnostics)

It is recommended that a physical examination always be performed and that special attention be paid to the following symptoms: Skin lesions that may indicate neurofibromatosis or tuberous cerebral sclerosis (with Wood lamp), signs of injury (self-harm, other injury, child abuse), evidence of congenital malformations, and dsymorphic signs including microcephaly and macrocephaly. These source guidelines also systematically examined and meta-analytically calculated possible internal neurological disorders that are common in autism spectrum disorders. Compared with healthy children, increased prevalences were reported in children with autism for infantile cerebral palsy (5%, 95%-CI 4-6), sleep problems (37%, 95%-CI 11-68), epilepsy (24%; 95%-CI 8-46), vision problems (7%, 95%-CI 0-26), hearing problems (3%, 95%-CI 0-9); motor difficulties (13%), and gastrointestinal complaints (3%). In children with autism spectrum disorders, the following prevalences were reported: infantile cerebral palsy (5%, 95%-CI 1-13), sleep problems (61%, 95%-CI 31-88), epilepsy (15%; 95%-CI 7-26), epileptic seizures (5%, 95%-CI 2-69), vision problems (6%, 95%-CI 0-21), hearing problems (8%, 95%-CI 1-20); motor difficulties (25%), and gastrointestinal complaints (62%). Based on this evidence, as well as other comorbid conditions and risk factors, it is recommended that the following conditions be considered for differential diagnosis during the internal medicine-neurology examination and that further laboratory testing be performed as needed: Intellectual disability,

motor coordination or developmental disorder, muscular dystrophy, epilepsy or epileptic encephalopathy, chromosomal disorders, other genetic disorders including fragile X syndrome, tuberous cerebral sclerosis, neurofibromatosis; eating disorders including restrictive eating, urinary incontinence and enuresis, constipation, encopresis, sleep disorders, hearing and visual disorders. In the explanations on the necessary components of diagnostics (see above, B.4.4), an internal neurological examination is recommended as a component of every diagnostic clarification.

NICE Adult

In these source guidelines, it is recommended that the following differential diagnoses or comorbid diseases be examined or kept in mind: other developmental neurological diseases, other mental disorders, neurological diseases, physical diseases, speech and language disorders, selective mutism, sensory hypersensitivity or hyposensitivity. In the remarks on the necessary components of the diagnosis (see above, B.4.4), an internal neurological examination is not mentioned.

SIGN

In SIGN, particular attention is drawn to the anamnestic finding of linguistic regression, which is more frequently associated with EEG changes and Landau-Kleffner syndrome, especially when it occurs above the age of three. The typical characteristics of Rett syndrome or mitochondrial disease should also be considered. Once again, the possible genetic causes of autism spectrum disorders are pointed out, which on the one hand implies the clarification of tuberous cerebral sclerosis as well as signs of dysmorphia in the physical examination. Indications of intellectual disability and its possible causes should be followed up. An internal neurological examination with focus on neurological findings and signs of dysmorphia is recommended (grade D: based on studies with evidence grade 3 and 4).

B.4.10.2 Current situation in Germany, formulation of own recommendations

In Germany, it is usually the case that a physical examination also takes place during the initial diagnosis of preschool children. In the case of primary school children, adolescents or adults, it can be assumed that this often does not take place, as it is possibly assumed that all relevant organic diseases have been detected at an early stage if the preventive examinations (U examinations) are carried out regularly by paediatricians and adolescent doctors. Furthermore, physicians with neurological and internal medicine expertise are not always involved in the diagnostic process. Here, the guideline groups see a clear need for improvement.

[28]	**Consensus-based recommendation** *Key question 26: What is the significance of the internal medicine-neurology examination in the diagnostic process? → on the significance of the internal neurological examination*
KKP	Every person with a suspected autism spectrum disorder should undergo a complete internal neurological examination as part of the diagnostic process. Attention should be paid to indications of (self) injury, compulsive washing, eating disorders and physical abuse.
	Strong consensus (13 of 14, 1 abstention)

B.4.11 Laboratory testing

B.4.11.1 Summary from the source guidelines

NICE children (diagnostics)

It is recommended not to perform routine laboratory tests, but to perform the following tests individually, based on the physical examination, clinical assessment and profile of the child/adolescent with autism spectrum disorder: Genetic testing (as suggested by the regional genetics center) for signs of dysmorphia, congenital malformations, or intelligence impairment, and EEG (see below) for evidence of epilepsy. Further laboratory tests are not recommended.

NICE Adult

Laboratory tests, EEG, hearing and vision tests should be performed on an individual basis, based on the results of the physical examination as well as the clinical assessment. Genetic testing should be performed (based on the recommendation of the regional genetics center) in the presence of dysmorphic signs, congenital malformations, or intellectual disability. Further laboratory testing should be performed as clinically indicated, for example, if there is a sudden change in behavior, a sudden change in weight, or possibly pain conditions that cannot be communicated.

SIGN

Genetic diagnostics should be performed in cases of suspected tuberous cerebral sclerosis, fragile X syndrome, and in the presence of signs of dysmorphia or reduced intelligence. In addi-

tion, all suspected diagnoses based on medical history and physical examination should be clarified lege artis. It is recommended to perform a chromosomal analysis as well as an examination for fragile X syndromes in case of corresponding clinical indications.

B.4.11.2 Current situation in Germany, adoption of the recommendations from the source guidelines with extension

There are no systematic studies on which laboratory tests are performed in routine pediatric diagnostics for children and adolescents with autism spectrum disorder in Germany. It can be assumed that different agencies proceed very differently here, depending on the training of the treating physicians and the availability of laboratory tests. For example, for a long period of time, it was common practice to screen for inborn errors of metabolism beyond newborn screening as part of the pediatric neurological examination. Here, however, the study evidence is clear: inborn *errors of metabolism are* very rare in individuals with autism spectrum disorder in systematic clinically collected samples (Schiff et al. 2011). When individuals are considered to have a diagnosis of inborn errors of metabolism, they are more likely to have a comorbidity of autism spectrum disorder, which should then be assessed in individuals with metabolic disorders. A recent systematic review article discusses the following inborn errors of metabolism with increased risk for autism spectrum disorders: Phenylketonuria, disorders of branched-chain amino acid (leucine, isoleucine, and valine) metabolism, aminoacidurias, disorders of purine and pyrimidine metabolism, vitamin- and cofactor-based disorders, mitochondrial disorders, glucose-6-phosphate dehydrogenase deficiency, Smith-Lemli-Opitz syndrome, succinine semialdehyde dehydrogenase deficiency, Sanfilippo syndrome (Ghaziuddin and Al-Owain 2013). All of these disorders are very rare conditions, so the presence of autism spectrum disorder should not be concluded by implication that these disorders should be routinely screened for. Further metabolic diagnostics should therefore only be carried out in the case of further acute or chronic physical symptoms of a metabolic disease by appropriately specialised centres with corresponding (paediatric) neurological expertise. General symptoms of a metabolic disease are e.g. sudden onset of lethargy, cyclic vomiting, epileptic seizures as a young child. In children who were not born in Germany and come from countries where screening for inborn errors of metabolism does not take place, special attention should be paid to symptoms of metabolic diseases and, if necessary, clarification should be initiated.

It is often debated whether increased *gastrointestinal problems are* present in individuals with autism spectrum disorder. In a consensus report from the USA as well as from the NICE children's guidelines after a systematic search, it was emphasised that these problems and diseases

are not increased in autism spectrum disorders (Buie et al. 2010). Therefore, a work-up for gastrointestinal disorders should only be performed in cases of clinical suspicion based on specific symptoms, such as recurrent abdominal pain or diarrhoea.

It can be assumed, although not empirically proven, that in Germany *genetic examinations* are carried out relatively frequently in children with autism spectrum disorders, and less frequently in adolescents and adults with a late diagnosis. Here, too, there is no uniform practice in Germany. In Germany, there is certainly also a high degree of sensitivity and frequent scepticism towards genetic diagnostics for mental disorders in general, which is much less pronounced in other countries. However, knowledge about etiologically relevant genetic findings has increased significantly in recent years, and some genetic diagnoses also imply specific further treatments (e.g. Prader-Will syndrome, Klinefelter syndrome). The guideline group therefore adopts and expands the recommendations of the NICE and SIGN source guidelines and refers to a recently published clinical review (Carter and Scherer 2013).

[29]	**Consensus-based recommendation** *Key question 27: What is the significance of a human genetic examination in the context of diagnostics?→ on the significance of human genetic examination*
KKP	A human genetic examination should be recommended to the person concerned and/or the legal guardians or the legal representative if there is a clinical indication.
	Strong consensus (14 out of 14)

[30]	**Supplementary consensus-based recommendation on laboratory tests**
KKP	In principle, laboratory tests should only be performed in children, adolescents and adults when clinically indicated. In particular, examinations for gastroenterological and metabolic disorders are unnecessary if there are no corresponding clinical symptoms.
	Strong consensus (14 out of 14)

B.4.12 Apparatus diagnostics

B.4.12.1 Summary from the source guidelines

In the source guidelines, EEG, MRI, CT, SPECT and PET examinations were systematically examined with regard to apparative diagnostics.

NICE children (diagnostics)

Regarding the apparative diagnostics it is pointed out that the evaluation of the results of EEG or MRI examinations are often very subjective and do not always imply a therapy. In particular, findings such as "abnormal EEG" without epileptic seizures occur frequently, but are rather unspecific. Structural changes detected on cranial MR imaging also do not usually imply therapy.

An EEG examination is recommended in cases of clinical suspicion of epileptic encephalopathy, Landau-Kleffner syndrome and epilepsy.

With regard to cranial imaging, only MRI studies were found. Here, too, it is recommended to perform an MRI only if there is a clinical indication and if action-guiding indications can be expected from the result.

NICE Adult

It is emphasized here that a diagnosis cannot be made based on MRI data. EEG is recommended if clinically indicated. Imaging techniques are not specifically addressed. A hearing or vision test is also recommended if clinically indicated.

SIGN

Here, a routine examination of EEG and MRI is rejected. Only in case of clinical indication an EEG should be performed, e.g. suspicion of Landau-Kleffner syndrome or regression of cognitive skills. No statement is made regarding indicated MRI examinations.

B.4.12.2 Current situation in Germany, adoption of the recommendations from the source guidelines

In Germany it is much more common than in the UK to perform EEG and MRI examinations as part of routine diagnostics, because there is much more diagnostic equipment available here than in the UK. However, these examinations are often very distressing, especially for children with autism spectrum disorder, and careful clinical consideration must be given to whether they

are really indicated. Certain EEG patterns associated with clinical characteristics, especially language or cognitive regression, can sometimes indicate treatable disorders such as Landau-Kleffner syndrome, continuous spike wave activity during sleep (CSWS), or even mitochondriopathies, so that an EEG is indicated especially when these disorders are suspected as well as when epilepsy is suspected. Cranial imaging is also only recommended if action-guiding indications are to be expected, as may be the case, for example, in the presence of certain mitochondriopathies or storage disorders.

[31]	**Consensus-based recommendation** *Key question 27: What is the significance of a human genetic examination in the context of diagnostics?→ on the significance of instrumental diagnostics*
KKP	Apparative diagnostics, above all EEG, MRT, but if necessary also apparative diagnostics for the clarification of other internal-neurological findings, should only be carried out if there is a clear clinical indication based on the somatic anamnesis and the internal-neurological examination. Possible hearing and visual disturbances should be excluded.
	Strong consensus (14 out of 14)

B.4.13 Best age for (early) diagnosis; follow-up examinations

Since, especially in the USA, the earliest possible diagnosis is strongly propagated and, in addition, the possibility of a cure has recently been frequently discussed, the question of the optimal age of an initial diagnosis and the topic of the necessary follow-up examinations are also raised here as a supplement to the description of the diagnostic process.

B.4.13.1 Summary from the source guidelines

For the question of early diagnosis, only NICE Children (diagnosis) and SIGN should be consulted. Both source guidelines recommend a diagnosis as early as possible if there are corresponding indicative symptoms (see also B.2). The two guidelines do not comment on the question of systematic follow-up diagnostics (see also B.7).

NICE Children (Diagnostics) additionally notes that there can be great diagnostic uncertainty in children with chronological ages below 24 months or developmental ages below 18 months,

and further in children and young people about whom no early childhood development information is available. Also, psychiatric differential diagnoses such as ADHD or social behavior disorders can often be very difficult to distinguish. Repeated presentation is recommended especially when there is diagnostic uncertainty.

NICE Adult

It is noted here that the symptoms of autism spectrum disorder are poorly understood in adulthood. For this reason, many adults with the disorder are underdiagnosed. It is recommended to ensure more knowledge about the classic symptoms of an autism spectrum disorder in the training of relevant professional groups and to think of the clinical picture in terms of differential diagnosis. The guideline does not comment on the question of systematic follow-up diagnostics (see also B.7).

B.4.13.2 Current situation in Germany, formulation of own recommendations

As mentioned above, the age of diagnosis in Germany is significantly higher than in the USA. There are long waiting times for diagnostic appointments in specialized offices/facilities. Furthermore, there are also additional waiting times for an adequate therapy offer. For this reason, it is still necessary to demand that Germany establish diagnostics as early as possible. The currently published diagnostic instruments are only valid for children with a developmental age > 18 months, so that a diagnosis for a developmental age < 18 months seems rather difficult. However, this will change after the publication of the ADOS Infant Module (expected in Germany before the end of 2015). This can be used from a developmental age of 12 months (Luyster et al. 2009).

In order to obtain evidence-based statements regarding early diagnosis, a systematic search was conducted for studies on the stability of a diagnosis at preschool age, divided into diagnosis before the age of 2 years or diagnosis from the age of two years to before the age of six years. Where possible, the results were meta-analytically aggregated (see Methods Report/Appendix).

Diagnosis before the age of two:

The results show (see Methods Report/Appendix) that when any diagnosis from the autism spectrum (ICD-10: F84.0, F84.1, F84.5, F84.8, F84.9; DSM-IV (TR): 299.00, 299.80) was assigned, this diagnosis category was absolutely stable over one year in both population-based and case-control studies (meta-analysis population-based studies 1 [95% CI 0.9764; 1.0236].

None of the children no longer had an autism spectrum diagnosis after the one-year follow-up. However, some children who did not receive an autism spectrum disorder diagnosis at baseline but had developmental abnormalities met the diagnostic criteria for autism spectrum disorder at one year (9/34; 26%). However, the subdiagnoses of autism spectrum disorders into early childhood autism, atypical autism/PDD-NOS or Asperger syndrome were not always stable at this young age, but there were changes in both directions, from autism to spectrum diagnoses and from spectrum diagnoses to autism.

After two years of follow-up, two case-control studies also showed that when any diagnosis from the autism spectrum (ICD-10: F84.0, F84.1, F84.5, F84.8, F84.9; DSM-IV (TR): 299.00, 299.80) was assigned, this diagnostic category was completely stable over two years (meta-analysis case-control studies 1 [95%-CI 0.98; 1.02]). Again, some children with developmental abnormalities at baseline who did not have an autism spectrum diagnosis received such a diagnosis within the following two years (3/28; 11%). Subdiagnoses within the autism spectrum were not always stable in these studies either, with the following pooled estimated percent stability rates found: T1 autism - T2 autism: 0.73 [95%-CI 0.63; 0.83]; T1 autism - T2 spectrum 0.27 [95%-CI 0.17; 0.37]; T1 spectrum - T2 spectrum 0.93 [95%-CI 0.77; 1.09], T1 spectrum - T2 autism 0.07 [95%-CI -0.09; 0.23].

Summary interpretation: These studies clearly show that an early diagnosis before the age of two years remains stable within the autism spectrum, and that a relatively high percentage of children with developmental abnormalities before the age of two years also receive a diagnosis from the autism spectrum after one to two years. The overall study quality was adequate, but the sample size was relatively small.

Diagnosis between the ages of two years and under six years:

Since only two studies on the course after one year were available, which could not be aggregated meta-analytically, these studies were not included in the following presentation (see Method Report/Appendix). The number of studies on the stability of the diagnosis after two years, on the other hand, is so good that two meta-analyses, one on population-based studies and the other on case-control studies, could be calculated. The results of both meta-analyses are very comparable.

If any autism spectrum diagnosis was present at T1, the population-based studies showed a pooled estimated percent stability rate of 0.91 [95%-CI 0.84; 0.97] of also continuing to have

an autism spectrum diagnosis after two years. A proportion of patients no longer met the diagnostic criteria after two years and no longer had a disorder on the autism spectrum (0.09 [95%-CI 0.03; 0.16]). Stability rates of individual diagnoses were as follows: T1 autism - T2 autism: 0.85 [95%-CI 0.73; 0.96]; T1 autism - T2 spectrum 0.07 [95%-CI -0.03; 0.16]; T1 autism - T2 no more autism spectrum diagnosis 0.08 [95%-CI -0.02; 0.18]; T1 spectrum - T2 spectrum 0.52 [95%-CI 0.34; 0.69]; T1 spectrum - T2 autism 0.15 [95%-CI -0.06; 0.36]; T1 spectrum - T2 no autism spectrum diagnosis more 0.29 [95%-CI -0.07; 0.65].

If any diagnosis from the autism spectrum was present at T1, the case-control studies showed a pooled estimated percent stability rate of 0.91 [95%-CI 0.86; 0.97] of also continuing to have a diagnosis from the autism spectrum after two years. A proportion of patients no longer met diagnostic criteria after two years (0.10 [95%-CI 0.03; 0.16]). Stability rates of individual diagnoses were as follows: T1 autism - T2 autism: 0.84 [95%-CI 0.74; 0.94]; T1 autism - T2 spectrum 0.10 [95%-CI 0.05; 0.15]; T1 autism - T2 no more autism spectrum diagnosis 0.04 [95%-CI -0.01; 0.08]; T1 spectrum - T2 spectrum 0.47 [95%-CI 0.13; 0.80]; T1 spectrum - T2 autism 0.26 [95%-CI 0.05; 0.47]; T1 spectrum - T2 no autism spectrum diagnosis more 0.20 [95%-CI 0.06; 0.35]. Of the children with developmental delay at T1, some also developed an autism spectrum disorder diagnosis after two years (13/48; 27%).

Summary interpretation: When diagnosing an autism spectrum disorder between the ages of two to six years, the diagnostic stability is somewhat lower than when diagnosing an autism spectrum disorder before the age of two years. Just under 10% of children do not meet diagnostic criteria after two years. This is mainly due to children with a diagnosis of Asperger's syndrome or atypical autism/PDD-NOS at T1 no longer meeting diagnostic criteria after two years. However, there continues to be a relatively high percentage of children with developmental disabilities at T1 who receive an autism spectrum disorder diagnosis after two years of follow-up.

[32]	**Evidence based statement** *Key question 16: At what earliest can ASD be reliably diagnosed? →on the stability of the diagnosis at preschool age*
	A diagnosis from the autism spectrum remains stable on the spectrum (100%) especially with an early diagnosis before the age of two. With a diagnosis between the ages of two to six years, 10% of children lose the diagnosis especially with initial diagnoses of Asperger syndrome or atypical autism/PDD-NOS. A proportion of children (approximately 10-30%) who show developmental abnormalities before and after the age of two develop the diagnostic criteria for a diagnosis on the autism spectrum over the course of 1-2 years. Within the autism spectrum, the children with an early diagnosis at the age before two years mainly show changes from an autism diagnosis towards a spectrum diagnosis (Asperger syndrome, atypical autism/PDD-NOS). Among the children with a diagnosis between the ages of two and six years, changes in the range of spectrum diagnoses are mainly seen in two directions, towards autism, but also towards no autism spectrum diagnosis anymore.
Evidence level **1**	Sources: see evidence tables in the appendix.
	Strong consensus (14 out of 14)

[33]	**Consensus-based recommendation** *Key question 16: At what earliest can ASD be reliably diagnosed? on →conclusions for the diagnostic process*
KKP	Since the diagnosis of autism spectrum disorder has been shown to be stable before the age of two, it should be made and named when symptoms are clear. Children with developmental disabilities should also be monitored for the development of autism spectrum disorder throughout their preschool years. Children with an initial diagnosis of Asperger's syndrome or atypical autism at preschool age should have their diagnosis rechecked no later than the year before they start school. For all children with autism spectrum disorder, a multidimensional intelligence diagnosis should be carried out before school enrolment if the child cooperates. If clinically indicated, further developmental areas should be checked, especially language.
	Strong consensus(14 out of 14)

B.5 Examination of comorbid disorders, differential diagnosis

Inge Kamp-Becker

B. 5.1 Comorbid disorders

B. 5.1.1 Introduction

This chapter presents the disorders or conditions that the diagnostician should consider when conducting a diagnostic evaluation of a child, adolescent, or young adult for the presence of autism spectrum disorder. There are a number of disorders and diagnoses that co-occur with autism spectrum disorder at an increased rate, these are referred to as comorbid disorders. In some cases, these disorders can be considered simultaneously as risk factors (see Chapter A.5), but also as differential diagnoses (see Chapter B.5.2). The reasons why some disorders are more frequently associated with autism are not yet sufficiently understood.

Comorbid disorders must be considered and treated according to these guidelines, they influence the long-term course of autism spectrum disorder. The most important comorbid disorders are those that occur frequently (high prevalence rate), have a significant impact on quality of life or influence the developmental course. These should be identified with the key question named below. Thus, the prevalence rate of comorbid disorders is of particular importance for diagnostics; these are presented in Chapters 3a and 3b (Chapter A.3 Descriptive Epidemiology), to which reference is made here.

The following key questions are answered and recommended in the text:

30. what comorbidities should be looked out for?

B.5.1.2 Summary from the source guidelines

The NICE guidelines come to the following recommendations after analysing the prevalence of comorbid disorders (see Chapter A.3.3):

Consideration should be given to whether a child or young person may have any of the following co-existing disorders. If this is suspected, then appropriate investigations should be initiated:

- Developmental Disabilities: Global developmental delays or intelligence impairment; circumscribed developmental disorders of motor functions; learning disorders; language disorders.

- Mental or behavioral problems and disorders: Attention deficit/hyperactivity disorder (ADHD); anxiety disorders and phobias; affective disorders; oppositional behavior; tics or Tourette's syndrome; obsessive-compulsive disorder; self-injurious behavior;
- Physical neurological abnormalities and disorders: Epilepsy and epileptic encephalopathy; chromosomal disorders; genetic abnormalities, including fragile X syndrome; tuberous sclerosis; muscular dystrophy; neurofibromatosis.
- Functional problems and disorders: Feeding problems, including restrictive diets; urinary incontinence or enuresis; constipation, bowel problems, fecal incontinence, or encopresis; sleep disturbances; visual or hearing impairments.

B. 5.1.3 Updating

For the question of the general frequency of comorbid conditions, the prevalence figures for another comorbid disorder are approximately 70 - 85% (Abdallah et al. 2011; Gjevik et al. 2011; Levy et al. 2010; Mattila et al. 2010; Simonoff et al. 2008). However, quite a few individuals with autism spectrum disorder have more than one comorbid condition (Levy et al. 2010; Melville et al. 2008; Simonoff et al. 2008). In a German study, 54% had one other psychiatric diagnosis, and 19% had two (Noterdaeme and Wriedt 2010). The most common diagnosis in this study was that of an externalizing disorder; internalizing and other disorders occurred only half as often. Various reasons for the high number of comorbidities are discussed. On the one hand, common biological/genetic and/or environmental risk factors could be responsible for this. However, the possibility that the high comorbidity can be explained by the difficulty in distinguishing from and overlapping with other disorders is also discussed (Caron and Rutter 1991; Gillberg and Fernell 2014; Mazefsky et al. 2012). In this case, the "comorbid" abnormalities (e.g., anxiety symptoms, attention problems) would already be explainable by the diagnosis of autism spectrum disorder and an additional diagnosis would be unnecessary. Therefore, it must be critically examined in each individual case whether there is actually a symptomatology that goes beyond the extent to be expected in autism spectrum disorder and thus whether there is actually an additional, further psychopathology.

Developmental Disabilities: Intelligence impairment and language development disorders

Current research consistently indicates that more than 55% of individuals with autism spectrum disorder have below average cognitive aptitude (IQ<85) (Baird et al. 2006; Yeargin-Allsopp et al. 2003). However, only 16% have moderate to severe intelligence impairment (IQ<50). About 28% have average intelligence (IQ 85-115), but only 3% had above-average intelligence

(IQ>115) (Charman et al. 2011). Very similar results were also found in a German study (Noterdaeme and Wriedt 2010). In a study of 1129 children born in 1994 and diagnosed with Autism Spectrum Disorder at age 8 within the Autism and Developmental Disabilities Monitoring (ADDM) Network, 38% had IQ in the low intelligence range (IQ<70) and 24% in the below average intelligence range (IQ = 70-84) (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators and Centers for Disease Control and Prevention. 2012). Risk for comorbid intelligence deficits was associated with prematurity and being too short for gestational age. Data on patients having an average IQ vary widely across studies. In a recent systematic review, the percentage of affected individuals with an average IQ is reported as 15.6-86.7% for early childhood autism and 45-85.3% for all profound developmental disorders (Elsabbagh et al. 2012). In the NICE guidelines, the prevalence of intelligence impairment (IQ<70) is reported as 65-76%. Consistently, many studies show that girls are more likely to have intelligence impairment (Wiggins et al. 2014; Lai et al. 2014). Heterogeneous intelligence profiles are often present, which also indicate individual performance strengths (Bölte et al. 2009; Dawson et al. 2007). Recent studies also indicate that there is an age effect that necessitates test repetition at around 8 years of age to avoid misclassification of cognitive performance (Barneveld et al. 2014).

Since language development disorders are very often associated with autism, it is important to determine whether language skills have developed in line with the child's age. Since language skills are of decisive importance for the prognosis (see chapter B.4), it is very important to assess them diagnostically and, if necessary, to promote them or include them in the therapy. In addition, motor deficits or developmental disorders should also be considered and treated.

Mental disorders

Sleep disorders are very common in **preschool age:** Every second child with an autism spectrum disorder is affected. In particular, frequent waking and difficulty falling asleep are complaints to be named here (Krakowiak et al. 2008).

In the **age group of 6 - 13 year old children, hyperactive** behaviour up to comorbid **ADHD** is particularly frequent. There is also an increased rate of **excretory disorders** (encopresis, urinary incontinence, enuresis). **Anxiety disorders**, including social phobia, should be considered as a possible comorbidity according to the empirical data. There are very different data on the prevalence of social phobia (Tyson and Cruess 2012), which vary considerably. In patients with high-functioning autism spectrum disorder, social phobia must be considered both as a comorbid and as one of the most relevant differential diagnoses (see B.5.2). A meta-analysis

(van Steensel et al. 2013) showed that 39.6% of children and adolescents with autism spectrum disorder met criteria for an anxiety disorder according to DSM-IV (29.8% specific phobia, 17.4% obsessive-compulsive disorder, 16.6% social anxiety disorder). Anxiety disorders were found mostly in older children, and obsessive-compulsive disorder and separation anxiety were found more in younger children. Overall, the study indicates a higher prevalence of anxiety disorders in the PDD-NOS subtype. In addition, low IQ was associated with a higher prevalence of anxiety disorders. **Eating behavior** abnormalities are present in many children, particularly in relation to selectivity in eating (Twachtman-Reilly et al. 2008), which is reported to be approximately 60%. **Depressive disorders are** significantly less common than anxiety disorders (Levy et al. 2010; Simonoff et al. 2008), but recent studies find higher rates of depression in patients with high-functioning autism spectrum disorder than in the general population (Mazzone et al. 2012). Furthermore, externalizing **behavior problems** also play an important role; in particular, social behavior disorders with oppositional behavior (Simonoff et al. 2008), but also **tic disorders** (Mattila et al. 2010) can occur simultaneously with autism spectrum disorder.

In a study of 4089 individuals with intelligence impairment (including 9.7% with autism spectrum disorder; Tsiouris et al. 2011), physically **aggressive behavior** toward other people, objects, and self was significantly associated with autism spectrum disorder (31% higher rate). Aggressive behavior against oneself was most frequently found in individuals with autism spectrum disorder, female gender, and significant intelligence impairment. Autoaggressive behavior was most common in severe intelligence impairment in a German study. A significant association was found between the occurrence of (auto-)aggressive behavior and the extent of psychosocial adjustment (Noterdaeme and Wriedt 2010). An association between autism spectrum disorder and **psychotic symptoms was found in** 12-year-old children (Rai et al. 2012a).

In **adulthood,** the data so far are based on few studies. Here, too, further studies with larger samples would therefore be desirable. In a study of 129 adult patients with autism spectrum disorder (Eaves 2006), who were diagnosed in childhood, 56% of the patients examined showed comorbid disorders, with **anxiety** disorders having the highest prevalence both in relation to the current time and in the course of life (39% and 53% respectively). Anxiety disorder and depression were found significantly less frequently in patients with intelligence impairment. A study of adult patients with autism spectrum disorder and intelligence impairment (Melville et al. 2008) found a rather low number of comorbid disorders compared to the prevalence figures for childhood and adolescence. **Problem behaviors** clearly predominated. In a study of 147 adults with intelligence impairment and autism, no increased rate of comorbid disorders was

found compared to 605 adults with intelligence impairment (without autism) (Tsakanikos et al. 2006).

In contrast, studies of adult patients with high-functioning autism spectrum disorder or Asperger syndrome found a high prevalence rate for comorbid disorders (especially personality disorders, depression, and anxiety disorders) (Hofvander et al. 2009; Lugnegård et al. 2011), also compared to a psychiatric sample without autism spectrum disorder (Joshi et al. 2013). The group of individuals with autism spectrum disorder had a significantly increased risk of comorbid depressive disorder and anxiety disorder (lifetime prevalence) compared to the psychiatric sample. In a sample of 54 patients with Asperger syndrome, more than half met criteria for a personality disorder (males: 65%, females 32%). In particular, the criteria for schizoid as well as obsessive-compulsive personality disorder were met. This is interpreted as an indication that there is a clear overlap of symptoms of the disorders Asperger syndrome and personality disorder. Comorbid antisocial personality disorder as well as substance abuse was found in the PDD-NOS subgroup (Hofvander et al. 2009). In a German study (Strunz et al. 2014a) of high-functioning adults with autism spectrum disorder, a comorbid psychiatric disorder (DSM-IV, Axis-I) was present in 36% of the 59 patients studied, with affective disorders (24%) and social phobias (14%) being the most common. 44.8% of the patients with autism spectrum disorder met the criteria for a personality disorder, most frequently schizoid and obsessive-compulsive personality disorder, and in rare cases self-confident or paranoid personality disorder.

