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Marja-Leena Mattila

AUTISM SPECTRUM DISORDERS

AN EPIDEMIOLOGICAL AND CLINICAL STUDY

UNIVERSITY OF OULU GRADUATE SCHOOL; UNIVERSITY OF OULU, FACULTY OF MEDICINE, INSTITUTE OF CLINICAL MEDICINE, DEPARTMENT OF PAEDIATRICS, CLINIC OF CHILD PSYCHIATRY; THULE INSTITUTE; OULU UNIVERSITY HOSPITAL



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MARJA-LEENA MATTILA

AUTISM SPECTRUM DISORDERS

An epidemiological and clinical study

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Abstract

Background: Autism spectrum disorders (ASDs), defined as pervasive developmental disorders (PDDs) in DSM-IV and ICD-10, become manifest in childhood, ranging from a severe form, autism, to milder forms, Asperger syndrome (AS) and pervasive developmental disorder not otherwise specified (PDD-NOS)/atypical autism. AS is also specified in criteria by Gillberg and by Szatmari *et al.* Different diagnostic criteria sets, overlaps, inaccuracies and exclusion criteria of many comorbid psychiatric disorders in PDDs have caused confusion. In DSM-5, PDDs were replaced by one diagnosis called ASD.

Aims and methods: This is an epidemiological study of 8-year-old children and a clinical study of 9- to 16-year-old high-functioning outpatients with AS/autism (HFA). The epidemiological target population (n = 4,422) was rated via the Autism Spectrum Screening Questionnaire (ASSQ) by parents and/or teachers and a screened sample was examined in order to estimate the prevalence of ASDs, to discover deficits in the diagnostic criteria of ASDs, to evaluate DSM-5 draft criteria for ASD, and to assess cut-off scores for the Finnish ASSQ. Comorbid psychiatric disorders were identified and overall level of functioning rated in 50 subjects with AS/HFA.

Results: The prevalence of AS according to DSM-IV was 2.5, to ICD-10 2.9, to Gillberg 2.7, and to Szatmari *et al.* 1.6 per 1,000. The prevalence of autism was 4.1 and that of ASDs 8.4 per 1,000 (DSM-IV). DSM-5 draft criteria were less sensitive in detecting AS/HFA. For 7- to 12-year-old children (IQ \ge 50), the optimal cut-off scores were 30 in clinical settings and 28 in total population screening using summed parent-rated and teacher-rated ASSQ scores. Comorbid psychiatric disorders were common (prevalence 74%) and often multiple; behavioral disorders in 44%, anxiety disorders in 42%, and tic disorders in 26%. Oppositional defiant disorder, depressive disorder and anxiety disorders as comorbidities indicated significantly lower levels of functioning.

Conclusions: Our results indicate the need to standardize the diagnostic criteria. The ICD-11 criteria should be uniform and harmonize with DSM-5. Determining cut-off scores for ASD screening instruments in different languages and cultures is of utmost importance. Clinicians are reminded to investigate psychiatric comorbidity in ASDs in order to target treatment and rehabilitation precisely.

Keywords: Asperger syndrome, ASSQ, autism, autism spectrum disorder, diagnosis, DSM-5, epidemiology, prevalence, psychiatric comorbidity, screening

Mattila, Marja-Leena, Autismikirjon häiriöt. Epidemiologinen ja kliininen tutkimus

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Tiivistelmä

Lähtökohdat: Autismikirjon häiriöt, ICD-10:ssä ja DSM-IV:ssä nimellä laaja-alaiset kehityshäiriöt, ilmenevät lapsuudessa. Niihin luetaan autismi, Aspergerin oireyhtymä (AS) ja tarkemmin määrittelemätön laaja-alainen kehityshäiriö/epätyypillinen autismi. Gillberg sekä Szatmari työtovereineen ovat myös määritelleet AS:n kriteerit. Useat diagnostiset kriteerit, päällekkäisyydet, epätarkkuudet ja monien psykiatristen liitännäishäiriöiden poissulkeminen laaja-alaisissa kehityshäiriöissä ovat aiheuttaneet sekaannuksia. DSM-5:ssä laaja-alaiset kehityshäiriöt korvattiin yhdellä diagnoosilla: autismikirjon häiriö.

Menelmät ja tavoitteet: Väitöstyö muodostui 8-vuotiaita lapsia koskeneesta epidemiologisesta tutkimuksesta sekä 9–16-vuotiaita AS- ja autistisia (HFA) lapsia ja nuoria koskeneesta kliinisestä tutkimuksesta. Vanhemmat ja/tai opettajat täyttivät epidemiologisen kohderyhmän lapsista (n = 4 422) suomennetun autismikirjon seulontalomakkeen (ASSQ), ja seuloutuneille tehtiin diagnostiset tutkimukset. Tämän jälkeen määritettiin autismikirjon esiintyvyys, kartoitettiin diagnostisten kriteerien puutteita, arvioitiin DSM-5-luonnoskriteerit autismikirjon häiriölle ja määritettiin ASSQ:n seulontarajat. Psykiatrinen komorbiditeetti ja sen merkitys toiminnalliseen tasoon tutkittiin AS-/HFA-lapsilla ja -nuorilla (n = 50).

Tulokset: AS:n esiintyvyys oli 2,5/1000 DSM-IV:n, 2,9/1000 ICD-10:n, 2,7/1000 Gillbergin ja 1,6/1000 Szatmarin mukaan. Autismin esiintyvyys oli 4,1/1000 ja koko autismikirjon 8,4/1000 (DSM-IV). DSM-5-luonnoskriteerit olivat epäherkät tunnistamaan AS:ää ja HFA:ta. Parhaiten soveltuviksi ASSQ:n seulontarajoiksi alakouluikäisille ($\text{AO} \ge 50$) osoittautuivat 30 kliinisiä tilanteita ja 28 väestöseulontoja varten laskemalla yhteen vanhempien arvioinnin ja opettajan arvioinnin pisteet. Psykiatrisia liitännäishäiriöitä oli 74 %:lla, ja monilla oli useita. Käytöshäiriöitä oli 44 %:lla, ahdistuneisuushäiriöt alensivat merkitsevästi toiminnallista tasoa.

Päätelmät: Tulokset osoittivat diagnostisten kriteereiden yhtenäistämistarpeen. ICD-11:een on syytä laatia yhdenmukaiset kriteerit DSM-5:n kanssa. Autismikirjon seulontalomakkeille on tarpeen määrittää eri kieliin ja kulttuureihin soveltuvat pisterajat. Psykiatrisen komorbiditeetin selvittäminen autismikirjon häiriöissä on tärkeää, jotta hoito ja kuntoutus voidaan kohdentaa oikein.

Asiasanat: Aspergerin oireyhtymä, autismi, autismikirjon häiriö, diagnoosi, DSM-5, epidemiologia, esiintyvyys, psykiatrinen komorbiditeetti, seulonta

Whatever you do, work at it with all your heart, as working for the Lord - COLOSSIANS 3:23 -

With love to all my family

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In the 1990s as a newly qualified pediatrician, I had a permanent position in Tahkokangas Service Center in Oulu, which is a rehabilitation center for people with mental retardation as well as for people with autism. I learned a lot there, but struggled with cases of severe epilepsy, which were so difficult. To learn more, I took a break from Tahkokangas and accepted a temporary post at the pediatric neurologic department at Oulu University Hospital, directed by Professor Heikki Rantala. In the first days of this millennium, Heikki asked me: "Are you interested in research?" This was the first day of this long journey to the public defense of my doctoral thesis. Heikki advised me to contact Professor Irma Moilanen in the Clinic of Child Psychiatry at the University of Oulu, where a research project was waiting for a researcher to begin. I would like to thank Professor Heikki Rantala sincerely for the confidence shown by offering me this opportunity. Research matured gradually for me like a fascinating hobby involving my heart and soul – a mission.

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Oulu, November 29, 2013

fraya-bene flattile

Abbreviations

ACI-PL	Autism Comorbidity Interview–Present and Lifetime Version
AD	Autistic disorder
ADHD	Attention Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ANOVA	Analysis of variance
APA	American Psychiatric Association
AS	Asperger syndrome
ASD	Autism spectrum disorder
ASDI	Asperger Syndrome (and high-functioning autism) Diagnostic Interview
ASSQ	Autism Spectrum Screening Questionnaire
ASSQ-REV	Autism Spectrum Screening Questionnaire–Revised Extended Version
AUC	Area under the curve
CD	Conduct disorder
CGAS	Children's Global Assessment Scale
CI	Confidence interval
CIA	Confidence interval analysis
DD-CGAS	Developmental Disability-Child Global Assessment Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-I	Diagnostic and Statistical Manual of Mental Disorders, First Edition
DSM-II	Diagnostic and Statistical Manual of Mental Disorders, Second Edition
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

FSIQ	Full-scale intelligence quotient
HFA	High-functioning autism
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases, 9th Revision
ICD-10	International Classification of Diseases, 10th Revision
ICD-11	International Classification of Diseases, 11th Revision
IQ	Intelligence quotient
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for
	School-Age Children–Present and Lifetime Version
LR	Likelihood ratio
MDD	Major depressive disorder
NPV	Negative predictive value
OCD	Obsessive-compulsive disorder
OCPD	Obsessive-compulsive personality disorder
ODD	Oppositional defiant disorder
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder not otherwise specified
PPV	Positive predictive value
ROC	Receiver operating characteristic
SCD	Social communication disorder
Se	Sensitivity
Sp	Specificity
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization
WISC-III	Wechsler Intelligence Scale for Children–Third Edition

List of Original Publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals.

- I Mattila ML, Kielinen M, Jussila K, Linna SL, Bloigu R, Ebeling H & Moilanen I (2007) An epidemiological and diagnostic study of Asperger syndrome according to four sets of diagnostic criteria. J Am Acad Child Adolesc Psychiatry 46(5): 636–646.
- II Mattila ML, Kielinen M, Linna SL, Jussila K, Ebeling H, Bloigu R, Joseph RM & Moilanen I (2011) Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. J Am Acad Child Adolesc Psychiatry 50(6): 583–592.
- III Mattila ML, Jussila K, Linna SL, Kielinen M, Bloigu R, Kuusikko-Gauffin S, Joskitt L, Ebeling H, Hurtig T & Moilanen I (2012) Validation of the Finnish Autism Spectrum Screening Questionnaire (ASSQ) for clinical settings and total population screening. J Autism Dev Disord 42(10): 2162–2180.
- IV Mattila ML, Hurtig T, Haapsamo H, Jussila K, Kuusikko-Gauffin S, Kielinen M, Linna SL, Ebeling H, Bloigu R, Joskitt L, Pauls DL & Moilanen I (2010) Comorbid psychiatric disorders associated with Asperger syndrome/high-functioning autism: a community- and clinic-based study. J Autism Dev Disord 40(9): 1080–1093.

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1 Introduction

Since Kanner's classic report of "early infantile autism" in 1943, remarkable progress has been made in our understanding of autism and autism spectrum disorders (ASDs) (Kanner 1943, Volkmar et al. 2012). During these 70 years, there have been many clarifications regarding aspects of autism and ASDs and approaches to diagnosis. The two major diagnostic frameworks for ASDs are defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) by the American Psychiatric Association (APA) and in the International Classification of Diseases (ICD) by the World Health Organization (WHO). According to DSM-IV (APA 1994) and ICD-10 (WHO 1993), ASDs are referred to as pervasive developmental disorders (PDDs) and described by three defining dimensions of behavior: 1) deficits in social reciprocity, 2) deficits in communication, and 3) presence of restricted, repetitive and stereotyped patterns of behavior, interests and activities, causing severe and pervasive impairments and lacks in the ability to relate to others, as well in language, thinking and feeling. These disorders become manifest in childhood and range from a severe form, classified as autism, through a milder form called Asperger syndrome (AS) to some aspects of a "broader autism spectrum" named pervasive developmental disorder not otherwise specified (PDD-NOS)/atypical autism. The operational criteria of AS were outlined by Gillberg and Gillberg in 1989 (Gillberg & Gillberg 1989). Also, Szatmari et al. proposed criteria for AS in 1989 (Szatmari et al. 1989). According to DSM-IV and ICD-10, two rare conditions, Rett's disorder and childhood disintegrative disorder, are also included in PDDs; these conditions have been excluded from the topic of the present doctoral thesis.

The prevalence of autism in the Provinces of Oulu and Lapland in Northern Finland was estimated by collecting data from hospital records in 1996 and 1997 (Kielinen *et al.* 2000). Only a few subjects with AS had been registered in hospital records, reflecting the fact that the Finnish ICD-10 was taken into use at the beginning of 1996. Different diagnostic criteria sets of AS and overlapping and inaccuracy in the criteria of PDDs have caused confusion in research as well as in clinical practice. An epidemiological study would give us the possibility to consider the prevalence and diagnostic criteria sets of ASDs.

In recent years, the publication of DSM-5 was one of the most anticipated events in the mental health field. The first DSM-5 draft criteria for ASD were posted by the APA in February 2010 and the revised draft in January 2011. The final DSM-5 was released at the APA's Annual Meeting in May 2013 and it marked the

end of a 14-year process in revising the criteria for the diagnosis and classification of mental disorders (APA 2013). In DSM-5, the whole spectrum of PDDs was replaced with one disorder named "autism spectrum disorder" described by two defining dimensions of behavior: 1) deficits in social communication and social interaction, and 2) presence of restrictive and repetitive patterns of behavior, interests and activities. Our thoroughly diagnosed epidemiological data gave us the opportunity to compare DSM-IV and the DSM-5 draft criteria posted in February 2010 and to be the first to publish the results.

In clinical practice, a screening instrument is an aid in recognizing the features of autism spectrum in order to speed up the diagnostic process. The Autism Spectrum Screening Questionnaire (ASSQ) was developed in Swedish as a screen for ASDs (Ehlers *et al.* 1999), and it has been translated into many languages (Ehlers & Gillberg 1993, Georgsdottir *et al.* 2013, Guo *et al.* 2011, Jakab *et al.* 2013, Kim *et al.* 2011, Kobayashi *et al.* 2013, Lesinskiene 2000, Mattila *et al.* 2009, Petersen *et al.* 2006, Posserud *et al.* 2006). The ASSQ was translated into Finnish in the 1990s and has been used in clinical settings in Finland ever since. Validation studies show broad variability of established cut-off scores in different languages and cultures (Ehlers *et al.* 1999, Guo *et al.* 2011, Posserud *et al.* 2006). Unfortunately, the Finnish ASSQ had not been validated and the cut-off scores had not been determined prior to the present work.