Some - mainly exploratory - studies find an increased rate of **psychotic disorders** in adults with autism spectrum disorder (Hofvander et al. 2009; Kohane et al. 2012; Lugnegård et al. 2012; Nylander et al. 2013; Stahlberg et al. 2004). With regard to the comorbid presence of catatonia, only case studies are available to date; a recent review (Mazzone et al. 2014) points out that catatonic symptoms can indeed be found in autism spectrum disorder patients, but the prevalence rate is difficult to state, also due to the difficult differential diagnostic delimitation.

Physical-neurological diseases

For comorbid epilepsy, a recent study (Mouridsen et al. 2013b) found an OR of 21.6 (95% CI 8.1-57.3) in patients with early childhood autism. A study in patients with Asperger syndrome found an increased rate (3.9% of the patient group studied) of comorbid epilepsy compared to the general population (Mouridsen et al. 2013b). Individuals with atypical autism were found to have an OR of 6.5 (95% CI 3.0-14.2). A population-based study of adults also found a significant association between epilepsy and autism spectrum disorder (OR = 7.4, 95% CI 1.5 - 35.5; Rai et al. 2012a). Thus, epilepsies are among the most common physical neurological

comorbid conditions, especially in the presence of a comorbid intellectual disability (Canal-Bedia et al. 2011).

A 2003 systematic review concluded that there is no evidence that gastrointestinal disorders are more common in individuals with autism spectrum disorder than in the general population (Kuddo and Nelson 2003). In children with atypical autism, a recent study found no increased rate of disorders affecting the stomach, intestines, and liver (Mouridsen et al. 2013a) compared to a control group. In a study of 487 children with autism spectrum disorder, only 7.2% had gastrointestinal problems, and there was a significant correlation with problems with sleep behavior, eating behavior, and oppositional behavior (Maenner et al. 2012). Another population-based study that included a group of individuals with early childhood autism (N = 121) and control group (N = 242) also found no overall increased rate of gastrointestinal disorders (Ibrahim et al. 2009). However, the group of individuals with early childhood autism did show increased rates of constipation and dietary peculiarities/selective eating behaviors. Allergies are not more common in children with autism according to a study with age-matched control group (N = 69) (Bakkaloglu et al. 2008).

Based on the prevalence data (see Chapter A.3.1), chromosomal and genetic disorders should also be considered. Sensory impairments can also be comorbid and do not exclude the diagnosis of an autism spectrum disorder (Dammeyer, 2014).

[34]	**Consensus statement** *Key Question 30: What comorbidities should be watched for?*
	The presence of comorbid disorders should be considered in the diagnostic process and, if necessary, further clarified and treated diagnostically. A differentiated assessment should be made as to whether the symptoms are additional to or go beyond those of an autism spectrum disorder and whether they meet the respective diagnostic criteria of other disorders.
	Strong consensus (14 out of 14)

B.5.2 Differential diagnoses

Inge Kamp-Becker

31. which differential diagnoses should be considered?

B5.2.1 Introduction

Many developmental, mental, and behavioral disorders are associated with symptoms similar to those of autism spectrum disorder. These must be differentially diagnosed from autism spectrum disorder. Consideration of possible differential diagnoses is of great importance in making a valid and reliable diagnosis, so they must be considered throughout the diagnostic process. Accurate diagnosis is crucial to initiate appropriate treatment. Failure to make an accurate diagnosis has far-reaching implications for the further development and prognosis of the affected person. A false positive diagnosis of autism spectrum disorder (a diagnosis of autism is made, but another disorder is actually present) has negative consequences, as does a false negative diagnosis (autism is present, but not diagnosed). The fact that many of the relevant differential diagnoses also occur as comorbid disorders in the presence of an autism spectrum disorder once again underscores the need for specialized diagnostics against the background of diverse experience with all relevant disorders (see Chapter B.4.2).

However, not only the differential diagnostic differentiation from other disorders must be considered, but autism spectrum disorder must also be differentiated from subclinical symptoms that occur in the general population and do not lead to clinically relevant impairment. So-called autistic "traits" or "autistic-like traits" (Lundström et al. 2011; Lundström 2012) occur in healthy individuals as well as in many other psychiatric disorders (see below). For example, special interests occur not only in autism spectrum disorder, but also in healthy individuals or individuals with other disorders (Turner-Brown et al. 2011), as do sensory abnormalities (Van Hulle et al. 2012). It is true that there are individuals who show subclinical features of autism spectrum disorder or Asperger's syndrome and for whom the diagnosis might also help them to better understand themselves and their problems or to identify with the disorder pattern. However, if there is no clinically relevant impairment in everyday life, then according to these guidelines the diagnosis must not be given.

Differentially, many disorders must be considered that are also associated with abnormalities in the area of social interaction, communication or repetitive, stereotyped behaviours. A diagnostic assessment must therefore include the core symptoms of autism spectrum disorders on

the one hand (see Chapter B.4.4), but also take into account their differential diagnostic differentiation from other disorders. In many cases, it is necessary to treat e.g. pronounced hyperactivity, impulsivity and lack of concentration, oppositional behaviour, anxiety symptoms or similar, before it can be diagnostically assessed whether these are present in addition to an underlying autistic disorder or whether the "autistic-like symptoms" exist in the context of another disorder. In the following, we will systematically consider which disorders should be given special attention and make appropriate recommendations. Therefore, in the following, the information from the source guidelines is presented first, then this is supplemented by more recent literature.

B.5.2.2 Summary from the source guidelines

19 studies were included (Allen et al. 2007; Arvidsson et al. 1997; Baron-Cohen et al. 2000; Beighley et al. 2013; Corsello et al. 2007; Dietz et al. 2006; Ehlers et al. 1999; Gray and Tonge 2005; Hastings 2003; Honda et al. 2009; Kamp-Becker et al. 2009; Lord 1995; Perry et al. 2005; Rellini et al. 2004b; Scheirs and Timmers 2009; Snow and Lecavalier 2008; Sponheim and Spurkland 1996; Stone et al. 2008; Webb et al. 2003). All studies were uncontrolled observational studies and were assessed as being of low quality.

The NICE children's guidelines make the following recommendations: The following differential diagnoses should be considered and specifically investigated in order to properly assess the findings obtained (autism-specific history and behavioural observation):

- Neural and mental development disorders: language development delay or language development disorder; intelligence impairment or global development delay; developmental coordination disorder.
- Mental and behavioral disorders: Attention-deficit/hyperactivity disorder (ADHD); affective disorders; anxiety disorders; attachment disorders; oppositional disorders; conduct disorders; obsessive-compulsive disorders; psychoses.
- Other disorders: Severe hearing or visual impairment, maltreatment, selective mutism.
- Disorders associated with developmental regression: Rett syndrome; epileptic encephalopathy.

NICE adult guidelines list as differential diagnoses: Obsessive-Compulsive Disorder, Personality Disorder. In the DSM-5 (Falkai and Döpfner 2015), the following additional differential diagnoses are named: social (pragmatic) communication disorder, stereotypic movement disorder.

B.5.2.3 Updating

Individual symptoms of autism spectrum disorder have low specificity for autism spectrum disorder, i.e. they also occur in many other disorders. For example, reduced eye contact, facial expressions, and gestures also occur in many emotional disorders (Tyson and Cruess 2012; van Steensel et al. 2013), as well as in schizophrenia, depression, and ADHD. Abnormalities in reciprocal social interaction skills are present in many disorders (over time) and are therefore not specific to autism spectrum disorder (Meyer-Lindenberg and Tost 2012). Deficits in the ability to allocate emotions occur in many disorders and can therefore have very different backgrounds (Collin et al. 2013). Impairments in the capacity for empathy and in the capacity for Theory of Mind are also found in many disorders (see below). In the following, various disorders are presented and their differential diagnostic differentiation is discussed (taking into account the explanations from the NICE guidelines for children, Appendix K).

Language development delay or language development disorder

These disorders involve a use or understanding of language that is not age appropriate. Play skills as well as the ability to use imagination may also not be age appropriate. This is associated with problems in social communication and interaction skills, which also extend beyond preschool age. Language abnormalities in terms of echolalia, stereotypical language use or neologisms may also be present (Bishop 2010; Bishop and Norbury 2002). In terms of differential diagnosis, it is relevant to note that children with language disorders do use nonverbal means of communication (eye contact, divided attention, gestures, etc.) in a compensatory manner (McArthur and Adamson 1996). Social motivation (especially in familiar relationships) is not impaired and children show only minor abnormalities in social interaction and empathy skills (Ventola et al. 2007). However, impairments in Theory of Mind ability are also present (Andrés-Roqueta et al. 2013; Dyck and Piek 2010; Farrar et al. 2009; Wisdom et al. 2007). Difficulties in the ability to recognize and correctly interpret emotions may also be present (Homer and Rutherford 2008). In a German study, items in the Reciprocal Social Interaction and Communication and Language domains of the ADI-R were found to separate the two comparison groups - F80.2 Receptive Language Disorder vs. Early Childhood Autism - well (Mildenberger et al. 2001). Two longitudinal follow-up studies of boys/young men with autism spectrum disorder and receptive language disorder, respectively (Howlin et al. 2000; Mawhood et al. 2000), show that over the course of development, males with autism had significantly more impairments in the area of stereotypic behaviors. Although only 10% in the group of individuals with receptive language impairment exhibited severe social problems (in contrast

to 74% of the autism group), 65% exhibited moderate social problems. The differences between the two groups became less pronounced as development progressed.

Since both language and communication difficulties as well as problems in social interaction occur in both disorders, the precise recording and assessment of these skills in the course of development is of crucial importance. Especially in children, the intensive promotion of language skills as well as accompanying further diagnostic examinations should be initiated.

Reduced intelligence or global developmental delay

In persons with intelligence impairment, many abnormalities are found that also occur in autism spectrum disorders. For example, repetitive, stereotyped behaviors are common in individuals with cognitive impairment (Carcani-Rathwell et al. 2006; Ventola et al. 2007). Play behaviors are also prominent, and abilities to form social interactions and engage in friendly relationships may be limited. However, unlike autism spectrum disorders, social motivation and orientation (eye contact, divided attention, nonverbal communication) are not impaired according to general developmental levels (Jones et al. 2008; Matson et al. 2008b). However, it is currently unclear whether a differential diagnostic differentiation is possible in the case of a very severe intellectual disability in combination with motor or sensory impairments.

Developmental coordination disorder

These individuals are motor clumsy and show poor motor coordination overall. This may be associated with a reduced spatial perception ability, which may also affect proximity-distance behaviour to other people. Social problems may also be present. However, in differentiation to autism spectrum disorder, these individuals show good communicative skills and inconspicuous play behaviour.

Attention Deficit Hyperactivity Disorder (ADHD)

The ADHD disorder is characterized by attention that is not age-appropriate (excessively focused and/or easily distracted), hyperactivity and motor restlessness. The symptoms usually persist into adulthood (Barbaresi et al. 2013) and not only represent one of the most relevant differential diagnoses of autism spectrum disorder, but are present as a comorbid disorder in approximately 30% of autism spectrum disorder cases (Mazefsky et al. 2014; Simonoff et al. 2008; see Chapter A.3.3). Very intensive research has been done on the similarities and differences (for a review see: Taurines et al. 2012). These exist with respect to genetic background (Rommelse et al. 2010; Rommelse et al. 2011), social cognitions (Bühler et al. 2011; Nydén et

al. 2010; Rumpf et al. 2012; Uekermann et al. 2010), social interaction skills (Ames and White 2011; Reiersen 2011) and neural correlates (Brieber et al. 2007; Gargaro et al. 2011). Deficits in social skills are common in individuals with ADHD, as are difficulties in the ability to recognize and correctly interpret emotions (Reiersen 2011). These multiple genetic and neuropsychological findings suggest an etiopathogenetic link between the two disorders. However, recent studies indicate that the disorders are only partially overlapping (van der Meer et al. 2012).

In delineating the two disorders, it appears that individuals with ADHD show fewer deficits in social reciprocity, nonverbal communication, and repetitive, stereotypic behaviors (Mayes et al. 2012). A clear distinction between the two disorders is possible in many cases. However, due to the overlap of the disorders, it is necessary to treat the symptoms of ADHD in accordance with the guidelines (see corresponding AWMF guideline ADHD in children, adolescents and adults) and to repeat the diagnosis of an autism spectrum disorder in the course of the treatment.

Affective disorders

Withdrawal, reduced verbal and non-verbal communication, little interest in age-appropriate activities and contacts are, among other things, symptoms of a depressive disorder. However, the course of development distinguishes the disorders, since in affective disorders the symptoms are mostly episodic.

Emotional and anxiety disorders

Autism spectrum disorders are often accompanied by emotional and anxiety disorders, however, individuals with emotional and anxiety disorders also often exhibit some symptoms that appear autistic. For example, fear of change is a common symptom in emotional disorders (Guttmann-Steinmetz et al. 2010; Pine et al. 2008; Renno and Wood 2013; Towbin et al. 2005; van Steensel et al. 2013) and therefore has low specificity for autism spectrum disorders. More than one-third of all children with anxiety disorders who did not have an autism spectrum disorder exceeded at least one of the three cut-off values of the ADI-R in a recent study (van Steensel et al. 2013). Therefore, it must be critically examined whether all criteria for an autism spectrum disorder are actually present in addition to the anxiety symptomatology, in particular whether there is an underlying impairment in the area of social communication and imaginative ability (Cath et al. 2008). Since comorbid anxiety disorders exacerbate the core symptoms of autism spectrum disorders (Kamp-Becker et al. 2009; Spiker et al. 2012; Sukhodolsky et al. 2008), a diagnosis of an anxiety disorder should rather be assigned in the case of very mild symptoms

of an autism spectrum disorder and appropriate treatment should be initiated in order to then repeat the diagnosis with regard to an autism spectrum disorder in the course of time.

Social phobia and anxious-avoidant personality disorder are classified as social anxiety disorders (Reich 2009). The main characteristic of social anxiety disorders is the pronounced fear of situations in which the affected person is the focus of attention and the use of avoidance strategies to escape these situations. In extreme cases, this can lead to a complete withdrawal from all social contacts. The cause is a profound fear of criticism and negative evaluation by the social environment. Longitudinally, social behavioural inhibitions, e.g. avoidance of eye contact and reduced communicative expressive behaviour, have frequently been reported since childhood (Tyson and Cruess 2012). Emotion recognition weaknesses are characterized by selective perception of social cue stimuli that suggest negative evaluation, e.g., rejection or disdain. Outside of socially demanding situations, such as in a family setting, adequate emotional perspective taking is usually possible. Individuals with social phobia report greater anxiety in social situations and reduced social skills than individuals with Asperger syndrome (Dissanayake 2012).

Selective mutism is understood as a clear, emotionally conditioned selectivity of speech in the presence of existing speech skills. As a result, there are clear problems in social interaction and communication. In contrast to autism spectrum disorder, however, these abnormalities are situation-specific (e.g. especially in unfamiliar, public situations such as school, kindergarten, etc.).

Overall, it appears that differential diagnostic differentiation from emotional/anxiety disorders is a challenge in diagnosis and screening methods are not appropriate for this purpose (Cholemkery et al. 2014b; Warren et al. 2012).

Oppositional disorders/social behaviour disorder

What oppositional/ social behavior disorder and autism spectrum disorder have in common is that there are problems in social interaction as well as deficits in the area of theory of mind/empathy (O'Nions et al. 2014; Pasalich et al. 2014; Schwenck et al. 2014; Sebastian et al. 2012). However, the underlying impairment in the area of social communication is absent in oppositional disorder/social behavior disorder. In these disorders, individuals often exhibit provocative, attention-seeking behaviors as well as instrumental, goal-directed aggressive behaviors that highlight intact social orientations. Cognitive aspects of the Theory of Mind are mostly unimpaired, whereas affective aspects are impaired. Especially with these differential diagnoses, a false positive diagnosis of autism spectrum disorder has long-term negative consequences.

Personality Disorders

Of note is the finding of recent studies outlining considerable overlap in the symptomatology of adults with high-functioning autism spectrum disorders (especially Asperger syndrome) and diverse personality disorders (Anckarsäter et al. 2006; Anckarsäter 2006; Barneveld et al. 2011; Hofvander et al. 2009; Hurst et al. 2007; Lugnegård et al. 2012; Strunz et al. 2014b; Strunz et al. 2014a; Tantam and Girgis 2009). These findings highlight the difficulty in distinguishing between the two disorders in adulthood, particularly when there is insufficient other-anamnestic information about the onset of the disorder in childhood. Deficits in Theory of Mind/empathic ability are also present in individuals with personality disorders (Blair 2008; Dziobek et al. 2011; Harari et al. 2010; Jones et al. 2010; Shamay-Tsoory et al. 2010; Strunz et al. 2014b; Wiehe 2003). Other common features include overarching and severe problems in social relationships, communication, and self-experience, loneliness, obsessive-rigid actions and attitudes, and significant impairments in many domains of life. In both disorders, symptomatology is experienced as belonging to the personality (ego-syntonic), although a diagnosis of autism spectrum disorder is experienced as less stigmatizing and more likely to imply identification with the disorder (Durand-Zaleski et al. 2012; Farrugia 2009; Kapp et al. 2013; Ruiz Calzada et al. 2012). Self-report instruments are not helpful in differential diagnostic assessment for the personality disorders (Bishop and Seltzer 2012; Brugha et al. 2012; Lehnhardt et al. 2013). The following personality disorders should be considered for differential diagnosis: Schizotypal, Schizoid, Narcissistic, Obsessive-Compulsive, Avoidant, Antisocial, Self-Insecure, Borderline Personality Disorder. It must be examined very carefully, taking into account information from other people, whether the onset of the disorder with a clinically relevant impairment is in early childhood, whether all the symptoms of an autism spectrum disorder have been present since early childhood and whether the symptoms present cannot be adequately explained by the presence of a personality disorder. A largely unremarkable course into adolescence is an exclusion criterion.

Social (pragmatic) communication disorder (according to DSM-5)

This disorder is characterized by persistent difficulties in the social use of verbal and nonverbal communication. Deficits exist in the social use of communication, difficulty adapting communication style to the context or needs of the listener, or following rules for conversation, and in understanding non-explicit messages. Repetitive, stereotypic behaviors are not present to the degree that would be expected in the presence of an autism spectrum disorder (Swineford et al. 2014). However, comorbid disorders (AHDS, social behavior disorder, and disorders with

known genetic background; Norbury 2014) are often found in individuals with this disorder. Unfortunately, there are no well-studied diagnostic inventories to date to capture the disorder well.

Obsessive Compulsive Disorder

Obsessive-compulsive disorders are associated with a pronounced adherence to rituals of action, systems of order or collecting habits. Often this also leads to increasing problems in social interactions, withdrawal and lack of contact. In contrast to autism spectrum disorder, however, the basic ability to interact and communicate socially is preserved and the compulsive actions are usually perceived as nonsensical and inappropriate by the adult affected.

Attachment disorders/Fetal Alcohol Syndrome

In the symptomatology of the disturbance patterns of an attachment disorder and autism spectrum disorder, clear overlaps are found. For example, more than 60% of the children studied with reactive attachment disorder exceeded the cut-off values of the ADI-R in the area of communication, 46% in the area of social interaction and 20% in the area of repetitive, stereotyped behaviours (Sadiq et al. 2012). However, children with attachment disorders benefit better from a psychoeducational program than children with autism spectrum disorders (Mukaddes et al. 2004). The developmental history is crucial; if emotional or physical abuse is present, appropriate measures should be taken (see AWMF guidelines on this).

There are also overlaps between Fetal Alcohol Syndrome and Autism Spectrum Disorders (Bishop et al. 2007) that need to be noted and considered in diagnostic assessment. Commonalities are evident in the presence of socially inappropriate behaviour and difficulties with peers. However, difficulties in initiating social interactions, reduced shared enjoyment, and nonverbal communication are more prevalent in children with autism spectrum disorder than in children with fetal alcohol syndrome (Bishop et al. 2007; Stevens et al. 2013).

Stereotypic movement disorder

The main feature of this disorder is repetitive, arbitrary, repetitive, non-functional and often rhythmic motor behaviours (e.g. shaking out or waving hands, swaying body movements, head banging, biting oneself, hitting oneself). The movements may or may not be stopped by appropriate effort (usually in children without intelligence impairment) (more difficult in children with intelligence impairment). However, unlike autism spectrum disorder, there are no fundamental deficits in social communication and reciprocity.

Psychotic disorders

There are also many similarities (genetics, neurobiology, social-cognitive impairments) and differences in relation to psychotic disorders (Baribeau and Anagnostou 2013; Bora and Pantelis 2013; Cochran et al. 2013). In the acute phase of a psychotic disorder, differentiation is difficult (Reaven et al. 2008); the developmental history is crucial.

visual or hearing impairments

In cases of significant visual impairment, non-verbal communication is also impaired (gaze behaviour, gestures, mimic expression). In speech development, echolalia and stereotypical word repetitions occur. Overall language development may be delayed, especially in relation to the understanding of abstract word meanings. Development of play behavior is conspicuous and sensory interests or sensory explorations occur frequently. Interests are often restricted and repetitive mannerisms are also common. Social interest is present, however, and the capacity for social reciprocity is not markedly impaired.

In cases of severe hearing impairment, language development is also conspicuous and communication skills are impaired. However, there are fewer abnormalities in the area of non-verbal communication, social reciprocity, play behaviour and less repetitive, stereotypical behaviour.

Rett syndrome, epileptic encephalopathy, Landau-Kleffner syndrome

These disorders are accompanied by a clear regression in development. A clear reduction of already acquired skills is at the heart of the symptomatology. In Landau-Kleffner syndrome, there is a loss of language, and about one third of those affected retain a severe receptive language deficit. Rett syndrome is an encephalopathy that follows an X-linked dominant inheritance and is associated with marked loss of language, cognitive, and motor functions. In contrast to autism spectrum disorder, however, the focus of these disorders is on the loss of previously acquired abilities.

[35]	**Consensus-based recommendation -** *key issue 31* *What are the differential diagnoses to look out for?*
KKP	In addition to an accurate assessment of the core symptoms of an autism spectrum disorder, differential diagnosis is of crucial importance for making a correct diagnosis. It must be assessed in a differentiated manner whether the present symptoms are not sufficiently explained by the presence of one of the following disorders. Therefore, specific examinations should also be considered throughout the diagnostic process if indicated. Developmental Disabilities: • Speech disorders • Global developmental disorders or intelligence impairment Mental and behavioral problems or disorders: • Attention Deficit Hyperactivity Disorder (ADHD) • Emotional and anxiety disorders • Affective disorders • Oppositional behaviour/disturbance of social behaviour • Personality Disorders • Obsessive Compulsive Disorder • Attachment Disorders • stereotypic movement disorder • Psychotic disorders
	Strong consensus (14 out of 14)

B.6 Clarification

Judith Sinzig & Matthias Dose
Collaboration: Marianne Menze on literature research and selection

B.6.1 Introduction

The following key questions are answered and recommended in the text [17]:

How should the diagnostic assessment be communicated to affected persons and their relatives/carers? Which factors are experienced as supportive or burdensome by the persons concerned and their relatives?
What is the significance of the diagnosis for those affected and their relatives?

B.6.2 Who should carry out the reconnaissance?

B.6.2.1 Summary from the source guidelines

The ***NICE Children (diagnosis) guideline states that*** discussions should be held in advance with parents/carers and/or, where appropriate, with the child/young person about how (including communication of the diagnosis) information should be shared during the assessment in the context of a diagnosis regarding autism spectrum disorder and afterwards.

The ***NICE adult guideline*** also states that before investigations are initiated, it should be discussed with the person concerned how the results should be reported, but not by whom.

The ***SIGN guideline does*** not specifically address this issue.

B.6.2.2 Current situation in Germany, formulation of own recommendations

Currently, there is no consensus as to which professional groups (specialists in child and adolescent psychiatry and psychotherapy, specialists in psychiatry/psychotherapy, paediatricians, psychologists, (child and adolescent) psychotherapists, social pedagogues) and institutions (institutional outpatient clinics, practices, early intervention facilities, social paediatric centres, autism therapy centres, etc.) can/should offer diagnostics. Accordingly, there is also no consensus on who, when and how to communicate the diagnosis and conduct an educational interview.

[17] To answer the key questions in this chapter, the following sources were consulted: Carr and Lord 2013; Carter et al. 2009; Cassidy et al. 2008; Coplan 2000; Coulthard and Fitzgerald 1999; Dale et al. 2006; Estes et al. 2013; Glasberg 2000; Hastings 2003; Head and Abbeduto 2007; Herring et al. 2006; Hodge 2005; Karst and Van Hecke, Amy Vaughan 2012; Ludlow et al. 2012; Macks and Reeve 2007; Mercer et al. 2006; Milshtein et al. 2010; Moh and Magiati 2012; Montes and Halterman 2008; Quirantes 2009; Reed and Osborne 2012; Siklos and Kerns 2007.

[36]	**Consensus-based recommendation** - *key issue 34* *How should the diagnostic assessment be communicated to affected persons and their relatives/carers? Which factors are experienced as supportive or burdensome by affected persons and their relatives?*
KKP	The diagnostic assessment should be mediated by the specialized body.
	Strong consensus (12 out of 12)

B.6.3 How should an educational interview proceed?

B.6.3.1 Summary from the source guidelines

NICE children (diagnostics)

Upon completion of the assessments, the results (including findings) should be gently discussed with the parents/guardians and/or the child/adolescent, as appropriate, without delay. If no autism spectrum diagnosis has been made, the reasons should be explained.

Notification of the diagnosis should provide education about what autism is and how autism may affect the individual's development and functioning. Where possible, a written report of the assessment should be provided to the parent/guardian and/or, if appropriate, to the child/young person, explaining the findings and reasons for the conclusions reached. The information (including the written report) should also be shared with the GP and, if appropriate consent has been obtained, with all 'key people' involved with the patient (including educators/teachers and social care staff). A follow-up appointment should be allocated within 6 weeks for further discussion. If an autism spectrum disorder has been diagnosed, the risk of autism spectrum disorders in siblings and offspring should be discussed.

NICE Adult

Communication of the results of the investigation should include a comprehensive and informative profile of the individual's needs and risks, including a treatment plan, in a manner appropriate to the individual's understanding of the problem.

SIGN Guideline

It is noted that it may be appropriate to communicate the diagnosis to parents or guardians and (where appropriate) children and young people separately, sequentially or together. As the communication of the diagnosis can be stressful, it is recommended to establish contact with local

professional groups. Diagnosis should be explained against ICD-10/DSM-IV criteria. Findings (including explanations) should be in writing. Clarification should be made as to who these findings/reports will be made available to. Basic information should be provided regarding current knowledge of causes, treatment options, prognosis, and appropriate multiprofessional support. If diagnosis is uncertain, next steps for clarification should be discussed. Relevant professional groups should be involved. Specific therapeutic interventions (including those for any comorbidities) should be addressed. Consequences for school, training etc. should be discussed, sources of information and a fixed contact person for further questions should be named.

B.6.3.2 Current situation in Germany, formulation of own recommendations

See above: There is no reliable knowledge about this. Very different approaches and thus different quality can be assumed.

[37]	**Consensus-based recommendation** *Key question 34*
KKP	Factors that are experienced as supportive by the persons concerned and their relatives in the educational discussion or process are a detailed explanation of symptoms, causes, prognosis, effective as well as dispensable interventions, youth welfare measures as well as educational, vocational and legal aspects. Furthermore, early planning of necessary help and therapeutic interventions as well as the naming of a contact person are important. An empathetic approach and a high level of professionalism on the part of the person providing the information have a supporting effect, so that the questions of those affected and their guardians can be answered with certainty. It is very important to specifically address fears and feelings of guilt regarding the causes and consequences of the disorder.
	Strong consensus (12 out of 12)

B.6.4 What is important from the point of view of the person concerned or the parents or guardians during an information session?

B.6.4.1 Summary from the source guidelines

NICE children (diagnostics)

Examples of good practice were the interview with a multiprofessional team that listens to the views of the parents or guardians, the rapid and clear communication of the examination result, the provision, explanation and discussion of written reports (also from the individual examinations), the presence only of those persons who were involved with the child/adolescent, and the advance information about the participants in the educational interview.

SIGN

The SIGN guideline emphasises that it is beneficial for the satisfaction of parents or guardians and/or affected persons if they are provided with good quality information and have sufficient opportunity to ask questions.

B. 6.4.2 Current situation in Germany, formulation of own recommendations

See above: There is no reliable knowledge about this. Very different approaches and thus different quality can be assumed.

[38]	**Consensus-based recommendation** *Bowl question 35*
KKP	The diagnosis is of great importance for the affected persons and their relatives. With the communication of the diagnosis, an education about the disorder adapted to age and developmental stage should take place.
	Strong consensus (12 out of 12)

B.7 Progressive diagnostics

Diana Will, Christine M. Friday

B.7.1 Introduction

In this chapter it will be presented which diagnostic procedures are suitable to measure and map changes and developmental processes in people with autism.

In addition to documenting therapeutic progress, the diagnosis should also be reexamined at preschool age, especially for individuals with Asperger syndrome (F84.5), atypical autism (F 84.1), or an unspecified pervasive developmental disorder (F 84.8 or F84.9). As already described in chapter A.4 Course and prognosis, the diagnoses are not always stable at this age.

The following key questions are answered and recommended in the text:

33. which procedures can also be recommended for follow-up diagnostics?

36. what follow-up diagnostics are necessary?

B.7.2 Which of the diagnostic procedures are also suitable for follow-up diagnostics?

B.7.2.1 Summary from the source guidelines

Neither the NICE children's (diagnostic)/adult guidelines nor the SIGN guideline make explicit recommendations for follow-up diagnostics.

B.7.2.2 Current situation in Germany

In Germany, there are currently no studies and no recommendations on follow-up diagnostics.

B.7.3 Which diagnostic procedures can also be used for follow-up diagnostics?

B.7.3.1 Summary from the source guidelines

Neither the NICE paediatric (diagnostic)/adult guidelines nor the SIGN guideline make recommendations for specific procedures for follow-up diagnosis.

B.7.3.2 Current situation in Germany

In Germany, there are currently no studies and no recommendations on procedures for progress diagnostics. However, some diagnostic procedures are currently used to measure changes and to document developmental processes and therapeutic progressions. When using these and other scales, it is important to ensure that the standardization is up to date and that the tests can be administered well to children, adolescents and adults with autism spectrum disorder, even in the presence of intelligence impairment. Unfortunately, this is true for only a few instruments, which are mentioned below. A compilation of international scales that can measure progress in different domains in preschool children has been done in a recently published systematic review, which concluded that there are few valid instruments, none of which can be recommended as necessary. The most important instruments from this review, which are also translated into German and (partially) standardised, have been included in the following compilation and supplemented by others (McConachie et al. 2015).

Instruments for the study of the developmental and intelligence trajectories

Bayley-III (Bayley Scales of Infant Development Bayley-III Bayley 2006):

The Bayley Scales of Infant Development are a pediatric developmental test and were developed for children aged 1 - 42 months. They represent the most internationally studied developmental diagnostic instrument. The instrument allows for the assessment of three basic skill areas with the cognitive, language and motor scales. The cognitive scale tasks capture habituation, problem solving skills, classification and categorization skills, imitation, and symbolic play. The language scale is divided into two subscales, receptive and expressive language. The receptive language subscale contains items that measure reactions to linguistic stimuli and word comprehension, and is primarily asked through pointing gestures. The expressive language subscale measures vocalization and speech ability. Some items in this scale also relate to early social-communicative skills, such as social smiling. The motor skills scale also divides into two subscales: Fine and Gross Motor Skills. The fine motor subscale covers, for example, grasping, holding, or using pens, while the gross motor subscale covers skills such as crawling, sitting, standing, walking, or jumping. The standards available to date are based on US studies from 2004, and a German standardization is in progress. Clinically, the Bayley III scales are frequently used in young children with ASD and are well established. In general, when examining developmental status, at least 6 months should elapse between repeated testing using the same instrument.

SON-R 2 ½ - 7 (Snijders-Oomen Intelligence Test; Tellegen et al. 1998):

Standardized non-verbal intelligence test for children aged 2.6 - 7.0 years. It can be used up to the age of 7.11 years for children with an existing intelligence impairment. It consists of six subtests, which can also be evaluated individually. In its entirety, it provides an overview of non-verbal cognitive skills. There are tasks focusing on "action" or on "thinking", which can be scored separately. No verbal instructions are necessary. All tasks can be understood by facial expressions and gestures of the test administration. So far, only Dutch norms are available for this test instrument, but they can be transferred to German children. Clinically, the SON-R 2 ½- 7 is frequently used with young children with ASD and reduced linguistic skills and is well proven for the examination of non-verbal cognitive skills. The test cannot be used to make a statement about the status of verbal skills or verbal IQ. In general, when testing cognitive skills, at least 6 months should elapse between repeated tests using the same instrument.

SON-R 6 - 40 (Snijders-Oomen Intelligence Test; Tellegen et al. 2012):

This test is applicable to individuals between the ages of 6 and 40.11 and includes the same four subtests: analogies, mosaics, categories, and sign patterns. The norming was conducted in 2009 - 2011 in Germany and the Netherlands. Clinically, the SON-R 6 - 40 is widely used with individuals with ASD and reduced verbal skills and is well established for the examination of non-verbal cognitive skills. The test cannot be used to make a statement about the status of verbal skills or verbal IQ. In general, when testing cognitive skills, at least 6 months should elapse between repeated tests using the same instrument.

IDS and IDS-P (Intelligence and Development Scales and Intelligence and Development Scales - preschool, Grob 2013a and b):

The intelligence and development scales are available for ages 5-10 and 3;0-5;11. With the scales for preschool children, developmental delays can be identified at an early stage. In doing so, the IDS provide both an intelligence score and a comprehensive developmental profile analysis. Five areas are examined: cognition, psychomotor skills, social-emotional competence, logical-mathematical thinking and language. The entire test takes approx. 60 - 90 minutes to complete and has been standardised on the basis of 700 children in Germany, Austria and Switzerland. The retest reliability after approx. 5 months is r = 0.9 for the functional area of cognition, r = 0.85 for psychomotor skills, r = *0.*53 for social-emotional skills, r = 0.8 for logical-mathematical thinking and r = 0.69 for language.

The IDS for children aged 5;0 - 10;11 years comprises six subscales: cognition, psychomotor skills, social-emotional competence, mathematics, language and achievement motivation. The duration is approx. 90 - 120 minutes and again a current German-language norming is available on the basis of 1330 children in Germany, Austria and Switzerland. Here, too, retest reliability was determined after an average of 15 months, varying between r = 0.45 and r = 0.81 in the cognitive development subtests and between r = 0.34 and r = *0.*88 in the general development subtests. For the intelligence score, the non-disattenuated retest reliability is r = 0.83.

It should be noted that, unlike the Bayley III and the two SON tests, there is no experience with children with autism spectrum disorders.

WPPSI-III (Wechsler Preschool and Primary Scale of Intelligence - Third Edition, 2014):

The Intelligence and Development Scales (Wechsler Scales for Young Children) measure general (total IQ) and specific cognitive abilities (1st verbal, 2nd action, 3rd processing speed, and 4th general language scales) in the age range of 3.0 to 7.2 years. The test battery consists of 14 subtests, some of which can be used optionally or additionally. The core tests can take

between 20 and 50 minutes to complete. The test was normed in 2009 on the basis of 710 children in Germany. The reliability of the subtests varies between r = 0.77 and 0.88; for the overall test it is r = 0.95.

Clinically, the WIPPSI can be used meaningfully in young children with ASD only when good verbal skills are present; here it is well established for testing cognitive skills in the average range. In the area of below-average cognitive skills, it shows a reduced ability to differentiate and a floor effect. In general, when examining cognitive skills, there should be at least 6 months between repeated tests using the same instrument.

WISC-IV (formerly HAWIK; Wechsler Intelligence Scale for Children; Petermann and Petermann 2011):

This instrument is composed of 15 subtests, with only 10 core tests used to calculate the total IQ. The areas of language comprehension, perceptual reasoning, working memory and processing speed, and general cognitive level are assessed. The procedure is appropriate for children and adolescents with a developmental age range of 6.0 - 16.11 years and has been re-normed. Clinically, the WISC-IV is widely used in children and adolescents with ASD and good verbal skills and is well established for testing cognitive skills in the average range. In the area of below average cognitive skills, it shows reduced differentiation ability and a floor effect. Generally, when examining cognitive skills, there should be at least 6 months between repeated testing using the same instrument.

WAIS-IV (formerly WIE or HAWIE; Wechsler Adult Intelligence Scale - Fourth edition; Petermann 2012):

This procedure is suitable for persons between the ages of 16.0 and 89.1 years. The test battery consists of ten subtests, which are composed of the same scales as the WISC-IV. The norming is up to date. Clinically, the WAIS-IV is widely used with adolescents and adults with ASD and good verbal skills and is well established for testing cognitive skills in the average range. In the below average range of cognitive skills, it shows reduced discriminative ability and a floor effect. Generally, when examining cognitive skills, there should be at least 6 months between repeated testing using the same instrument.

Instruments for measuring language development

Unfortunately, there is no homogeneous language development test in Germany in which the change of language skills can be examined in a standardized way over the course of the entire toddler, preschool and school age. The existing language development tests are only suitable

for diagnostic purposes. Some of the above-mentioned developmental tests contain subscales for different language skills, which can be used for the evaluation of progress.

Instruments for measuring daily living skills and adaptive behaviour

GES (Griffiths Developmental Scales, Brandt and Sticker 2001):

This developmental diagnostic is standardized for German children, but very old. Therefore, this test may easily overestimate the level of development. However, the GES offer the advantage that it includes a conversation with the parents or a close caregiver in addition to the behavioral observation. If young children with ASD do not cooperate on any other test (e.g., the Bayley III scales), a rough estimate of developmental status can be made by talking with parents alone. Five functional areas (Motor, Personal and Social, Hearing and Speech, Eye and Hand, Achievement) are assessed. The results can provide information for advising parents or guardians as well as for planning and implementing targeted early intervention measures. The procedure has been developed for children with a developmental age of 1 - 24 months. The standardization is based on 1750 examinations in the developmental course of 102 children. The calculation of the developmental status gives the impression that these were standardised values. However, this is not the case. The position of the tasks in the stage ladders is based on the age at which 50% of a large group of children were able to solve these tasks (see also Petermann & Macha 2005). This means that the variability of normal development is not taken into account. The scale is therefore only suitable for the rough clinical assessment of developmental level up to the age of 24 months in infants who cannot be tested in any other way. However, the ceiling effect from 18 months restricts its use, particularly in follow-up examinations (Esser & Petermann 2010).

ICF (International Classification of Functioning, Disability and Health, German Institute of Medical Documentation and Information, DIMDI WHO Collaborating Centre for the System of International Classifications):

The ICF is a uniform and standardized classification system for describing a person's functional health status, disability, social impairment and relevant environmental factors. It can be used to show the bio-psycho-social aspects of disease outcomes, taking into account contextual factors. It is applicable over the entire lifespan. The primary aim of the ICF is to provide a common language for describing functional health. The instrument allows for the inclusion of individual contextual factors, such as environmental factors and person-related factors. The ICF does not classify disease-related specificities, but rather findings and symptoms related to functional capacity. With its help, the individual need for help can be ascertained and communicated across different professions. However, working with the ICF is very time-consuming. Autism-specific aspects of a child's functioning from the ICF have not yet been compiled and empirically investigated; however, corresponding research projects are currently planned.

Instruments for autism-specific progression diagnostics

BOSCC (Brief Observation of Social Communication Change):

This instrument is currently still under development. It is intended to record the course of autistic symptoms in a differentiated manner for young children and preschoolers (Kitzerow et al. 2015).

ADOS-severity score (Autism Diagnostic Observation Schedule Severity score; Gotham et al. 2008; Hus et al., 2014):

The ADOS-2 can also be used repeatedly by using the same or different modules. This instrument can be used from a developmental age of 18 months. The severity score, which can be easily calculated from the ADOS-2, allows the results of the different modules to be compared with each other. It is somewhat less sensitive than the BOSCC (Kitzerow et al. 2015).

CARS (Childhood Autism Rating Scale, Schopler et al. 1980)

CARS is less oriented towards the criteria of the classification systems (ICD-10/DSM-IV). It records the areas of relationships with people, imitation (verbal and motor), affect, use of the body, relationships with inanimate objects, adaptation to environmental changes, visual responsiveness, auditory responsiveness, near-receptor response, fear response, verbal communication, non-verbal communication, activity level (movement patterns), and functional level of intelligence. The instrument is suitable for children from a developmental age of two years and was edited by Steinhausen (1993) for the German-speaking world under the name "Autismus Beurteilungsskala". [18]

SRS (Scale for the Assessment of Social Reactivity, Constantino and Gruber 2005/German version Bölte and Poustka 2008b):

The scale maps autism spectrum disorder as a dimensional characteristic that is normally distributed in the general population. The SRS can be used to locate children and adolescents between the ages of 4 - 18 who have a very mild level of autism spectrum disorder but still require treatment. Social, communicative and rigid behaviors are recorded as dimensions, which means that autism is considered a "trait" and is psychopathological only in the extreme. The scale is thus particularly suitable for identifying and classifying the severity of an autism spectrum disorder. A particular strength of this instrument lies in its use for course diagnosis (Tse et al. 2007; Freitag et al. 2013). In addition, this scale can be used to assess comorbid autistic traits. The five subscales (social awareness, social cognition, social communication, social motivation, and autistic mannerisms) can also be used for profile analysis and for planning and evaluating therapeutic interventions. [19]

[18] For more information on this instrument, see chapter B.4.
[19] For more information on this instrument, see chapter B.3.

Comorbid psychopathology in the course

CBCL 1 ½ - 5 (Child Behavior Checklist 1 ½ - 5, Achenbach 2000a): instrument for the diagnosis of children with behavioral problems aged 18 months to 5 years.

CBCL 4 - 18 (Child Behavior Checklist 4 - 18, Working Group German Child Behavior Checklist 1998): Instrument for the diagnosis of children and adolescents with behavioural problems from 4 - 18 years. Both instruments record the assessments of parents or guardians regarding the competencies and problems of their children. The evaluation of this questionnaire includes the following scales and scores: three competence scales (activity, social competence and school), eight cross-assessment syndromes (social withdrawal, physical complaints, anxiety/depressiveness, social problems, schizoid/compulsive, attention deficit disorder, dissocial behaviour, aggressive behaviour), where a comparison is possible across parent, teacher and self-report forms of this questionnaire system. Scales of internalizing and externalizing behavior, as well as an overall problem behavior score, are formed from the syndrome scales.

TRF 1½ - 5 (The Caregiver-Teacher Report Form, Achenbach et al. 2000b): This questionnaire for caregivers of young children and preschoolers contains 99 items, 83 of which are counterparts to the parent version. These items then result in five problem scales (Emotional Reactivity; Anxious/Depressed; Physical Complaints; Social Withdrawal; Attention Problems; and Aggressive Behavior) as well as three superordinate scales: externalizing conspicuousness, internalizing conspicuousness, and overall conspicuousness. It is used for the general assessment of behavioural problems and behavioural skills.

TRF 6 - 18 (Teacher's Report Form of the Child Behavior Checklist, Döpfner et al. 2014): Teacher's questionnaire on the behavior of children and adolescents aged 6 - 18. It is structured analogously to the parent questionnaire and covers social skills and academic performance as well as the behaviour of children and adolescents. It can be used to assess behavioural problems and behavioural skills.

[39]	**Consensus-based recommendation** - *Key questions 33 and 36* *Which methods can also be used for course diagnostics?* *What progress diagnostics are necessary?*
KKP	Within the framework of therapy and support, the current developmental status and any new physical or mental disorders of the person with an autism spectrum disorder should be regularly reviewed so that it is possible to modify the therapy or support goals according to current needs.
	Strong consensus (12 out of 12)

B.7.4 Recommendation for research

Currently, there are no special procedures for follow-up diagnostics in Germany that can make an assessment of therapy and support successes visible. It seems necessary to establish targeted follow-up research with the aim of improving therapy planning and measuring achieved therapy successes. Furthermore, it seems reasonable and necessary to translate proven foreign language instruments and to standardize and validate them for the German market.

List of tables

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List of abbreviations

AAA	Adult Asperger Assessment
ABC	Autism Behavior Checklist
ABI	Autistic Behavior Interview
ADI	Autism Diagnostic Interview - Revised
ADOS	Autism Diagnostic Observation Schedule
ADHD	attention-deficit/hyperactivity disorder
AQ	Autism Spectrum Quotient
AS	Asperger's syndrome
ASAS	Australian Scale of As¬perger`s Syndrome
ASD / ASS	Autism Spectrum Disorder / Autism Spectrum Disorder
ASD-DA	Autism Spectrum Disorders-Diagnosis for Intellectually Disabled Adults
ASD-OC	Autism Spectrum Disorder Observation for Children
ASDI	Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview
ASSQ	Autism Spectrum Screening Questionnaire
AUC	Area under the curve
AWMF	consortium of scientific medical societies
ÄZQ	Medical Centre for Quality in Medicine
BAG	Federal Working Group of Head Clinicians for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy e. V.
BDK	Federal Directors' Conference Adult Psychiatric Clinics
BDP	Professional Association of German Psychologists
BKJPP	Professional Association for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy in Germany e. V.
BMBF	Federal Ministry of Education and Research
BOS	Behaviour observation scale
BVDP	Professional Association of German Psychiatrists e.V.
BVKJ	Professional Association of Paediatricians and Adolescents
CARS	Childhood Autism Rating Scale
CAST	Childhood Autism Spectrum Test
CDC's	Centers for Disease Control and Prevention's
CEBM	Centre for Evidence-Based Medicine
CHAT	Checklist for Autism in Toddlers
DBC-ES	Developmental Behaviour Checklist - Early Screen
DELBI	German instrument for methodological guideline evaluation
DGKJ	German Society for Pediatric and Adolescent Medicine e.V.
DGKJP	German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy e.V.
DGPPN	German Society for Psychiatry , Psychotherapy and Neurology
DGSPJ	German Society for Social Pediatrics and Adolescent Medicine
DGVT	German Society for Behaviour Therapy e.V.
DISCO	Diagnostic Interview for Social and Communication Disorders schedule
DSM	Diagnostic and Statistical Manual
DVT	Umbrella organization for behavioral therapy
FARE	Society for Rehabilitation in Pediatric and Adolescent Medicine
FSC/SCQ	Questionnaire on social communication/ Social Communication Questionnaire
HF	Highfunctioning
ICD	International Classification of Mental Disorders
ICF	International Classification of Functioning, Disability and Health
ID	Intelectual Disabilty
AI / CI	Confidence interval
KKP	Clinical consensus point
KG	Control group

MBAS	Marburg Assessment Scale for Asperger's Syndrome
M-CHAT	Modified Checklist for Autism in Toddlers
NICE	National Institute of Clinical Excellence
NVL	National health care guidelines
OR	odds ratio
PDD-Nos	Pervasive developmental disorder not otherwise specified/ profound developmental disorder not otherwise classified
QUADAS	Quality assessment of diagnostic accuracy studies
RAADS-R	Ritvo Autism Asperger Diagnostic Scale-Revised
RCT	Randomized controlled trial
ROC	Receiver Operating Characteristic
SCDC	Social and Communication Disorder Checklist
SCQ	Social Communication Questionnaire
Sens	Sensitivity
Spec/ Spec	Specificity
SF	Key question
SRS	Social Responsiveness Scale
SIGN	Scottish Intercollegiate Guidelines Network
T1, T2, etc.	Measurement time 1, measurement time 2, etc.
VIFF	Association for interdisciplinary early intervention
WGAS	Scientific Society Autism Spectrum
WPS	Western Psychological Services
3di	Developmental, Dimensional and Diagnostic Interview

Bibliography

Abdallah, Morsi W.; Greaves-Lord, Kirstin; Grove, Jakob; Nørgaard-Pedersen, Bent; Hougaard, David M.; Mortensen, Erik L. (2011): Psychiatric comorbidities in autism spectrum disorders: findings from a Danish Historic Birth Cohort. In: *Eur Child Adolesc Psychiatry* 20 (11-12), pp. 599-601. DOI: 10.1007/s00787-011-0220-2.

Achenbach, T. M. (2000a): CBCL 1½-5 Child Behavior Checklist 1 ½ - 5 German version Parent questionnaire for young children and preschoolers.

Achenbach, T. M., & Ruffle, T. M. (2000b). The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. Pediatrics in Review, 21(8), 265-271.

Aldridge, Fiona J.; Gibbs, Vicki M.; Schmidhofer, Katherine; Williams, Megan (2012): Investigating the Clinical Usefulness of the Social Responsiveness Scale (SRS) in a Tertiary Level, Autism Spectrum Disorder Specific Assessment Clinic. In: *J Autism Dev Disord* 42 (2), pp. 294-300. doi: 10.1007/s10803-011-1242-9.

Allen, C. W.; Silove, N.; Williams, K.; Hutchins, P. (2007): Validity of the Social Communication Questionnaire in Assessing Risk of Autism in Preschool Children with Developmental Problems. In: *J Autism Dev Disord* 37 (7), pp. 1272-1278. DOI: 10.1007/s10803-006-0279-7.

Allik, Hiie; Larsson, Jan-Olov; Smedje, Hans (2006): Insomnia in school-age children with Asperger syndrome or high-functioning autism. In: *BMC Psychiatry* 6 (1), p. 18. DOI: 10.1186/1471-244X-6-18.

American Psychiatric Association (1984): Diagnostic and statistical manual of mental disorders, 3rd ed. - DSM-III. Washington, DC: American Psychiatric Association.

American Psychiatric Association (1987): Diagnostic and statistical manual of mental disorders, revised 3rd ed. - DSM-III-R. Washington, D.C.: American Psychiatric Association.

American Psychiatric Association (2000): Diagnostic and statistical manual of mental disorders, 4th ed., text revision - DSM-IV-TR. Washington, D.C.: American Psychiatric Association.

Ames, Catherine S.; White, Sarah J. (2011): Brief Report: Are ADHD Traits Dissociable from the Autistic Profile? Links Between Cognition and Behaviour. In: *J Autism Dev Disord* 41 (3), pp. 357-363. DOI: 10.1007/s10803-010-1049-0.

Amin, Sanjiv B.; Smith, Tristram; Wang, Hongyue (2011): Is Neonatal Jaundice Associated with Autism Spectrum Disorders: A Systematic Review. In: *J Autism Dev Disord* 41 (11), pp. 1455-1463. DOI: 10.1007/s10803-010-1169-6.

Anckarsäter, H.; Stahlberg, O.; Larson, T.; Hakansson, C.; Jutblad, S. B.; Niklasson, L. et al. (2006): The Impact of ADHD and Autism Spectrum Disorders on Temperament, Character, and Personality Development. In: *Am J Psychiatry* 163 (7), p. 1239. DOI: 10.1176/appi.ajp.163.7.1239.

Anckarsäter, Henrik (2006): Central nervous changes in social dysfunction: autism, aggression, and psychopathy. In: *Brain Research Bulletin* 69 (3), pp. 259-265. DOI: 10.1016/j.brainresbull.2006.01.008.

Anckarsäter, Henrik; Nilsson, Thomas; Saury, Jean-Michel; Råstam, Maria; Gillberg, Christopher (2008): Autism spectrum disorders in institutionalized subjects. In: *Nord J Psychiatry* 62 (2), pp. 160-167. DOI: 10.1080/08039480801957269.

Andrés-Roqueta, Clara; Adrian, Juan E.; Clemente, Rosa A.; Katsos, Napoleon (2013): Which are the best predictors of theory of mind delay in children with specific language impairment? In: *International Journal of Language & Communication Disorders* 48 (6), pp. 726-737. DOI: 10.1111/1460-6984.12045.

German Child Behavior Checklist Working Group (1998): CBCL/4-18. Elternfragebogen über das Verhalten von Kindern und Jugendlichen. 2nd ed.

Arvidsson, T.; Danielsson, B.; Forsberg, P.; Gillberg, C.; Johansson, M.; Kjellgren, G. (1997): Autism in 3-6-Year-Old Children in a Suburb of Goteborg, Sweden. In: *Autism* 1 (2), pp. 163-173. doi: 10.1177/1362361397012004.

Asperger, H. (1944): The "Autistic Psychopaths" in Childhood. In: *Archiv für Psychiatrie und Nervenkrankheite* 117, pp. 73-136.

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators; Centers for Disease Control and Prevention. (2012): Prevalence of autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. In: *MMWR Surveill Summ* 61 (3), pp. 1-19.

Auyeung, Bonnie; Baron-Cohen, Simon; Wheelwright, Sally; Allison, Carrie (2008): The Autism Spectrum Quotient: Children's Version (AQ-Child). In: *J Autism Dev Disord* 38 (7), pp. 1230-1240. DOI: 10.1007/s10803-007-0504-z.

Avchen, Rachel Nonkin; Wiggins, Lisa D.; Devine, Owen; Van Naarden Braun, Kim; Rice, Catherine; Hobson, Nancy C. et al. (2011): Evaluation of a Records-Review Surveillance System Used to Determine the Prevalence of Autism Spectrum Disorders. In: *J Autism Dev Disord* 41 (2), pp. 227-236. DOI: 10.1007/s10803-010-1050-7.

Bachmann, Christian J.; Manthey, Thomas; Kamp-Becker, Inge; Glaeske, Gerd; Hoffmann, Falk (2013): Psychopharmacological treatment in children and adolescents with autism spectrum disorders in Germany. In: *Research in Developmental Disabilities* 34 (9), pp. 2551-2563. DOI: 10.1016/j.ridd.2013.05.028.

Badawi, Nadia; Dixon, Glenys; Felix, Janine F.; Keogh, John M.; Petterson, Beverly; Stanley, Fiona J.; Kurinczuk, Jennifer J. (2006): Autism following a history of newborn encephalopathy: more than a coincidence? In: *Dev Med Child Neurol* 48 (02), pp. 85-89. DOI: 10.1017/S001216220600020X.

Baghdadli, A.; Pascal, C.; Grisi, S.; Aussilloux, C. (2003a): Risk factors for self-injurious behaviours among 222 young children with autistic disorders. In: *J Intellect Disabil Res* 47 (8), pp. 622-627. DOI: 10.1046/j.1365-2788.2003.00507.x.

Baghdadli, Amaria; Picot, Marie C.; Pascal, Céline; Pry, René; Aussilloux, Charles (2003b): Relationship between age of recognition of first disturbances and severity in young children with autism. In: *European Child & Adolescent Psychiatry* 12 (3), pp. 122-127. DOI: 10.1007/s00787-003-0314-6.

Baio J. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators (2014): Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. In: *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002)* 63 (2), pp. 1-21.

Baird, Gillian; Charman, Tony; Baron-Cohen, Simon; Cox, Antony; Swettenham, John; Wheelwright, Sally; Drew, Auriol (2000): A Screening Instrument for Autism at 18 Months of Age: A 6-Year Follow-up Study. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 39 (6), pp. 694-702. DOI: 10.1097/00004583-200006000-00007.

Baird, Gillian; Simonoff, Emily; Pickles, Andrew; Chandler, Susie; Loucas, Tom; Meldrum, David; Charman, Tony (2006): Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). In: The *Lancet* 368 (9531), pp. 210-215. DOI: 10.1016/S0140-6736(06)69041-7.

Bakkaloglu, Betul; Anlar, Banu; Anlar, F. Yasar; Öktem, Ferhunde; Pehlivantürk, Berna; Ünal, Fatih et al. (2008): Atopic features in early childhood autism. In: *European Journal of Paediatric Neurology* 12 (6), pp. 476-479. DOI: 10.1016/j.ejpn.2007.12.008.

Barbaresi, W. J.; Colligan, R. C.; Weaver, A. L.; Voigt, R. G.; Killian, J. M.; Katusic, S. K. (2013): Mortality, ADHD, and Psychosocial Adversity in Adults With Childhood ADHD: A Prospective Study. In: *PEDIATRICS* 131 (4), pp. 637-644. DOI: 10.1542/peds.2012-2354.

Barbaresi, William J.; Colligan, Robert C.; Weaver, Amy L.; Katusic, Slavica K. (2009): The Incidence of Clinically Diagnosed Versus Research-Identified Autism in Olmsted County, Minnesota, 1976-1997: Results from a Retrospective, Population-Based Study. In: *J Autism Dev Disord* 39 (3), pp. 464-470. DOI: 10.1007/s10803-008-0645-8.

Barbaresi, William J.; Katusic, Slavica K.; Colligan, Robert C.; Weaver, Amy L.; Jacobsen, Steven J. (2005): The Incidence of Autism in Olmsted County, Minnesota, 1976-1997. in *Arch Pediatr Adolesc Med* 159 (1), p. 37. doi: 10.1001/archpedi.159.1.37.

Barbaro, J.; Dissanayake, C. (2013): Early markers of autism spectrum disorders in infants and toddlers prospectively identified in the Social Attention and Communication Study. In: *Autism* 17 (1), pp. 64-86. DOI: 10.1177/1362361312442597.

Barger, Brian D.; Campbell, Jonathan M.; McDonough, Jaimi D. (2013): Prevalence and Onset of Regression within Autism Spectrum Disorders: A Meta-analytic Review. In: *J Autism Dev Disord* 43 (4), pp. 817-828. DOI: 10.1007/s10803-012-1621-x.

Baribeau, Danielle A.; Anagnostou, Evdokia (2013): A Comparison of Neuroimaging Findings in Childhood Onset Schizophrenia and Autism Spectrum Disorder: A Review of the Literature. In: *Front. Psychiatry* 4. DOI: 10.3389/fpsyt.2013.00175.

Barnard-Brak, Lucy; Sulak, Tracey; Ivey Hatz, Julie K. (2011): Macrocephaly in Children With Autism Spectrum Disorders. In: *Pediatric Neurology* 44 (2), pp. 97-100. DOI: 10.1016/j.pediatrneurol.2010.09.011.

Barneveld, Petra S.; Pieterse, Jolijn; Sonneville, Leo de; van Rijn, Sophie; Lahuis, Bertine; van Engeland, Herman; Swaab, Hanna (2011): Overlap of autistic and schizotypal traits in adolescents with Autism Spectrum Disorders. In: *Schizophrenia Research* 126 (1-3), pp. 231-236. DOI: 10.1016/j.schres.2010.09.004.

Barneveld, Petra Suzanne; Swaab, Hanna; van Engeland, Herman; Sonneville, Leo de (2014): Cross-Sectional Evidence for a Decrease in Cognitive Function With Age in Children With Autism Spectrum Disorders? In: *Autism Res* 7 (5), pp. 527-534. DOI: 10.1002/aur.1380.

Baron-Cohen, S; Wheelwright, S; Cox, A.; Baird, G.; Charman, T.; Swettenham, J.; Doehrin, P. (2000): Early identification of autism by the CHecklist for Autism in Toddlers (CHAT). In: *Journal of the Royal Society* 93 (10), pp. 521-525.

Baron-Cohen, S.; Cox, A.; Baird, G.; Swettenham, J.; Nightingale, N.; Morgan, K. et al. (1996): Psychological markers in the detection of autism in infancy in a large population. In: *The British Journal of Psychiatry* 168 (2), pp. 158-163. DOI: 10.1192/bjp.168.2.158.

Baron-Cohen, S.; Wheelwright, S.; Skinner, R.; Martin, J.; Clubley, E. (2001): The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. In: *J Autism Dev Disord.* (31(1)), S. 5–17.

Baron-Cohen, Simon; Hoekstra, Rosa A.; Knickmeyer, Rebecca; Wheelwright, Sally (2006): The Autism-Spectrum Quotient (AQ)-Adolescent Version. In: *J Autism Dev Disord* 36 (3), pp. 343-350. DOI: 10.1007/s10803-006-0073-6.

Baron-Cohen, Simon; Lombardo, Michael V.; Auyeung, Bonnie; Ashwin, Emma; Chakrabarti, Bhismadev; Knickmeyer, Rebecca (2011): Why Are Autism Spectrum Conditions More Prevalent in Males? In: *PLoS Biol* 9 (6), p. e1001081. DOI: 10.1371/journal.pbio.1001081.

Baron-Cohen, Simon; Wheelwright, Sally; Robinson, Janine; Woodbury-Smith, Marc (2005): The Adult Asperger Assessment (AAA): a diagnostic method. In: *Journal of Autism and Developmental Disorders* 35 (6), pp. 807-819. DOI: 10.1007/s10803-005-0026-5.

Bastiaansen, Jojanneke A.; Meffert, Harma; Hein, Simone; Huizinga, Petra; Ketelaars, Cees; Pijnenborg, Marieke et al. (2011): Diagnosing Autism Spectrum Disorders in Adults: the Use of Autism Diagnostic Observation Schedule (ADOS) Module 4. In: *J Autism Dev Disord* 41 (9), pp. 1256-1266. DOI: 10.1007/s10803-010-1157-x.