A high degree of psychiatric comorbidity is associated with ASDs (Gadow *et al.* 2004, Ghaziuddin *et al.* 1998, Gjevik *et al.* 2011, Leyfer *et al.* 2006, Mukaddes *et al.* 2010, Simonoff *et al.* 2008). However, in DSM-IV and ICD-10, many psychiatric comorbidities are excluded, which is a source of confusion. For example, the diagnosis of PDD rules out attention deficit/hyperactive disorder (ADHD; DSM-IV, ICD-10), and the diagnostic criteria of AS exclude obsessive-compulsive disorder (OCD; ICD-10) and schizophrenia (DSM-IV, ICD-10). Studies concerning comorbid psychiatric disorders in ASDs have mainly revealed one or just a few comorbidities, and only relatively few investigators have dealt with the whole spectrum of comorbid psychiatric disorders in ASDs or have used standardized instruments (Ghaziuddin *et al.* 1998, Gjevik *et al.* 2011, Leyfer *et al.* 2006, Mukaddes *et al.* 2010, Simonoff *et al.* 2008). To our knowledge, only one population-based study has dealt previously with psychiatric comorbid disorders in subjects with ASDs (Simonoff *et al.* 2008). In addition, psychiatric comorbidity in ASDs was previously an unstudied research area in Finland.

The lack of research in the above-mentioned areas gave rise to the present doctoral thesis.

2 Review of the literature

2.1 History

The word "autism" has been used for about 100 years. It comes from the combination of the Greek prefix "auto" meaning "self" and the Greek suffix "ism" which means "the act, state, or theory of". The term describes a condition in which a person withdraws from social interaction – hence an isolated self. Eugen Bleuler (1911, 1983), a Swiss psychiatrist, was the first person to use the term "autism", in 1911, to refer to detachment from reality with the relative and absolute predominance of the inner life in individuals with schizophrenia. The word autism first took its modern sense in 1938 when Hans Asperger, an Austrian pediatrician at Vienna University Hospital, adopted Bleuler's terminology "autistic psychopaths" in a paper in German about child psychology (Asperger 1938). In the 1940s, Leo Kanner (1943), a Jewish American child psychiatrist and native Austrian, was the first to use the term "autism" in English in its modern sense.

Autism was probably first described under the title Rapport et memoires sur le Sauvage de l'Aveyron ("The Wild Boy of Aveyron") by a French physician Jean-Marc-Gaspard Itard (1962) in the second decade of the nineteenth century. Itard named his descriptions "intellectual mutism" and he effectively separated these cases from cases of mental retardation. Known for his attempts at rehabilitation of the "feral" child, the Wild Boy of Aveyron, Itard wrote a largely unacknowledged paper in 1828 on the different causes of "intellectual mutism", the result of 28 years of observations at the Institut des Sourd-Muets in Paris. (Carrey 1995.) In the mid-1920s, Grunja Jefimovna Ssucharewa, a Russian neurologist, published a paper in which she described "schizoid personality disorder" in children (Ssucharewa 1926). Ssucharewa's paper was not translated into English until seventy years later, when it became clear that she had described the core deficits and major hallmarks of autism (Wolff 1996).

In the 1940s, Kanner (1943) introduced the label "early infantile autism" by publishing a paper entitled "Autistic Disturbances of Affective Contact", in which he described a distinct syndrome in 11 children with unusual behavior similarities instead of previous depictions of such children as feeble-minded, retarded, moronic, idiotic or schizoid. Several traits that Kanner described in these children, including "autistic aloneness," and "insistence on sameness" or "resistance to change," form the essential criteria in current conceptualizations of ASD. Kanner's publication went

on to become a classic in the field of clinical psychiatry. It also caught professional attention and was internationally acknowledged among English-speaking researchers. Only one year after Kanner's publication of "early infantile autism", Asperger (1944) published his paper on four school-age boys, usually with normal intelligence, and referred to the condition as "autistic psychopathy". Asperger's paper was published in German and did not receive any attention among Englishspeaking researchers for decades, until the Dutch child psychiatrist Dirk Arnold van Krevelen (1971) presented an opportunity for English readers to become familiar with these descriptions. He distinguished the features between Kanner's group with "early infantile autism" and Asperger's group with "autistic psychopathy". In 1981, the English child psychiatrist Lorna Wing induced huge interest in AS by publishing a review and a series of 34 case reports based on Asperger's descriptions. In her publication, Wing chose the name "Asperger's syndrome" in order to use a neutral name instead of "autistic psychopathy", which had led to misunderstanding because of "the popular tendency to equate psychopathy with sociopathic behavior" (Wing 1981). In 1989, Asperger's descriptions were operationalized for a diagnosis by Gillberg and Gillberg (1989). However, Asperger's original paper was not translated into English until 1991 (Frith 1991).

Although autism was recognized as a unique condition in the 1930s (Asperger 1938) and 1940s (Asperger 1944, Kanner 1943), autism and schizophrenia mainly remained linked over the decades. Autism was not included in DSM-I in 1952 or in DSM-II in 1968. In both the first and the second editions of the DSM the terms "autism" and "autistic" were used to describe behaviors manifested in schizophrenia. Children who exhibited autistic-like symptoms were diagnosed as schizophrenic, childhoodtype. However, increasingly, researchers and medical professionals began to have an understanding of autism as a condition separate from schizophrenia in children, and gradually an understanding of autism as having a neurodevelopmental origin. In 1979, the WHO recognized autism for the first time, in ICD-9, in which it was referred to as infantile autism ("Kanner's autism"), while childhood schizophrenia was explicitly excluded. ICD-9 also referred to the condition described by Asperger, although it was not named there. Instead, it was defined under a new category of "other specified pervasive developmental disorders". (Feinstein 2010.) In turn, in DSM-III, autism was dissociated from schizophrenia in 1980, recognizing it as a separate diagnostic category with one autism designation, "infantile autism". Both ICD-9 and DSM-III defined infantile autism by narrow criteria, reflecting the more severe and classical Kanner-type of autism. Inclusion of infantile autism as an explicitly defined category was a major accomplishment (Volkmar et al. 2012). In 1987, with the revision of DSM-III (DSM-III-R) "infantile autism" was expanded to "autistic disorder" (AD), the criteria of which became less restrictive; in consequence, many more subjects were given the diagnosis of autism. DSM-III-R criteria were, thus, criticized for their low specificity, *i.e.*, overdiagnosis of autism in more cognitively impaired individuals where high rates of stereotyped behaviors are frequent (Szatmari 1992, Volkmar *et al.* 2012) and relative underdiagnosis in more cognitively able groups (Volkmar *et al.* 2012). Low specificity of DSM-III-R was one concern informing the changes in DSM-IV. Another concern included the potential for possible differences as regards the changes to be made in ICD-10 scheduled to appear at about the same time as the new DSM-IV. Given the concern that two competing diagnostic approaches for autism would have an impact on research, some consideration was made for a joint effort to derive a diagnostic approach suitable for both publications. (Volkmar *et al.* 2012.)

The category of ASDs was named PDDs for the first time in ICD-9 and DSM-III. In the most recent release of ICD, ICD-10 in 1993, as well as in the complete release of DSM, DSM-IV in 1994, and in the text revision of DSM-IV (DSM-IV-TR) in 2000, the category of PDDs was retained, but several subtypes were added. Both DSM-IV and ICD-10 adopted an explicit categorical approach (Volkmar *et al.* 2012). Although the two systems differ in some respects for PDDs, the definitions are virtually identical for AD/childhood autism. The DSM-5 criteria were published in May 2013. In contrast to the categorical approach of DSM-IV and ICD-10, in DSM-5 a dimensional approach was adopted. All subcategories of PDDs were replaced with one disorder named "autism spectrum disorder" including specified severity levels. The next version of ICD (ICD-11) is due to be published in 2015.

2.2 Autism spectrum disorders

In DSM-IV and ICD-10, ASDs are referred to as PDDs. However, the diagnostic names of PDDs are different in the two major diagnostic frameworks (Table 1). In 2000, the text of DSM-IV was revised (DSM-IV-TR; APA 2000), but the criteria themselves were retained unchanged. In DSM-IV, a diagnosis can be made under five subcategories, AD, childhood disintegrative disorder, Rett's disorder, Asperger's disorder and PDD-NOS, and correspondingly, in ICD-10, under eight subcategories, childhood autism, atypical autism, Rett's syndrome, other childhood disintegrative disorder, overactive disorder associated with mental retardation and stereotyped movements, AS, other pervasive developmental disorders, and pervasive developmental disorder, unspecified.

DSM-IV	ICD-10		
Pervasive developmental disorders	F84 Pervasive developmental disorders		
299.00 Autistic disorder	F84.0 Childhood autism		
299.80 Pervasive developmental disorder not	F84.1 Atypical autism		
otherwise specified			
	F84.10 Atypicality in age of onset		
	F84.11 Atypicality in symptomatology		
	F84.12 Atypicality in both age of onset and		
	symptomatology		
299.80 Rett's disorder	F84.2 Rett's syndrome		
299.10 Childhood disintegrative disorder	F84.3 Other childhood disintegrative disorder		
	F84.4 Overactive disorder associated with mental		
	retardation and stereotyped movements		
299.80 Asperger's disorder	F84.5 Asperger's syndrome		
	F84.8 Other pervasive developmental disorders		
	F84.9 Pervasive developmental disorder,		
	unspecified		

Table 1. Pervasive developmental disorders.

2.2.1 Autistic disorder/childhood autism

The definitions of AD in DSM-IV and that of childhood autism in ICD-10 are almost identical, including 12 criteria grouped into three domains (social, communication-play, and restricted interests and behaviors) with a minimum requirement of a total of six criteria, two of which had to be social (highlighting the strength of social dysfunction as being the best predictor of diagnosis of autism), one of which had to be communicative, and one needing to be behavioral, with the remaining two capable of coming from any domain (Appendices 1 and 2); over 2,000 combinations of criteria can meet this threshold (Volkmar *et al.* 2012). To meet the criteria for AD in DSM-IV, delays or abnormal functioning must be evident in at least one of the following areas, with onset prior to the age of 3 years: 1) social interaction, 2) language as used in social communication, and 3) symbolic or imaginative play, and correspondingly to meet the criteria for childhood autism in ICD-10: 1) receptive or expressive language as used in social communication, 2) the development of selective social attachments or of reciprocal social interaction, and 3) functional or symbolic play.

2.2.2 Asperger syndrome

Asperger syndrome belongs to the category of PDDs typically characterized by the same kind of qualitative impairments in reciprocal social interaction that typify autism, together with restricted, repetitive, and stereotyped behaviors, interests and activities. Throughout the present study, the operational criteria of AS developed by Gillberg and Gillberg in 1989 and elaborated by Gillberg in 1991 are referred to as Gillberg's criteria (Ehlers & Gillberg 1993, Gillberg 1991, Gillberg & Gillberg 1989; Appendix 3). The criteria for AS proposed by Szatmari *et al.* (1989) are presented in Appendix 4, the research criteria for AS, recognized in ICD-10, in Appendix 5, and the corresponding criteria for AS, *i.e.*, Asperger's disorder in DSM-IV, in Appendix 6. Table 2 shows a comparison of four sets of diagnostic criteria. In DSM-5 (2013) the label of AS was no longer recognized; instead, it was incorporated into the category of ASD.

The prevailing sense is that AS is a variant of autism and located at the milder end of ASDs. Diagnostic manuals (DSM-IV, ICD-10) help with the definition of AS only up to a point. The label "high-functioning autism" (HFA) is much used of the high-functioning subjects with autism and it is often considered to be interchangeable with AS, although development in the first 36 months is not defined as being delayed in AS and only two of the three main domains of autistic behavior are stated in AS. The most workable distinction between AS and autism, requirements of normal early language and cognitive development in AS, can be regarded as being to some extent artificial. Reliable early development hallmarks are also hard to apply, especially for adult cases. In addition, early language criteria do not demarcate distinct groups, e.g., distinguishable at later ages. The requirements of normal early language and cognitive function in AS are mentioned in DSM-IV and ICD-10, while speech delay is allowed in Gillberg's criteria. The presence of mental retardation in AS has been under discussion from the very beginning. Wing (1981), the initiator of interest in AS, accepted mental retardation, although Asperger (1944, 1979) himself did not.

In AS, marked social difficulties (of the type seen in autism) develop, particularly with peers, and come to attention somewhat later in life than in autism. Social impairments are stated in all these four sets of diagnostic criteria for AS, but the emphases of the limitations of social functioning are different; for example, in the criteria of Szatmari *et al.*, solitariness is emphasized. In turn, communication difficulties are not stated in DSM-IV and ICD-10. However, difficulties in prosody (Chevallier *et al.* 2011, Paul *et al.* 2005, Shriberg *et al.*

Clinical feature	DSM-IV	ICD-10	Gillberg ¹	Szatmari et al. ²
1. Manifestation				
delays in speech	no	no	may be	not defined
delays in cognitive development	no	no	not defined	not defined
delays in self-help skills, adaptive	no	no	not defined	not defined
behavior and curiosity about the				
environment				
2. Social impairments	yes ³	yes ³	yes	yes
impaired nonverbal communication	may be	may be	yes	yes
inadequate friendships	may be	may be	may be	yes
lack of empathy	may be	may be	may be	may be
lack of sharing	may be	may be	may be	may be
3. Odd speech and language	not defined	not defined	yes	yes
formal, pedantic language	not defined	not defined	may be	not defined
odd prosody	not defined	not defined	may be	may be
misinterpretations of literal/implied	not defined	not defined	may be	not defined
meanings				
repetitive patterns of speech	not defined	not defined	not defined	may be
idiosyncratic use of words	not defined	not defined	not defined	may be
4. Stereotyped, repetitive behavior	yes ⁴	yes ⁴	yes	not defined
all-absorbing interest	may be	may be	yes	not defined
routines or rituals	may be	may be	yes	not defined
repetitive motor mannerisms	may be	may be	not defined	not defined
preoccupation with parts of objects	may be	may be	not defined	not defined
5. Motor clumsiness	not defined	may be	yes	not defined
6. Isolated special skills	not defined	common	not defined	not defined
7. Clinically significant impairments in social, occupational or other important areas of functioning	yes	not defined	not defined	not defined
8. Exclusion of AD/other PDDs	yes	yes	no	yes

Table 2. Comparison of four sets of diagnostic criteria of AS.