Bayley, N. (2006): Bayley Scales of Infant and Toddler Development III. 3rd ed. San Antonio: Psychological Corporation.

Bedford, Rachael; Elsabbagh, Mayada; Gliga, Teodora; Pickles, Andrew; Senju, Atsushi; Charman, Tony; Johnson, Mark H. (2012): Precursors to Social and Communication Difficulties in Infants At-Risk for Autism: Gaze Following and Attentional Engagement. In: *J Autism Dev Disord* 42 (10), pp. 2208-2218. DOI: 10.1007/s10803-012-1450-y.

Beighley, Jennifer S.; Matson, Johnny L.; Rieske, Robert D.; Jang, Jina; Cervantes, Paige E.; Goldin, Rachel L. (2013): Comparing challenging behavior in children diagnosed with autism spectrum disorders according to the DSM-IV-TR and the proposed DSM-5. In: *Dev Neurorehabil* 16 (6), pp. 375-381. DOI: 10.3109/17518423.2012.760119.

Berg, A. T.; Plioplys, S.; Tuchman, R. (2011): Risk and Correlates of Autism Spectrum Disorder in Children With Epilepsy: A Community-Based Study. In: *Journal of Child Neurology* 26 (5), pp. 540-547. DOI: 10.1177/0883073810384869.

Bertrand, J.; Mars, A.; Boyle, C.; Bove, F.; Yeargin-Allsopp, M.; Decoufle, P. (2001): Prevalence of Autism in a United States Population: The Brick Township, New Jersey, Investigation. In: *PEDIATRICS* 108 (5), pp. 1155-1161. DOI: 10.1542/peds.108.5.1155.

Bettelheim, B. (1967): The empty fortress: infantile autism and the birth of the self. New York: The Free Press.

Billstedt, Eva; Carina Gillberg, I.; Gillberg, Christopher (2007): Autism in adults: symptom patterns and early childhood predictors. Use of the DISCO in a community sample followed from childhood. In: *J Child Psychol & Psychiat* 48 (11), pp. 1102-1110. DOI: 10.1111/j.1469-7610.2007.01774.x.

Bishop, D. V. M. (2010): Overlaps Between Autism and Language Impairment: Phenomimicry or Shared Etiology? In: *Behav Genet* 40 (5), pp. 618-629. DOI: 10.1007/s10519-010-9381-x.

Bishop, Dorothy V.M.; Norbury, Courtenay Frazier (2002): Exploring the borderlands of autistic disorder and specific language impairment: a study using standardised diagnostic instruments. In: *Journal of Child Psychology and Psychiatry* 43 (7), pp. 917-929. DOI: 10.1111/1469-7610.00114.

Bishop, Somer; Gahagan, Sheila; Lord, Catherine (2007): Re-examining the core features of autism: a comparison of autism spectrum disorder and fetal alcohol spectrum disorder. In: *Journal of Child Psychology and Psychiatry* 48 (11), pp. 1111-1121. DOI: 10.1111/j.1469-7610.2007.01782.x.

Bishop, Somer L.; Seltzer, Marsha Mailick (2012): Self-Reported Autism Symptoms in Adults with Autism Spectrum Disorders. In: *J Autism Dev Disord* 42 (11), pp. 2354-2363. DOI: 10.1007/s10803-012-1483-2.

Black, C. (2002): Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. In: *BMJ* 325 (7361), pp. 419-421. DOI: 10.1136/bmj.325.7361.419.

Blair, R. J. R. (2008): Fine cuts of empathy and the amygdala: Dissociable deficits in psychopathy and autism. In: The *Quarterly Journal of Experimental Psychology* 61 (1), pp. 157-170. DOI: 10.1080/17470210701508855.

Bleil Walters, Jessica; Hughes, Tammy L.; Sutton, Lawrence R.; Marshall, Stephanie N.; Crothers, Laura M.; Lehman, Cathryn et al. (2013): Maltreatment and Depression in Adolescent Sexual Offenders with an Autism Spectrum Disorder. In: *Journal of Child Sexual Abuse* 22 (1), pp. 72-89. DOI: 10.1080/10538712.2013.735357.

Bleuler, Egon (1911): Dementia praecox oder Gruppe der Schizophrenien. Leipzig, Vienna: Verlag Franz Deuticke.

Bölte, S.; Poustka, F. (2008a): Skala zur Erfassung sozialer Reaktivität (SRS). Bern: Huber.

Bölte, S.; Poustka, F. (2008b): SRS. Social reactivity scale - dimensional autism diagnostics. Bern: Huber.

Bölte, S.; Poustka, F.; Rutter, M. (2006): Social Communication-Autism Screening Questionnaire. Mannheim: Huber.

Bölte, Sven; Dziobek, Isabel; Poustka, Fritz (2009): Brief Report: The Level and Nature of Autistic Intelligence Revisited. In: *J Autism Dev Disord* 39 (4), pp. 678-682. DOI: 10.1007/s10803-008-0667-2.

Bölte, Sven; Poustka, Fritz (2005): Psychodiagnostic procedures for the assessment of autistic disorders. In: *Journal of Child and Adolescent Psychiatry and Psychotherapy* 33 (1), pp. 5-14. DOI: 10.1024/1422-4917.33.1.5.

Bölte, Sven; Westerwald, Eva; Holtmann, Martin; Freitag, Christine; Poustka, Fritz (2011): Autistic Traits and Autism Spectrum Disorders: The Clinical Validity of Two Measures Presuming a Continuum of Social Communication Skills. In: *J Autism Dev Disord* 41 (1), pp. 66-72. DOI: 10.1007/s10803-010-1024-9.

Bora, Emre; Pantelis, Christos (2013): Theory of mind impairments in first-episode psychosis, individuals at ultra-high risk for psychosis and in first-degree relatives of schizophrenia: Systematic review and meta-analysis. In: *Schizophrenia Research* 144 (1-3), pp. 31-36. DOI: 10.1016/j.schres.2012.12.013.

Brandler, William M.; Sebat, Jonathan (2015): From De Novo Mutations to Personalized Therapeutic Interventions in Autism. In: *Annu. Rev. Med.* 66 (1), pp. 487-507. DOI: 10.1146/annurev-med-091113-024550.

Brandt, I.; Sticker, E. J. (2001): GES. Griffiths developmental scales. For assessing development in the first two years of life. 2nd ed. Weinheim: Beltz.

Bretherton, I (1984): Symbolic play : the development of social understanding. Orlando, Fla: Academic Press.

Brieber, Sarah; Neufang, Susanne; Bruning, Nicole; Kamp-Becker, Inge; Remschmidt, Helmut; Herpertz-Dahlmann, Beate et al. (2007): Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. In: *Journal of Child Psychology and Psychiatry* 48 (12), pp. 1251-1258. DOI: 10.1111/j.1469-7610.2007.01799.x.

Brisson, J.; Warreyn, P.; Serres, J.; Foussier, S.; Adrien-Louis, J. (2012): Motor anticipation failure in infants with autism: a retrospective analysis of feeding situations. In: *Autism* 16 (4), pp. 420-429. doi: 10.1177/1362361311423385.

Bromley, R. L.; Mawer, G. E.; Briggs, M.; Cheyne, C.; Clayton-Smith, J.; Garcia-Finana, M. et al. (2013): The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. In: *Journal of Neurology, Neurosurgery & Psychiatry* 84 (6), pp. 637-643. DOI: 10.1136/jnnp-2012-304270.

Brooks, Whitney T.; Benson, Betsey A. (2013): The validity of the social communication questionnaire in adults with intellectual disability. In: *Research in Autism Spectrum Disorders* 7 (2), pp. 247-255. DOI: 10.1016/j.rasd.2012.10.002.

Brugha, T. S.; McManus, S.; Smith, J.; Scott, F. J.; Meltzer, H.; Purdon, S. et al. (2012): Validating two survey methods for identifying cases of autism spectrum disorder among adults in the community. In: *Psychological Medicine* 42 (03), pp. 647-656. doi: 10.1017/S0033291711001292.

Brugha, Traolach S.; McManus, Sally; Bankart, John; Scott, Fiona; Purdon, Susan; Smith, Jane et al. (2011): Epidemiology of Autism Spectrum Disorders in Adults in the Community in England. In: *Arch Gen Psychiatry* 68 (5), pp. 459-465. DOI: 10.1001/archgenpsychiatry.2011.38.

Bruining, Hilgo; Swaab, Hanna; Kas, Martien; van Engeland, Herman (2009): Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. In: *PEDIATRICS* 123 (5), pp. e865-e870. Available online at http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=psyc6&NEWS=N&AN=2010-04323-008.

Buchmayer, S.; Johansson, S.; Johansson, A.; Hultman, C. M.; Sparen, P.; Cnattingius, S. (2009): Can Association Between Preterm Birth and Autism be Explained by Maternal or Neonatal Morbidity? In: *PEDIATRICS* 124 (5), pp. e817-e825. DOI: 10.1542/peds.2008-3582.

Buck, Tara R.; Viskochil, Joseph; Farley, Megan; Coon, Hilary; McMahon, William M.; Morgan, Jubel; Bilder, Deborah A. (2014): Psychiatric Comorbidity and Medication Use in Adults with Autism Spectrum Disorder. In: *J Autism Dev Disord* 44 (12), pp. 3063-3071. doi: 10.1007/s10803-014-2170-2.

Bühler, Eva; Bachmann, Christian; Goyert, Hannah; Heinzel-Gutenbrunner, Monika; Kamp-Becker, Inge (2011): Differential Diagnosis of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder by Means of Inhibitory Control and 'Theory of Mind'. In: *J Autism Dev Disord* 41 (12), pp. 1718-1726. DOI: 10.1007/s10803-011-1205-1.

Buie, T.; Campbell, D. B.; Fuchs, G. J.; Furuta, G. T.; Levy, J.; VandeWater, J. et al. (2010): Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report. In: *PEDIATRICS* 125 (Supplement), pp. 1-18. DOI: 10.1542/peds.2009-1878C.

Canal-Bedia, Ricardo; García-Primo, Patricia; Martín-Cilleros, María Victoria; Santos-Borbujo, José; Guisuraga-Fernández, Zoila; Herráez-García, Lorena et al. (2011): Modified Checklist for Autism in Toddlers: Cross-Cultural Adaptation and Validation in Spain. In: *J Autism Dev Disord* 41 (10), pp. 1342-1351. DOI: 10.1007/s10803-010-1163-z.

Canitano, R.; Luchetti, A.; Zappella, M. (2005): Epilepsy, Electroencephalographic Abnormalities, and Regression in Children With Autism. In: *Journal of Child Neurology* 20 (1), pp. 27-31. DOI: 10.1177/08830738050200010401.

Canitano, R.; Vivanti, G. (2007): Tics and Tourette syndrome in autism spectrum disorders. In: *Autism* 11 (1), pp. 19-28. DOI: 10.1177/1362361307070992.

Carcani-Rathwell, Iris; Rabe-Hasketh, Sophia; Santosh, Paramala J. (2006): Repetitive and stereotyped behaviours in pervasive developmental disorders. In: *Journal of Child Psychology and Psychiatry* 47 (6), pp. 573-581. DOI: 10.1111/j.1469-7610.2005.01565.x.

Caron, Chantal; Rutter, Michael (1991): Comorbidity in Child Psychopathology: Concepts, Issues and Research Strategies. In: *Journal of Child Psychology and Psychiatry* 32 (7), pp. 1063-1080. DOI: 10.1111/j.1469-7610.1991.tb00350.x.

Carr, Themba; Lord, Catherine (2013): Longitudinal study of perceived negative impact in African American and Caucasian mothers of children with autism spectrum disorder. In: *Autism : the international journal of research and practice* 17 (4), pp. 405-417. DOI: 10.1177/1362361311435155.

Carter, Alice S.; Martínez-Pedraza, Frances de L; Gray, Sarah A. O. (2009): Stability and individual change in depressive symptoms among mothers raising young children with ASD: maternal and child correlates. In: *Journal of clinical psychology* 65 (12), pp. 1270-1280. DOI: 10.1002/jclp.20634.

Carter, M. T.; Scherer, S. W.. (2013): Autism spectrum disorder in the genetics clinic: a review. In: *Clin Genet* 83 (5), pp. 399-407. DOI: 10.1111/cge.12101.

Cassidy, Arlene; McConkey, Roy; Truesdale-Kennedy, Maria; Slevin, Eamonn (2008): Preschoolers with autism spectrum disorders: the impact on families and the supports available to them. In: *Early Child Development and Care* 178 (2), pp. 115-128. DOI: 10.1080/03004430701491721.

Cath, Danielle C.; Ran, Natalie; Smit, Johannes H.; van Balkom, Anton J. L. M.; Comijs, Hannie C. (2008): Symptom Overlap between Autism Spectrum Disorder, Generalized Social Anxiety Disorder and Obsessive-Compulsive Disorder in Adults: A Preliminary Case-Controlled Study. In: *Psychopathology* 41 (2), pp. 101-110. DOI: 10.1159/000111555.

Cederlund, M.; Hagberg, B.; Billstedt, E.; Gillberg, I. C.; Gillberg, C. (2008): Asperger syndrome and autism: a comparative longitudinal follow-up study more than 5 years after original diagnosis. In: *J Autism Dev Disord* 38, pp. 72-85.

Center for Disease Control (2007a): Prevalence of autism spectrum disorder-autism and developmental disabilities monitoring network, six sites, United States (2000). In: *MMWR Surveillance Summary* 56, pp. 1-11.

Center for Disease Control (2007b): Prevalence of autism spectrum disorders-autism and developmental disabilities monitoring network, 14 sites, United States (2002). In: *MMWR Surveillance Summary* 56, pp. 12-28.

Center for Disease Control (2009): Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring network, United States, 2006. In: *Morbidity and Mortality Weekly Report Surveillance Summary* 58, pp. 1-14.

Centers for Disease Control and Prevention (2012): Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. In: *Morbidity and Mortality Weekly Report Surveillance Summary* 61 (3), pp. 1-24.

Centers for Disease Control Prevention (2014): Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. In: *Morbidity and Mortality Weekly Report Surveillance Summary* 63 (2), pp. 1-21.

Chakrabarti, Suniti (2001): Pervasive Developmental Disorders in Preschool Children. In: *JAMA* 285 (24), p. 3093. DOI: 10.1001/jama.285.24.3093.

Chakrabarti, Suniti; Fombonne, Eric (2005): Pervasive Developmental Disorders in Preschool Children: Confirmation of High Prevalence. In: *AJP* 162 (6), pp. 1133-1141. DOI: 10.1176/appi.ajp.162.6.1133.

Chandler, Susie; Charman, Tony; Baird, Gillian; Simonoff, Emily; Loucas, Tom; Meldrum, David et al. (2007): Validation of the Social Communication Questionnaire in a Population Cohort of Children With Autism Spectrum Disorders. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 46 (10), pp. 1324-1332. DOI: 10.1097/chi.0b013e31812f7d8d.

Charman, T.; Baird, G.; Simonoff, E.; Loucas, T.; Chandler, S.; Meldrum, D.; Pickles, A. (2007): Efficacy of three screening instruments in the identification of autistic-spectrum disorders. In: *The British Journal of Psychiatry* 191 (6), pp. 554-559. DOI: 10.1192/bjp.bp.107.040196.

Charman, T.; Pickles, A.; Simonoff, E.; Chandler, S.; Loucas, T.; Baird, G. (2011): IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). In: *Psychological Medicine* 41 (03), pp. 619-627. DOI: 10.1017/S0033291710000991.

Charman, Tony; Baron-Cohen, Simon; Swettenham, John; Baird, Gillian; Drew, Auriol; Cox, Antony (2003): Predicting language outcome in infants with autism and pervasive developmental disorder. In: *Int J Lang Commun Disord* 38 (3), pp. 265-285. DOI: 10.1080/136820310000104830.

Charman, Tony; Swettenham, John; Baron-Cohen, Simon; Cox, Antony; Baird, Gillian; Drew, Auriol (1997): Infants with autism: An investigation of empathy, pretend play, joint attention, and imitation. In: *Developmental Psychology* 33 (5), pp. 781-789. DOI: 10.1037/0012-1649.33.5.781.

Chawarska, Katarzyna; Campbell, D; Chen, L; Shic, F; Klin, A; Chang, J (2011): Early Generalized Overgrowth in Boys With Autism. In: *Arch Gen Psychiatry* 68 (10), pp. 1021-1031. DOI: 10.1001/archgenpsychiatry.2011.106.

Chawarska, Katarzyna; Macari, Suzanne; Shic, Frederick (2013): Decreased Spontaneous Attention to Social Scenes in 6-Month-Old Infants Later Diagnosed with Autism Spectrum Disorders. In: *Biological Psychiatry* 74 (3), pp. 195-203. doi: 10.1016/j.biopsych.2012.11.022.

Cheely, Catherine A.; Carpenter, Laura A.; Letourneau, Elizabeth J.; Nicholas, Joyce S.; Charles, Jane; King, Lydia B. (2012) The Prevalence of Youth with Autism Spectrum Disorders in the Criminal Justice System. In: *J Autism Dev Disord* 42 (9), pp. 1856-1862. DOI: 10.1007/s10803-011-1427-2.

Chen, C.-Y.; Liu, C.-Y.; Su, W.-C.; Huang, S.-L.; Lin, K.-M. (2007): Factors Associated With the Diagnosis of Neurodevelopmental Disorders: A Population-Based Longitudinal Study. In: *PEDIATRICS* 119 (2), pp. e435-e443. DOI: 10.1542/peds.2006-1477.

Chess, S (1971): Autism in children with congenital rubella. In: *Journal of Autism and Childhood Schizophrenia* 1 (1), pp. 33-47.

Chess, S (1977): Follow-up report on autism in congenital rubella. In: *Journal of Autism and Childhood Schizophrenia* 7 (1), pp. 69-81.

Chess, S; Fernandez, P; Korn, S (1978): Behavioral consequences of congenital rubella. In: *Journal of pediatrics* 93 (4), pp. 699-703.

Chlebowski, Colby; Green, James A.; Barton, Marianne L.; Fein, Deborah (2010): Using the Childhood Autism Rating Scale to Diagnose Autism Spectrum Disorders. In: *J Autism Dev Disord* 40 (7), pp. 787-799. DOI: 10.1007/s10803-009-0926-x.

Cholemkery, Hannah; Kitzerow, Janina; Rohrmann, Sonja; Freitag, Christine M. (2014a): Validity of the social responsiveness scale to differentiate between autism spectrum disorders and disruptive behaviour disorders. In: *Eur Child Adolesc Psychiatry* 23 (2), pp. 81-93. DOI: 10.1007/s00787-013-0427-5.

Cholemkery, Hannah; Mojica, Laura; Rohrmann, Sonja; Gensthaler, Angelika; Freitag, Christine M. (2014b): Can Autism Spectrum Disorders and Social Anxiety Disorders be Differentiated by the Social Responsiveness Scale in Children and Adolescents? In: *J Autism Dev Disord* 44 (5), pp. 1168-1182. DOI: 10.1007/s10803-013-1979-4.

Chuthapisith, J.; Taycharpipranai, P.; Ruangdaraganon, N.; Warrington, R.; Skuse, D. (2012): Translation and validation of the developmental, dimensional and diagnostic interview (3Di) for diagnosis of autism spectrum disorder in Thai children. In: *Autism* 16 (4), pp. 350-356. DOI: 10.1177/1362361311433770.

Cochran, David M.; Dvir, Yael; Frazier, Jean A. (2013) "Autism-plus" Spectrum Disorders. In *Child and Adolescent Psychiatric Clinics of North America* 22 (4), pp. 609-627. doi: 10.1016/j.chc.2013.04.005.

Coghill, David; Sonuga-Barke, Edmund J.S. (2012): Annual Research Review: Categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders - implications of recent empirical study. In: *Journal of Child Psychology and Psychiatry* 53 (5), pp. 469-489. DOI: 10.1111/j.1469-7610.2011.02511.x.

Coid, J. (2006): Prevalence and correlates of personality disorder in Great Britain. In: The *British Journal of Psychiatry* 188 (5), pp. 423-431. DOI: 10.1192/bjp.188.5.423.

Collin, Lisa; Bindra, Jasmeet; Raju, Monika; Gillberg, Christopher; Minnis, Helen (2013): Facial emotion recognition in child psychiatry: A systematic review. In: *Research in Developmental Disabilities* 34 (5), pp. 1505-1520. DOI: 10.1016/j.ridd.2013.01.008.

Constantino, J. N.; Gruber, C. P. (2005a): The social responsiveness scale manual. Los Angeles, CA: Western Psychological Services.

Constantino, J. N.; Gruber, C. P. (2005): Social responsiveness scale (SRS). Los Angeles, CA: Western Psychological Services.

Constantino, John N.; LAVESSER, PATRICIA D.; ZHANG, Y. I.; ABBACCHI, ANNA M.; GRAY, TEDDI; Todd, Richard D. (2007): Rapid Quantitative Assessment of Autistic Social Impairment by Classroom Teachers. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 46 (12), pp. 1668-1676. DOI: 10.1097/chi.0b013e318157cb23.

Constantino, John N.; Todd, Richard D. (2005b): Intergenerational transmission of subthreshold autistic traits in the general population. In: *Biological Psychiatry* 57 (6), pp. 655-660. DOI: 10.1016/j.biopsych.2004.12.014.

Coplan, J. (2000): Counseling Parents Regarding Prognosis in Autistic Spectrum Disorder. In: *PEDIATRICS* 105 (5), p. e65. DOI: 10.1542/peds.105.5.e65.

Corsello, Christina; Hus, Vanessa; Pickles, Andrew; Risi, Susan; Cook, Edwin H.; Leventhal, Bennett L.; Lord, Catherine (2007): Between a ROC and a hard place: decision making and making decisions about using the SCQ. In: *Journal of Child Psychology and Psychiatry* 48 (9), pp. 932-940. DOI: 10.1111/j.1469-7610.2007.01762.x.

Coulthard, Patricia; Fitzgerald, Michael (1999): In God we trust? Organised religion and personal beliefs as resources and coping strategies, and their implications for health in parents with a child on the autistic spectrum. In: *Mental Health, Religion & Culture* 2 (1), pp. 19-33. DOI: 10.1080/13674679908406329.

Courchesne, Eric; Campbell, Kathleen; Solso, Stephanie (2011): Brain growth across the life span in autism: Age-specific changes in anatomical pathology. In: *Brain Research* 1380, pp. 138-145. DOI: 10.1016/j.brainres.2010.09.101.

Croen, Lisa A. (2011): Antidepressant Use During Pregnancy and Childhood Autism Spectrum Disorders. In: *Arch Gen Psychiatry* 68 (11), pp. 1104-1112. DOI: 10.1001/archgenpsychiatry.2011.73.

Croen, Lisa A.; Grether, Judith K.; Hoogstrate, Jenny; Selvin, Steve (2002): The Changing Prevalence of Autism in California. In: *Journal of Autism and Developmental Disorders* 32 (3), pp. 207-215. DOI: 10.1023/A:1015453830880.

Croen, Lisa A.; Grether, Judith K.; Yoshida, Cathleen K.; Odouli, Roxana; Van de Water, Judy (2005): Maternal Autoimmune Diseases, Asthma and Allergies, and Childhood Autism Spectrum Disorders. In: *Arch Pediatr Adolesc Med* 159 (2), pp. 151-157. DOI: 10.1001/archpedi.159.2.151.

Curran, Eileen A.; Dalman, Christina; Kearney, Patricia M.; Kenny, Louise C.; Cryan, John F.; Dinan, Timothy G.; Khashan, Ali S. (2015): Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder. In: *JAMA Psychiatry* 72 (9), p. 935. DOI: 10.1001/jamapsychiatry.2015.0846.

Dale, Emily; Jahoda, Andrew; Knott, Fiona (2006): Mothers' attributions following their child's diagnosis of autistic spectrum disorder: exploring links with maternal levels of stress,depression and expectations about their child's future. In: *Autism : the international journal of research and practice* 10 (5), pp. 463-479. DOI: 10.1177/1362361306066600.

Daniels, A. M.; Mandell, D. S. (2014): Explaining differences in age at autism spectrum disorder diagnosis: A critical review. In: *Autism* 18 (5), pp. 583-597. DOI: 10.1177/1362361313480277.

Daniels, J. L.; Forssen, U.; Hultman, C. M.; Cnattingius, S.; Savitz, D. A.; Feychting, M.; Sparen, P. (2008): Parental Psychiatric Disorders Associated With Autism Spectrum Disorders in the Offspring. In: *PEDIATRICS* 121 (5), pp. e1357-e1362. DOI: 10.1542/peds.2007-2296.

Danielsson, Susanna; Gillberg, I. Carina; Billstedt, Eva; Gillberg, Christopher; Olsson, Ingrid (2005): Epilepsy in Young Adults with Autism: A Prospective Population-based Follow-up Study of 120 Individuals Diagnosed in Childhood. In: *Epilepsia* 46 (6), pp. 918-923. DOI: 10.1111/j.1528-1167.2005.57504.x.

Darrou, C.; Pry, R.; Pernon, E.; Michelon, C.; Aussilloux, C.; Baghdadli, A. (2010): Outcome of young children with autism: Does the amount of intervention influence developmental trajectories? In: *Autism. DOI:* 10.1177/1362361310374156.

Davidovitch, Michael; Hemo, Beatriz; Manning-Courtney, Patricia; Fombonne, Eric (2013): Prevalence and Incidence of Autism Spectrum Disorder in an Israeli Population. In: *J Autism Dev Disord* 43 (4), pp. 785-793. DOI: 10.1007/s10803-012-1611-z.

Dawson, G.; Rogers, S.; Munson, J.; Smith, M.; Winter, J.; Greenson, J. et al. (2010): Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model. In: *PEDIATRICS* 125 (1), pp. e17-e23. DOI: 10.1542/peds.2009-0958.

Dawson, M.; Soulieres, I.; Ann Gernsbacher, M.; Mottron, L. (2007): The Level and Nature of Autistic Intelligence. In: *Psychological Science* 18 (8), pp. 657-662. DOI: 10.1111/j.1467-9280.2007.01954.x.

de Bildt, Annelies; Sytema, Sjoerd; Ketelaars, Cees; Kraijer, Dirk; Mulder, Erik; Volkmar, Fred; Minderaa, Ruud (2004): Interrelationship between Autism Diagnostic Observation Schedule-Generic (ADOS-G), Autism Diagnostic Interview-Revised (ADI-R), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) Classification in Children and Adolescents with Mental Retardation. In: *Journal of Autism and Developmental Disorders* 34 (2), pp. 129-137.

de Bildt, Annelies; Sytema, Sjoerd; van Lang, Natasja D. J.; Minderaa, Ruud B.; van Engeland, Herman; de Jonge, Maretha V. (2009): Evaluation of the ADOS Revised Algorithm: The Applicability in 558 Dutch Children and Adolescents. In: *J Autism Dev Disord* 39 (9), pp. 1350-1358. DOI: 10.1007/s10803-009-0749-9.

de Bruin, Esther I.; Ferdinand, Robert F.; Meester, Sjifra; de Nijs, Pieter F. A.; Verheij, Fop (2007): High Rates of Psychiatric Co-Morbidity in PDD-NOS. In: *J Autism Dev Disord* 37 (5), pp. 877-886. DOI: 10.1007/s10803-006-0215-x.

Deal, Cheri L.; Tony, Michèle; Höybye, Charlotte; Allen, David B.; Tauber, Maïthé; Christiansen, Jens Sandahl et al. (2013): Growth Hormone Research Society Workshop Summary: Consensus Guidelines for Recombinant Human Growth Hormone Therapy in Prader-Willi Syndrome. In: *The Journal of Clinical Endocrinology & Metabolism* 98 (6), pp. E1072-E1087. DOI: 10.1210/jc.2012-3888.

Depienne, Christel; Moreno-De-Luca, Daniel; Heron, Delphine; Bouteiller, Delphine; Gennetier, Aurélie; Delorme, Richard et al. (2009): Screening for Genomic Rearrangements and Methylation Abnormalities of the 15q11-q13 Region in Autism Spectrum Disorders. In: *Biological Psychiatry* 66 (4), pp. 349-359. DOI: 10.1016/j.biopsych.2009.01.025.

German Institute of Medical Documentation and Information, DIMDI WHO Collaborating Centre for the System of International Classifications: International Classification of Functioning, Disability and Health (ICF). Geneva.

Dietz, Claudine; Swinkels, Sophie; van Daalen, Emma; van Engeland, Herman; Buitelaar, Jan K. (2006): Screening for Autistic Spectrum Disorder in Children Aged 14-15 Months. II: Population Screening with the Early Screening of Autistic Traits Questionnaire (ESAT). Design and General Findings. In: *J Autism Dev Disord* 36 (6), pp. 713-722. DOI: 10.1007/s10803-006-0114-1.

DiGuiseppi, Carolyn; Hepburn, Susan; Davis, Jonathan M.; Fidler, Deborah J.; Hartway, Sara; Lee, Nancy Raitano et al. (2010): Screening for autism spectrum disorders in children with Down syndrome: Population prevalence and screening test characteristics. In: *Journal of Developmental and Behavioral Pediatrics* 31 (3), pp. 181-191. DOI: 10.1192/bjp.175.5.444.

Dissanayake, C. (2012): Children with social phobia have distinct social skills deficit and vocal characteristics to children with Asperger's disorder and typically developing children. In: *Evidence-Based Mental Health* 15 (2), p. 37. DOI: 10.1136/ebmental-2011-100259.

Döpfner, M; Berner, W; Flechtner, H; Lehmkuhl,, G; Steinhausen, H-C (1999): Psychopathological Assessment System for Children and Adolescents (CASCAP-D). Findings sheet, glossary and exploration guide. With the collaboration of Manfred Döpfner. Göttingen: Hogrefe Verl. for Psychology.

Döpfner, M.; Plück, J.; Kinnen, C. (2014): TRF/6-18R. Teacher questionnaire on child and adolescent behavior.

Döpfner, Manfred; Görtz-Dorten, A; Lehmkuhl, Gerd; Breuer,, D; Goletz, H (2008): DISYPS-II. Diagnostic system for mental disorders according to ICD-10 and DSM-IV for children and adolescents - II: Hogrefe.

Durand-Zaleski, Isabelle; Scott, Jan; Rouillon, Frédéric; Leboyer, Marion (2012): A first national survey of knowledge, attitudes and behaviours towards schizophrenia, bipolar disorders and autism in France. In: *BMC Psychiatry* 12 (1), p. 128. DOI: 10.1186/1471-244X-12-128.