AS, Asperger syndrome; AD, autistic disorder; PDD, pervasive developmental disorder ¹ Ehler & Gillberg 1993, Gillberg 1991, Gillberg & Gillberg 1989 ² Szatmari *et al.* 1989 ³ at least two required ⁴ at least one required

2001) and pragmatic impairments in both language expression and comprehension (Lam & Yeung 2012, Landa 2000, Loukusa *et al.* 2007) are significant features in high-functioning subjects with ASDs. Pragmatic difficulties in ASDs are evident when understanding requires interpretation of indirect, ambiguous or figurative language utilizing contextual information (Dennis *et al.* 2001, Jolliffe & Baron-Cohen 1999, Loukusa *et al.* 2007, Loukusa & Moilanen 2009). Also, difficulties in interactional language use and deficiencies in narrative and discourse abilities are common in ASDs (Adams *et al.* 2002, Losh & Capps 2003, Volden 2004). In recent studies, impaired perception of speech prosody in AS caused by deficient auditory processing has been suggested (Jansson-Verkasalo *et al.* 2005, Korpilahti *et al.* 2007, Kujala *et al.* 2005, 2007, 2010, Lepistö *et al.* 2006, 2007, 2008, O'Connor 2012). In contrast to DSM-IV and ICD-10, Gillberg and Szatmari *et al.* did include odd speech and language in their criteria.

Circumscribed interests are marked and are a source of disability in AS. One of four stereotyped repetitive interests and/or activities is required to be met for the diagnosis of AS according to DSM-IV and ICD-10, and two of them should be detected according to Gillberg's criteria, whereas Szatmari *et al.* did not mention them at all. Abnormal idiosyncratic negative responses to specific sensory stimuli (touch, light, sounds, taste, and smell) are not stated in any of the four sets of criteria, although hyper- or hypo-reactivity to sensory input have been associated with ASDs (Jasmin *et al.* 2009, Nieminen-von Wendt *et al.* 2005).

Motor clumsiness may be present in AS (ICD-10, Gillberg & Gillberg 1991) or is not defined (DSM-IV, Szatmari *et al.* 1989). Clinically significant impairments in social, occupational or other important areas of functioning are required for the diagnosis of AS in DSM-IV, but are not mentioned at all in ICD-10, Gillberg's criteria or those of Szatmari *et al.* Other PDDs are an exclusion criterion from AS in DSM-IV and ICD-10, and AD in Szartmari *et al.*'s criteria, respectively, but not in Gillberg's criteria.

In addition to difficulty with several diagnostic criteria regarding AS, confusion also arises from the question of whether it is known what an AS case is (Frith 2004, Sharma *et al.* 2012). Asperger syndrome comprises a heterogeneous group including cases of well below average ability and poor social adaptation as well as those with superior and good social adaptation. The behavioral features of a child with AS vary from one individual to another, depending on the combination of features present. Not all cases described by Asperger would meet the criteria of Asperger's disorder defined in DSM-IV (Miller & Ozonoff 1997).

All the features that characterize AS can be found in varying degrees in the normal population. People differ in their levels of skill in social interaction and in their ability to read nonverbal social cues. There is an equally wide distribution in motor skills. Many who are capable and independent as adults have special interests that they pursue with marked enthusiasm. Collecting objects such as stamps, old glass bottles, or railway engine numbers are socially accepted hobbies. Asperger (1979) pointed out that the capacity to withdraw into an inner world of one's own special interests is available in a greater or lesser measure to all human beings. He emphasised that this ability has to be present to marked extent in those who are creative artists or scientists. The difference between someone with AS and the normal person who has a complex inner world is that the latter does take part appropriately in two-way social interaction at times, while the former does not. Also, the normal person, however elaborate his inner world, is influenced by his social experiences, whereas the person with AS seems cut off from the effects of outside contacts. A number of normal adults have outstandingly good rote memories and even retain eidetic imagery into adult life. Pedantic speech and a tendency to take things literally can also be found in normal people. It is possible that some people could be classified as suffering from AS because they are at the extreme end of the normal continuum on all these features. In others, one particular aspect may be so marked that it affects the whole of their functioning. -- Even though AS does appear to merge into the normal continuum, there are many cases in whom the problems are so marked that the suggestion of a distinct pathology seems a more plausible explanation than a variant of normality. (Wing 1981.)

2.2.3 Pervasive developmental disorder not otherwise specified/ atypical autism

Both DSM-IV and ICD-10 include these subthreshold PDD diagnoses, with very slight differences in description. These diagnoses are used when symptoms do not meet specific criteria for a PDD, but there are major social or communication difficulties or the presence of restricted behaviors of the type seen in autism. These cases are likely to represent some aspects of a "broader autism spectrum" (Towbin 2005). (Volkmar *et al.* 2012.) In DSM-IV, this category is called PDD-NOS including atypical autism, and in ICD-10, it is called atypical autism and defined separately from other PDDs and unspecified PDDs. Atypical autism does not meet the criteria for autism because of (1) late age at onset (criteria as for AD except for age at manifestation), (2) atypical

or subthreshold symptomatology (criteria as for AD except insufficient demonstrable abnormalities in one or two of the three domains of psychopathology required for the diagnosis of autism in spite of characteristic abnormalities in the other domain[s]), or (3) all of these. No specific minimum number of ASD diagnostic symptoms is required for PDD-NOS or for atypical autism.

2.2.4 Autism spectrum disorder according to DSM-5

The nosology of ASD is at a critical point in its history as regards better defining the dimensions of social-communication deficits and restricted/repetitive behaviors on an individual level for both clinical and neurobiological purposes (Lord & Jones 2012). The first DSM-5 draft criteria for ASD in February 2010 and the revised draft in January 2011 are presented in Appendices 7 and 8, and the finally settled DSM-5 criteria in Appendix 9, correspondingly.

In DSM-5, the diagnostic criteria and taxonomic structure of PDDs changed in several regards (APA 2013). First, four subcategories of PDDs in DSM-IV, *i.e.* AD, AS, childhood disintegrative disorder and PDD-NOS, were incorporated within one category of "autism spectrum disorder" that replaced the term PDD. In addition, Rett's Disorder was removed from ASD. The unified ASD category aims to produce a clear diagnostic system that identifies the common characteristics of ASDs across all ages and ability levels. ASD encompasses conditions previously referred to as early infantile autism, childhood autism, Kanner's autism, HFA, atypical autism, PDD-NOS, childhood disintegrative disorder, and Asperger's disorder (APA 2013). Second, compared with DSM-IV, there are major changes to conceptualize and diagnose ASD. To describe the single category of ASD, the triad of deficient behavior was merged into a dyad defining dimensions of behavior: (1) deficits in social communication and social interaction, and (2) presence of restricted, repetitive behaviors, interests or activities. Third, the history of the behaviors is now taken into consideration. The symptoms in these two domains of behavior should be manifest currently or they should have become manifested by history. Fourth, by merging the communication and social interaction domains, eight ASD diagnostic symptoms used in DSM-IV were reduced to three, all of them having to be met currently or by history in order for there to be a diagnosis of ASD, instead of a longer list of individual symptoms under DSM-IV, of which an individual must meet a subset. Fifth, restrictive and repetitive patterns of behaviors consist of four ASD diagnostic symptoms and also include, for the first time, an ASD diagnostic symptom concerning hyper- or hypo-reactivity to sensory input

or unusual interest in sensory aspects of the environment. At least two out of the four ASD diagnostic symptoms in the repetitive patterns of behavior have to be endorsed currently or by history, an increase from the possibility of meeting criteria for PDD-NOS in DSM-IV in the absence of symptoms in the domain of repetitive patterns of behavior. Sixth, the revised diagnostic system adds a universal onset criterion, *i.e.*, "symptoms must be present in early developmental period, but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life".

In DSM-IV, the criteria reflect examples from multiple levels of analysis, including specific behaviors such as shared interests (e.g., not showing objects of interest to other people), general qualities such as social reciprocity and important contexts such as peer interactions. In contrast to DSM-IV, DSM-5 identifies a smaller number of more general principles in social communication. These principles are expected to be present in all individuals with ASD currently or historically regardless of age and developmental level, but can be manifested in many different ways. (Mahjouri & Lord 2012.) These changes also reflect a substantial amount of literature that has shown that, in many cases, the way in which a particular behavior is classified under social or communication domains is arbitrary (Gotham *et al.* 2007). For example, nonverbal forms of behavior such as eye contact, gesture and facial expression are social and communicative; conversation is social use of language (Lord & Jones 2012). Many factor-analytic studies of children with ASD have shown one social-communication factor (Gotham *et al.* 2007).

In DSM-5, the restricted, repetitive behaviors domain again includes insistence on sameness, which has been reinstated from Kanner's original paper and DSM-III-R. This area could be particularly important to characterize individuals across the lifespan who may not have "typical" restricted, repetitive behaviors (e.g., hand flapping, spinning), but have difficulty with changes in routine and schedule, both of which affect their overall level of functioning (Mahjouri & Lord 2012).

In DSM-5 the definitions for language and early development that categorized the diagnostic subtypes in DSM-IV have been removed. Diagnoses of PDDs in DSM-IV, *i.e.*, the subtypes, were also used to describe the severity of ASD. Instead, DSM-5 includes severity specifiers, *i.e.*, three severity levels of autism symptoms, cognitive skills and adaptive functioning, defined by the level of support required for an individual (Appendix 10). Both intellectual functioning and language level determine these severity levels, thus being now important considerations in an ASD diagnosis. (Mahjouri & Lord 2012.) Manifestations of the disorder therefore vary greatly depending on the severity of the autistic condition, developmental

level and chronological age (APA 2013). Also, the results of a multisite study of the clinical diagnoses of different ASDs support the move from existing subgroupings of ASDs to dimensional descriptions of core features of social affect and fixated, repetitive behaviors, together with characteristics such as language level and cognitive function (Lord *et al.* 2012).

In addition to the above, DSM-5 introduces two distinct, novel diagnoses, "social (pragmatic) communication disorder" (SCD) and "stereotypic movement disorder". SCD describes individuals who display impairments in social communication and social interactions without showing any restrictive and repetitive behavior or interests. Individuals diagnosed with DSM-IV PDD-NOS who do not meet DSM-5 criteria for ASD (currently or by history), but who have deficits in social communication should be evaluated for SCD. The diagnosis of ASD supersedes that of SCD whenever the criteria of ASD are met, and care should be taken to enquire carefully regarding past or current restricted/repetitive behavior. (APA 2013.) Stereotypic movement disorder describes individuals who display repetitive, seemingly driven, and apparently purposeless motor behavior (e.g., hand shaking or waving, body rocking, head banging, self-biting). Motor stereotypes are among the diagnostic characteristics of ASD, so an additional diagnosis of stereotypic movement disorder is not given when such forms of repetitive behavior are better explained by the presence of ASD. However, when stereotypes cause self-injury and become a focus of treatment, both diagnoses may be appropriate. (APA 2013.)

2.3 Prevalence of autism spectrum disorders

Estimates of the prevalence of ASDs are close to 6 to 7 in 1,000 based on recent publications (Fombonne 2009, Leyy *et al.* 2009, Mahjouri & Lord 2012). Results vary markedly in different studies depending on methods, sample sizes, procedures involving administrative databases or national registers, or a two-stage or multistage approach in underlying populations, sources of information, diagnostic instruments used, diagnostic criteria, and the period of time when the study was conducted (Fombonne 2009).

In a review article, AD accounts for approximately 2 in 1,000 (Fombonne 2009), and its prevalence ranges from 0.07 (Treffert 1970) to 7.3 (Kadesjö *et al.* 1999) in 1,000 in various studies.

Estimates of the prevalence of AS vary from 0.03 to 6.0 in 1,000 (Baird *et al.* 2000, Chakrabarti & Fombonne, 2001, 2005, Ehlers & Gillberg 1993, Fombonne

2009, Kadesjo *et al.* 1999, Lesinskiene, 2000, Lesinskiene & Puras 2001, Levy *et al.* 2009, Sponheim & Skjeldal 1998). With an older target population, aged 8 to 12 years, and co-operation with teachers, the prevalence of AS is suggested to be higher (Chakrabarti & Fombonne 2001, Fombonne 2001, Posserud *et al.* 2006).

In a review article it was concluded that the prevalence of PDD-NOS was approximately 3 in 1,000 (Fombonne 2009). However, PDD-NOS subtypes of late onset or late onset plus sub-threshold symptomatology could also be labeled AS because of overlaps in diagnostic criteria. Therefore, the choice between a diagnosis of PDD-NOS versus AS may have an influence on prevalence figures.

In the Provinces of Oulu and Lapland in Northern Finland, the prevalence of "classic autism" was estimated to be 5.6 in 10,000 (8.2 in 10,000 for boys and 2.5 in 10,000 for girls) by collecting data from hospital records in 1996 and 1997 (Kielinen et al. 2000). When ICD-10 and DSM-IV criteria were used in that study, the age-specific prevalence was lowest, 6.1 in 10,000, in the oldest age group of 15to 18-year-old children, and highest, 20.7 in 10,000, in the age group of 5 to 7 years, possibly reflecting more active recognition of autism in recent years. Of the subjects with autism, 50% had mental retardation (intelligence quetient [IQ] < 70) (Kielinen et al. 2000). In the most recent publication based on hospital records and concerning the complete Finnish population of those aged 19 years or younger, born between 1987 and 2005 and followed as regards ASD diagnoses up to 2007, prevalence estimates were 38.1 in 10,000 for ASDs, 9 in 10,000 for childhood autism, 14.5 in 10,000 for AS, and 14.6 in 10,000 for PDD-NOS, including a diagnosis of "other PDD" or "PDD, unspecified" (Lampi et al. 2012). The majority of the 5,019 cases in that study were diagnosed via ICD-10 and only 19 cases via ICD-9; the less common ASD subtypes, such as Rett's syndrome, were excluded.

2.4 Screening of autism spectrum disorders

Recognizing autistic forms of behavior is regarded as challenging and diagnosis of ASD is a time-consuming and highly specialized task. Parents are more satisfied with the diagnostic process when they see fewer professionals in order to obtain the diagnosis and when the children are diagnosed at younger ages (Goin-Kochel *et al.* 2006). Over the past decade, children with ASDs have been diagnosed at increasingly younger ages, with screening tools possibly being one contributor to this. In reports from the 1990s, parents became aware of their childrens' developmental problems between the ages of 18–30 months, but the average age of these children at the time of a confirmed diagnosis was around 5.5 years for AD and 11 years for AS (Howlin

& Asgharian 1999). More recently, the average age at diagnosis of AD with learning disabilities or mental retardation has decreased to 3–4 years and that of AS and atypical autism to 5–6 years (Fernell & Gillberg 2010, Mulvihill *et al.* 2009).