Dyck, Murray; Piek, Jan (2010): How to distinguish normal from disordered children with poor language or motor skills. In: *International Journal of Language & Communication Disorders* 45 (3), pp. 336-344. DOI: 10.3109/13682820903009503.

Dziobek, Isabel; Preißler, Sandra; Grozdanovic, Zarko; Heuser, Isabella; Heekeren, Hauke R.; Roepke, Stefan (2011): Neuronal correlates of altered empathy and social cognition in borderline personality disorder. In: *NeuroImage* 57 (2), pp. 539-548. DOI: 10.1016/j.neuroimage.2011.05.005.

Eaves, L. C. (2006): Screening for autism: agreement with diagnosis. In: *Autism* 10 (3), pp. 229-242. DOI: 10.1177/1362361306063288.

Eaves, L. C.; Wingert, H. D.; Ho, H. H.; Mickelson, E. C. (2006a): Screening for autism spectrum disorders with the social communication questionnaire. In: *Journal of Developmental & Behavioral Pediatrics, 27(2), S95-S103.* 27 (2), pp. 95-103.

Ehlers, Stephan; Gillberg, Christopher; Wing, Lorna (1999): A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. In: *J Autism Dev Disord* 29 (2), pp. 129-141. DOI: 10.1023/A:1023040610384.

Eisenberg, L. (1957): The fathers of autistic children. In: *American Journal of Orthopsychiatry* 17, pp. 715-724.

Eliasen, M.; Tolstrup, J. S.; Nybo Andersen, A.-M.; Gronbaek, M.; Olsen, J.; Strandberg-Larsen, K. (2010): Prenatal alcohol exposure and autistic spectrum disorders--a population-based prospective study of 80 552 children and their mothers. In: *International Journal of Epidemiology* 39 (4), pp. 1074-1081. DOI: 10.1093/ije/dyq056.

Elsabbagh, Mayada; Divan, Gauri; Koh, Yun-Joo; Kim, Young Shin; Kauchali, Shuaib; Marcín, Carlos et al. (2012): Global Prevalence of Autism and Other Pervasive Developmental Disorders. In: *Autism Res* 5 (3), pp. 160-179. DOI: 10.1002/aur.239.

Elsabbagh, Mayada; Fernandes, Janice; Jane Webb, Sara; Dawson, Geraldine; Charman, Tony; Johnson, Mark H. (2013a): Disengagement of Visual Attention in Infancy is Associated with Emerging Autism in Toddlerhood. In: *Biological Psychiatry* 74 (3), pp. 189-194. doi: 10.1016/j.biopsych.2012.11.030.

Elsabbagh, Mayada; Gliga, Teodora; Pickles, Andrew; Hudry, Kristelle; Charman, Tony; Johnson, Mark H. (2013b): The development of face orienting mechanisms in infants at-risk for autism. In *Behavioural Brain Research* 251, pp. 147-154. doi: 10.1016/j.bbr.2012.07.030.

Eriksson, Mats Anders; Westerlund, Joakim; Anderlid, Britt Marie; Gillberg, Christopher; Fernell, Elisabeth (2012): First-degree relatives of young children with autism spectrum disorders: Some gender aspects. In: *Research in Developmental Disabilities* 33 (5), pp. 1642-1648. DOI: 10.1016/j.ridd.2012.03.025.

Esposito, Gianluca; Venuti, Paola; Maestro, Sandra; Muratori, Filippo (2009): An exploration of symmetry in early autism spectrum disorders: Analysis of lying. In: *Brain and Development* 31 (2), pp. 131-138. DOI: 10.1016/j.braindev.2008.04.005.

Esser, G.; Petermann, F. (2010): Entwicklungsdiagnostik: Hogrefe Verlag. Available online at https://books.google.de/books?id=GgzeWGidr1kC, last checked 15.03.2016.

Estes, Annette; Olson, Erin; Sullivan, Katherine; Greenson, Jessica; Winter, Jamie; Dawson, Geraldine; Munson, Jeffrey (2013): Parenting-related stress and psychological distress in mothers of toddlers with autism spectrum disorders. In *Brain & development* 35 (2), pp. 133-138. doi: 10.1016/j.braindev.2012.10.004.

Falkai, Peter; Döpfner, Manfred (eds.) (2015): Diagnostic and statistical manual of mental disorders DSM-5. American Psychiatric Association. Göttingen et al: Hogrefe.

Farrar, M. Jeffrey; Johnson, Bonnie; Tompkins, Virginia; Easters, Molly; Zilisi-Medus, Andrea; Benigno, Joann P. (2009): Language and theory of mind in preschool children with specific language impairment. In: *Journal of Communication Disorders* 42 (6), pp. 428-441. DOI: 10.1016/j.jcomdis.2009.07.001.

Farrugia, David (2009): Exploring stigma: medical knowledge and the stigmatisation of parents of children diagnosed with autism spectrum disorder. In: *Sociology of Health & Illness* 31 (7), pp. 1011-1027. DOI: 10.1111/j.1467-9566.2009.01174.x.

Fein, Deborah; Barton, Marianne; Eigsti, Inge-Marie; Kelley, Elizabeth; Naigles, Letitia; Schultz, Robert T. et al. (2013): Optimal outcome in individuals with a history of autism. In: *Journal of Child Psychology and Psychiatry* 54 (2), pp. 195-205. DOI: 10.1111/jcpp.12037.

Flanagan, J. E.; Landa, R.; Bhat, A.; Bauman, M. (2012): Head Lag in Infants at Risk for Autism: A Preliminary Study. In: *American Journal of Occupational Therapy* 66 (5), pp. 577-585. DOI: 10.5014/ajot.2012.004192.

Folstein, S.; Rutter, M. (1977): Genetic influences and infantile autism. In: *Nature* 165, pp. 726-728.

Fombonne, E.; Du Mazaubrun, C.; Cans, C.; Grandjean, H. (1997): Autism and associated medical disorders in a French epidemiological survey. In: *J Am Acad Child Adolesc Psychiatry* 36 (11), pp. 1561-1569.

Fombonne, E.; Quirke, S.; Hagen, A. (2011): Epidemiology of pervasive developmental disorders. In: D. G. Amaral, G. Dawson, and D. H. Geschwind (Eds.): Autism Spectrum Disorders. New York: Oxford University Press, pp. 90-111.

Fombonne, E.; Zakarian, R.; Bennett, A.; Meng, L.; McLean-Heywood, D. (2006): Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations. In: *PEDIATRICS* 118 (1), pp. e139-e150. DOI: 10.1542/peds.2005-2993.

Fombonne, Eric (2009): Epidemiology of Pervasive Developmental Disorders. In: *Pediatr Res* 65 (6), pp. 591-598. DOI: 10.1203/PDR.0b013e31819e7203.

FORD, TAMSIN; Goodman, Robert; Meltzer, Howard (2003): The British Child and Adolescent Mental Health Survey 1999: The Prevalence of DSM-IV Disorders. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 42 (10), pp. 1203-1211. DOI: 10.1097/00004583-200310000-00011.

Fountain, C.; Winter, A. S.; Bearman, P. S. (2012): Six Developmental Trajectories Characterize Children With Autism. In: *PEDIATRICS* 129 (5), pp. e1112-e1120. DOI: 10.1542/peds.2011-1601.

Frazier, T. W.; Youngstrom, E. A.; Sinclair, L.; Kubu, C. S.; Law, P.; Rezai, A. et al. (2010): Autism Spectrum Disorders as a Qualitatively Distinct Category From Typical Behavior in a Large, Clinically Ascertained Sample. In: *Assessment* 17 (3), pp. 308-320. DOI: 10.1177/1073191109356534.

Frazier, Thomas W.; Thompson, Lee; Youngstrom, Eric A.; Law, Paul; Hardan, Antonio Y.; Eng, Charis; Morris, Nathan (2014): A Twin Study of Heritable and Shared Environmental Contributions to Autism. In: *J Autism Dev Disord* 44 (8), pp. 2013-2025. doi: 10.1007/s10803-014-2081-2.

Frazier, Thomas W.; Youngstrom, Eric A.; Speer, Leslie; Embacher, Rebecca; Law, Paul; Constantino, John et al. (2012): Validation of Proposed DSM-5 Criteria for Autism Spectrum Disorder. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 51 (1), pp. 28-40.e3. DOI: 10.1016/j.jaac.2011.09.021.

Freitag, Christine M. (2008): Autismus-Spektrum-Störungen. München u.a.: Reinhardt (3).

Freitag, Christine M. (2011): Genetic risk in autism: new associations and clinical testing. In: *Expert Opin. Med. Diagn.* 5 (4), pp. 347-356. DOI: 10.1517/17530059.2011.579101.

Freitag, Christine M. (2014): Autism spectrum disorder according to DSM-5. In: *Journal of Child and Adolescent Psychiatry and Psychotherapy* 42 (3), pp. 185-192. DOI: 10.1024/1422-4917/a000288.

Freitag, Christine M.; Cholemkery, Hannah; Elsuni, Leyla; Kroeger, Anne K.; Bender, Stephan; Kunz, Cornelia Ursula; Kieser, Meinhard (2013): The group-based social skills training SOSTA-FRA in children and adolescents with high functioning autism spectrum disorder - study protocol of the randomised, multi-centre controlled SOSTA - net trial. In: *Trials* 14 (1), p. 6. DOI: 10.1186/1745-6215-14-6.

Freitag, Christine M.; Retz-Junginger, Petra; Retz, Wolfgang; Seitz, Christiane; Palmason, Haukur; Meyer, Jobst et al. (2007): Evaluation of the German version of the Autism Spectrum Quotient (AQ) - the short version AQ-k. In: *Journal of Clinical Psychology and Psychotherapy* 36 (4), pp. 280-289. DOI: 10.1026/1616-3443.36.4.280.

Freud, Sigmund (1940 //1998): Mass Psychology and Ego Analysis. In: Sigmund Freud: Collected Works. Arranged Chronologically, 13: Beyond the Pleasure Principle. Mass Psychology and Ego-Analysis. The Ego and the Id. And other works from the years 1920-1924. 10th edition. Edited by Anna Freud, Marie Bonaparte, E. Bibring, W. Hoffer, E. Kris, and O. Osakower. Frankfurt am Main: S. Fischer, p. 73f.

Frith, U. (ed.) (1991): Autism and Asperger syndrome. Cambridge: Cambridge University Press.

Fukumoto, Aya; Hashimoto, Toshiaki; Mori, Kenji; Tsuda, Yoshimi; Arisawa, Kokichi; Kagami, Shoji (2011): Head circumference and body growth in autism spectrum disorders. In: *Brain and Development* 33 (7), pp. 569-575. doi: 10.1016/j.braindev.2010.09.004.

Gadow, K. D.; DeVincent, C. J. (2005): Clinical significance of tics and attention-deficit hyperactivity disorder (ADHD) in children with pervasive developmental disorder. In: *J Child Neurol.* 20 (6), pp. 481-488.

Gail Williams, P.; Sears, Lonnie L.; Allard, AnnaMary (2004): Sleep problems in children with autism. In: *J Sleep Res* 13 (3), pp. 265-268. DOI: 10.1111/j.1365-2869.2004.00405.x.

Gargaro, Belinda A.; Rinehart, Nicole J.; Bradshaw, John L.; Tonge, Bruce J.; Sheppard, Dianne M. (2011): Autism and ADHD: How far have we come in the comorbidity debate? In: *Neuroscience & Biobehavioral Reviews* 35 (5), pp. 1081-1088. DOI: 10.1016/j.neubiorev.2010.11.002.

Garnett, M. S.; Attwood, A. J. (1995): The Australian Scale of Asperger's Syndrome. Brisbane, Australia.

Gaugler, Trent; Klei, Lambertus; Sanders, Stephan J.; Bodea, Corneliu A.; Goldberg, Arthur P.; Lee, Ann B. et al. (2014): Most genetic risk for autism resides with common variation. In: *Nat Genet* 46 (8), pp. 881-885. DOI: 10.1038/ng.3039.

Georgiades, Stelios; Szatmari, Peter; Zwaigenbaum, Lonnie; Bryson, Susan; Brian, Jessica; Roberts, Wendy et al. (2013): A Prospective Study of Autistic-Like Traits in Unaffected Siblings of Probands With Autism Spectrum Disorder. In: *JAMA Psychiatry* 70 (1), p. 42. DOI: 10.1001/2013.jamapsychiatry.1.

Geschwind, Daniel H. (2011): Genetics of autism spectrum disorders. In: *Trends in Cognitive Sciences* 15 (9), pp. 409-416. DOI: 10.1016/j.tics.2011.07.003.

Ghaziuddin, Mohammad; Al-Owain, Mohammed (2013): Autism spectrum disorders and inborn errors of metabolism: an update. In: *Pediatric Neurology* 49 (4), pp. 232-236. DOI: 10.1016/j.pediatrneurol.2013.05.013.

Giarelli, Ellen; Wiggins, Lisa D.; Rice, Catherine E.; Levy, Susan E.; Kirby, Russell S.; Pinto-Martin, Jennifer; Mandell, David (2010): Sex differences in the evaluation and diagnosis of autism spectrum disorders among children. In: *Disability and Health Journal* 3 (2), pp. 107-116. DOI: 10.1016/j.dhjo.2009.07.001.

Gillberg, C.; Råstam, M.; Wentz, E. (2001): The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. In: *Autism : the international journal of research and practice* 5 (1), pp. 57-66.

Gillberg, Christopher; Fernell, Elisabeth (2014): Autism Plus Versus Autism Pure. In: *J Autism Dev Disord* 44 (12), pp. 3274-3276. DOI: 10.1007/s10803-014-2163-1.

Gillberg, I. C.; Gillberg, C. (1989): Asperger syndrome-some epidemiological considerations: a research note. In: *J Child Psychol Psychiatry* 30, pp. 631-638.

Gjevik, Elen; Eldevik, Sigmund; Fjæran-Granum, Torill; Sponheim, Eili (2011): Kiddie-SADS Reveals High Rates of DSM-IV Disorders in Children and Adolescents with Autism Spectrum Disorders. In: *J Autism Dev Disord* 41 (6), pp. 761-769. DOI: 10.1007/s10803-010-1095-7.

Glasberg, B. A. (2000): The development of siblings' understanding of autism spectrum disorders. In: *J Autism Dev Disord* 30 (2), pp. 143-156.

Glasson, E J; Bower, C; Petterson, B; de Klerk, N; Chaney, G; Hallmayer, J F (2004): Perinatal factors and the development of autism: a population study. In: *Arch Gen Psychiatry* 61 (6), pp. 618-627.

Golding, Jean; Steer, Colin; Pembrey, Marcus; Wang, Chenxi (2010): Parental and Grandparental Ages in the Autistic Spectrum Disorders: A Birth Cohort Study. In: *PLoS ONE* 5 (4), p. e9939. DOI: 10.1371/journal.pone.0009939.

Goldstein, Sam; Schwebach, Adam J. (2004): The Comorbidity of Pervasive Developmental Disorder and Attention Deficit Hyperactivity Disorder: Results of a Retrospective Chart Review. In: *J Autism Dev Disord* 34 (3), pp. 329-339. DOI: 10.1023/B:JADD.0000029554.46570.68.

Gotham, Katherine; Risi, Susan; Dawson, Geraldine; Tager-Flusberg, Helen; JOSEPH, ROBERT; CARTER, ALICE et al. (2008): A Replication of the Autism Diagnostic Observation Schedule (ADOS) Revised Algorithms. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 47 (6), pp. 642-651. DOI: 10.1097/CHI.0b013e31816bffb7.

Gotham, Katherine; Risi, Susan; Pickles, Andrew; Lord, Catherine (2007): The Autism Diagnostic Observation Schedule: Revised Algorithms for Improved Diagnostic Validity. In: *J Autism Dev Disord* 37 (4), pp. 613-627. DOI: 10.1007/s10803-006-0280-1.

Gray, Kylie M.; Tonge, Bruce J. (2005): Screening for autism in infants and preschool children with developmental delay. In: *Aust NZ J Psychiatry* 39 (5), pp. 378-386. DOI: 10.1080/j.1440-1614.2005.01585.x.

Gray, Kylie M.; Tonge, Bruce J.; Sweeney, Deborah J. (2008): Using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule with Young Children with Developmental Delay: Evaluating Diagnostic Validity. In: *J Autism Dev Disord* 38 (4), pp. 657-667. DOI: 10.1007/s10803-007-0432-y.

Green, Dido; Charman, Tony; Pickles, Andrew; Chandler, Susie; Loucas, Tom; Simonoff, Emily; Baird, Gillian (2009): Impairment in movement skills of children with autistic spectrum disorders. In: *Developmental Medicine & Child Neurology* 51 (4), pp. 311-316. DOI: 10.1111/j.1469-8749.2008.03242.x.

Grob A, Meyer CS, Hagmann-von Arx P (2013a) Intelligence and Development Scales. Intelligence and development scales for children 5-10 years. Hans Huber, Bern

Grob A, Reimann G, Frischknecht M-C, Gut J (2013b) Intelligence and Development Scale - preschool. Intelligence and development scales for preschool age. Hans Huber, Bern

Guttmann-Steinmetz, Sarit; Gadow, Kenneth D.; DeVincent, Carla J.; Crowell, Judy (2010): Anxiety Symptoms in Boys with Autism Spectrum Disorder, Attention-Deficit Hyperactivity Disorder, or Chronic Multiple Tic Disorder and Community Controls. In: *J Autism Dev Disord* 40 (8), pp. 1006-1016. DOI: 10.1007/s10803-010-0950-x.

Haglund, N. G. S.; Kallen, K. B. M. (2011): Risk factors for autism and Asperger syndrome: Perinatal factors and migration. In: *Autism* 15 (2), pp. 163-183. DOI: 10.1177/1362361309353614.

Hallmayer, Joachim; Cleveland, S; Torres, A; Phillips, J; Cohen, B; Torigoe, T et al. (2011): Genetic Heritability and Shared Environmental Factors Among Twin Pairs With Autism. In: *Arch Gen Psychiatry* 68 (11), p. 1095. DOI: 10.1001/archgenpsychiatry.2011.76.

Hansen, Stefan N.; Schendel, Diana E.; Parner, Erik T. (2015): Explaining the Increase in the Prevalence of Autism Spectrum Disorders. In: *JAMA Pediatr* 169 (1), pp. 56-62. DOI: 10.1001/jamapediatrics.2014.1893.

Harari, Hagai; Shamay-Tsoory, Simone G.; Ravid, Milli; Levkovitz, Yechiel (2010): Double dissociation between cognitive and affective empathy in borderline personality disorder. In: *Psychiatry Research* 175 (3), pp. 277-279. DOI: 10.1016/j.psychres.2009.03.002.

Hartley, S. L.; Sikora, D. M.; McCoy, R. (2008): Prevalence and risk factors of maladaptive behaviour in young children with autistic disorder. In: *Journal of Intellectual Disability Research* 52 (10), pp. 819-829. DOI: 10.1111/j.1365-2788.2008.01065.x.

Hastings, Richard P. (2003): Behavioral adjustment of siblings of children with autism. In: *J Autism Dev Disord* 33 (1), pp. 99-104. DOI: 10.1023/A:1022290723442.

Head, Lara S.; Abbeduto, Leonard (2007): Recognizing the role of parents in developmental outcomes: a systems approach to evaluating the child with developmental disabilities. In: *Mental retardation and developmental disabilities research reviews* 13 (4), pp. 293-301. DOI: 10.1002/mrdd.20169.

Heller, Theodor (1908): Uber dementia infantilis. In: *Z Erforsch Behandl Jugndl Schwachsinns* 2, S. 17-28.

Henderson, S E; Sugden, D A (1992): The Movement Assessment Battery for Children. London, UK: The Psychological Corporation.

Herring, Eli; Epstein, Rachel; Elroy, Sarit; Iancu, Daisy R.; Zelnik, Nathanel (1999): Sleep patterns in autistic children. In: *Journal of Autism and Developmental Disorders* 29 (2), pp. 143-147. DOI: 10.1023/A:1023092627223.

Herring, S.; Gray, K.; Taffe, J.; Tonge, B.; Sweeney, D.; Einfeld, S. (2006): Behaviour and emotional problems in toddlers with pervasive developmental disorders and developmental delay: associations with parental mental health and family functioning. In: *Journal of intellectual disability research : JIDR* 50 (Pt 12), pp. 874-882. DOI: 10.1111/j.1365-2788.2006.00904.x.

Hodge, Nick (2005): Reflections on diagnosing autism spectrum disorders. In: *Disability & Society* 20 (3), pp. 345-349. DOI: 10.1080/09687590500060810.

Hoffmann, Thomas J.; Windham, Gayle C.; Anderson, Meredith; Croen, Lisa A.; Grether, Judith K.; Risch, Neil (2014): Evidence of Reproductive Stoppage in Families With Autism Spectrum Disorder. In: *JAMA Psychiatry* 71 (8), pp. 943-951. DOI: 10.1001/jamapsychiatry.2014.420.

Hoffmann, Wiebke; Heinzel-Gutenbrunner, M; Becker, K; Kamp-Becker, Inge (in press): Screening of children and adolescents with high-functioning autism spectrum disorder using selected items of the ADI-R. In: *Journal of Child and Adolescent Psychiatry and Psychotherapy*.

Hoffmann, Wiebke; König, Udo; Heinzel-Gutenbrunner, Monika; Mattejat, Fritz; Becker, Katja; Kamp-Becker, Inge (2013): Early identification of Asperger syndrome in young children. In: *Research in Developmental Disabilities* 34 (1), pp. 640-649. DOI: 10.1016/j.ridd.2012.09.013.

Hofvander, Bjorn; Delorme, Richard; Chaste, Pauline; Nyden, Agneta; Wentz, Elisabet; Stahlberg, Ola et al. (2009): Psychiatric and psychosocial problems in adults with normal-intelligence autism spectrum disorders. In: *BMC Psychiatry* 9 (1), p. 35. DOI: 10.1186/1471-244X-9-35.

Homer, Michelle; Rutherford, M. D. (2008): Individuals with Autism can Categorize Facial Expressions. In: *Child Neuropsychology* 14 (5), pp. 419-437. DOI: 10.1080/09297040802291715.

Honda, Hideo; Shimizu, Yasuo; Nitto, Yukari; Imai, Miho; Ozawa, Takeshi; Iwasa, Mitsuaki et al. (2009): Extraction and Refinement Strategy for detection of autism in 18-month-olds: a guarantee of higher sensitivity and specificity in the process of mass screening. In: *Journal of Child Psychology and Psychiatry* 50 (8), pp. 972-981. DOI: 10.1111/j.1469-7610.2009.02055.x.

Honda, Hideo; Shimizu, Yasuo; Rutter, Michael (2005): No effect of MMR withdrawal on the incidence of autism: a total population study. In: *J Child Psychol & Psychiat* 46 (6), pp. 572-579. DOI: 10.1111/j.1469-7610.2005.01425.x.

Howlin, P; Asgharian, A (1999): The diagnosis of autism and Asperger syndrome: findings from a survey of 770 families. In: *Dev Med Child Neurol* 41 (12), pp. 834-839.

Howlin, P. (1997): Prognosis in autism: do specialist treatments affect long-term outcome? In: *European Child & Adolescent Psychiatry* 6 (2), pp. 55-72. DOI: 10.1007/BF00566668.

Howlin, Patricia (2003): Outcome in high-functioning adults with autism with and without early language delays: implications for the differentiation between autism and Asperger syndrome. In: *Journal of Autism and Developmental Disorders* 33 (1), pp. 3-13. DOI: 10.1023/A:1022270118899.

Howlin, Patricia; Goode, Susan; Hutton, Jane; Rutter, Michael (2004): Adult outcome for children with autism. In: *J Child Psychol & Psychiat* 45 (2), pp. 212-229. DOI: 10.1111/j.1469-7610.2004.00215.x.

Howlin, Patricia; Mawhood, Lynn; Rutter, Michael (2000): Autism and Developmental Receptive Language Disorder-a Follow-up Comparison in Early Adult Life. II: Social, Behavioural, and Psychiatric Outcomes. In: *J Child Psychol & Psychiat* 41 (5), pp. 561-578. DOI: 10.1111/1469-7610.00643.

Hultman, C M; Sandin, S; Levine, S Z; Lichtenstein, P; Reichenberg, A (2011): Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. In: *Mol Psychiatry* 16 (12), pp. 1203-1212.

Hultman, C M; Sparén, p; Cnattingius, S (2002): Perinatal risk factors for infantile autism. In: *Epidemiology* 13 (4), pp. 417-423.

Hurst, Ruth M.; Nelson-Gray, Rosemery O.; Mitchell, John T.; Kwapil, Thomas R. (2007): The Relationship of Asperger's Characteristics and Schizotypal Personality Traits in a Non-clinical Adult Sample. In: *J Autism Dev Disord* 37 (9), pp. 1711-1720. DOI: 10.1007/s10803-006-0302-z.

Hus V1, Gotham K, Lord C. (2014). Standardizing ADOS domain scores: separating severity of social affect and restricted and repetitive behaviors. *Journal of autism and developmental disorders*, 44(10), 2400-2412.

Ibanez, L. V.; Messinger, D. S.; Newell, L.; Lambert, B.; Sheskin, M. (2008): Visual disengagement in the infant siblings of children with an autism spectrum disorder (ASD). In: *Autism* 12 (5), pp. 473-485. doi: 10.1177/1362361308094504.

Ibrahim, S. H.; Voigt, R. G.; Katusic, S. K.; Weaver, A. L.; Barbaresi, W. J. (2009): Incidence of Gastrointestinal Symptoms in Children With Autism: A Population-Based Study. In: *PEDIATRICS* 124 (2), pp. 680-686. DOI: 10.1542/peds.2008-2933.

Idring, Selma; Rai, Dheeraj; Dal, Henrik; Dalman, Christina; Sturm, Harald; Zander, Eric et al. (2012): Autism Spectrum Disorders in the Stockholm Youth Cohort: Design, Prevalence and Validity. In: *PLoS ONE* 7 (7), p. e41280. DOI: 10.1371/journal.pone.0041280.

Jacobi, Frank; Höfler, Michael; Siegert, Jens; Mack, Simon; Gerschler, Anja; Scholl, Lucie et al. (2014): Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: the Mental Health Module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). In: *Int. J. Methods Psychiatr. Res.* 23 (3), pp. 304-319. DOI: 10.1002/mpr.1439.

Ji, N. Y.; Capone, G. T.; Kaufmann, W. E. (2011): Autism spectrum disorder in Down syndrome: cluster analysis of Aberrant Behaviour Checklist data supports diagnosis. In: *J Intellect Disabil Res* 55 (11), pp. 1064-1077.

Johnson, S.; Hollis, C.; Hennessy, E.; Kochhar, P.; Wolke, D.; Marlow, N. (2010): Screening for autism in preterm children: diagnostic utility of the Social Communication Questionnaire. In: *Archives of disease in childhood* 96 (1), pp. 73-77. DOI: 10.1136/adc.2010.194795.

Jones, Alice P.; Happé, Francesca G.E.; Gilbert, Francesca; Burnett, Stephanie; Viding, Essi (2010): Feeling, caring, knowing: different types of empathy deficit in boys with psychopathic tendencies and autism spectrum disorder. In: *Journal of Child Psychology and Psychiatry* 51 (11), pp. 1188-1197. DOI: 10.1111/j.1469-7610.2010.02280.x.

Jones, Warren; Carr, Katelin; Klin, Ami (2008): Absence of Preferential Looking to the Eyes of Approaching Adults Predicts Level of Social Disability in 2-Year-Old Toddlers With Autism Spectrum Disorder. In: *Arch Gen Psychiatry* 65 (8), p. 946. DOI: 10.1001/archpsyc.65.8.946.

Jones, Warren; Klin, Ami (2013): Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. In: *Nature* 504 (7480), pp. 427-431. DOI: 10.1038/nature12715.

Joshi, Gagan; Wozniak, Janet; Petty, Carter; Martelon, Mary Kate; Fried, Ronna; Bolfek, Anela et al. (2013): Psychiatric Comorbidity and Functioning in a Clinically Referred Population of Adults with Autism Spectrum Disorders: A Comparative Study. In: *J Autism Dev Disord* 43 (6), pp. 1314-1325. DOI: 10.1007/s10803-012-1679-5.

Kamio, Y. (2002): Self-injurious and aggressive behavior in adolescents with intellectual disabilities: A comparison of adolescents with and without autism. In: *Japanese Journal of Special Education* 39 (6), pp. 143-154.

Kamp-Becker, I.; Ghahreman, M.; Heinzel-Gutenbrunner, M.; Peters, M.; Remschmidt, H.; Becker, K. (2013): Evaluation of the revised algorithm of Autism Diagnostic Observation Schedule (ADOS) in the diagnostic

investigation of high-functioning children and adolescents with autism spectrum disorders. In: *Autism* 17 (1), pp. 87-102. DOI: 10.1177/1362361311408932.

Kamp-Becker, Inge; Ghahreman, Mardjan; Smidt, Judith; Remschmidt, Helmut (2009): Dimensional Structure of the Autism Phenotype: Relations Between Early Development and Current Presentation. In: *J Autism Dev Disord* 39 (4), pp. 557-571. DOI: 10.1007/s10803-008-0656-5.

Kamp-Becker, Inge; Mattejat, Fritz; Wolf-Ostermann, Karin; Remschmidt, Helmut (2005): Die Marburger Beurteilungsskala zum Asperger-Syndrom (MBAS) - ein Screening-Verfahren für autistische Störungen auf hohem Funktionsniveau. In: *Journal of Child and Adolescent Psychiatry and Psychotherapy* 33 (1), pp. 15-26. DOI: 10.1024/1422-4917.33.1.15.

Kamp-Becker, Inge; Smidt, Judith; Ghahreman, Mardjan; Heinzel-Gutenbrunner, Monika; Becker, Katja; Remschmidt, Helmut (2010a): Categorical and Dimensional Structure of Autism Spectrum Disorders: The Nosologic Validity of Asperger Syndrome. In: *J Autism Dev Disord* 40 (8), pp. 921-929. DOI: 10.1007/s10803-010-0939-5.

Kamp-Becker, Inge; Wulf, Claudia; Bachmann, Christian J.; Ghahreman, Mardjan; Heinzel-Gutenbrunner, Monika; Gerber, Gerti et al. (2010b): Frühsymptome des Asperger-Syndroms im Kindesalter. In: *Childhood and Development* 19 (3), pp. 168-176. DOI: 10.1026/0942-5403/a000021.

Kanner, L. (1943): Autistic disturbances of affective contact. In: *Nervous Child* 2, pp. 217-250.