Based on retrospective videotape analyses of children's social events, early signs of autistic behavior can be recognized at the age of 12 months; four forms of behavior (pointing, showing objects, looking at others and orienting to name) correctly classified 90% of children with autism and 90% of normally developing children (Osterling & Dawson 1994), and ASD can be distinguished from mental retardation and typical development between the ages of 12 and 30 months (Mars et al. 1998, Osterling et al. 2002). Indeed, many screening instruments have been developed to focus on early years for more severely handicapped children with high levels of autistic behavior (Baron-Cohen et al. 1992, 1996, Krug et al. 1980, Swinkels et al. 2006) and for children with autistic behavior at all intelligence levels (Berument et al. 1999, Constantino et al. 2003, Rutter et al. 2003). However, identification of a broader autism spectrum is regarded as being even more challenging because of milder symptoms. Autistic traits in a broader spectrum often become manifest at pre-school or school-age (Mattila et al. 2009), when social demands exceed limited capacities, and diagnoses of AS/HFA may be delayed until early adulthood or even adulthood (Woodbury-Smith et al. 2005). Therefore, some screening instruments have been developed to capture higher-functioning primaryschool-aged phenotypes (Ehlers & Gillberg 1993, Ehlers et al. 1999, Scott et al. 2002, Williams et al. 2005) and adults with normal intelligence and autistic traits (Andersen et al. 2011, Booth et al. 2013, Woodbury-Smith et al. 2005)

The Autism Spectrum Screening Questionnaire (ASSQ; Ehlers & Gillberg 1993) was the first instrument developed as a screener specifically for AS. Originally, it was known as the Asperger Syndrome Screening Questionnaire and designed in Swedish. The ASSQ has been translated into many languages (English [Ehlers & Gillberg 1993], Lithuanian [Lesinskiene 2000], Norwegian [Posserud *et al.* 2006], Danish [Petersen *et al.* 2006], Finnish [Mattila *et al.* 2009], Korean [Kim *et al.* 2011], Mandarin Chinese [Guo *et al.* 2011], Hungarian [Jakab *et al.* 2013], Icelandic [Georgsdottir *et al.* 2013], and Japanese [Kobayashi *et al.* 2013]). Cut-off scores for the Swedish (Ehlers *et al.* 1999), Norwegian (Posserud *et al.* 2009) and Mandarin Chinese (Guo *et al.* 2011) ASSQs have been established (Table 3), but to our knowledge, the English, Lithuanian, Danish, Korean, Hungarian, Icelandic, and Japanese ASSQs have not yet been validated.

The cut-off scores for Swedish and Mandarin Chinese ASSQs were estimated in clinical samples, whereas the cut-off score for the Norwegian ASSQ was estimated in

a total population sample. For the Swedish ASSQ, a parent-rated cut-off score of 19, with a sensitivity of 62–82% and a specificity of 90%, and a teacher-rated cut-off score of 22, with a sensitivity of 70% and a specificity of 91%, were suggested in clinical settings (Ehlers *et al.* 1999). The Mandarin Chinese ASSQ distinguished clinically diagnosed ASD patients from unaffected controls using a parent-rated cut-off score of 12, with a sensitivity of 96% and a specificity of 83% (Guo *et al.* 2011). For the Norwegian ASSQ, an optimal cut-off score of 17, with a sensitivity of 91% and a specificity of 86%, was indicated in a total population sample when using the higher of either parent-rated or teacher-rated ASSQ scores (Posserud *et al.* 2009). Most recently, a revised and extended version of the ASSQ, the Autism Spectrum Screening Questionnaire-Revised Extended Version (ASSQ-REV) has been developed in Swedish to better catch the female phenotype of ASDs (Kopp & Gillberg 2011).

Language Clinical settings		al settings	Total population
	Parent-rated (se/sp)	Teacher-rated (se/sp)	Higher of parent-rated
			or teacher-rated (se/sp)
Swedish	19 (62-82%/90%)	22 (70%/91%)	
Mandarin Chinese	12 (96%/83%)		
Norwegian			17 (91%/86%)

Table 3. Cut-off scores for the ASSQs in different languages.

ASSQ, Autism Spectrum Screening Questionnaire; se, sensitivity; sp, specificity

2.5 Diagnosis of autism spectrum disorders

From the very beginning, the diagnosis of ASDs has been founded on behavioral descriptions. However, in the last few decades, attention has been focused on genetic and neurobiological findings that might identify or lead to clear etiologies. There is strong evidence that genetic factors play a critical role in vulnerability to ASD (Losh *et al.* 2008), with heritability estimates from twin studies being as high as 90% (Bailey *et al.* 1995) and recurrence risk estimates of ASDs from sibling studies coming close to 20% (Ozonoff *et al.* 2011). The most significant scientific challenges to the concept of autism as one "disease" or even "diseases" have had limited success because of the heterogeneity of the genetic findings (Geschwind 2008, Veenstra-Vanderweele *et al.* 2004); as a consequence, the actual genetic
model indicates polygenetic heredity (Geschwind 2008, 2011). Epigenetic factors are also important (James *et al.* 2010). Endophenotypes (*i.e.*, different features in language, social interaction, behavior and cognition) in ASDs help us to understand the influence of hereditary factors. Genes may have an effect on many ASD features at the extremity of the continuum for each feature and which can also become manifest in other developmental and neuropsychiatric conditions. Because there is still a lack of a unique or universal "autism gene", genetic descriptions will in no way replace a behavioral diagnosis (Lord & Jones 2012).

Efforts at identification of individuals with ASD through brain imaging algorithms (Ecker *et al.* 2010) and of clear discriminability of children at risk for autism have been made (Hughes 2010). However, these approaches seldom provide data on an individual level, do not as yet have well-accepted standards for replicability across time or site (Lotspeich *et al.* 2004) and have rarely addressed questions of specificity of findings to ASD (Lord & Jones 2012). Therefore, it is too early to build diagnostic systems based on structural and functional neuroimaging measurements. (Lord & Jones 2012.)

In order to access the information typically associated with a diagnosis, e.g., disease course or response to treatment, one still has to come back to behavior (Lord & Jones 2012). For families learning about their child's diagnosis, individuals with ASD seeking to understand their own strengths and challenges, educators and therapists designing individualized rehabilitation, investigators developing new non-medical forms of intervention and researchers in general, behavioral conceptualizations remain critical (Charman *et al.* 2011, Lord & Jones 2012, Shattuck *et al.* 2009). Thus, despite significant genetic and neuroimaging findings, diagnoses of ASDs are still founded on behavioral descriptions.

Best-estimate clinical diagnoses of specific ASDs (AD, AS and PDD-NOS) have been used as the diagnostic gold standard (Chakrabarti & Fombonne 2005, Charman & Baird 2002, Volkmar *et al.* 2005). Typically, a diagnosis of ASD is made through obtaining behavioral history as well as observing the child using standardized clinical tools (Volkmar *et al.* 1999). Currently, most researchers use standardized measures such as the Autism Diagnostic Interview-Revised (ADI-R; Le Couteur *et al.* 2003), the Developmental, Dimensional and Diagnostic Interview (3di; Skuse *et al.* 2004), and the Diagnostic Interview for Social Communication Disorders (DISCO; Leekam *et al.* 2002, Wing *et al.* 2002) to obtain early developmental history from parents, along with semi-structured, standardized tools such as the Autism Diagnostic Observation Schedule (ADOS; Lord *et al.* 2000, ADOS-2; Lord *et al.* 2012) to observe a child in order to make diagnostic

decisions. Diagnostic instruments have been helpful in defining populations (Beglinger & Smith 2001), merging samples (Lord et al. 2006), comparing results across studies (Gotham et al. 2008, Risi et al. 2006), and in genotyping (Weiss et al. 2009). In addition, clinicians often use observational instruments or may use interview instruments and broader screening tools such as the Childhood Autism Rating Scale (CARS; Schopler et al. 1980) and collect information from day-care centers, schools and therapists. These sources of information allow clinicians in multiprofessional teams to generate an overall impression of the subject, which corresponds with a diagnostic classification from either the DSM-IV or ICD-10. Using a combination of the standardized instruments, a reliable and valid diagnosis can be made by the age of 2 in the case of autism (Cox et al. 1999, Kim & Lord 2012, Lord et al. 2006, Stone et al. 1999). However, recognizing broader phenotypes is more challenging; as a consequence, the diagnoses are often not completed until pre-school or school age (Fernell & Gillberg 2010, Howlin & Asgharian 1999, Mattila et al. 2009), or the diagnoses are delayed even right up to and during adulthood (Valkanova et al. 2013, Woodbury-Smith et al. 2005).

2.6 Comorbid psychiatric disorders

Autism spectrum disorders are not conditions with precise boundaries, but there are a number of overlapping disorders and behavioral symptoms that are not accounted for by the diagnosis of ASD (Gadow *et al.* 2004, Ghaziuddin *et al.* 1998, Gjevik *et al.* 2011, Leyfer *et al.* 2006, Mukaddes & Fateh 2010, Simonoff *et al.* 2008).

According to DSM-IV, symptoms of inattention and hyperactivity are described as occurring frequently in children with PDD, but there is an exclusionary criterion concerning comorbid diagnosis of ADHD with a PDD in both DSM-IV and ICD-10. In spite of this, many investigators have looked at the evidence linking PDDs and ADHD (Gadow *et al.* 2006, Goldstein & Schwebach 2004, Keehn *et al.* 2010, Kochhar *et al.* 2011, Lee & Ousley 2006, Yerys *et al.* 2009, Yoshida & Uchiyama 2004). Additionally, the coexistence of ADHD in children with PDDs may have important consequences as regards treatment (Posey *et al.* 2007) as well as genetic research (Ronald *et al.* 2008). Of behaviors, aggression, often found in oppositional defiant disorder (ODD) (Gjevik *et al.* 2011, Simonoff *et al.* 2008) and in conduct disorder (CD), is also regarded as being common in children with ASDs.

The symptomatology of obsessive-compulsive personality disorder (OCPD, DSM-IV) seems to be strikingly similar to that of "autistic psychopathy" as

Pervasive developmental disorder	Exclusion
Autistic disorder (DSM-IV)	Psychiatric disorder
	Rett's disorder
	Childhood disintegrative disorder
Childhood autism (ICD-10)	Psychiatric disorder
	Other varieties of pervasive developmental disorders
	F20 Schizophrenia of unusually early onset
	F70-F72 Mental retardation with some associated emotional or behavioral disorders
	F80.2 Specific development disorder of receptive
	language with secondary socio-emotional problems
	F84.12 Rett's syndrome
	F94.1 Reactive attachment disorder
	F94.2 Disinhibited attachment disorder
Asperger's disorder (DSM-IV)	Psychiatric disorder
	Another specific pervasive developmental disorder
	Schizophrenia
Asperger's syndrome (ICD-10)	Psychiatric disorder
	Other varieties of pervasive developmental disorder
	F20.6 Simple schizophrenia
	F21 Schizotypal disorder
	F42 Obsessive-compulsive disorder
	F60.5 Obsessional personality disorder
	F94.1 Reactive attachment disorder of chlidhood
	F94.2 Disinhibited attachment disorder of chlidhood

Table 4. Exclusion criteria in pervasive developmental disorders.

described by Asperger (1944). Co-occurrence of anxiety and anxiety disorders, including OCD, has been demonstrated to be at greater than chance levels in high-functioning individuals with ASDs (Gillott *et al.* 2001, Gjevik *et al.* 2011, Jacob *et al.* 2009, Kim *et al.* 2000, Kuusikko *et al.* 2008, Mack *et al.* 2010, Russell *et al.* 2005, Sukhodolsky *et al.* 2008, van Steensel *et al.* 2011, White *et al.* 2009, White & Roberson-Nay 2009). However, the diagnostic criteria of AS according to ICD-10 exclude OCD. In turn, DSM-IV does not mention OCD as an exclusion criterion.

Autism was originally considered to be childhood schizophrenia, but it was later separated from schizophrenia. In DSM-IV and ICD-10, AS diagnostic criteria even exclude schizophrenia. However, similarities and differential diagnostics concerning ASD and schizophrenia have recently been studied (Gadow & Devincent 2012, King & Lord 2011, Lugnegård 2012, Murphy 2006, Raja & Azzoni 2010, Rapoport *et al.* 2009, Unenge Hallerbäck *et al.* 2012).

In contrast to ADHD, OCD and schizophrenia, tic disorders are not exclusion criteria in autism or AS. Again, Tourette's syndrome, motor and vocal tics are considered to be diagnoses overlapping with PDDs (Baron-Cohen *et al.* 1999, Canitano & Vivanti 2007, Ehlers & Gillberg 1993, Ringman & Jankovic 2000).

Of mood disorders, depression is often associated with ASDs as a comorbid disorder (Ghaziuddin *et al.* 1998, Joshi *et al.* 2013, Kim *et al.* 2000, Lugnegård *et al.* 2011). Many studies have demonstrated major depressive disorder (MDD) as a comorbid condition in adults with ASDs (Joshi *et al.* 2013, Lugnegård *et al.* 2011), but a high prevalence of mood disorders in children with ASD has also been reported (Mukaddes & Fateh 2010).

Psychiatric patients are significantly more often smokers than the general population (Poirier *et al.* 2002), the exceptions being those with OCD (Bejerot & Humble 1999) and those with disorganized and catatonic subtypes of schizophrenia (Beratis *et al.* 2001). A low prevalence of smoking in patients with ASDs was shown in a Swedish study, supporting the theory of a biological link between ASD and OCD (Bejerot & Nylander 2003). Clinically significant ADHD symptoms are associated with levels of cigarette smoking (Tercyak *et al.* 2002). Recently, nicotine dependency in subjects with AS was also shown to be closely linked to comorbid ADHD (Hallerbäck *et al.* 2012).

It has long been common knowledge among clinicians that subjects with ASDs suffer from insomnia and other sleep disturbances. During the past few years, researchers have shown a growing interest in sleep disturbances in cases of ASDs (Allik *et al.* 2006a, 2006b, 2008 Johnson *et al.* 2012, Krakowiak *et al.* 2008, Paavonen *et al.* 2008, Rossignol & Frye 2011, Tani *et al.* 2003). Melatonin administration in cases of ASD is associated with improved sleep parameters, better daytime behavior, and minimal side effects (Rossignol & Frye 2011, 2013).

In spite of the research results presented above, many psychiatric diagnoses are exclusion criteria as regards PDDs according to DSM-IV and ICD-10 (Table 4). However, having an ASD does not protect a child from having other psychiatric disorders, but increases the risk of a number of co-occurring behaviors and difficulties (Amr *et al.* 2012, Guttmann-Steinmetz *et al.* 2009, Magnuson & Constantino 2011, Mazzone *et al.* 2012, Sukhodolsky *et al.* 2008).

3 Aims of the study

The main aims of the present study were

- 1. to estimate the prevalence of AS according to four sets of diagnostic criteria (DSM-IV, ICD-10, Gillberg's criteria and Szatmari *et al.*'s criteria), to estimate the prevalence of autism and ASDs according to DSM-IV criteria, and to reveal overlaps and inaccuracies concerning the diagnostic criteria of ASDs (I and II)
- 2. to evaluate the DSM-5 draft criteria for ASD posted in February 2010, compare the results with those obtained using DSM-IV criteria, and present modifications to the DSM-5 draft criteria (II)
- 3. to assess the validity of and provide optimal cut-off scores for the Finnish ASSQ for clinical settings and total population screening (III)
- 4. to estimate the prevalence and identify the types of comorbid psychiatric disorders associated with AS/HFA and to rate the overall level of functioning in relation to psychiatric comorbidity in children/adolescents with AS/HFA (IV)

4 Subjects and methods

4.1 Participants

The Finnish population was homogeneous at the time of our study, mainly of Finnish extraction and Finno-Ugric origin. In Finland, everyone has an equal right to basic education, healthcare and social security.

Compulsory education offers equal educational possibilities for every child aged 7–16 years, and prolonged compulsory education for every child with mental retardation aged 6–17 years. Mainstream comprehensive schooling is divided into two phases, primary school from 1st to 6th grade, with pupils aged 7–12 years, and secondary school from 7th to 9th grade, with pupils aged 13–16 years.

Finnish child health clinic services are part of primary healthcare guided by the Ministry of Social Affairs and Health. The Finnish child health clinic system is a population-based, municipal service for every child below school age, *i.e.*, until the age of seven years. Services are a continuation of maternal healthcare, with the general aim of promoting the health of the child and the entire family. Public-health nurses collaborating with physicians are the primary caregivers monitoring children's physical, cognitive and social development as well as implementing the national vaccination program. It is recommended that all Finnish children should visit the child health clinic 9 times by their first birthday, twice between their first and second birthdays and then once a year until school age of seven years. If any developmental abnormalities are identified or suspected, the child undergoes more comprehensive diagnostic and neurocognitive assessment in his/her own municipality and in the closest hospital, if needed, after which children with mental retardation are referred to prolonged compulsory education. In the Oulu University Hospital area, children diagnosed with mental retardation are referred to Tahkokangas Service Center for rehabilitation follow-up.

In Publications I–III, the participants were involved in an epidemiological study. In Publication IV, the participants were involved in both the epidemiological study and a clinical study.

4.1.1 Epidemiological study (I, II, III, IV)

In order to optimize the target age population and teachers as raters in ASD screening, we chose a target population of primary school children, 8 years old.

The total number of schools in the study area was 329, including 22 special and 2 private schools. In addition, many of the schools had special classes or integrated special education for pupils with special needs. At primary school, there is one main teacher for each class group who teaches the same pupils for several hours per day for one to several years. It is common that the same teacher teaches the same pupils for the first two years. Thus, most of the children in the epidemiological study were in the second grade, probably having the same teacher as in the first grade.

Screening for ASDs was targeted at a total population of all 8-year-old children born in 1992 and living in the Northern Ostrobothnia Hospital District, the catchment area of the University Hospital of Oulu, Finland, in autumn 2000 (n = 5,484; Statistics Finland 2000). No exclusion criteria were used. A total of 4,422 children (81%, mean age 8.3, range 7.8–8.8) comprised the final population with ASSQ data and with parental consent to participate. Based on the screening results (see Procedure, Epidemiological study), 125 children (high-/medium-risk sample) with parents were invited to and 110 (88%) participated in diagnostic examinations for ASDs at the outpatient Clinic of Child Psychiatry, University Hospital of Oulu (Fig. 1) in the school year 2001–2002 and autumn 2002.

The prevalence of AS, autism and ASDs was determined in the total population of 4,422 children. The DSM-5 draft criteria posted by the APA in February 2010 were evaluated in a sample of 82 children (full-scale intelligence quotient [FSIQ] \geq 50) from the high-/medium-risk sample (see Procedure, Epidemiological study). (Fig. 1)

For validation of the Finnish ASSQ, a "total population validation sample" was also drawn from the epidemiological study and consisted of 4,408 children with an FSIQ \geq 50 (mean age 8.3, range 7.8–8.8), 28 of them with a diagnosis of ASD, and the final "high-/medium-risk sample" comprised 104 screened (see Procedure, Epidemiological study) children (mean age 8.3, range 7.8–8.8) from the epidemiological study, 26 of them with a diagnosis of ASD. (Fig. 1)

4.1.2 Clinical study (IV)

In the clinical study, as part of our genetic study (Weiss *et al.* 2009), the target population included all registered children and adolescents with AS or AS traits (*i.e.*, features of AS or autism) or AS suspected and an FSIQ \geq 80 at Oulu University Hospital prior to 2003. In our hospital district (*i.e.*, our research area), the diagnostic examinations of all children with suspected ASDs were performed in Oulu University Hospital at the time of our study. Thus, the outpatient participants were not selected (by socioeconomic status, for example) when the outpatient data were collected. All

outpatients had been diagnosed by multiprofessional teams at the child psychiatric or pediatric neurology clinic, supervised by a child psychiatrist or a child neurologist. Clinical diagnoses had then been assigned regarding current behavior (without regarding development during the first 3 years), and as a consequence, the subjects with normal intelligence had been diagnosed as having AS/AS traits/AS suspected.

In 2005, the prevalence and types of comorbid psychiatric disorders were determined using a sample of participants that comprised high-functioning 12- to 13-year-old subjects with AS/HFA (n = 18) from the epidemiological study and 9- to 16-year-old subjects with AS/HFA (n = 32) from the clinical study (Weiss *et al.* 2009), making a combined sample of 50 (mean age 12.7, SD 1.5, age range 9.8–16.3; FSIQ \geq 70) (Tables 5a and 5b, Fig. 2).

The population-based sample (called "community-based sample" in Publication IV) consisted of 18 subjects with AS/HFA (FSIQ \geq 70, mean age 12.7, SD 0.3, age range 12.2–13.1) from the epidemiological study, and the clinical sample consisted of 40 subjects with AS/HFA (FSIQ \geq 70, mean age 12.7, SD 1.7, age range 9.8–16.3), 32 of them from the clinical study plus 8 subjects from the epidemiological study. These eight subjects were born in 1992 and belonged to the epidemiological population, but they were also registered as ASD patients in medical records and belonged to the clinical sample. Thus, the samples were partly overlapping concerning these eight participants. (Tables 5a and 5b, Fig. 2)

4.2 Measures

4.2.1 The Autism Spectrum Screening Questionnaire

The Autism Spectrum Screening Questionnaire (ASSQ; Ehlers & Gillberg 1993) was used as a screening instrument in the epidemiological study. It is an informantbased rating scale with 27 items, identical for parents and teachers, requiring the respondent to indicate if "the rated child stands out as different from other children of his/her age", for each item. It can be completed in 10 min and was designed with a 3-point scale as follows: "no" (score 0 indicating normal), "somewhat" (score 1 indicating some abnormality), or "yes" (score 2 indicating definite abnormality). The total scale score (range 0 to 54) serves as an index of severity of ASD traits, with higher scores indicating more severe levels of social impairment. The original Swedish ASSQ was validated for ASDs in children aged 6–17 years with normal intelligence or mild mental retardation (FSIQ \geq 50), and cut-off scores of 22 for teachers' ratings and 19 for parents' ratings were recommended for screening in clinical settings. (Ehlers *et al.* 1999.)

The ASSQ items were originally designed to measure 4 factors: (1) social interaction (11 items), (2) communication problems (6 items), (3) restricted and repetitive behavior (5 items), and (4) motor clumsiness and other associated symptoms including motor and vocal tics (5 items) (Ehlers *et al.* 1999). This categorization was outlined by Ehlers and Gillberg, two of the three developers of the screening instrument (personal communication with Professor Gillberg). More recently, a three-factor solution has been identified using the Norwegian ASSQ (Posserud *et al.* 2008). In their study, the first factor was labeled "social difficulties", and included difficulties in friendship, prosocial behavior and social communication. The second factor covered repetitive, stereotyped behavior and autism-associated problems, such as motor difficulties and tics, and was called "tics/motor/obsessive-compulsive disorder". The items allocated to the third factor were identified as "autistic style", a kind of social-cognitive and speaking style often seen in high-functioning individuals with autism/AS, regarded by other children, for instance, as "eccentric professor", "old-fashioned", or having "robot-like language".

Originally, the ASSQ was translated from Swedish into Finnish by two clinical psychologists in the 1990s and it has been used in clinical settings in Finland ever since. At the beginning of our study in 2000, it was back-translated into Swedish by an official Swedish-Finnish translator, and after comparison of the original Swedish and the back-translated Swedish forms, the final Finnish version was completed (Autismi- ja Aspergerliitto ry 2012)¹. For the Finnish version, the ASSQ rating expression of two points (Swedish definition "stämmer absolut", meaning "fits definitely"), was toned down to "fits" because our clinical experience suggested that Finnish parents are reluctant to assess their children's features as "definite". The Finnish expression "fits" was also considered analogous to the English ASSQ rating expression of two points ("yes").

4.2.2 The Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule

The Autism Diagnostic Interview-Revised (ADI-R; Lord *et al.* 1995) and the Autism Diagnostic Observation Schedule (ADOS; Lord *et al.* 2000), module 3 (*i.e.*, for verbally fluent children), were used as ASD assessment tools in the

¹ Marja-Leena Mattila, Sirkka-Liisa Linna and Irma Moilanen

epidemiological and clinical studies. The physicians², clinical psychologist³ and Master of Education graduate⁴ who participated in the diagnostic process had been trained in the use of the ADI-R and ADOS for research purposes, but inter-rater reliabilities had not been established. The ADI-R and ADOS were not used to make diagnostic classifications in the present study (*i.e.*, the diagnostic algorithms were not used). Instead, these instruments were used to obtain structured information from parents and for semi-structured observation of a child. A clinical best estimate was used to make the diagnosis.

The ADI-R is a standardized investigator-based, structured clinical interview for parents/caregivers of children, primarily concerning children's behavior between the ages of four to five years. It was developed to elicit a full range of information across all three main symptom areas, 1) Reciprocal social interaction, 2) Language/ communication, and 3) Repetitive, restricted and stereotyped behavior and interests, needed to produce a diagnosis of autism and to assist in the assessment of related PDDs. The ADI-R used in our study contained 111 items (Lord *et al.* 1995). The subsequently revised version created in 2003 contains 93 items (Le Couteur *et al.* 2003). The cut-off scores of the algorithm are standardized for autism.

The ADI-R was translated from English into Finnish by a group of professionals in the field of ASDs and then back-translated into English by an official English translator. After comparison, the final Finnish version (Hogrefe Psykologisk Forlag 2009) was completed by a group of professionals⁵, all of whom were extensively trained in the use of the ADI-R.

The ADOS is for semi-structured assessment of an individual's current social interaction, communication and play or imaginative use of materials, with 10 to 15 different tasks (e.g., Make-Believe Play, Joint Interactive Play, Telling a Story from a Book, Conversation and Reporting a Non-Routine Event). The ADOS comprises four modules based on the verbal level and chronological age of the subject: 1) Module 1 for a child who does not use phrase speech, *i.e.*, a pre-verbal child or a child who uses single words, 2) Module 2 for a child who uses phrase speech, but is not verbally fluent, 3) Module 3 for a child/adolescent with fluent speech, and 4) Module 4 for an adolescent/adult with fluent speech. The cut-off scores of the algorithm are separately standardized for autism and ASDs.

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Module 3, with 14 tasks, was translated from English into Finnish by an official English translator. After comparison of the original and the back-translated English version, the final Finnish version (Hogrefe Psykologisk Forlag 2009) was completed by two clinical psychologists⁶ in the field of ASDs, both of them extensively trained in use of the ADOS.

4.2.3 The Asperger Syndrome (and high-functioning autism) Diagnostic Interview

The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI; Gillberg *et al.* 2001) was used as an AS assessment tool in the epidemiological study to complement Gillberg's criteria list. The ASDI is an investigator-based interview consisting of 20 items covering all diagnostic items for AS in Gillberg's criteria list. The ASDI was recommended for use as an aid in guiding the direction of further in-depth clinical examination. Preliminary data from a clinical study suggested that inter-rater reliability and test-retest stability may be excellent, with κ exceeding 0.90 in both instances. The validity appeared to be relatively good. (Gillberg *et al.* 2001.)

4.2.4 The Wechsler Intelligence Scale for Children-Third Edition

Intelligence quotients (IQs) were measured by means of the full-scale Wechsler Intelligence Scale for Children-Third Edition (WISC-III; Wechsler 1991) in the epidemiological study. WISC-III is an individual cognitive ability test for 6- to 16-year-old children and does not require reading or writing. WISC-III evaluates participants' verbal IQ, performance IQ and FSIQ. Verbal subtests (Information, Similarities, Arithmetic, Vocabulary, and Comprehension) are oral questions without time limits except for Arithmetic. Performance subtests (Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly) are nonverbal tasks, all of which are timed and some of which allow bonus points for extra fast work.

⁶ Sanna Kuusikko-Gauffin and Katja Jussila

4.2.5 The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version

The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL; Kaufman *et al.* 1997) was used in the clinical study to diagnose psychiatric comorbidity. K-SADS-PL is a semi-structured interview designed to assess current and past episodes of psychopathology in children and adolescents between the ages of 6–18 according to DSM-IV criteria via parent and child/adolescent interviews. K-SADS-PL has well-established reliability and validity (Kaufman *et al.* 1997). In our study, the primary K-SADS diagnoses (affective, psychotic, anxiety, behavioral, eating, tic and post-traumatic stress disorders as well as substance abuse and dependence) and the question on sleep disturbances, with several response options, concerned all participants. Definite current and past DSM-IV psychiatric diagnoses were assessed. Lifetime diagnosis included current and past diagnoses. Diagnostic endorsements did not involve use of the exclusionary rules in DSM-IV with regard to autism and AS.