Kanner, L. (1973): Childhood Psychosis: Initial Studies and New Insights. New York: Winston/Wiley.

Kapp, Steven K.; Gillespie-Lynch, Kristen; Sherman, Lauren E.; Hutman, Ted (2013): Deficit, difference, or both? Autism and neurodiversity. In: *Developmental Psychology* 49 (1), pp. 59-71. DOI: 10.1037/a0028353.

Karst, Jeffrey S.; Van Hecke, Amy Vaughan (2012): Parent and family impact of autism spectrum disorders: a review and proposed model for intervention evaluation. In: *Clin Child Fam Psychol Rev* 15 (3), pp. 247-277. DOI: 10.1007/s10567-012-0119-6.

Kawamura, Yuichi; Takahashi, Osamu; Ishii, Takashi (2008): Reevaluating the incidence of pervasive developmental disorders: Impact of elevated rates of detection through implementation of an integrated system of screening in Toyota, Japan. In: *Psychiatry Clin Neurosci* 62 (2), pp. 152-159. DOI: 10.1111/j.1440-1819.2008.01748.x.

Keil, Alexander; Daniels, Julie L.; Forssen, Ulla; Hultman, Christina; Cnattingius, Sven; Söderberg, Karin C. et al. (2010): Parental Autoimmune Diseases Associated With Autism Spectrum Disorders in Offspring. In: *Epidemiology* 21 (6), pp. 805-808. DOI: 10.1097/EDE.0b013e3181f26e3f.

Kielinen, Marko; Rantala, Heikki; Timonen, Eija; Linna, Sirkka-Liisa; Moilanen, Irma (2004): Associated Medical Disorders and Disabilities in Children with Autistic Disorder: A Population-based Study. In: *autism* 8 (1), pp. 49-60. DOI: 10.1177/1362361304040638.

Kim, J. A.; Szatmari, P.; Bryson, S. E.; Streiner, D. L.; Wilson, F. J. (2000): The Prevalence of Anxiety and Mood Problems among Children with Autism and Asperger Syndrome. In: *Autism* 4 (2), pp. 117-132. DOI: 10.1177/1362361300004002002.

Kim, So Hyun; Lord, Catherine (2012a): Combining information from multiple sources for the diagnosis of autism spectrum disorders for toddlers and young preschoolers from 12 to 47 months of age. In: *Journal of Child Psychology and Psychiatry* 53 (2), pp. 143-151. DOI: 10.1111/j.1469-7610.2011.02458.x.

Kim, So Hyun; Lord, Catherine (2012b): New Autism Diagnostic Interview-Revised Algorithms for Toddlers and Young Preschoolers from 12 to 47 Months of Age. In: *J Autism Dev Disord* 42 (1), pp. 82-93. DOI: 10.1007/s10803-011-1213-1.

Kim, So Hyun; Thurm, Audrey; Shumway, Stacy; Lord, Catherine (2013): Multisite Study of New Autism Diagnostic Interview-Revised (ADI-R) Algorithms for Toddlers and Young Preschoolers. In: *J Autism Dev Disord* 43 (7), pp. 1527-1538. DOI: 10.1007/s10803-012-1696-4.

Kim, Young Shin; Leventhal, Bennett L. (2015): Genetic Epidemiology and Insights into Interactive Genetic and Environmental Effects in Autism Spectrum Disorders. In: *Biological Psychiatry* 77 (1), pp. 66-74. DOI: 10.1016/j.biopsych.2014.11.001.

Kim, Young Shin; Leventhal, Bennett L.; Koh, Yun-Joo; Fombonne, Eric; Laska, Eugene; Lim, Eun-Chung et al. (2011): Prevalence of Autism Spectrum Disorders in a Total Population Sample. In: *AJP* 168 (9), pp. 904-912. DOI: 10.1176/appi.ajp.2011.10101532.

King, Claire; Murphy, Glynis H. (2014): A Systematic Review of People with Autism Spectrum Disorder and the Criminal Justice System. In: *J Autism Dev Disord* 44 (11), pp. 2717-2733. DOI: 10.1007/s10803-014-2046-5.

Kirby, Russell S.; Wingate, Martha S.; Van Naarden Braun, Kim; Doernberg, Nancy S.; Arneson, Carrie L.; Benedict, Ruth E. et al. (2011): Prevalence and functioning of children with cerebral palsy in four areas of the United States in 2006: A report from the Autism and Developmental Disabilities Monitoring Network. In: *Research in Developmental Disabilities* 32 (2), pp. 462-469. DOI: 10.1016/j.ridd.2010.12.042.

Kitzerow, Janina; Teufel, Karoline; Wilker, Christian; Freitag, Christine M. (2015): Using the brief observation of social communication change (BOSCC) to measure autism-specific development. In: Autism Research, pp. n/a-n/a. DOI: 10.1002/aur.1588.

Kitzerow, Janina; Wilker, Christian; Teufel, Karoline; Soll, Sophie; Schneider, Monika; Westerwald, Eva et al. (2014): Das Frankfurter Frühinterventionsprogramm (FFIP) für Vorschulkinder mit Autismus-Spektrum-Störungen (ASS). In: *Childhood and Development* 23 (1), pp. 34-41. DOI: 10.1026/0942-5403/a000133.

Kleinman, Jamie M.; Ventola, Pamela E.; Pandey, Juhi; Verbalis, Alyssa D.; Barton, Marianne; Hodgson, Sarah et al. (2008): Diagnostic Stability in Very Young Children with Autism Spectrum Disorders. In: *J Autism Dev Disord* 38 (4), pp. 606-615. DOI: 10.1007/s10803-007-0427-8.

Klin, A.; Volkmar, F. R. (2003): Asperger syndrome: diagnosis and external validity. In: *Child Adolesc Psychiatr Clin N Am* 12, pp. 1-13.

Koelkebeck, K.; Riedel, A.; Ohrmann, P.; Biscaldi, M.; Tebartz van Elst, L. (2014): Autism spectrum disorders with high functioning in adulthood. In: *Nervenarzt* 85 (7), pp. 891-902. DOI: 10.1007/s00115-014-4050-6.

Kogan, M. D.; Blumberg, S. J.; Schieve, L. A.; Boyle, C. A.; Perrin, J. M.; Ghandour, R. M. et al. (2009): Prevalence of Parent-Reported Diagnosis of Autism Spectrum Disorder Among Children in the U.S., 2007. In: *PEDIATRICS* 124 (5), pp. 1395-1403. DOI: 10.1542/peds.2009-1522.

Kohane, Isaac S.; McMurry, Andrew; Weber, Griffin; MacFadden, Douglas; Rappaport, Leonard; Kunkel, Louis et al. (2012): The Co-Morbidity Burden of Children and Young Adults with Autism Spectrum Disorders. In: *PLoS ONE* 7 (4), p. e33224. DOI: 10.1371/journal.pone.0033224.

Krakowiak, P.; Goodlin-Jones, B.; Hertz-Picciotto, I.; Croen, L. A.; Hansen, R. L. (2008): Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: a population-based study. In: *J Sleep Res* 17 (2), pp. 197-206. DOI: 10.1111/j.1365-2869.2008.00650.x.

Krakowiak, P.; Walker, C. K.; Bremer, A. A.; Baker, A. S.; Ozonoff, S.; Hansen, R. L.; Hertz-Picciotto, I. (2012): Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders. In: *PEDIATRICS* 129 (5), pp. e1121-e1128. DOI: 10.1542/peds.2011-2583.

Kröger, Anne; Hänig, Susann; Seitz, Christiane; Palmason, Haukur; Meyer, Jobst; Freitag, Christine M. (2011): Risk factors of autistic symptoms in children with ADHD. In: *Eur Child Adolesc Psychiatry* 20 (11-12), pp. 561-570. DOI: 10.1007/s00787-011-0221-1.

Kuddo, T.; Nelson, K. B.. (2003): How common are gastrointestinal disorders in children with autism? In: *Curr Opin Pediatr* 15 (3), pp. 339-343.

Kulage, Kristine M.; Smaldone, Arlene M.; Cohn, Elizabeth G. (2014): How Will DSM-5 Affect Autism Diagnosis? A Systematic Literature Review and Meta-analysis. In: *J Autism Dev Disord* 44 (8), pp. 1918-1932. DOI: 10.1007/s10803-014-2065-2.

Lai, Meng-Chuan; Baron-Cohen, Simon; Buxbaum, Joseph D. (2015): Understanding autism in the light of sex/gender. In: *Molecular Autism* 6 (1), p. 90. DOI: 10.1186/s13229-015-0021-4.

Lai, Meng-Chuan; Lombardo, Michael V.; Auyeung, Bonnie; Chakrabarti, Bhismadev; Baron-Cohen, Simon (2014): Sex/Gender Differences and Autism: Setting the Scene for Future Research. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 54 (1), pp. 11-24. DOI: 10.1016/j.jaac.2014.10.003.

Lampi, Katja M.; Lehtonen, Liisa; Tran, Phuong Lien; Suominen, Auli; Lehti, Venla; Banerjee, P. Nina et al. (2012): Risk of Autism Spectrum Disorders in Low Birth Weight and Small for Gestational Age Infants. In: *The Journal of Pediatrics* 161 (5), pp. 830-836. DOI: 10.1016/j.jpeds.2012.04.058.

Landa, Rebecca; Garrett-Mayer, Elizabeth (2006): Development in infants with autism spectrum disorders: a prospective study. In: *J Child Psychol & Psychiat* 47 (6), pp. 629-638. DOI: 10.1111/j.1469-7610.2006.01531.x.

Landa, Rebecca J.; Holman, Katherine C.; Garrett-Mayer, Elizabeth (2007): Social and Communication Development in Toddlers With Early and Later Diagnosis of Autism Spectrum Disorders. In: *Arch Gen Psychiatry* 64 (7), p. 853. DOI: 10.1001/archpsyc.64.7.853.

Latif, A.H.A.; Williams, W. R. (2007): Diagnostic trends in autistic spectrum disorders in the South Wales valleys. In: *Autism* 11 (6), pp. 479-487. DOI: 10.1177/1362361307083256.

Lauritsen, M. B.; Pedersen, C. B.; Mortensen, P. B. (2004): The incidence and prevalence of pervasive developmental disorders: a Danish population-based study. In: *Psychol. Med.* 34 (7), pp. 1339-1346. DOI: 10.1017/S0033291704002387.

Le Couteur, Ann; Haden, Gyles; Hammal, Donna; McConachie, Helen (2008): Diagnosing Autism Spectrum Disorders in Pre-school Children Using Two Standardised Assessment Instruments: The ADI-R and the ADOS. In: *J Autism Dev Disord* 38 (2), pp. 362-372. DOI: 10.1007/s10803-007-0403-3.

Le Couteur, Ann Le (2003): National Autism Plan for Children (NAPC): Plan for the Identification, Assessment, Diagnosis and Access to Early Interventions for Pre-School to Primary School Aged Children with Autism Spectrum Disorders (ASD). Ed. by National Initiative for Autism: Available online at http://iier.isciii.es/autismo/pdf/aut_napc.pdf, last checked 04.09.2015.

Lee, L C; Zachary, A A; Leffell, M S; Newschaffer, C J; Matteson, K J; Tyler, J D; Zimmerman, A W (2006): HLA-DR4 in families with autism. In: *Pediatr Neurol* 35 (5), pp. 303-307.

Leekam, S.; Libby, S.; Wing, L.; Gould, J.; Gillberg, C. (2000): Comparison of ICD-10 and Gillberg's Criteria for Asperger Syndrome. In: *Autism* 4 (1), pp. 11-28. DOI: 10.1177/1362361300004001002.

Lehnhardt, F. G.; Gawronski, A.; Pfeiffer, K.; Kockler, H.; Schilbach, L.; Vogeley, K. (2013): The investigation and differential diagnosis of Asperger syndrome in adults. In: *Deutsches Arzteblatt international* 110 (45), pp. 755-763.

Lemcke, Sanne; Juul, Svend; Parner, Erik T.; Lauritsen, Marlene B.; Thorsen, Poul (2013): Early Signs of Autism in Toddlers: A Follow-Up Study in the Danish National Birth Cohort. In: *J Autism Dev Disord* 43 (10), pp. 2366-2375. doi: 10.1007/s10803-013-1785-z.

Levy, Susan E.; Giarelli, Ellen; Lee, Li-Ching; Schieve, Laura A.; Kirby, Russell S.; Cunniff, Christopher et al. (2010): Autism Spectrum Disorder and Co-occurring Developmental, Psychiatric, and Medical Conditions Among Children in Multiple Populations of the United States. In: *Journal of Developmental & Behavioral Pediatrics* 31 (4), pp. 267-275. DOI: 10.1097/DBP.0b013e3181d5d03b.

Leyfer, Ovsanna T.; Folstein, Susan E.; Bacalman, Susan; Davis, Naomi O.; Dinh, Elena; Morgan, Jubel et al. (2006): Comorbid Psychiatric Disorders in Children with Autism: Interview Development and Rates of Disorders. In: *J Autism Dev Disord* 36 (7), pp. 849-861. DOI: 10.1007/s10803-006-0123-0.

Lichtenstein, Paul; Carlström, Eva; Råstam, Maria; Gillberg, Christopher; Anckarsäter, Henrik (2010): The Genetics of Autism Spectrum Disorders and Related Neuropsychiatric Disorders in Childhood. In: *AJP* 167 (11), pp. 1357-1363. DOI: 10.1176/appi.ajp.2010.10020223.

Lindquist, Barbro; Carlsson, Göran; Persson, Eva-Karin; Uvebrant, Paul (2006): Behavioural problems and autism in children with hydrocephalus. In: *Eur Child Adolesc Psychiatry* 15 (4), pp. 214-219. DOI: 10.1007/s00787-006-0525-8.

Lord, C; Bailey, A (2002): Autism spectrum disorders. In: M. Rutter and E. Taylor (eds): Child and adolescent psychiatry. 4th ed. Oxford: Blackwell Scientific, pp. 664-681.

Lord, Catherine (1995): Follow-Up of Two-Year-Olds Referred for Possible Autism. In: *Journal of Child Psychology and Psychiatry* 36 (8), pp. 1365-1382. DOI: 10.1111/j.1469-7610.1995.tb01669.x.

Lord, Catherine (2012): A Multisite Study of the Clinical Diagnosis of Different Autism Spectrum Disorders. In: *Arch Gen Psychiatry* 69 (3), p. 306. DOI: 10.1001/archgenpsychiatry.2011.148.

Lord, Catherine; Risi, Susan; Lambrecht, Linda; Cook, Jr., Edwin H.; Leventhal, Bennett L.; DiLavore, Pamela C. et al. (2000): The Autism Diagnostic Observation schedule - Generic. A Standard Measure of Social and Communication Deficits Associated with the Spectrum of Autism. In: *Journal of Autism and Developmental Disorders* 30 (3), pp. 205-223. DOI: 10.1023/A:1005592401947.

Lord, Catherine; Rutter, Michael; Le Couteur, Ann (1994): Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. In: *Journal of Autism and Developmental Disorders* 25 (4), pp. 659-685.

Ludlow, Amanda; Skelly, Charlotte; Rohleder, Poul (2012): Challenges faced by parents of children diagnosed with autism spectrum disorder. In: *Journal of health psychology* 17 (5), pp. 702-711. DOI: 10.1177/1359105311422955.

Lugnegård, Tove; Hallerbäck, Maria Unenge; Gillberg, Christopher (2011): Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. In: *Research in Developmental Disabilities* 32 (5), pp. 1910-1917. DOI: 10.1016/j.ridd.2011.03.025.

Lugnegård, Tove; Hallerbäck, Maria Unenge; Gillberg, Christopher (2012): Personality disorders and autism spectrum disorders: what are the connections? In: *Comprehensive Psychiatry* 53 (4), pp. 333-340. DOI: 10.1016/j.comppsych.2011.05.014.

Lundström, S.; Chang, Z.; Kerekes, N.; Gumpert, C. H.; Råstam, M.; Gillberg, C. et al. (2011): Autistic-like traits and their association with mental health problems in two nationwide twin cohorts of children and adults. In: *Psychological Medicine* 41 (11), pp. 2423-2433. doi: 10.1017/S0033291711000377.

Lundström, Sebastian (2012): Autism Spectrum Disorders and Autisticlike Traits. In: *Arch Gen Psychiatry* 69 (1), p. 46. DOI: 10.1001/archgenpsychiatry.2011.144.

Luyster, Rhiannon; Gotham, Katherine; Guthrie, Whitney; Coffing, Mia; Petrak, Rachel; Pierce, Karen et al. (2009): The Autism Diagnostic Observation Schedule-Toddler Module: A New Module of a Standardized Diagnostic Measure for Autism Spectrum Disorders. In: *J Autism Dev Disord* 39 (9), pp. 1305-1320. DOI: 10.1007/s10803-009-0746-z.

Macks, Ryan J.; Reeve, Ronald E. (2007): The adjustment of non-disabled siblings of children with autism. In: *J Autism Dev Disord* 37 (6), pp. 1060-1067. DOI: 10.1007/s10803-006-0249-0.

Maenner, Matthew J.; Arneson, Carrie L.; Levy, Susan E.; Kirby, Russell S.; Nicholas, Joyce S.; Durkin, Maureen S. (2012): Brief Report: Association Between Behavioral Features and Gastrointestinal Problems Among Children with Autism Spectrum Disorder. In: *J Autism Dev Disord* 42 (7), pp. 1520-1525. DOI: 10.1007/s10803-011-1379-6.

Maestro, S.; Muratori, F.; Cesari, A.; Cavallaro, M. C.; Paziente, A.; Pecini, C. et al. (2005): Course of Autism Signs in the First Year of Life. In: *Psychopathology* 38 (1), pp. 26-31. DOI: 10.1159/000083967.

Magnusson, C.; Rai, D.; Goodman, A.; Lundberg, M.; Idring, S.; Svensson, A. et al. (2012): Migration and autism spectrum disorder: population-based study. In: The *British Journal of Psychiatry* 201 (2), pp. 109-115. DOI: 10.1192/bjp.bp.111.095125.

Magnússon, Páll; Saemundsen, Evald (2001): Prevalence of autism in Iceland. In: *Journal of Autism and Developmental Disorders* 31 (2), pp. 153-163. DOI: 10.1023/A:1010795014548.

Mahoney, W. J.; Szatmari, P.; MacLean, J. E.; Bryson, S. E.; Bartolucci, G.; Walter, S. D. et al. (1998): Reliability and accuracy of differentiating pervasive developmental disorder subtypes. In: *Journal of the American Academy of Child and Adolescent Psychiatry* 37 (3), pp. 278-285. DOI: 10.1097/00004583-199803000-00012.

Maimburg, R. D.; Vaeth, M. (2006): Perinatal risk factors and infantile autism. In: *Acta Psychiatr Scand* 114 (4), pp. 257-264. DOI: 10.1111/j.1600-0447.2006.00805.x.

Maimburg, Rikke Damkjaer; Vaeth, Michael; Schendel, Diana Elizabeth; Bech, Bodil Hammer; Olsen, Jørn; Thorsen, Poul (2008): Neonatal jaundice: a risk factor for infantile autism? In: *Paediatric and Perinatal Epidemiology* 22 (6), pp. 562-568. DOI: 10.1111/j.1365-3016.2008.00973.x.

Maljaars, J.; Noens, I.; Scholte, E.; van Berckelaer-Onnes, I. (2012): Evaluation of the criterion and convergent validity of the Diagnostic Interview for Social and Communication Disorders in young and low-functioning children. In: *Autism* 16 (5), pp. 487-497. DOI: 10.1177/1362361311402857.

Mandell, David S.; Walrath, Christine M.; Manteuffel, Brigitte; Sgro, Gina; Pinto-Martin, Jennifer A. (2005): The prevalence and correlates of abuse among children with autism served in comprehensive community-based mental health settings. In: *Child Abuse & Neglect* 29 (12), pp. 1359-1372. DOI: 10.1016/j.chiabu.2005.06.006.

Mandy, William; Charman, Tony; Gilmour, Jane; Skuse, David (2011): Toward specifying pervasive developmental disorder-not otherwise specified. In: *Autism Res* 4 (2), pp. 121-131. DOI: 10.1002/aur.178.

Margari, Lucia; Buttiglione, Maura; Legrottaglie, Anna R.; Presicci, Anna; Craig, Francesco; Curatolo, Paolo (2012): Neuropsychiatric impairment in children with Continuous Spikes and Waves during slow Sleep: A long-term follow-up study. In: *Epilepsy & Behavior* 25 (4), pp. 558-562. doi: 10.1016/j.yebeh.2012.08.007.

Matson, J L; Smiroldo, B B; Hastings, T L (1998): Validity of the autism/pervasive developmental disorder subscale of the Diagnostic Assessment for the Severely Handicapped-II. In: *Journal of Autism and Developmental Disorders* 28 (1), pp. 77-81.

Matson, Johnny L.; Boisjoli, Jessica; Rojahn, Johannes; Hess, Julie (2009): A factor analysis of challenging behaviors assessed with the Baby and Infant Screen for Children with aUtism Traits (BISCUIT-Part 3). In: *Research in Autism Spectrum Disorders* 3 (3), pp. 714-722. DOI: 10.1016/j.rasd.2009.01.008.

Matson, Johnny L.; Dempsey, Timothy; Rivet, Tessa (2008a): A comparison of Asperger symptom rating scales with children and adolescents. In: *Research in Autism Spectrum Disorders* 2 (4), pp. 643-650. DOI: 10.1016/j.rasd.2008.01.001.

Matson, Johnny L.; Wilkins, Jonathan; Ancona, Martin (2008b): Autism in adults with severe intellectual disability: An empirical study of symptom presentation. In: *J Intellect Dev Dis* 33 (1), pp. 36-42. DOI: 10.1080/13668250701829837.

Matson, Johnny L.; Wilkins, Jonathan; Boisjoli, Jessica A.; Smith, Kimberly R. (2008c): The validity of the autism spectrum disorders-diagnosis for intellectually disabled adults (ASD-DA). In: *Research in Developmental Disabilities* 29 (6), pp. 537-546. DOI: 10.1016/j.ridd.2007.09.006.

Mattila, Marja-Leena; Hurtig, Tuula; Haapsamo, Helena; Jussila, Katja; Kuusikko-Gauffin, Sanna; Kielinen, Marko et al. (2010): Comorbid Psychiatric Disorders Associated with Asperger Syndrome/High-functioning Autism: A Community- and Clinic-based Study. In: *J Autism Dev Disord* 40 (9), pp. 1080-1093. DOI: 10.1007/s10803-010-0958-2.

Mawhood, Lynn; Howlin, Patricia; Rutter, Michael (2000): Autism and Developmental Receptive Language Disorder-a Comparative Follow-up in Early Adult Life. I: Cognitive and Language Outcomes. In: *J Child Psychol & Psychiat* 41 (5), pp. 547-559. DOI: 10.1111/1469-7610.00642.

Mayes, Susan Dickerson; Calhoun, Susan L.; Mayes, Rebecca D.; Molitoris, Sarah (2012): Autism and ADHD: Overlapping and discriminating symptoms. In: *Research in Autism Spectrum Disorders* 6 (1), pp. 277-285. DOI: 10.1016/j.rasd.2011.05.009.

Mayes, Susan Dickerson; Calhoun, Susan L.; Murray, Michael J.; Morrow, Jill D.; Yurich, Kirsten K L; Mahr, Fauzia et al. (2009): Comparison of scores on the Checklist for Autism Spectrum Disorder, Childhood Autism Rating Scale, and Gilliam Asperger's Disorder Scale for children with low functioning autism, high functioning autism, Asperger's disorder, ADHD, and typical development. In: *Journal of Autism and Developmental Disorders* 39 (12), pp. 1682-1693. DOI: 10.1007/s10803-009-0812-6.

Mazefsky, C. A.; Oswald, D. P. (2006): The discriminative ability and diagnostic utility of the ADOS-G, ADI-R, and GARS for children in a clinical setting. In: *Autism* 10 (6), pp. 533-549. DOI: 10.1177/1362361306068505.

Mazefsky, Carla A.; Borue, Xenia; Day, Taylor N.; Minshew, Nancy J. (2014): Emotion Regulation Patterns in Adolescents With High-Functioning Autism Spectrum Disorder: Comparison to Typically Developing Adolescents and Association With Psychiatric Symptoms. In: *Autism Res* 7 (3), pp. 344-354. DOI: 10.1002/aur.1366.

Mazefsky, Carla A.; Conner, Caitlin M.; Oswald, Donald P. (2010): Association between depression and anxiety in high-functioning children with autism spectrum disorders and maternal mood symptoms. In: *Autism Res* 3 (3), pp. 120-127, DOI: 10.1002/aur.133.

Mazefsky, Carla A.; Herrington, John; Siegel, Matthew; Scarpa, Angela; Maddox, Brenna B.; Scahill, Lawrence; White, Susan W. (2013): The Role of Emotion Regulation in Autism Spectrum Disorder. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 52 (7), pp. 679-688. DOI: 10.1016/j.jaac.2013.05.006.

Mazefsky, Carla A.; Oswald, Donald P.; Day, Taylor N.; Eack, Shaun M.; Minshew, Nancy J.; Lainhart, Janet E. (2012): ASD, a Psychiatric Disorder, or Both? Psychiatric Diagnoses in Adolescents with High-Functioning ASD. In: *Journal of Clinical Child & Adolescent Psychology* 41 (4), pp. 516-523. DOI: 10.1080/15374416.2012.686102.

Mazzone, Luigi; Postorino, Valentina; Valeri, Giovanni; Vicari, Stefano (2014): Catatonia in Patients with Autism: Prevalence and Management. In: *CNS Drugs* 28 (3), pp. 205-215. DOI: 10.1007/s40263-014-0143-9.

Mazzone, Luigi; Ruta, Liliana; Reale, Laura (2012): Psychiatric comorbidities in asperger syndrome and high functioning autism: diagnostic challenges. In: *Ann Gen Psychiatry* 11 (1), p. 16. DOI: 10.1186/1744-859X-11-16.

McArthur, Duncan; Adamson, Lauren B. (1996): Joint attention in preverbal children: autism and developmental language disorder. In: *J Autism Dev Disord* 26 (5), pp. 481-496. DOI: 10.1007/BF02172271.

McConachie, Helen; Parr, Jeremy R.; Glod, Magdalena; Hanratty, Jennifer; Livingstone, Nuala; Oono, Inalegwu P. et al. (2015): Systematic review of tools to measure outcomes for young children with autism spectrum disorder. In: *Health technology assessment (Winchester, England)* 19 (41), pp. 1-506. DOI: 10.3310/hta19410.

McDermott, S.; Moran, R.; Platt, T.; Issac, T.; Wood, H.; Dasari, S. (2005): Depression in adults with disabilities, in primary care. In: *Disability & Rehabilitation* 27 (3), pp. 117-123.

McPartland, James C.; Reichow, Brian; Volkmar, Fred R. (2012): Sensitivity and Specificity of Proposed DSM-5 Diagnostic Criteria for Autism Spectrum Disorder. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 51 (4), pp. 368-383. DOI: 10.1016/j.jaac.2012.01.007.

Melfsen, Siebke; Walitza, Susanne; Attwood, Anthony; Warnke, Andreas (2005): Validation of the German version of the Australian Scale of Asperger's Syndrome (ASAS). In: *Journal of Child and Adolescent Psychiatry and Psychotherapy* 33 (1), pp. 27-34. DOI: 10.1024/1422-4917.33.1.27.

Melville, Craig A.; Cooper, Sally-Ann; Morrison, Jill; Smiley, Elita; Allan, Linda; Jackson, Alison et al. (2008): The Prevalence and Incidence of Mental Ill-Health in Adults with Autism and Intellectual Disabilities. In: *J Autism Dev Disord* 38 (9), pp. 1676-1688. DOI: 10.1007/s10803-008-0549-7.

Mercer, L.; Creighton, S.; Holden, J. J. A.; Lewis, M. E. S. (2006): Parental perspectives on the causes of an autism spectrum disorder in their children. In: *Journal of genetic counseling* 15 (1), pp. 41-50. DOI: 10.1007/s10897-005-9002-7.

Meyer-Lindenberg, Andreas; Tost, Heike (2012): Neural mechanisms of social risk for psychiatric disorders. In: *Nat Neurosci* 15 (5), pp. 663-668. DOI: 10.1038/nn.3083.

Miano, Silvia; Bruni, Oliviero; Elia, Maurizio; Trovato, Alessia; Smerieri, Arianna; Verrillo, Elisabetta et al. (2007): Sleep in children with autistic spectrum disorder: A questionnaire and polysomnographic study. In: *Sleep Medicine* 9 (1), pp. 64-70. DOI: 10.1016/j.sleep.2007.01.014.

Mildenberger, K.; Sitter, S.; Noterdaeme, M.; Amorosa, H. (2001): The use of the ADI-R as a diagnostic tool in the differential diagnosis of children with infantile autism and children with a receptive language disorder. In: *Eur Child Adolesc Psychiatry* 10 (4), pp. 248-255. DOI: 10.1007/s007870170014.

Miller, Judith N.; Ozonoff, Sally (2000): The external validity of Asperger disorder: Lack of evidence from the domain of neuropsychology. In: *Journal of Abnormal Psychology* 109 (2), pp. 227-238. DOI: 10.1037/0021-843X.109.2.227.

Milshtein, Shahaf; Yirmiya, Nurit; Oppenheim, David; Koren-Karie, Nina; Levi, Shlomit (2010): Resolution of the diagnosis among parents of children with autism spectrum disorder: associations with child and parent characteristics. In: *J Autism Dev Disord* 40 (1), pp. 89-99. DOI: 10.1007/s10803-009-0837-x.

Mizejewski, Gerald J.; Lindau-Shepard, Barbara; Pass, Kenneth A. (2013): Newborn screening for autism: in search of candidate biomarkers. In: *Biomarkers Med.* 7 (2), pp. 247-260. DOI: 10.2217/bmm.12.108.

Moh, Teresa Ailing; Magiati, Iliana (2012): Factors associated with parental stress and satisfaction during the process of diagnosis of children with Autism Spectrum Disorders. In: *Research in Autism Spectrum Disorders* 6 (1), pp. 293-303. DOI: 10.1016/j.rasd.2011.05.011.

Molloy, C. A.; Murray, D. S.; Akers, R.; Mitchell, T.; Manning-Courtney, P. (2011): Use of the Autism Diagnostic Observation Schedule (ADOS) in a clinical setting. In: *Autism* 15 (2), pp. 143-162. doi: 10.1177/1362361310379241.

Montes, Guillermo; Halterman, Jill S. (2008): Association of childhood autism spectrum disorders and loss of family income. In: *PEDIATRICS* 121 (4), p. e821-6. DOI: 10.1542/peds.2007-1594.

Montiel-Nava, C.; Pena, J. A. (2008): Epidemiological findings of pervasive developmental disorders in a Venezuelan study. In: *Autism* 12 (2), pp. 191-202. DOI: 10.1177/1362361307086663.

Moore, Vanessa; Titcomb, Josie; Johnson, Chris; Cronk, Elaine; Baker, Sue; Thysson, Laura; Rolles, Chris (1998): Developing an Autism Assessment Service II: Analysis of the First 81 Cases Seen. In: *Child Psychol. Psychiat. Rev.* 3 (3), pp. 121-127. DOI: 10.1017/S1360641798001634.

Mordre, Marianne; Groholt, Berit; Knudsen, Ann Kristin; Sponheim, Eili; Mykletun, Arnstein; Myhre, Anne Margrethe (2012): Is Long-Term Prognosis for Pervasive Developmental Disorder Not Otherwise Specified Different from Prognosis for Autistic Disorder? Findings from a 30-Year Follow-Up Study. In: *J Autism Dev Disord* 42 (6), pp. 920-928. DOI: 10.1007/s10803-011-1319-5.

Mouridsen, S. E.; Isager, T.; Rich, B. (2013a): Diseases of the gastrointestinal tract in individuals diagnosed as children with atypical autism: A Danish register study based on hospital diagnoses. In: *Autism* 17 (1), pp. 55-63. DOI: 10.1177/1362361312455110.

Mouridsen, S. E.; Rich, B.; Isager, T.; Nedergaard, N. J. (2008): Pervasive Developmental Disorders and Criminal Behaviour: A Case Control Study. In: *International Journal of Offender Therapy and Comparative Criminology* 52 (2), pp. 196-205. DOI: 10.1177/0306624X07302056.

Mouridsen, Svend Erik; Rich, Bente; Isager, Torben (2011a): A longitudinal study of epilepsy and other central nervous system diseases in individuals with and without a history of infantile autism. In: *Brain and Development* 33 (5), pp. 361-366. DOI: 10.1016/j.braindev.2010.07.002.

Mouridsen, Svend Erik; Rich, Bente; Isager, Torben (2011b): Epilepsy and other central nervous system diseases in atypical autism: a case control study. In: *J Neural Transm* 118 (4), pp. 621-627. DOI: 10.1007/s00702-010-0566-5.

Mouridsen, Svend Erik; Rich, Bente; Isager, Torben (2013b): Epilepsy in Individuals with a History of Asperger's Syndrome: A Danish Nationwide Register-Based Cohort Study. In: *J Autism Dev Disord* 43 (6), pp. 1308-1313. DOI: 10.1007/s10803-012-1675-9.

Mouridsen, Svend Erik; Rich, Bente; Isager, Torben; Nedergaard, Niels Jørgen (2007): Autoimmune diseases in parents of children with infantile autism: a case-control study. In: *Developmental Medicine & Child Neurology* 49 (6), pp. 429-432. DOI: 10.1111/j.1469-8749.2007.00429.x.

Mukaddes, Nahit M.; Kaynak, F. Nimet; Kinali, Gülsevim; Beşikci, Hümeyra; Issever, Halim (2004): Psychoeducational Treatment of Children with Autism and Reactive Attachment Disorder. In: *Autism* 8 (1), pp. 101-109. DOI: 10.1177/13623613040642.

Mukaddes, Nahit Motavalli; Kilincaslan, Ayse; Kucukyazici, Gokce; Sevketoglu, Timur; Tuncer, Samuray (2007): Autism in visually impaired individuals. In: *Psychiatry Clin Neurosci* 61 (1), pp. 39-44. DOI: 10.1111/j.1440-1819.2007.01608.x.

Mundy, Peter; Newell, Lisa (2007): Attention, Joint Attention, and Social Cognition. In: *Current Directions in Psychol Sci* 16 (5), pp. 269-274. DOI: 10.1111/j.1467-8721.2007.00518.x.

Murdoch, John D.; State, Matthew W. (2013): Recent developments in the genetics of autism spectrum disorders. In: *Current Opinion in Genetics & Development* 23 (3), pp. 310-315. DOI: 10.1016/j.gde.2013.02.003.

Nadig, Aparna S.; Ozonoff, Sally; Young, Gregory S.; Rozga, Agata; SIGMAN, MARIAN; Rogers, Sally J. (2007): A Prospective Study of Response to Name in Infants at Risk for Autism. In: *Arch Pediatr Adolesc Med* 161 (4), p. 378. DOI: 10.1001/archpedi.161.4.378.

NICE (ed.) (2011): Autism diagnosis in children and young people. Recognition, referral and diagnosis of children and young people on the autism spectrum. Clinical Guideline no. 128. London: National Institute for Health and Clinical Excellence.

NICE (ed.) (2012): Autism: recognition, referral, diagnosis and management of adults on the autism spectrum. Clinical Guideline no. 142. London: National Institute for Health and Care Excellence.

NICE (ed.) (2013): Autism. The management and support of children and young people on the autism spectrum. Clinical Guideline no. 170. London: National Institute for Health and Care Excellence.

Nieschlag, E (2013): Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. In: *Dtsch. Arztebl. Int* 110, p. 347-353.

Norbury, Courtenay F. (2014): Practitioner Review: Social (pragmatic) communication disorder conceptualization, evidence and clinical implications. In: *Journal of Child Psychology and Psychiatry* 55 (3), pp. 204-216. DOI: 10.1111/jcpp.12154.

Noterdaeme, M.; Hutzelmeyer-Nickels, A. (2010): Early symptoms and recognition of pervasive developmental disorders in Germany. In: *Autism* 14 (6), pp. 575-588. DOI: 10.1177/1362361310371951.

Noterdaeme, Michele A.; Wriedt, Elke (2010): Concomitant symptomatology in profound developmental disorders. In: *Journal of Child and Adolescent Psychiatry and Psychotherapy* 38 (4), pp. 257-266. DOI: 10.1024/1422-4917/a000045.

Nydén, Agneta; Niklasson, Lena; Stahlberg, Ola; Anckarsater, Henrik; Wentz, Elisabet; Rastam, Maria; Gillberg, Christopher (2010): Adults with autism spectrum disorders and ADHD neuropsychological aspects. In: *Research in Developmental Disabilities* 31 (6), pp. 1659-1668. DOI: 10.1016/j.ridd.2010.04.010.

Nylander, Lena; Holmqvist, Maria; Gustafson, Lars; Gillberg, Christopher (2013): Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in adult psychiatry. A 20-year register study. In: *North J Psychiatry* 67 (5), pp. 344-350. doi: 10.3109/08039488.2012.748824.

Oliveira, G.; Diogo, L.; Grazina, M.; Garcia, P.; Ataíde, A.; Marques, C. et al. (2005): Mitochondrial dysfunction in autism spectrum disorders: a population-based study. In: *Dev Med Child Neurol* 47 (3), pp. 185-189. DOI: 10.1017/S0012162205000332.

Oliveras-Rentas, Rafael E.; Kenworthy, Lauren; Roberson, Richard B.; Martin, Alex; Wallace, Gregory L. (2012): WISC-IV profile in high-functioning autism spectrum disorders: impaired processing speed is associated with increased autism communication symptoms and decreased adaptive communication abilities. In: *Journal of Autism and Developmental Disorders* 42 (5), pp. 655-664. DOI: 10.1007/s10803-011-1289-7.

O'Nions, Elizabeth; Sebastian, Catherine L.; McCrory, Eamon; Chantiluke, Kaylita; Happé, Francesca; Viding, Essi (2014): Neural bases of Theory of Mind in children with autism spectrum disorders and children with conduct problems and callous-unemotional traits. In: *Dev Sci* 17 (5), pp. 786-796. DOI: 10.1111/desc.12167.

Oosterling, Iris; Rommelse, Nanda; Jonge, Maretha de; van der Gaag, Rutger Jan; Swinkels, Sophie; Roos, Sascha et al. (2010a): How useful is the Social Communication Questionnaire in toddlers at risk of autism spectrum disorder? In: *Journal of Child Psychology and Psychiatry* 51 (11), pp. 1260-1268. DOI: 10.1111/j.1469-7610.2010.02246.x.

Oosterling, Iris; Roos, Sascha; de Bildt, Annelies; Rommelse, Nanda; Jonge, Maretha de; Visser, Janne et al. (2010b): Improved Diagnostic Validity of the ADOS Revised Algorithms: A Replication Study in an Independent Sample. In: *J Autism Dev Disord* 40 (6), pp. 689-703. DOI: 10.1007/s10803-009-0915-0.

Oosterling, Iris J.; Swinkels, Sophie H.; van der Gaag, Rutger Jan; Visser, Janne C.; Dietz, Claudine; Buitelaar, Jan K. (2009): Comparative Analysis of Three Screening Instruments for Autism Spectrum Disorder in Toddlers at High Risk. In: *J Autism Dev Disord* 39 (6), pp. 897-909. DOI: 10.1007/s10803-009-0692-9.

Oslejsková, H.; Dusek, L.; Makovská, Z.; Pejcochová, J.; Autrata, R.; Slapák, I. (2008): Complicated relationship between autism with regression and epilepsy. In: *Neuro Endocrinol Lett* 29 (4), pp. 558-570.

Ozonoff, S.; Young, G. S.; Carter, A.; Messinger, D.; Yirmiya, N.; Zwaigenbaum, L. et al. (2011a): Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study. In: *PEDIATRICS* 128, pp. e488-e495. DOI: 10.1542/peds.2010-2825.

Ozonoff, Sally; Heung, Kelly; Byrd, Robert; Hansen, Robin; Hertz-Picciotto, Irva (2008): The onset of autism: patterns of symptom emergence in the first years of life. In: *Autism Res* 1 (6), pp. 320-328. DOI: 10.1002/aur.53.

Ozonoff, Sally; Iosif, Ana-Maria; Baguio, Fam; Cook, Ian C.; Hill, Monique Moore; Hutman, Ted et al. (2010): A Prospective Study of the Emergence of Early Behavioral Signs of Autism. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 49 (3), pp. 256-266.e2. DOI: 10.1016/j.jaac.2009.11.009.

Ozonoff, Sally; Iosif, Ana-Maria; Young, Gregory S.; Hepburn, Susan; Thompson, Meagan; Colombi, Costanza et al. (2011b): Onset Patterns in Autism: Correspondence Between Home Video and Parent Report. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 50 (8), pp. 796-806.e1. DOI: 10.1016/j.jaac.2011.03.012.

Page, J.; Boucher, J. (1998): Motor impairments in children with autistic disorder. In: *child lang teach ther* 14 (3), pp. 233-259. DOI: 10.1191/026656998673400901.

Palma, Giuseppe de; Catalani, Simona; Franco, Anna; Brighenti, Maurizio; Apostoli, Pietro (2012): Lack of Correlation Between Metallic Elements Analyzed in Hair by ICP-MS and Autism. In: *J Autism Dev Disord* 42 (3), pp. 342-353. DOI: 10.1007/s10803-011-1245-6.

Palmer, Raymond F.; Blanchard, Stephen; Jean, Carlos R.; Mandell, David S. (2005): School District Resources and Identification of Children With Autistic Disorder. In: *Am J Public Health* 95 (1), pp. 125-130. DOI: 10.2105/AJPH.2003.023077.

Palmer, Raymond F.; Walker, Tatjana; Mandell, David; Bayles, Bryan; Miller, Claudia S. (2010): Explaining Low Rates of Autism Among Hispanic Schoolchildren in Texas. In: *Am J Public Health* 100 (2), pp. 270-272. DOI: 10.2105/AJPH.2008.150565.

Papanikolaou, Katerina; Paliokosta, Elena; Houliaras, Giorgos; Vgenopoulou, Sofia; Giouroukou, Eleni; Pehlivanidis, Artemios et al. (2009): Using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic for the Diagnosis of Autism Spectrum Disorders in a Greek Sample with a Wide Range of Intellectual Abilities. In: *J Autism Dev Disord* 39 (3), pp. 414-420. DOI: 10.1007/s10803-008-0639-6.

Pasalich, Dave S.; Dadds, Mark R.; Hawes, David J. (2014): Cognitive and affective empathy in children with conduct problems: Additive and interactive effects of callous-unemotional traits and autism spectrum disorders symptoms. In: *Psychiatry Research* 219 (3), pp. 625-630. DOI: 10.1016/j.psychres.2014.06.025.

Patten, Elena; Belardi, Katie; Baranek, Grace T.; Watson, Linda R.; Labban, Jeffrey D.; Oller, D. Kimbrough (2014): Vocal Patterns in Infants with Autism Spectrum Disorder: Canonical Babbling Status and Vocalization Frequency. In: *J Autism Dev Disord* 44 (10), pp. 2413-2428. doi: 10.1007/s10803-014-2047-4.

Perry, Adrienne; Condillac, Rosemary A.; Freeman, Nancy L.; Dunn-Geier, Jennifer; Belair, Joanne (2005): Multi-site Study of the Childhood Autism Rating Scale (CARS) in Five Clinical Groups of Young Children. In: *J Autism Dev Disord* 35 (5), pp. 625-634. DOI: 10.1007/s10803-005-0006-9.

Persico, Antonio M.; Napolioni, Valerio (2013): Autism genetics. In: *Behavioural Brain Research* 251, pp. 95-112. DOI: 10.1016/j.bbr.2013.06.012.

Petermann, F. (2012): WAIS-IV. Wechsler Adult Intelligence Scale. Manual 1: Basic principles, test scoring, and interpretation. 4th ed. Frankfurt: Pearson Assessment & Information GmbH.

Petermann, F.; Petermann, U. (2011): WISC-IV. Wechsler Intelligence Scale for Children - Fourth Edition. Frankfurt: Pearson Assessment & Information GmbH.

Petermann, Franz; Macha, Thorsten (2005): Psychological tests for pediatricians. Göttingen: Hogrefe.

Pierce, Karen; Conant, David; Hazin, Roxana; Stoner, Richard; Desmond, Jamie (2011): Preference for Geometric Patterns Early in Life as a Risk Factor for Autism. In: *Arch Gen Psychiatry* 68 (1), p. 101. DOI: 10.1001/archgenpsychiatry.2010.113.

Pine, D. S.; Guyer, A. E.; Goldwin, M.; Towbin, K. A.; Leibenluft, E. (2008): Autism Spectrum Disorder Scale Scores in Pediatric Mood and Anxiety Disorders. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 47 (6), pp. 652-661. DOI: 10.1097/CHI.0b013e31816bffa5.

Plasschaert, Ellen; Descheemaeker, Mie-Jef; van Eylen, Lien; Noens, Ilse; Steyaert, Jean; Legius, Eric (2015): Prevalence of autism spectrum disorder symptoms in children with neurofibromatosis type 1. In: *Am. J. Med. Genet.* 168 (1), pp. 72-80. doi: 10.1002/ajmg.b.32280.

Pondé, Milena Pereira; Novaes, Camila Marinho; Losapio, Mirella Fiuza (2010): Frequency of symptoms of attention deficit and hyperactivity disorder in autistic children. In: *Arq. Neuro-Psiquiatr.* 68 (1), pp. 103-106. DOI: 10.1590/S0004-282X2010000100022.

Posserud, M.; Lundervold, Astri J.; Lie, Stein Atle; Gillberg, Christopher (2010): The prevalence of autism spectrum disorders: impact of diagnostic instrument and non-response bias. In: *Soc Psychiat Epidemiol* 45 (3), pp. 319-327. DOI: 10.1007/s00127-009-0087-4.

Poustka, Luise; Rühl, D; Feineis-Matthews, S; Bölte, S; Poustka, Fritz; Hartung, M (2015): ADOS-2. Diagnostic Observation Scale for Autistic Disorders 2: German language version of the Autism Diagnostic Observation Schedule - 2 by C. Lord, M. Rutter, P. C. Dilavore, S. Risi, K. Gotham and S. L. Bishop (Modules 1-4) and C. Lord, R. J. Luyster, K. Gotham, and W. Guthrie (Toddler Module). Bern: Huber.

Powell, J. E.; Edwards, A.; Edwards, M.; Pandit, B. S.; Sungum-Paliwal, S. R.; Whitehouse, W. (2000): Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas in the West Midlands, UK. In: *Dev Med Child Neurol* 42 (9), pp. 624-628. DOI: 10.1017/S001216220000116X.

Quirantes, Deborah (2009): Collaborative approach to autism: a parent's perspective. In: *Journal for specialists in pediatric nursing : JSPN* 14 (3), pp. 203-205. DOI: 10.1111/j.1744-6155.2009.00199.x.

Rai, D.; Lee, B. K.; Dalman, C.; Golding, J.; Lewis, G.; Magnusson, C. (2013): Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. In: *BMJ* 346 (apr19 1), pp. f2059. DOI: 10.1136/bmj.f2059.

Rai, Dheeraj; Kerr, Michael P.; McManus, Sally; Jordanova, Vesna; Lewis, Glyn; Brugha, Traolach S. (2012a): Epilepsy and psychiatric comorbidity: A nationally representative population-based study. In: *Epilepsia* 53 (6), pp. 1095-1103. doi: 10.1111/j.1528-1167.2012.03500.x.

Rai, Dheeraj; Lewis, Glyn; Lundberg, Michael; Araya, Ricardo; Svensson, Anna; Dalman, Christina et al. (2012b): Parental Socioeconomic Status and Risk of Offspring Autism Spectrum Disorders in a Swedish Population-Based Study. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 51 (5), pp. 467-476. DOI: 10.1016/j.jaac.2012.02.012.

Ravens-Sieberer, U.; Wille, N.; Bettge, S.; Erhart, M. (2007): Mental Health of Children and Adolescents in Germany. In: *Bundesgesundheitsbl.* 50 (5-6), pp. 871-878. DOI: 10.1007/s00103-007-0250-6.

Raznahan, Armin; Wallace, Gregory L.; Antezana, Ligia; Greenstein, Dede; Lenroot, Rhoshel; Thurm, Audrey et al. (2013): Compared to What? Early Brain Overgrowth in Autism and the Perils of Population Norms. In: *Biological Psychiatry* 74 (8), pp. 563-575. doi: 10.1016/j.biopsych.2013.03.022.

Reaven, J. A.; Hepburn, S. L.; Ross, R. G. (2008): Use of the ADOS and ADI-R in Children with Psychosis: Importance of Clinical Judgment. In: *Clinical Child Psychology and Psychiatry* 13 (1), pp. 81-94. DOI: 10.1177/1359104507086343.

Reed, Phil; Osborne, Lisa A. (2012): Diagnostic practice and its impacts on parental health and child behaviour problems in autism spectrum disorders. In: *Archives of disease in childhood* 97 (10), pp. 927-931. DOI: 10.1136/archdischild-2012-301761.

Reich, James (2009): Avoidant Personality Disorder and Its Relationship to Social Phobia, pp. 207-222. DOI: 10.1016/B978-0-12-375096-9.00008-0.

Reichenberg, A; Gross, R; Weiser, M; Bresnahan, M; Silverman, J; Harlap, S et al. (2006): Advancing paternal age and autism. In: *Arch Gen Psychiatry* 63 (9), pp. 1026-1032.

Reiersen, Angela M. (2011): Links Between Autism Spectrum Disorder and ADHD Symptom Trajectories: Important Findings and Unanswered Questions. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 50 (9), pp. 857-859. DOI: 10.1016/j.jaac.2011.06.012.

Rellini, E; Tortolani, D; Trillo, S; Carbone, S; Montecchi, F (2004a): Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) correspondence and conflicts with DSM-IV criteria in diagnosis of autism. In: *Journal of Autism and Developmental Disorders* 34 (6), pp. 703-708.

Rellini, E.; Tortolani, D.; Trillo, S.; Carbone, S.; Montecchi, F. (2004b): Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) Correspondence and Conflicts with DSM-IV Criteria in Diagnosis of Autism. In: *J Autism Dev Disord* 34 (6), pp. 703-708. DOI: 10.1007/s10803-004-5290-2.

Remschmidt, Helmut; Kamp-Becker, Inge (2006): Asperger syndrome. Berlin, Heidelberg: Springer.

Renno, Patricia; Wood, Jeffrey J. (2013): Discriminant and Convergent Validity of the Anxiety Construct in Children with Autism Spectrum Disorders. In: *J Autism Dev Disord* 43 (9), pp. 2135-2146. DOI: 10.1007/s10803-013-1767-1.

Reszka, Stephanie S.; Boyd, Brian A.; McBee, Matthew; Hume, Kara A.; Odom, Samuel L. (2014): Brief report: concurrent validity of autism symptom severity measures. In: *Journal of Autism and Developmental Disorders* 44 (2), pp. 466-470. doi: 10.1007/s10803-013-1879-7.

Rice, Catherine E.; Baio, Jon; Van Naarden Braun, Kim; Doernberg, Nancy; Meaney, F. John; Kirby, Russell S. (2007): A public health collaboration for the surveillance of autism spectrum disorders. In: *Paediatr Perinat Epidemiol* 21 (2), pp. 179-190. DOI: 10.1111/j.1365-3016.2007.00801.x.

Ringman, J. M.; Jankovic, J. (2000): Occurrence of tics in Asperger's syndrome and autistic disorder. In: *J Child Neurol* 15 (6), pp. 394-400.

Risi, Susan; Lord, Catherine; Gotham, Katherine; Corsello, Christina; CHRYSLER, CHRISTINA; Szatmari, Peter et al. (2006): Combining Information From Multiple Sources in the Diagnosis of Autism Spectrum Disorders. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 45 (9), pp. 1094-1103. DOI: 10.1097/01.chi.0000227880.42780.0e.

Robins, D. L.; Casagrande, K.; Barton, M.; Chen, C.-M. A.; Dumont-Mathieu, T.; Fein, D. (2014): Validation of the Modified Checklist for Autism in Toddlers, Revised With Follow-up (M-CHAT-R/F). In: *PEDIATRICS* 133 (1), pp. 37-45. DOI: 10.1542/peds.2013-1813.

Robins, Diana L.; Fein, Deborah; Barton, Marianne L.; Green, James A. (2001): The Modified Checklist for Autism in Toddlers: an initial study investigating the early detection of autism and pervasive developmental disorders. In: *Journal of Autism and Developmental Disorders* 31 (2), pp. 131-144.

Robinson, E. B.; Lichtenstein, P.; Anckarsater, H.; Happe, F.; Ronald, A. (2013): Examining and interpreting the female protective effect against autistic behavior. In: *Proceedings of the National Academy of Sciences* 110 (13), pp. 5258-5262. DOI: 10.1073/pnas.1211070110.

Rogers, Sally J.; Vismara, Laurie A. (2008): Evidence-Based Comprehensive Treatments for Early Autism. In: *Journal of Clinical Child & Adolescent Psychology* 37 (1), pp. 8-38. DOI: 10.1080/15374410701817808.

Rommelse, N. N. J.; Franke, B.; Geurts, H. M.; Hartman, C. A.; Buitelaar, J. K. (2010): Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. In: *Eur Child Adolesc Psychiatry* 19 (3), pp. 281-295. DOI: 10.1007/s00787-010-0092-x.

Rommelse, N. N. J.; Geurts, H. M.; Franke, B.; Buitelaar, J. K.; Hartman, C. A. (2011): A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. In: *Neuroscience & Biobehavioral Reviews* 35 (6), pp. 1363-1396. DOI: 10.1016/j.neubiorev.2011.02.015.

Ronald, Angelica; Hoekstra, Rosa A. (2011): Autism spectrum disorders and autistic traits: A decade of new twin studies. In: *Am. J. Med. Genet.* 156 (3), pp. 255-274. DOI: 10.1002/ajmg.b.31159.

Rossignol, D. A.; Frye, R. E. (2011): Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis. In: *Mol Psychiatry* 17 (3), pp. 290-314. DOI: 10.1038/mp.2010.136.

Rowberry, Justin; Macari, Suzanne; Chen, Grace; Campbell, Daniel; Leventhal, John M.; Weitzman, Carol; Chawarska, Katarzyna (2015): Screening for Autism Spectrum Disorders in 12-Month-Old High-Risk Siblings by Parental Report. In: *J Autism Dev Disord* 45 (1), pp. 221-229. doi: 10.1007/s10803-014-2211-x.

Rozga, Agata; Hutman, Ted; Young, Gregory S.; Rogers, Sally J.; Ozonoff, Sally; Dapretto, Mirella; SIGMAN, MARIAN (2011): Behavioral Profiles of Affected and Unaffected Siblings of Children with Autism: Contribution of Measures of Mother-Infant Interaction and Nonverbal Communication. In: *J Autism Dev Disord* 41 (3), pp. 287-301. DOI: 10.1007/s10803-010-1051-6.

Ruiz Calzada, Luisa; Pistrang, Nancy; Mandy, William (2012): High-Functioning Autism and Asperger's Disorder: Utility and Meaning for Families. In: *J Autism Dev Disord* 42 (2), pp. 230-243. DOI: 10.1007/s10803-011-1238-5.

Rumpf, Anna-Lena; Kamp-Becker, Inge; Becker, Katja; Kauschke, Christina (2012): Narrative competence and internal state language of children with Asperger Syndrome and ADHD. In: *Research in Developmental Disabilities* 33 (5), pp. 1395-1407. DOI: 10.1016/j.ridd.2012.03.007.

Rumsey, Judith M; Rapoport, Judith L; Sceery, Walter R (1985): Autistic children as adults. Psychiatric, social, and behavioral outcomes. In: *Journal of the American Academy of Child Psychiatry* 24 (4), pp. 465-473.

Russell, Paul S. S.; Daniel, Anna; Russell, Sushila; Mammen, Priya; Abel, Julie S.; Raj, Lydia E. et al. (2010): Diagnostic accuracy, reliability and validity of Childhood Autism Rating Scale in India. In: *World J Pediatr* 6 (2), pp. 141-147. DOI: 10.1007/s12519-010-0029-y.

Rutgers, Anna H.; Bakermans-Kranenburg, Marian J.; Ijzendoorn, Marinus H.; Berckelaer-Onnes, Ina A. (2004): Autism and attachment: a meta-analytic review. In: *J Child Psychol & Psychiat* 45 (6), pp. 1123-1134. DOI: 10.1111/j.1469-7610.2004.t01-1-00305.x.

Rutter, M. (1970): Autistic children: infancy to adulthood. In: *Seminars of Psychiatry* 2 (4), pp. 435-450.

Rutter, M. (1972): Childhood schizophrenia reconsidered. In: *Journal of Autism and Childhood Schizophrenia* 2, pp. 315-337.

Rutter, M. (1977): Brain damage syndromes in childhood: Concepts and findings. In: *Journal of Child Psychology and Psychiatry* 18, pp. 1-21.

Rutter, M.; Bailey, A.; Lord, C. (2003): Social communication questionnaire. Los Angeles: Western Psychological Services.

Rutter, M.; Sandberg, S. (1985): Epidemiology of child psychiatric disorder: Methodological issues and some substantive findings. In: *Child Psychiatry and Human Development* 15, pp. 209-233.

Sadiq, Fareeha Amber; Slator, Louise; Skuse, David; Law, James; Gillberg, Christopher; Minnis, Helen (2012): Social use of language in children with reactive attachment disorder and autism spectrum disorders. In: *Eur Child Adolesc Psychiatry* 21 (5), pp. 267-276. doi: 10.1007/s00787-012-0259-8.

Saemundsen, Evald; Ludvigsson, Petur; Hilmarsdottir, Ingibjorg; Rafnsson, Vilhjalmur (2007): Autism Spectrum Disorders in Children with Seizures in the First Year of Life-A Population-Based Study. In: *Epilepsia* 48 (9), pp. 1724-1730. DOI: 10.1111/j.1528-1167.2007.01150.x.

Saemundsen, Evald; Ludvigsson, Petur; Rafnsson, Vilhjalmur (2008): Risk of autism spectrum disorders after infantile spasms: A population-based study nested in a cohort with seizures in the first year of life. In: *Epilepsia* 49 (11), pp. 1865-1870. DOI: 10.1111/j.1528-1167.2008.01688.x.

Sandin, Sven; Lichtenstein, Paul; Kuja-Halkola, Ralf; Larsson, Henrik; Hultman, Christina M.; Reichenberg, Abraham (2014): The Familial Risk of Autism. In: *JAMA* 311 (17), p. 1770. DOI: 10.1001/jama.2014.4144.

Santosh, Paramala J.; Mandy, William P. L.; Puura, Kaija; Kaartinen, Miia; Warrington, Richard; Skuse, David H. (2009): The construction and validation of a short form of the developmental, diagnostic and dimensional interview. In: *Eur Child Adolesc Psychiatry* 18 (8), pp. 521-524. DOI: 10.1007/s00787-009-0004-0.

Sappok, T; Diefenbacher, A; Bergmann, T; Bölte, S; Gaul, I; Heinrich, M; Dziobek, I (2015): DIBAS-R. The Diagnostic Observation Sheet for Autism Spectrum Disorder-Revised. A screening instrument for adults with intelligence impairment and suspected autism. Bern: Huber.

Scambler, Douglas; Rogers, Sally J.; Wehner, Elizabeth (2001): Can the Checklist for Autism in Toddlers Differentiate Young Children With Autism From Those With Developmental Delays? In: *Journal of the American Academy of Child & Adolescent Psychiatry* 40 (12), pp. 1457-1463. DOI: 10.1097/00004583-200112000-00017.

Schanding, G. Thomas; Nowell, Kerri P.; Goin-Kochel, Robin P. (2012): Utility of the Social Communication Questionnaire-Current and Social Responsiveness Scale as Teacher-Report Screening Tools for Autism Spectrum Disorders. In: *J Autism Dev Disord* 42 (8), pp. 1705-1716. DOI: 10.1007/s10803-011-1412-9.

Scheirs, J. G. M.; Timmers, E. A. (2009): Differentiating Among Children with PDD-NOS, ADHD, and those with a Combined Diagnosis on the Basis of WISC-III Profiles. In: *J Autism Dev Disord* 39 (4), pp. 549-556. DOI: 10.1007/s10803-008-0657-4.

Schendel, Diana E.; Autry, Andrew; Wines, Roberta; Moore, Cynthia (2009): The co-occurrence of autism and birth defects: prevalence and risk in a population-based cohort. In: *Developmental Medicine & Child Neurology* 51 (10), pp. 779-786. DOI: 10.1111/j.1469-8749.2009.03310.x.