4.2.6 The Children's Global Assessment Scale

The Children's Global Assessment Scale (CGAS; Shaffer *et al.* 1983) was used in the clinical study to evaluate children's/adolescents' level of functioning in everyday life (e.g., at home, at school, with peers). CGAS scores range between 1 and 100, with higher scores indicating better functioning. CGAS scores below 70 are considered to indicate psychiatric disturbance and limited functioning. For subjects with no history of psychiatric disturbance, only a current CGAS score is assigned. For subjects with current and/or past psychiatric disorders, two CGAS scores can be estimated, one for current and one for worst lifetime functioning. In our study, the current and worst lifetime CGAS scores were used.

4.2.7 Medical Records

Early developmental milestones were checked from University Hospital of Oulu records for the screened subjects in the high-/medium-risk sample in the epidemiological study for whom verification was considered necessary after the ADI-R interviews and for all individuals diagnosed with ASDs in the epidemiological and clinical studies. Via the search conducted in the medical records of Oulu University Hospital in the clinical study in autumn 2002 (Weiss *et al.* 2009), we

could simultaneously check that all registered ASD patients born in 1992 were identified in our screening in the epidemiological study. Concerning the children with moderate, severe, or profound mental retardation in the epidemiological study, medical records of the University Hospital of Oulu and Tahkokangas Service Center were evaluated in order to identify diagnoses of ASDs.

4.3 Procedures

The studies were approved by the Ethics Committee of the Faculty of Medicine, University of Oulu, and the Ethics Committee of the Northern Ostrobothnia Hospital District. The school inspector, the superintendents of all 43 municipalities and all 329 school principals were informed and permission was requested to carry out the screening phase of the epidemiological study in their schools. Written informed consent was obtained from all parents and from all children of 12 years of age or more. The study design of the epidemiological study is shown in Fig. 1 and the study design of the clinical study in Fig. 2.

4.3.1 Epidemiological study (I, II, III and IV)

In the epidemiological study (Fig. 1), screening of ASDs was carried out in the target population of all children born in 1992 and living in the catchment area of the Northern Ostrobothnia Hospital District from September to November 2000 (n = 5,484). No exclusion criteria were used. Of the 329 schools, 321 (98%) with 5,319 (97%) children agreed to participate in our study. Nine schools (2.7%), including seven special schools, had no pupils born in 1992. Eight schools (2.5%) with 77 (1.4%) children born in 1992 did not return the study material. In sum, 304 (92%) schools with 5,242 (96%) children participated. The teachers of these children and the school principals, doctors and nurses were given an informative lecture (17 occasions in all)⁷, after which the research material was handed out to the teachers, who distributed the material to parents via the pupils. The parents were asked to complete the ASSQ and a developmental questionnaire, in which cognitive impairment, developmental disorders and illnesses were asked about. The parents of 4,424 (84%) children gave written informed consent to participate and ASSQs for 3,762 children (85%; 1-25 items missing in 187 cases) were completed by parents. After parental permission, the teachers of 4,396 children (99%; no items missing) completed the ASSQ, and indicated

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if the child's curriculum was general or special-needs education. Two children with the consent of parents were not rated by either parents or by teacher. Thus, 4,422 children with parents' consent having parent-rated and/or teacher-rated ASSQs remained for estimation of the prevalence of AS, autism and ASDs.



ASSQ, Autism Spectrum Screening Questionnaire; ASD, autism spectrum disorder; ADI-R, Autism Diagnostic Interview – Revised; ADOS, Autism Diagnostic Observation Schedule; WISC-III, Wechsler Intelligence Scale for Children – Third Edition; ASDI, Asperger Syndrome (and high-functioning autism) Diagnostic Interview; FSIQ, full-scale intelligence quotient; AS, Asperger syndrome; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edn; ICD-10, International Classification of Diseases, 10th edn; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th edn; APA, American Psychiatric Association

Fig. 1. Study design in the epidemiological study (I, II, III, IV).

On the developmental questionnaire completed by parents, eight children were reported to have moderate, severe or profound mental retardation, *i.e.*, an FSIQ < 50. Of the 4,414 children with a reported FSIQ \geq 50, a high-/medium-risk sample of 125 children was invited to take part in diagnostic examinations: (1) A "high-risk sample" of all children (n = 73) with teacher-rated ASSQ scores of \geq 22 and/or parent-rated ASSQ scores of \geq 19 based on the established Swedish cut-offs for clinical settings (Ehlers *et* al. 1999), and (2) a "medium-risk sample" of all children (n = 52) with teacher-rated ASSQ scores of 17-21 (n = 28) OR teacher-rated ASSQ scores of 9-16 and parentrated ASSQ scores of 7-18 (n = 24), in order to identify ASD cases as accurately as possible among the participants who were rated below the above-mentioned Swedish cut-off score recommendations (Ehlers et al. 1999). The children in the medium-risk sample were selected on the basis of data in two Swedish publications: 1) all subjects with AS had been scored ≥ 17 in teacher-rated ASSQs (Kadesjö *et al.* 1999), and 2) the Receiver Operating Characteristic (ROC) curves had shown a minimum of 9 points for teacher-rated ASSQ scores and a minimum of 7 points for parent-rated ASSQ scores, with a sensitivity of 95% for ASDs (Ehlers et al. 1999). The "low-risk sample", i.e., the rest of the children (n = 4,304), was not examined in our study.

Of the high-/medium-risk sample (n = 125), 110 children (88%), with (a) parent(s), participated in diagnostic examinations in the school year 2001–2002 and autumn 2002. The ADI-R⁸ and the ADOS, module 3⁸ were administered and videotaped and WISC-III tests performed (by a clinical and a research psychologist). Four children had FSIQ scores < 50 and two children with severe physical disability could not be tested reliably. These six children were eliminated from further analyses, leaving 4,408 children (FSIQ \geq 50) for the "total population validation sample" and 104 children (FSIQ \geq 50) for the "high-/medium-risk sample": 61 (84%) of them in the high-risk sample and 43 (83%) in the medium-risk sample. After that, school observations⁹ of 24 children were undertaken blind to previous results because more information was considered to be necessary (e.g., because of contradictory ratings in the ASSQ between parents and teachers or contradictory results in the ASSQ and the ADI-R). Medical records were reviewed⁸.

Of the 43 children in the medium-risk sample, (1) 15 had been scored at or above the threshold(s) in 1–3 area(s) in the ADI-R and were included in consensus diagnostics, and (2) 28 had been scored below all 3 thresholds in the ADI-R; 6 of them were included in consensus diagnostics to ensure reliability of diagnosis and

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the remaining children (n = 22) were excluded from further consensus diagnostics because they were not suspected of having ASDs. Finally, 82 children from the high-/ medium-risk sample were included in the consensus diagnostics procedure: all 61 children from the high-risk sample and 21 children from the medium-risk sample.

DSM-IV, ICD-10, Gillberg's criteria and Szatmari *et al.*'s criteria for AS and DSM-IV criteria for autism were used to make best estimate clinical consensus diagnoses concerning the 82 participants (FSIQ \geq 50), based on all information gathered (ASSQs, ADI-R, ADOS videotapes, ASDI, WISC-III, school observations, and medical records) by a pediatrician¹⁰ with extensive clinical experience of ASDs and other developmental disorders, and a child psychiatrist¹¹ with long-term clinical experience of ASDs and other psychiatric disorders. The school observer¹² participated in the evaluation meetings concerning the 24 children.

Medical records of the University Hospital of Oulu (n = 12) and Tahkokangas Service Center (n = 11) concerning the 12 children (0.27%) with moderate (FSIQ 35–49; n = 8), severe (FSIQ 20–34; n = 3), or profound (FSIQ < 20; n = 1) mental retardation were evaluated to identify diagnoses of ASDs¹⁰.

The prevalence of AS according to DSM-IV, ICD-10, Gillberg's criteria and Szatmari *et al.*'s criteria, and the prevalence of autism and ASDs according to DSM-IV criteria were estimated in the total population of 4,422 children in the epidemiological study.

DSM-5 draft criteria for ASD posted by the APA in February 2010 were evaluated concerning the 82 participants (FSIQ \geq 50) from the high-/medium-risk sample in connection with the detailed results obtained according to DSM-IV¹⁰. Unusual (Item 71 in ADI-R) and abnormal idiosyncratic (*i.e.*, hyper- or hyporeactivity to sensory input, Item 73 in ADI-R) forms of sensory behavior were assessed using the ADI-R data based on consensus among the researchers^{10,11}.

The 4,408 (80%) children with ASSQ data from the epidemiological study made up the "total population validation sample", including 4,382 (99%) with teacher and 3,565 (81%) with parent ASSQ data (67.0% rated by mothers, 2.9% by fathers, 25.8% by both parents, and information of raters missing in 4.3%), of whom 3,539 (80%) were rated by both teachers and parents, all of the children having an FSIQ \geq 50 with no items missing in the ASSQs, and of these, 28 had ASDs (26 diagnosed according to DSM-IV in our study and two with hospital-registered diagnoses of ASDs who refused to participate in diagnostic reassessment in our study). Of the total population validation sample (n = 4,408 children), 61 children in the high-risk sample

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and 43 children in the medium-risk sample were combined into a "high-/medium-risk sample" (n = 104), comparable with a clinical sample, all rated by parents (58.7% by mothers, 2.9% by fathers, 35.6% by both parents, information of raters missing in 2.9%) and 103 by teachers, and of these, 26 had ASDs diagnosed according to DSM-IV in our study. There were no statistically significant differences between the means of the ASSQ scores rated by mothers, fathers and both parents either in the total population validation sample or in the high-/medium-risk sample.

In order to identify all children with hospital-registered diagnoses of ASDs, we performed a search for ASDs and extensively evaluated medical records at Oulu University Hospital during autumn 2002 (e.g., Korpilahti *et al.* 2007, Kuusikko *et al.* 2008, 2009, Loukusa *et al.* 2007, Weiss *et al.* 2009). Of the 4,408 children (FSIQ \geq 50) in the total population validation sample, 17 had registered diagnoses of ASDs, all of whom met our inclusion criteria either for the high-risk sample (n = 15) or for the medium-risk sample (n = 2). Of these 17 children, 15 were reassessed in our study, and 13 were confirmed as having ASDs. Two children with hospital-registered diagnoses of "AS" and "AS traits" refused to participate in diagnostic reassessment despite meeting our inclusion criteria for the high-risk sample. We did not find any hospital-registered diagnoses of ASDs in the low-risk sample of 4,304 children; as a consequence, the validity of the ASSQ in the total population validation sample could be assessed, although random selection of low-risk individuals and examination of them could not be implemented in the epidemiological study.

The validity of the Finnish ASSQ was assessed in the total population validation sample (n = 4,408) and in the high-/medium-risk sample (n = 104) and the optimal cut-off scores of the Finnish ASSQ for total population screening and clinical settings were provided.

4.3.2 Clinical study (IV)

The study concerning psychiatric comorbidity (Tables 5a and 5b, Fig. 2) was part of our clinical study. Our hospital records were evaluated during autumn 2002 in order to identify all children and adolescents with ASDs and an FSIQ \geq 80, originally for the genetic substudy of our clinical study. Based on the results of additional clinical genetic examination, no child/adolescent had to be removed because of any known genetic disorder that was stated as an exclusion criterion in the genetic study (Weiss *et al.* 2009). The outpatients with AS or AS traits who had already participated in the epidemiological study were removed from the diagnostic phase of the clinical study. Finally, 53 outpatients with AS (n = 43), AS traits (n = 8) or AS suspected (n

= 2), aged 7–14 years, were invited to and 46 (87%) participated in a study carried out in order to define the AS/HFA diagnosis more closely, in 2003.

Table 5a. Participants in Publication IV.

Participants	Combined sample	Population-based sample ¹ from the epidemiological study	Clinical sample ¹ from the epidemiological and clinical studies
Participants (n [male/female])	50 (38/12)	18 (12/6)	40 (32/8)
Mean age/age range	12.7/9.8–16.3	12.7/12.2–13.1	12.7/9.8–16.3
FSIQ	≥ 70	≥ 70	≥ 70
AS (male/female)	27 (20/7)	8 (5/3)	22 (17/5)
HFA (male/female)	23 (18/5)	10 (7/3)	18 (15/3)
Primary school-aged (male/female)	36 (26/10)	18 (12/6)	26 (20/6)
AS/HFA	17/19	8/10	12/14
Secondary school-aged (male/female)	14 (12/2)	-	14 (12/2)
AS/HFA	10/4	-	10/4

FSIQ, full-scale intelligence quotient; AS, Asperger syndrome; HFA, high-functioning autism; ¹ Eight participants were in both samples

Table 5b. Procedures in Publication IV.

Condensed procedures	Epidemiological study	Clinical study
Participants (n [male/female])	18 (12/6)	32 (26/6)
Measures		
1. AS/HFA diagnosis	х	х
ASSQ	х	
ADI-R	х	х
ADOS, module 3	х	х
WISC-III	х	х
Medical records	х	х
School observation	х	
2. Psychiatric comorbidity examinations	х	х
K-SADS-PL	х	х
CGAS	х	х

AS, Asperger syndrome; HFA, high-functioning autism; x, included in procedure; ASSQ, Autism Spectrum Screening Questionnaire; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; WISC-III, Wechsler Intelligence Scale for Children-Third Edition; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version; CGAS, Children's Global Assessment Scale Asperger syndrome/HFA diagnostic examinations included ADI-R and ADOS, module 3¹³. The ADI-R interviews and ADOS observations were videotaped. Early development in all cases was verified from the medical records of Oulu University Hospital^{13,14}. After these investigations the diagnoses of AS/AS traits/AS suspected in the medical records were reassigned by the psychologist¹³ on the basis of all information gathered (ADI-R, ADOS, medical records), consulting the pediatrician¹⁵ in the case of subjects for whom a second opinion was considered to be essential. DSM-IV criteria were used in detail to derive the best clinical diagnosis of AS or HFA.

Of the 28 subjects with ASDs in the epidemiological study, four were excluded because of an FSIQ below 70. Two subjects with clinical AS/AS traits refused to participate in the diagnostic reassignment, and one with verified AS diagnosis announced refusal to continue. Finally, 21 subjects with AS/HFA (FSIQ \geq 70) in the epidemiological study remained.

Of the total number of 67 subjects with AS/HFA (FSIQ \geq 70) combined from the epidemiological study (n = 21) and clinical study (n = 46), 50 (75%) participated in the psychiatric comorbidity examinations in 2005.

In order to estimate the prevalence and identify the types of comorbid psychiatric disorders, the parents and children/adolescents were interviewed using the K-SADS-PL schedule, and to estimate the level of functioning in these children/adolescents, the CGAS was used. When both parents were available, they were interviewed together. The interviews were videotaped. The graduate-level interviewers^{14,16} were trained in administration of the K-SADS-PL schedule and the CGAS. First, a senior child psychiatrist¹⁷ was trained by a highly qualified child and adolescent psychiatrist, James J. McGough, MD, from the University of Los Angeles, California, US (Smalley *et al.* 2007). Second, the senior child psychiatrist¹⁷ trained an educational psychologist¹⁴ who then as a senior interviewer¹⁴ trained a junior interviewer¹⁶ in the administration of the K-SADS-PL schedule and the CGAS. A best-estimate procedure described by Leckman *et al.* (1982) and all the information available was used to make clinical psychiatrist¹⁷ had consensus meetings to confirm diagnostic assessments and CGAS scores when

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needed. In addition, the senior interviewer¹⁸, experienced in the use of K-SADS-PL administration and coding (Hurtig *et al.* 2007), reviewed every tenth interview by the junior interviewer¹⁹ to ensure consistency between the raters. Inter-rater reliability was assessed by means of Cohen's κ (κ for diagnoses 0.94, SD 0.06) and percentage agreement between the interviewers (percentage mean for diagnoses 99.7%).



FSIQ, full-scale intelligence quotient; ASD, autism spectrum disorder; AS, Asperger syndrome; HFA, high-functioning autism; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edn; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children (Diobal Assessment Scale



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¹⁹ Helena Haapsamo

4.4 Data analysis

Analyses were performed by using SPSS for Windows, release 16.0., 2008 (SPSS inc., Chicago, IL). Confidence intervals (CIs) were calculated by using Confidence Interval Analysis (CIA) for Windows, version 2.0.0. 2000 (BMJ Books, London).

The prevalence of AS was estimated according to DSM-IV, ICD-10, Gillberg's criteria and Szatmari *et al.*'s criteria and the prevalence of autism and ASDs was estimated according to DSM-IV in the total population of 4,422 children. Differences between means were tested using Student's *t*-test for two independent samples. Kappa statistics were calculated to illustrate agreement concerning the presence of an ASD according to different diagnostic criteria (DSM-IV, DSM-5 draft and our modification of the DSM-5 draft).

ROC analyses were performed to assess discriminant validity of the Finnish ASSQ in distinguishing ASD from non-ASD cases in the total population validation sample (n = 4,408) and in the high-/medium-risk sample (n = 104) using (1) parent-rated ASSQ scores only, (2) teacher-rated ASSQ scores only, and combining parents' and teachers' ratings in the ASSQ as follows: (3) summed parent-rated and teacher-rated ASSQ scores (both ratings had to be available), and (4) higher of parent-rated and teacher-rated ASSQ scores (both ratings had to be available). Area under the curve (AUC), sensitivity (*i.e.*, number of true positives divided by [number of true negatives]), specificity (*i.e.*, number of true negatives divided by [number of true negatives plus number of false positives]), positive predictive value (PPV; number of true positives divided by number of all positives), negative predictive value (NPV; number of true negatives divided by number of all positives) and likelihood ratio (LR; how many times more likely it is to be diagnosed as ASD than not to be diagnosed at a cut-off score in question) were calculated.

The prevalences of current and lifetime comorbid psychiatric disorders were determined according to DSM-IV. Co-occurring disorders and the effect of age (primary school vs. secondary school age) on comorbid disorders were analyzed by using Pearson's Chi-Square test or Fisher's Exact Test. Differences between mean current CGAS scores among AS/HFA subjects with and without comorbid psychiatric disorders were assessed by using Student's *t*-test. The influences of comorbid psychiatric disorders on CGAS scores were analyzed by using multiway ANOVA, having the CGAS score as response variable and comorbid psychiatric disorders as explanatory variables. No statistical comparison between the population-based sample and the clinical sample was carried out because there were eight overlapping participants. Statistical significance was evaluated using two-tailed 0.05-level tests.

5 Results

5.1 Prevalence and diagnosis of autism spectrum disorders in the epidemiological study (I and II)

The prevalence of AS according to DSM-IV was 2.5 in 1,000 (95% CI 1.4–4.4), according to ICD-10, 2.9 in 1,000 (95% CI 1.7–5.0), according to Gillberg's criteria, 2.7 in 1,000 (95% CI 1.6–4.7) and according to criteria of Szatmari *et al.*, 1.6 in 1,000 (95% CI 0.8–3.3) (Table 3 of Publication I, and Table 6). The prevalence of AS according to DSM-IV would have been 0.5 in 1,000 if the children with no communication impairments after 36 months had been counted in. The male-to-female ratios in AS according to DSM-IV, ICD-10, Gillberg, and Szatmari *et al.* were 0.8:1, 1.2:1, 2:1, and 0.8:1, respectively.

Of the 10 children originally with AS/AS traits (9 diagnosed as AS/AS traits at Oulu University Hospital, and the parents of one child had been told at the public health care center that the child had AS traits), 4 (40%) were assigned as having HFA (AS according to Gillberg's criteria) and 6 were assigned as having AS according to DSM-IV/ICD-10 criteria in our study.

Items G ("Solitary"; Szatmari *et al.*'s criteria), H ("Repetitive behavior"; ICD-10), I ("Narrow interest" and "Repetitive routines and interests"; Gillberg's criteria), J ("Speech and language problems"; Gillberg's criteria), and K ("Odd speech"; Szatmari *et al.*'s criteria) (see Publication I) showed the most remarkable overlaps and lack of overlaps across the sets of AS diagnostic criteria.

The prevalence of autism according to DSM-IV was 4.1 (95% CI 2.6–6.4) in 1,000; 61% were high-functioning with an FSIQ \geq 70. The prevalence of autism with mild mental retardation was 0.9 (95% CI 0.4–2.3) in 1,000, and with moderate mental retardation, 0.7 (95% CI 0.2–2.0) in 1,000. No subjects with severe or profound mental retardation were diagnosed as having autism. The male-to-female ratio was 2:1 in subjects with autism.

The prevalence of ASDs according to DSM-IV was 8.4 (95% CI 6.1–11.5) in 1,000; 65% of the subjects were high-functioning with an FSIQ \geq 70, 11% had mild mental retardation, 19% had moderate mental retardation, and 5% had severe mental retardation. The prevalence of ASDs with mild mental retardation (FSIQ 50–69) was 0.9 (95% CI 0.4–2.3) in 1,000, with moderate mental retardation (FSIQ 35–49), 1.6 (95% CI 0.8–3.3) in 1,000, and with severe mental retardation (FSIQ 20–34), 0.45 (95% CI 0.1–1.6) in 1,000. No subjects with profound mental

retardation (FSIQ < 20) were diagnosed as having ASDs. (Table 6.) The male-to-female ratio was 1.8:1 in subjects with ASDs, 1.7:1 in high-functioning subjects with ASDs, and 2.3:1 in subjects with ASDs and mental retardation.

During the diagnostic process our clinical insight was that seven cases could also have features of ASDs, but none of the diagnostic criteria sets could allow us to identify them (males 31, 37, 42, 63, 64, 70 and 72; Tables S7 and S8 of Publication II). If the seven cases had been included in those with ASDs using the diagnosis of PDD-NOS, the prevalence of ASDs according to DSM-IV would have risen to 10.0 (95% CI 7.4–13.3) in 1,000.

Diagnosis (FSIQ)	DSM-IV ar	nd medical	records	DSM-5 draft1	Our modification ²
	Prevalence/	95% CI	n (%)	n (% of DSM-IV	n (% of DSM-IV
	1,000			result)	result)
ASDs ³ (all)	8.4	6.1–11.5	37 (100)		
ASDs ^{4,5,6} (≥ 70) ^{4,7}	0.45	0.1–1.6	2 (5)		
ASDs ⁸ (≥ 50) ⁸			26	> 12 (46)	> 25 (96)
ASDs ⁸ (≥ 70) ^{7,8}	5.0	3.3–7.5	22 (60)	> 8 (36)	> 21 (95)
ASDs ⁸ (50–69) ⁸	0.9	0.4–2.3	4 (11)	> 4 (100)	> 4 (100)
ASDs ⁵ (35–49) ⁵	1.6	0.8–3.3	7 (19)		
ASDs ⁵ (20–34) ⁵	0.45	0.1–1.6	2 (5)		
ASDs ⁵ (< 20) ⁵			0 (0)		
Autism ^{5,8} (all)	4.1	2.6-6.4	18 (48.5)		
autism ⁸ (≥ 70) ⁸	2.5	1.4-4.4	11 (61)	> 8 (73)	> 11 (100)
autism ⁸ (50–69) ⁸	0.9	0.4–2.3	4 (22)	> 4 (100)	> 4 (100)
autism⁵ (35–49)⁵	0.7	0.2–2.0	3 (17)		
autism⁵ (20–34)⁵			0 (0)		
autism⁵ (< 20)⁵			0 (0)		
AS ⁸	2.5	1.4-4.4	11 (30)	> 0 (0)	> 10 (91)
The rest ^{4,5,9}	1.8	0.9–3.6	8 (21.5)		

Table 6. Diagnoses according to DSM-IV and medical records, DSM-5 draft, and modified DSM-5 draft suggested by us.

FSIQ, full-scale intelligence quotient; ASD, autism spectrum disorder; AS, Asperger syndrome; ¹ Evaluated in 82 participants (FSIQ \ge 50); ² Our modification of DSM-5 draft criteria; ³ Included autism, AS and "the rest"; ⁴ According to developmental questionnaire used by parents; ⁵ Drawn from medical records; ⁶ AS (*n* = 1), AS traits (*n* = 1); ⁷ Of all ASDs, 65% high-functioning; ⁸ Based on screening and examinations in the epidemiological study; ⁹ AS (*n* = 1), AS traits (*n* = 1), PDD (*n* = 1), autistic traits (*n* = 5) Of the 26 subjects with FSIQ \geq 50 diagnosed as having ASDs in our study, 13 had registered diagnoses of ASDs in the medical records: AS (n = 4), AS traits (n = 5), HFA (n = 1), AD (n = 2), autistic traits (n = 1), and the parents of one child had been told at the public healthcare center that the child had AS traits (although the child had not been referred to diagnostic examinations in the University Hospital of Oulu), while the remaining 12 subjects (46%) had not been diagnosed as having ASDs until we carried out our study (42% of them were males and 58% females). Of the 15 children in the high-/medium-risk sample who refused to participate in diagnostic examinations, one had AS and one had AS traits according to the developmental questionnaires completed by the parents, and medical records. Of the 104 subjects with FSIQ \geq 50 in the high-/medium-risk sample, two with diagnoses of AS traits/AS suspected (in the medical records) did not meet the DSM-IV criteria in our study. Of the 12 participants with an FSIQ < 50, nine had ASDs according to medical records; these participants included three with AD, one with PDD, and five with autistic traits.

5.2 DSM-5 draft criteria posted in February 2010 (II)

In Table 2 of Publication II, we suggested modifications to five details of DSM-5 draft criteria posted by the APA in February 2010. A summary of the modifications is presented in Table 7. Kappa agreement concerning any ASD diagnosis between DSM-5 draft and DSM-IV criteria was 0.54, and between our modification of DSM-5 draft criteria and DSM-IV criteria, 0.92.

Of the 26 subjects with ASDs (FSIQ \geq 50) according to DSM-IV, 12 (46%) could be identified according to DSM-5 draft criteria, whereas 25 (96%) could be identified according to our modification of DSM-5 draft criteria. DSM-5 draft criteria revealed 73% of the high-functioning subjects with autism (FSIQ \geq 70), but no subjects with AS, whereas our modification revealed 100% and 91%, respectively. All subjects with ASDs and mild mental retardation were identified according to both sets of criteria. (Table 6.)

The mean FSIQ of the 12 subjects with ASDs according to DSM-5 draft criteria (79; SD, 22; range 55–135) was significantly lower (p = 0.001, t = -3.812, df = 24) than that of the 14 subjects who did not meet these criteria (106; SD, 14; range 85–130).

Table 7. Our modifications (bold lower-case letters) to five details of DSM-5 draft criteria posted in February 2010 (compare with Appendix 7).

Autism spectrum disorder must meet criteria 1, 2, and 3

- 1. Clinically significant, persistent deficits in social communication and interactions, as manifest by at least two of three:
 - a. Marked deficits in nonverbal and/or verbal communication used for social interaction
 - b. Lack of social reciprocity
 - c. Failure to develop and maintain peer relationships appropriate to developmental level
- Restricted, repetitive patterns of behavior, interests, and activities, as manifested by at least two of the following:
 - a. Stereotyped motor or verbal behaviors, or unusual sensory behaviors,
 - or idiosyncratic sensory behaviors
 - b. Excessive adherence to routines and/or ritualized patterns of behavior
 - c. Restricted, fixated interests
- 3. Symptoms must be present in childhood

5.3 Psychometric properties of the Finnish Autism Spectrum Screening Questionnaire (III)

Figures 3 and 4 show ROC curves for (1) parent-rated and (2) teacher-rated ASSQ scores, (3) summed parent-rated and teacher-rated ASSQ scores, and (4) higher of parent-rated and teacher-rated ASSQ scores. The point in the ROC curve that comes closest to the top left corner (*i.e.*, maximizes sensitivity and specificity) is regarded as the best cut-off score.

In the high-/medium-risk sample (n = 104), the summed parent-rated and teacher-rated ASSQ scores showed the best discriminative ability between cases with and without ASD diagnoses (AUC = 92%, 95% CI = 87%–97%). A summed cut-off score of 30 indicated the best balance between sensitivity (89%) and specificity (82%), with PPV = 62%, NPV = 96% and LR = 4.9. A teacher-rated cut-off score of 22 was associated with sensitivity of 73% and specificity of 74% (PPV = 49%, NPV = 89% and LR = 2.8). An optimal cut-off score with high sensitivity and high specificity for parents' ASSQ ratings alone could not be established. More detailed statistics of the ASSQ scores in the high-/medium-risk sample are shown in Table 8.