Schieve, Laura A.; Baio, Jon; Rice, Catherine E.; Durkin, Maureen; Kirby, Russell S.; Drews-Botsch, Carolyn et al. (2010): Risk for cognitive deficit in a population-based sample of U.S. children with autism spectrum disorders: Variation by perinatal health factors. In: *Disability and Health Journal* 3 (3), pp. 202-212. DOI: 10.1016/j.dhjo.2009.12.001.

Schiff, Manuel; Benoist, Jean-François; Aïssaoui, Sofiane; Boespflug-Tanguy, Odile; Boepsflug-Tanguy, Odile; Mouren, Marie-Christine et al. (2011): Should metabolic diseases be systematically screened in nonsyndromic autism spectrum disorders? In: *PLoS ONE* 6 (7), p. e21932. DOI: 10.1371/journal.pone.0021932.

Schlack, R.; Mauz, E.; Hebebrand, J.; Hölling, H. (2014): Did the frequency of parent-reported diagnoses of attention-deficit/hyperactivity disorder (ADHD) increase in Germany between 2003-2006 and 2009-2012? In: *Bundesgesundheitsbl.* 57 (7), pp. 820-829. DOI: 10.1007/s00103-014-1983-7.

Schonauer, K.; Klar, M.; Kehrer, H. E.; Arolt, V. (2001): Life courses of early childhood autistic persons in adulthood - A review of long-term catamnestic data -. In: *Fortschr Neurol Psychiatr* 69 (5), pp. 221-235. doi: 10.1055/s-2001-13933.

Schopler, Eric; Reichler, Robert J.; DeVellis, Robert F.; Daly, Kenneth (1980): Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). In: *J Autism Dev Disord* 10 (1), pp. 91-103. DOI: 10.1007/BF02408436.

Schwenck, Christina; Freitag, Christine M. (2014): Differentiation between attention-deficit/hyperactivity disorder and autism spectrum disorder by the Social Communication Questionnaire. In: *ADHD Atten Def Hyp Disord* 6 (3), pp. 221-229. DOI: 10.1007/s12402-014-0147-9.

Schwenck, Christina; Gensthaler, Angelika; Romanos, Marcel; Freitag, Christine M.; Schneider, Wolfgang; Taurines, Regina (2014): Emotion recognition in girls with conduct problems. In: *Eur Child Adolesc Psychiatry* 23 (1), pp. 13-22. DOI: 10.1007/s00787-013-0416-8.

Scott, F. J.; Baron-Cohen, S.; Bolton, P.; Brayne, C. (2002): The CAST (Childhood Asperger Syndrome Test): Preliminary Development of a UK Screen for Mainstream Primary-School-Age Children. In: *Autism* 6 (1), pp. 9-31. DOI: 10.1177/1362361302006001003.

Sebastian, Catherine L.; McCrory, E. J. P.; Cecil, Charlotte A. M.; Lockwood, Patricia L.; De Brito, Stephane A.; Fontaine, Nathalie M. G.; Viding, Essi (2012): Neural Responses to Affective and Cognitive Theory of Mind in Children With Conduct Problems and Varying Levels of Callous-Unemotional Traits. In: *Arch Gen Psychiatry* 69 (8), p. 814. DOI: 10.1001/archgenpsychiatry.2011.2070.

Shamay-Tsoory, Simone G.; Harari, Hagai; Aharon-Peretz, Judith; Levkovitz, Yechiel (2010): The role of the orbitofrontal cortex in affective theory of mind deficits in criminal offenders with psychopathic tendencies. In: *Cortex* 46 (5), pp. 668-677. DOI: 10.1016/j.cortex.2009.04.008.

Sharp, William G.; Berry, Rashelle C.; McCracken, Courtney; Nuhu, Nadrat N.; Marvel, Elizabeth; Saulnier, Celine A. et al. (2013): Feeding Problems and Nutrient Intake in Children with Autism Spectrum Disorders: A Meta-analysis and Comprehensive Review of the Literature. In: *J Autism Dev Disord* 43 (9), pp. 2159-2173. DOI: 10.1007/s10803-013-1771-5.

Shen, Y.; Dies, K. A.; Holm, I. A.; Bridgemohan, C.; Sobeih, M. M.; Caronna, E. B. et al. (2010): Clinical Genetic Testing for Patients With Autism Spectrum Disorders. In: *PEDIATRICS* 125 (4), pp. e727-e735. DOI: 10.1542/peds.2009-1684.

SIGN (ed.) (2007): Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network.

Siklos, Susan; Kerns, Kimberly A. (2007): Assessing the diagnostic experiences of a small sample of parents of children with autism spectrum disorders. In: *Research in Developmental Disabilities* 28 (1), pp. 9-22. DOI: 10.1016/j.ridd.2005.09.003.

Simonoff, Emily; Pickles, Andrew; Charman, Tony; Chandler, Susie; Loucas, Tom; Baird, Gillian (2008): Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 47 (8), pp. 921-929. DOI: 10.1097/CHI.0b013e318179964f.

Sinzig, Judith (2011): Frühkindlicher Autismus. Berlin, Heidelberg: Imprint: Springer (Manuale psychischer Störungen bei Kindern und Jugendlichen, 0).

Skuse, D. H.; James, R. S.; Bishop, D. V. M.; Coppin, B.; Dalton, P.; Aamodt-Leeper, G. et al. (1997): Evidence from Turner's syndrome of an imprinted X-linked locus affecting cognitive function. In: *Nature* 387 (6634), pp. 705-708. DOI: 10.1038/42706.

Skuse, David; Warrington, R; Bishop, D; Chowdhury, U; Lau, U; Mandy, W; Place, M (2004): The Developmental, Dimensional and Diagnostic Interview (3di). A Novel Computerized Assessment for Autism Spectrum Disorders. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 43 (5), pp. 548-558.

Skuse, David H.; Mandy, William; Scourfield, Jane (2005): Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. In: The *British Journal of Psychiatry* 187 (6), pp. 568-572. DOI: 10.1192/bjp.187.6.568.

Smeeth, Liam; Cook, Claire; Fombonne, Eric; Heavey, Lisa; Rodrigues, Laura C.; Smith, Peter G.; Hall, Andrew J. (2004): MMR vaccination and pervasive developmental disorders: a case-control study. In: The *Lancet* 364 (9438), pp. 963-969. DOI: 10.1016/S0140-6736(04)17020-7.

Snow, A. V.; Lecavalier, L. (2008): Sensitivity and specificity of the Modified Checklist for Autism in Toddlers and the Social Communication Questionnaire in preschoolers suspected of having pervasive developmental disorders. In: *Autism* 12 (6), pp. 627-644. DOI: 10.1177/1362361308097116.

Spence, M. A. (1976): Generic studies. In: E. Ritvo (Ed.): Autism, Diagnosis, Current Research and Management. New York: Halstead/Wiley, pp. 169-174.

Spiker, M. A.; Lin, C. E.; van Dyke, M.; Wood, J. J. (2012): Restricted interests and anxiety in children with autism. In: *Autism* 16 (3), pp. 306-320. DOI: 10.1177/1362361311401763.

Sponheim, Eili; Spurkland, Ingrid (1996): Diagnosing childhood autism in clinical practice. In: *Nord J Psychiatry* 50 (1), pp. 5-9. DOI: 10.3109/08039489609081381.

Stahlberg, O.; Soderstrom, H.; Rastam, M.; Gillberg, C. (2004): Bipolar disorder, schizophrenia, and other psychotic disorders in adults with childhood onset AD/HD and/or autism spectrum disorders. In: *J Neural Transm* 111 (7). DOI: 10.1007/s00702-004-0115-1.

Ståhlberg, Ola; Anckarsäter, Henrik; Nilsson, Thomas (2010): Mental health problems in youths committed to juvenile institutions: prevalences and treatment needs. In: *Eur Child Adolesc Psychiatry* 19 (12), pp. 893-903. DOI: 10.1007/s00787-010-0137-1.

Starr, Elizabeth; Szatmari, Peter; Bryson, Susan; Zwaigenbaum, Lonnie (2003): Stability and change among high-functioning children with pervasive developmental disorders: a 2-year outcome study. In: *Journal of Autism and Developmental Disorders* 33 (1), pp. 15-22. DOI: 10.1023/A:1022222202970.

Steinhausen, H.-C. (1993): Mental disorders in children and adolescents. Textbook of child and adolescent psychiatry. 3rd ed. Munich: Urban and Schwarzenberg.

Steinsbekk, Silje; Berg-Nielsen, Turid S.; Wichstrøm, Lars (2013): Sleep Disorders in Preschoolers. In: *Journal of Developmental & Behavioral Pediatrics* 34 (9), pp. 633-641. DOI: 10.1097/01.DBP.0000437636.33306.49.

Stenberg, Nina; Bresnahan, Michaeline; Gunnes, Nina; Hirtz, Deborah; Hornig, Mady; Lie, Kari Kveim et al. (2014): Identifying Children with Autism Spectrum Disorder at 18 Months in a General Population Sample. In: *Paediatr Perinat Epidemiol* 28 (3), pp. 255-262. DOI: 10.1111/ppe.12114.

Stevens, Sara A.; Nash, Kelly; Koren, Gideon; Rovet, Joanne (2013): Autism characteristics in children with fetal alcohol spectrum disorders. In: *Child Neuropsychology* 19 (6), pp. 579-587. DOI: 10.1080/09297049.2012.727791.

Stone, W. L.; McMahon, C. R.; Henderson, L. M. (2008): Use of the Screening Tool for Autism in Two-Year-Olds (STAT) for children under 24 months: An exploratory study. In: *Autism* 12 (5), pp. 557-573. DOI: 10.1177/1362361308096403.

Stoppelbein, L.; Greening, L.; Kakooza, A. (2006): The importance of catatonia and stereotypies in autistic spectrum disorders. In: *Int Rev Neurobiol* 72, pp. 103-118.

Strunz, Sandra; Dziobek, Isabel; Roepke, Stefan (2014a): Comorbid psychiatric disorders and differential diagnosis in non-intelligent adults with autism spectrum disorder. In: *Psychother Psych Med* 64 (06), pp. 206-213. DOI: 10.1055/s-0033-1358708.

Strunz, Sandra; Westphal, Linda; Ritter, Kathrin; Heuser, Isabella; Dziobek, Isabel; Roepke, Stefan (2014b): Personality Pathology of Adults With Autism Spectrum Disorder Without Accompanying Intellectual Impairment in Comparison to Adults With Personality Disorders. In: *J Autism Dev Disord. DOI:* 10.1007/s10803-014-2183-x.

Sucharewa, G. (1926): The schizoid psychopathies in childhood. In: *Monatsschrift für Psychiatrie und Neurologie* 60, pp. 235-261.

Sukhodolsky, Denis G.; Scahill, Lawrence; Gadow, Kenneth D.; Arnold, L. Eugene; Aman, Michael G.; McDougle, Christopher J. et al. (2008): Parent-Rated Anxiety Symptoms in Children with Pervasive Developmental Disorders: Frequency and Association with Core Autism Symptoms and Cognitive Functioning. In: *J Abnorm Child Psychol* 36 (1), pp. 117-128. DOI: 10.1007/s10802-007-9165-9.

Sullivan, Sarah; Rai, Dheeraj; Golding, Jean; Zammit, Stan; Steer, Colin (2013): The Association Between Autism Spectrum Disorder and Psychotic Experiences in the Avon Longitudinal Study of Parents and Children (ALSPAC) Birth Cohort. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 52 (8), pp. 806-814.e2. DOI: 10.1016/j.jaac.2013.05.010.

Swineford, Lauren B.; Thurm, Audrey; Baird, Gillian; Wetherby, Amy M.; Swedo, Susan (2014): Social (pragmatic) communication disorder: a research review of this new DSM-5 diagnostic category. In: *J Neurodev Disord* 6 (1), p. 41. DOI: 10.1186/1866-1955-6-41.

Tantam, D.; Girgis, S. (2009): Recognition and treatment of Asperger syndrome in the community. In: *British Medical Bulletin* 89 (1), pp. 41-62. DOI: 10.1093/bmb/ldp006.

Taurines, Regina; Schwenck, Christina; Westerwald, Eva; Sachse, Michael; Siniatchkin, Michael; Freitag, Christine (2012): ADHD and autism: differential diagnosis or overlapping traits? A selective review. In: *ADHD Atten Def Hyp Disord* 4 (3), pp. 115-139. DOI: 10.1007/s12402-012-0086-2.

Taylor, Luke E.; Swerdfeger, Amy L.; Eslick, Guy D. (2014): Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. In: *Vaccine* 32 (29), pp. 3623-3629. doi: 10.1016/j.vaccine.2014.04.085.

Tebartz van Elst, Ludger (ed.) (2013): The Asperger Syndrome in Adulthood. And other high-functioning autism spectrum disorders. With the collaboration of M. Biscaldi. 1st ed. Berlin: Med.-Wiss. Verl.-Ges.

Tellegen, P. J.; Laros, J. A.; Petermann, F. (1998): SON 2 ½-7th non-verbal intelligence test. Göttingen: Hogrefe.

Tellegen, P. J.; Laros, J. A.; Petermann, F. (2012): SON-R 6-40. non-verbal intelligence test. Göttingen: Hogrefe.

Totsika, Vasiliki; Hastings, Richard P.; Emerson, Eric; Lancaster, Gillian A.; Berridge, Damon M. (2011): A population-based investigation of behavioural and emotional problems and maternal mental health: associations with autism spectrum disorder and intellectual disability. In: *Journal of Child Psychology and Psychiatry* 52 (1), pp. 91-99. DOI: 10.1111/j.1469-7610.2010.02295.x.

Towbin, Kenneth E.; Pradella, Anne; Gorrindo, Tristan; Pine, Daniel S.; Leibenluft, Ellen (2005): Autism Spectrum Traits in Children with Mood and Anxiety Disorders. In: *Journal of Child and Adolescent Psychopharmacology* 15 (3), pp. 452-464. DOI: 10.1089/cap.2005.15.452.

Tsakanikos, Elias; Costello, Helen; Holt, Geraldine; Bouras, Nick; Sturmey, Peter; Newton, Tim (2006): Psychopathology in Adults with Autism and Intellectual Disability. In: *J Autism Dev Disord* 36 (8), pp. 1123-1129. DOI: 10.1007/s10803-006-0149-3.

Tse, Jeanie; Strulovitch, Jack; Tagalakis, Vicki; Meng, Linyan; Fombonne, Eric (2007): Social Skills Training for Adolescents with Asperger Syndrome and High-Functioning Autism. In: *J Autism Dev Disord* 37 (10), pp. 1960-1968. DOI: 10.1007/s10803-006-0343-3.

Tsiouris, J. A.; Kim, S. Y.; Brown, W. T.; Cohen, I. L. (2011): Association of aggressive behaviours with psychiatric disorders, age, sex and degree of intellectual disability: a large-scale survey. In: *Journal of Intellectual Disability Research* 55 (7), pp. 636-649. DOI: 10.1111/j.1365-2788.2011.01418.x.

Tsuchiya, Kenji J.; Matsumoto, Kaori; Yagi, Atsuko; Inada, Naoko; Kuroda, Miho; Inokuchi, Eiko et al. (2013): Reliability and Validity of Autism Diagnostic Interview-Revised, Japanese Version. In: *J Autism Dev Disord* 43 (3), pp. 643-662. DOI: 10.1007/s10803-012-1606-9.

Turner, Lauren M.; Stone, Wendy L. (2007) Variability in outcome for children with an ASD diagnosis at age 2. In: *J Child Psychol & Psychiat* 48 (8), pp. 793-802. DOI: 10.1111/j.1469-7610.2007.01744.x.

Turner-Brown, L. M.; Lam, K. S. L.; Holtzclaw, T. N.; Dichter, G. S.; Bodfish, J. W. (2011): Phenomenology and measurement of circumscribed interests in autism spectrum disorders. In: *Autism* 15 (4), pp. 437-456. doi: 10.1177/1362361310386507.

Twachtman-Reilly, Jennifer; Amaral, Sheryl C.; Zebrowski, Patrecia P. (2008): Addressing Feeding Disorders in Children on the Autism Spectrum in School-Based Settings: Physiological and Behavioral Issues. In: *Lang Speech Hear Serv Sch* 39 (2), p. 261. DOI: 10.1044/0161-1461(2008/025).

Tyson, Katherine E.; Cruess, Dean G. (2012): Differentiating High-Functioning Autism and Social Phobia. In: *J Autism Dev Disord* 42 (7), pp. 1477-1490. DOI: 10.1007/s10803-011-1386-7.

Uekermann, J.; Kraemer, M.; Abdel-Hamid, M.; Schimmelmann, B. G.; Hebebrand, J.; Daum, I. et al. (2010): Social cognition in attention-deficit hyperactivity disorder (ADHD). In: *Neuroscience & Biobehavioral Reviews* 34 (5), pp. 734-743. DOI: 10.1016/j.neubiorev.2009.10.009.

Ünal, Özlem; Özcan, Özlem; Öner, Özgür; Akcakin, Melda; Aysev, Ayla; Deda, Gülhis (2009): EEG and MRI findings and their relation with intellectual disability in pervasive developmental disorders. In: *World J Pediatr* 5 (3), pp. 196-200. DOI: 10.1007/s12519-009-0037-y.

Valicenti-McDermott, Maria; McVicar, Kathryn; Rapin, Isabelle; Wershil, Barry K.; Cohen, Herbert; Shinnar, Shlomo (2006): Frequency of Gastrointestinal Symptoms in Children with Autistic Spectrum Disorders and Association with Family History of Autoimmune Disease. In: *Journal of Developmental & Behavioral Pediatrics* 27 (Supplement 2), pp. S128-S136. DOI: 10.1097/00004703-200604002-00011.

Valicenti-McDermott, Maria D.; McVicar, Kathryn; Cohen, Herbert J.; Wershil, Barry K.; Shinnar, Shlomo (2008): Gastrointestinal Symptoms in Children with an Autism Spectrum Disorder and Language Regression. In: *Pediatric Neurology* 39 (6), pp. 392-398. DOI: 10.1016/j.pediatrneurol.2008.07.019.

van der Meer, Jolanda M. J.; Oerlemans, Anoek M.; van Steijn, Daphne J.; Lappenschaar, Martijn G.A.; de Sonneville, Leo M. J.; Buitelaar, Jan K.; Rommelse, Nanda N. J. (2012): Are Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder Different Manifestations of One Overarching Disorder? Cognitive and Symptom Evidence From a Clinical and Population-Based Sample. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 51 (11), pp. 1160-1172.e3. DOI: 10.1016/j.jaac.2012.08.024.

Van Hulle, Carol A.; Schmidt, Nicole L.; Goldsmith, H. Hill (2012): Is sensory over-responsivity distinguishable from childhood behavior problems? A phenotypic and genetic analysis. In: *Journal of Child Psychology and Psychiatry* 53 (1), pp. 64-72. DOI: 10.1111/j.1469-7610.2011.02432.x.

Van Naarden Braun, K.; Pettygrove, S.; Daniels, J.; Miller, L.; Nicholas, J.; Baio, J. et al. (2007): Centers for Disease Control and Prevention. Evaluation of a methodology for a collaborative multiple source surveillance network for autism spectrum disorders--Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2002. In: *Morbidity and Mortality Weekly Report Surveillance Summary* 56 (1), pp. 29-40.

van Steensel, Francisca J. A.; Bögels, Susan M.; Wood, Jeffrey J. (2013): Autism Spectrum Traits in Children with Anxiety Disorders. In: *J Autism Dev Disord* 43 (2), pp. 361-370. doi: 10.1007/s10803-012-1575-z.

Vannucchi, Giulia; Masi, Gabriele; Toni, Cristina; Dell′Osso, Liliana; Erfurth, Andreas; Perugi, Giulio (2014): Bipolar disorder in adults with Asperger′s syndrome: A systematic review. In: *Journal of Affective Disorders* 168, pp. 151-160. DOI: 10.1016/j.jad.2014.06.042.

Ventola, Pamela; Kleinman, Jamie; Pandey, Juhi; Wilson, Leandra; Esser, Emma; Boorstein, Hilary et al. (2007): Differentiating between Autism Spectrum Disorders and Other Developmental Disabilities in Children Who Failed a Screening Instrument for ASD. In: *J Autism Dev Disord* 37 (3), pp. 425-436. DOI: 10.1007/s10803-006-0177-z.

Ventola, Pamela E.; Kleinman, Jamie; Pandey, Juhi; Barton, Marianne; Allen, Sarah; Green, James et al. (2006): Agreement among four diagnostic instruments for autism spectrum disorders in toddlers. In: *Journal of Autism and Developmental Disorders* 36 (7), pp. 839-847. DOI: 10.1007/s10803-006-0128-8.

Vogeley, Kai (2012): Being Different. Asperger syndrome and high-functioning autism in adulthood a guidebook. 1st ed. Weinheim u.a.: Beltz.

Voineagu, Irina; Yoo, Hee Jeong (2013): Current Progress and Challenges in the Search for Autism Biomarkers. In: *Disease Markers* 35 (5), pp. 55-65. DOI: 10.1155/2013/476276.

Volk, Heather E.; Hertz-Picciotto, Irva; Delwiche, Lora; Lurmann, Fred; McConnell, Rob (2011): Residential Proximity to Freeways and Autism in the CHARGE Study. In: *Environ Health Perspect* 119 (6), pp. 873-877. DOI: 10.1289/ehp.1002835.

Volk, Heather E.; Lurmann, Fred; Penfold, Bryan; Hertz-Picciotto, Irva; McConnell, Rob (2013): Traffic-Related Air Pollution, Particulate Matter, and Autism. In: *JAMA Psychiatry* 70 (1), pp. 71-77. DOI: 10.1001/jamapsychiatry.2013.266.

Walker, D. R.; Thompson, A.; Zwaigenbaum, L.; Goldberg, J.; Bryson, S. E.; Mahoney, W. J. et al. (2004): Specifying PDD-NOS: A Comparison of PDD-NOS, Asperger Syndrome, and Autism. In: *Journal of the American Academy of Child & Adolescent Psychiatry* 43 (2), pp. 172-180. DOI: 10.1097/00004583-200402000-00012.

Walsh, Pat; Elsabbagh, Mayada; Bolton, Patrick; Singh, Ilina (2011): In search of biomarkers for autism: scientific, social and ethical challenges. In: *Nat Rev Neurosci* 12 (10), pp. 603-612. DOI: 10.1038/nrn3113.

von Gontard, Alexander von; Niemczyk, Justine; Thomé-Granz, Sigrid; Nowack, Judith; Moritz, Anne-Michaela; Equit, Monika (2015a): Incontinence and parent-reported oppositional defiant disorder symptoms in young children-a population-based study. In: Pediatr Nephrol 30 (7), pp. 1147-1155. DOI: 10.1007/s00467-014-3040-z.

von Gontard, A. von; Pirrung, M.; Niemczyk, J.; Equit, M. (2015b): Incontinence in children with autism spectrum disorder. In: Journal of Pediatric Urology 11 (5), p. 264.e1. DOI: 10.1016/j.jpurol.2015.04.015.

Warren, Zachary; Vehorn, Alison; Dohrmann, Elizabeth; Nicholson, Amy; Sutcliffe, James S.; Veenstra-VanderWeele, Jeremy (2012): Accuracy of phenotyping children with autism based on parent report: what specifically do we gain phenotyping "rapidly"? In: *Autism Res* 5 (1), pp. 31-38, DOI: 10.1002/aur.230.

Webb, E.; Morey, J.; Thompsen, W.; Butler, C.; Barber, M.; Fraser, W. I. (2003): Prevalence of autistic spectrum disorder in children attending mainstream schools in a Welsh education authority. In: *Dev Med Child Neurol* 45 (06). DOI: 10.1017/S0012162203000720.

Weisbrot, Deborah M.; Gadow, Kenneth D.; DeVincent, Carla J.; Pomeroy, John (2005): The Presentation of Anxiety in Children with Pervasive Developmental Disorders. In: *Journal of Child and Adolescent Psychopharmacology* 15 (3), pp. 477-496. DOI: 10.1089/cap.2005.15.477.

Werling, Donna M.; Geschwind, Daniel H. (2015): Recurrence rates provide evidence for sex-differential, familial genetic liability for autism spectrum disorders in multiplex families and twins. In: *Molecular Autism* 6 (1), p. 63. DOI: 10.1186/s13229-015-0004-5.

Westman Andersson, Gunilla; Miniscalco, Carmela; Gillberg, Christopher (2013): Autism in Preschoolers: Does Individual Clinician's First Visit Diagnosis Agree with Final Comprehensive Diagnosis? In: The *Scientific World Journal* 2013 (1), pp. 1-7. DOI: 10.1155/2013/716267.

Wiehe, Vernon R. (2003): Empathy and narcissism in a sample of child abuse perpetrators and a comparison sample of foster parents. In: *Child Abuse & Neglect* 27 (5), pp. 541-555. DOI: 10.1016/S0145-2134(03)00034-6.

Wiggins, L. D.; Bakeman, R.; Adamson, L. B.; Robins, D. L. (2007): The Utility of the Social Communication Questionnaire in Screening for Autism in Children Referred for Early Intervention. In: *Focus on Autism and Other Developmental Disabilities* 22 (1), pp. 33-38. DOI: 10.1177/10883576070220010401.

Wiggins, L. D.; Piazza, V.; Robins, D. L. (2014): Comparison of a broad-based screen versus disorder-specific screen in detecting young children with an autism spectrum disorder. In: *Autism* 18 (2), pp. 76-84. doi: 10.1177/1362361312466962.

Wiggins, Lisa D.; Robins, Diana L. (2008): Brief Report: Excluding the ADI-R Behavioral Domain Improves Diagnostic Agreement in Toddlers. In: *J Autism Dev Disord* 38 (5), pp. 972-976. DOI: 10.1007/s10803-007-0456-3.

Williams, Emma; Thomas, Kate; Sidebotham, Helen; Emond, Alan (2008a): Prevalence and characteristics of autistic spectrum disorders in the ALSPAC cohort. In: *Developmental Medicine & Child Neurology* 50 (9), pp. 672-677. DOI: 10.1111/j.1469-8749.2008.03042.x.

Williams, K.; Glasson, E. J.; Wray, J.; Tuck, M.; Helmer, M.; Bower, C. I.; Mellis, C. M. (2005): Incidence of autism spectrum disorders in children in two Australian states. In: *Med J Aust* 182 (3), pp. 108-111.

Williams, K.; Helmer, M.; Duncan, G. W.; Peat, J. K.; Mellis, C. M. (2008b): Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia. In: *Child Care Health Dev* 34 (2), pp. 249-256. doi: 10.1111/j.1365-2214.2007.00796.x.

Wing, L. (1981): Asperger's syndrome: a clinical account. In: *Psychological Medicine* 11, pp. 115-129.

Wisdom, Sarah N.; Dyck, Murray J.; Piek, Jan P.; Hay, David; Hallmayer, Joachim (2007): Can autism, language and coordination disorders be differentiated based on ability profiles? In: *Eur Child Adolesc Psychiatry* 16 (3), pp. 178-186. DOI: 10.1007/s00787-006-0586-8.

Wong, V. C. N.; Hui, S. L. H. (2007): Epidemiological Study of Autism Spectrum Disorder in China. In: *Journal of Child Neurology* 23 (1), pp. 67-72. DOI: 10.1177/0883073807308702.

Wood, Claire L.; Warnell, Frances; Johnson, Mary; Hames, Annette; Pearce, Mark S.; McConachie, Helen; Parr, Jeremy R. (2015): Evidence for ASD Recurrence Rates and Reproductive Stoppage From Large UK ASD Research Family Databases. In: *Autism Res* 8 (1), pp. 73-81. DOI: 10.1002/aur.1414.

Woodbury-Smith, M. R.; Robinson, J.; Wheelwright, S.; Baron-Cohen, S. (2005): Screening Adults for Asperger Syndrome Using the AQ: A Preliminary Study of its Diagnostic Validity in Clinical Practice. In: *J Autism Dev Disord* 35 (3), pp. 331-335. DOI: 10.1007/s10803-005-3300-7.

Woodbury-Smith, Marc; Dein, Kalpana (2014): Autism Spectrum Disorder (ASD) and Unlawful Behaviour: Where Do We Go from Here? In: *J Autism Dev Disord* 44 (11), pp. 2734-2741. DOI: 10.1007/s10803-014-2216-5.

Woolfenden, Sue; Sarkozy, Vanessa; Ridley, Greta; Williams, Katrina (2012): A systematic review of the diagnostic stability of Autism Spectrum Disorder. In: *Research in Autism Spectrum Disorders* 6 (1), pp. 345-354. DOI: 10.1016/j.rasd.2011.06.008.

World Health Organization (1986): International Classification of Diseases, Injuries and Causes of Death (ICD) as revised by the 9th revision published by the Federal Ministry of Health. Cologne, Stuttgart, Berlin, Mainz: Kohlhammer.

World Health Organization (1992): International Classification of Mental Disorders. ICD-10. Bern: Huber.

Xu, Guifeng; Jing, Jin; Bowers, Katherine; Liu, Buyun; Bao, Wei (2014): Maternal Diabetes and the Risk of Autism Spectrum Disorders in the Offspring: A Systematic Review and Meta-Analysis. In: *J Autism Dev Disord* 44 (4), pp. 766-775. DOI: 10.1007/s10803-013-1928-2.

Yasuhara, Akihiro (2010): Correlation between EEG abnormalities and symptoms of autism spectrum disorder (ASD). In: *Brain and Development* 32 (10), pp. 791-798. DOI: 10.1016/j.braindev.2010.08.010.

Yeargin-Allsopp, Marshalyn; Rice, Catherine; Karapurkar, Tanya; Doernberg, Nancy; Boyle, Coleen; Murphy, Catherine (2003): Prevalence of Autism in a US Metropolitan Area. In: *JAMA* 289 (1). DOI: 10.1001/jama.289.1.49.

Wechsler preschool and primary scale of intelligence- III. (WPPSI-III) ; German version ; Manual ; [German adaptation after D. Wechsler] (2014). 3rd, revised and enlarged ed. Frankfurt, M: Pearson (Always learning).

Zwaigenbaum, Lonnie; Bryson, Susan; Garon, Nancy (2013): Early identification of autism spectrum disorders. In: *Behavioural Brain Research* 251, pp. 133-146. DOI: 10.1016/j.bbr.2013.04.004.

Zwaigenbaum, Lonnie; Bryson, Susan; Rogers, Tracey; Roberts, Wendy; Brian, Jessica; Szatmari, Peter (2005): Behavioral manifestations of autism in the first year of life. In: *International Journal of Developmental Neuroscience* 23 (2-3), pp. 143-152. DOI: 10.1016/j.ijdevneu.2004.05.001.