Table 8. Statistical outcome values in the high-/medium-risk sample (n = 104) based on 1) parent-rated ASSQ scores, 2) teacher-rated ASSQ scores, 3) summed parent-rated and teacher-rated ASSQ scores, and 4) higher of parent-rated and teacher-rated ASSQ scores.

ASSQ score	Se	Sp	Se+Sp	PPV	NPV	LR	ROC AUC (95% CI)
Parent-rated							0.70
ASSQ scores							(0.59, 0.81)
Parents 2	1.00	0.08	1.08	0.27	1.00	1.08	
Parents 7	0.96	0.33	1.29	0.32	0.96	1.44	
Parents 9	0.85	0.47	1.32	0.35	0.90	1.61	
Parents 19	0.46	0.77	1.23	0.40	0.81	2.00	
Teacher-rated							0.77
ASSQ scores							(0.66, 0.89)
Teacher 6	1.00	0.17	1.17	0.29	1.00	1.20	
Teacher 19	0.81	0.57	1.38	0.39	0.90	1.89	
Teacher 221	0.73	0.74	1.47	0.49	0.89	2.81	
Teacher 24	0.58	0.83	1.41	0.54	0.85	3.42	
Summed parent-rated and							0.92
teacher-rated ASSQ scores							(0.87, 0.97)
Parents + teacher 28	1.00	0.71	1.71	0.54	1.00	3.50	
Parents + teacher 29	0.96	0.75	1.72	0.57	0.98	3.90	
Parents + teacher 301	0.89	0.82	1.70	0.62	0.96	4.87	
Parents + teacher 31	0.81	0.82	1.63	0.60	0.93	4.44	
Parents + teacher 33	0.81	0.87	1.68	0.68	0.93	6.22	
Parents + teacher 35	0.73	0.87	1.60	0.66	0.91	5.63	
Higher of parent-rated and							0.83
teacher-rated ASSQ scores							(0.75, 0.92)
Parents or teacher 17	1.00	0.26	1.26	0.31	1.00	1.35	
Parents or teacher 19	1.00	0.36	1.36	0.35	1.00	1.57	
Parents or teacher 20	0.92	0.47	1.39	0.37	0.95	1.73	
Parents or teacher 22	0.89	0.61	1.50	0.43	0.94	2.27	
Parents or teacher 24	0.69	0.77	1.46	0.50	0.88	2.96	
Parents or teacher 25	0.65	0.82	1.47	0.55	0.88	3.60	

¹Cut-off score recommendations

ASSQ, Autism Spectrum Screening Questionnaire; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; ROC, receiver operating characteristic; AUC, area under the curve; 95% CI, confidence interval



ROC, receiver operating characteristic; ASSQ, Autism Spectrum Screening Questionnaire

Fig. 3. ROC curves of the high-/medium-risk sample (n = 104) based on 1) parent-rated ASSQ scores, 2) teacher-rated ASSQ scores, 3) summed parent-rated and teacher-rated ASSQ scores, and 4) higher of parent-rated and teacher-rated ASSQ scores.



ROC, receiver operating characteristic; ASSQ, Autism Spectrum Screening Questionnaire

Fig. 4. ROC curves of the total population validation sample (n = 4,408) based on 1) parent-rated ASSQ scores, 2) teacher-rated ASSQ scores, 3) summed parent-rated and teacher-rated ASSQ scores, and 4) higher of parent-rated and teacher-rated ASSQ scores.

ASSQ score	Se	Sp	Se+Sp	PPV	NPV	LR	ROC AUC
Parent-rated							0.97
ASSQ scores							(0.95, 0.99)
Parents 2	1.00	0.65	1.65	0.02	1.00	2.86	
Parents 7 ¹	0.96	0.93	1.89	0.10	1.00	13.75	
Parents 10	0.75	0.96	1.71	0.14	1.00	20.89	
Parents 15	0.61	0.99	1.59	0.26	1.00	44.74	
Teacher-rated							0.99
ASSQ scores							(0.988, 0.998)
Teacher 7 ¹	1.00	0.94	1.94	0.10	1.00	18.14	
Teacher 8	0.96	0.95	1.92	0.12	1.00	20.99	
Teacher 9	0.93	0.96	1.89	0.14	1.00	25.27	
Teacher12	0.89	0.98	1.87	0.20	1.00	38.88	
Teacher 16	0.86	0.99	1.84	0.30	1.00	66.64	
Summed parent-rated and							0.998
teacher-rated ASSQ scores							(0.997, 0.999)
Parents + teacher 281	1.00	0.99	1.99	0.50	1.00	125.39	
Parents + teacher 29	0.96	0.99	1.96	0.53	1.00	141.07	
Parents + teacher 30	0.89	0.995	1.89	0.58	1.00	174.16	
Parents + teacher 33	0.82	0.997	1.82	0.66	1.00	240.34	
Higher of parent-rated and							0.996
teacher-rated ASSQ scores							(0.994, 0.998)
Parents or teacher 19	1.00	0.98	1.98	0.33	1.00	60.53	
Parents or teacher 20	0.93	0.99	1.92	0.36	1.00	69.37	
Parents or teacher 22	0.89	0.99	1.88	0.42	1.00	92.20	
Parents or teacher 24	0.71	0.99	1.71	0.50	1.00	125.39	

Table 9. Statistical outcome values in the total population validation sample (n = 4,408) based on 1) parent-rated ASSQ scores, 2) teacher-rated ASSQ scores, 3) summed parent-rated and teacher-rated ASSQ scores, and 4) higher of parent-rated and teacher-rated ASSQ scores.

¹Cut-off score recommendations

ASSQ, Autism Spectrum Screening Questionnaire; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; ROC, receiver operating characteristic; AUC, area under the curve; 95% CI, confidence interval

In the total population validation sample (n = 4,408), the summed parent-rated and teacher-rated ASSQ scores showed the best discriminative ability between cases with and without ASD diagnoses (AUC = 99.8%, 95% CI = 99.7%–99.9%). A summed cut-off score of 28 was associated with sensitivity of 100% and specificity of 99% (PPV = 50%, NPV = 100% and LR = 125). A teacher-rated cut-off score of seven was associated with sensitivity of 100% and specificity of 99% (PPV = 10%, NPV = 100% and LR = 18). A parent-rated cut-off score of seven was associated with sensitivity of 93% (PPV = 10%, NPV = 100% and LR = 14). More detailed statistics of the ASSQ scores in the total population validation sample are shown in Table 9.

5.4 Comorbid psychiatric disorders (IV)

Current and lifetime comorbid psychiatric disorders in subjects with AS/HFA are presented in Table 10.

5.4.1 Prevalence in the combined population-based and clinical samples

One or more comorbid psychiatric disorders (current/lifetime) were diagnosed in 74%/84% of the cases. The most common disorders (current/lifetime) were behavioral (44%/50%), anxiety (42%/56%) and tic disorders (26%/38%). Of current comorbid psychiatric disorders, one disorder was diagnosed in 32%, two in 20%, three in 14% and four or more in 8% of the subjects with AS/HFA.

Current behavioral disorders (n = 22) often co-occurred (n = 13; p = 0.030, df 1) with current anxiety disorders (n = 21). Of current behavioral disorders, ODD (n = 8) co-occurred (n = 7; p = 0.007) significantly with current anxiety disorders (n = 21), especially (n = 4; p = 0.037, df = 1) with OCD (n = 11). About half of the 19 cases with current ADHD and about half of the 21 cases with current anxiety disorders simultaneously (n = 11; p = 0.075, df 1), although this was not statistically significant.

Current psychiatric disorders were more common in primary school-age (n = 30/36) than in secondary school-age (n = 7/14) participants (p = 0.029). Of all current comorbid psychiatric disorders, tic disorders (n = 13/36 vs. n = 0/14; p = 0.010) and behavioral disorders (n = 19/36 vs. n = 3/14; p = 0.045, df = 1) were more common in primary school-age (n = 36) than in secondary school-age (n = 14) participants. No secondary school-age participants had current tic disorders, but four of them were recalled as having had motor and/or vocal tics in the past.

Comorbid psychiatric disorder	Combined sample		Population-based	sample ¹	Clinical sample ¹	
	(n = 50; M = 38)		(n = 18; M = 12)	- 	(n = 40; M = 32)	
	mean age 12.7 (rai	nge 9.8–16.3)	mean age 12.7 (r	ange 12.2–13.1)	mean age 12.7 (rai	nge 9.8–16.3)
	Current/lifetime	95% CI	Current/lifetime	95% CI	Current/lifetime	95% CI
Behavioral disorders	22 (44%)/25 (50%)	31-58/37-63	7 (39%)/8 (44%)	20-61/25-66	19 (48%)/22 (55%)	33-62/40-69
Attention deficit/hyperactive disorder	19 (38%) ^{2,3,4} /22 (44%)	26-52/31-58	6 (33%)²/7 (39%)	16-56/20-61	16 (40%) ^{3,4} /19 (48%)	26-55/33-62
Combined type (current)	13 (68%)²/15		5 (83%)²/5		10 (62.5%)/12	
Inattentive type (current)	6 (32%) ^{3.4} /8		1 (17%)/2		6 (37.5%) ^{3.4} /7	
Hyperactive type (current)	0 (0%)/3		0/1		0/3	
Conduct disorder	1 (2%)/1 (2%)	0.4-10/0.4-10	1 (6%)/1 (6%)	1-26/1-26	1 (2.5%)/1 (2.5%)	0.4-13/0.4-13
Oppositional defiant disorder	8 (16%)/8 (16%)	8-28/8-28	3 (17%)/3 (17%)	6-39/6-39	8 (20%)/8 (20%)	10-35/10-35
Anxiety disorders	21 (42%)/28 (56%)	29-56/42-69	7 (39%)/9 (50%)	20-61/29-71	18 (45%)/23 (58%)	31-60/42-72
Separation anxiety disorder	1 (2%)/4 (8%)	0.4-10/3-19	1 (6%)/3 (17%)	1-26/6-39	1 (2.5%)/2 (5%)	0.4-13/1-16
Panic disorder with agoraphobia	1 (2%)/1 (2%)	0.4-10/0.4-10	1 (6%)/1 (6%)	1-26/1-26	1 (2.5%)/1 (2.5%)	0.4-13/0.4-13
Agoraphobia	1 (2%)/1 (2%)	0.4-10/0.4-10	0/0	0-18/1-18	1 (2.5%)/1 (2.5%)	0.4-13/0.4-13
Social phobia	2 (4%)/3 (6%)	1-14/2-16	1 (6%)/1 (6%)	1-26/1-26	1 (2.5%)/2 (5%)	0.4-13/1-16
Specific phobia	14 (28%)/17 (34%)	18-42/22-48	6 (33%)/7 (39%)	16-56/20-61	11 (28%)/13 (33%)	16-43/20-48
Obsessive-compulsive disorder	11 (22%)/14 (28%)	13-35/18-42	2 (11%)/2 (11%)	3-33/3-33	10 (25%)/13 (33%)	14-40/20-48
Tic disorders	13 (26%)/19 (38%)	16-40/26-52	8 (44%)/9 (50%)	25-66/29-71	9 (23%)/14 (35%)	12-38/22-50
Tourette's syndrome	7 (14%)/7 (14%)	7-26/7-26	5 (28%)/5 (28%)	12-51/12-51	5 (13%)/5 (13%)	6-26/6-26
Motor tics	3 (6%)/5 (10%)	2-16/4-21	1 (6%)/1 (6%)	1-26/1-26	3 (8%)/5 (13%)	3-20/6-26
Vocal tics	3 (6%)/8 (16%)	2-16/8-28	2 (11%)/3 (17%)	3-33/6-39	1 (2.5%)/5 (13%)	0.4-13/6-26
Mood and related disorders	3 (6%)/7 (14%)	2-16/7-26	1 (6%)/1 (6%)	1-26/1-26	3 (8%)/7 (18%)	3-20/9-32
Major depressive disorder	3 (6%)/7 (14%)	2-16/7-26	1 (6%)/1 (6%)	1-26/1-26	3 (8%)/7 (18%)	3-20/9-32
Enuresis	1 (2%)/8 (16%)	0.4-10/8-28	1 (6%)/4 (22%)	1-26/9-45	1 (2.5%)/7 (18%)	0.4-13/9-32
Encopresis	1 (2%)/3 (6%)	0.4-10/2-16	1 (6%)/1 (6%)	1-26/1-26	1 (2.5%)/3 (8%)	0.4-13/3-20
Insomnia (current) ⁵	18 (36%)	24-50	5 (28%)	12–51	15 (38%)	24–53
Initial	17 (34%) ⁶	22–48	5 (28%)	12–51	14 (35%)	22–50
Middle	2 (4%) ⁶	1-14	0	0-18	2 (5%)	1–16
Circadian	1 (2%) ⁶	0.4-10	0	0–18	1 (2.5%)	0.4-13
Nonrestorative	1 (2%) ⁶	0.4-10	0	0-18	1 (2.5%)	0.4-13
AS, Asperger syndrome; HFA, high-fun	ctioning autism; M, n	nale; 95% CI, con	fidence interval; ¹ Coi	mbined sample = po	opulation-based samp	ole + clinical
sample (eight outpatients overlapping t	between the population	on-based and the	clinical samples); ² C	ne had changed fro	m past ADHD inatter	itive type to current
ADHD combined type; ³ Two had chang	jed from past ADHD	combined type to	current ADHD inatte	ntive type; ⁴ One ha	d changed from past.	ADHD hyperactive
type to current ADHD inattentive type; [±]	⁵ None had terminal i	nsomnia; ⁶ One ha	ad initial, middle, circa	adian and nonrestor	ative insomnia	

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A significant number of ADHD features indicating lifelong comorbid diagnosis of combined, inattentive or hyperactive-impulsive types of ADHD was shown in 44% of the subjects. In turn, 38% met a current diagnosis of ADHD (68% of them combined type, 32% inattentive type, and none hyperactive, impulsive type). In 21% of the current cases, ADHD type had changed over the years. All ODD diagnoses (n = 8) were current; thus, no past ODD was diagnosed.

The most common current anxiety disorders were specific phobias (28%; fear of animals [dogs, bees], darkness, heights, confined spaces, bridges, and needles or injections), and OCD (22%). Two or three different current anxiety disorders were diagnosed in 14% of the participants.

None met the criteria for schizophrenia or related disorders, eating disorders or substance abuse disorders, and none had ever smoked.

5.4.2 Prevalence in the population-based sample and clinical sample

One or more current comorbid psychiatric disorders were diagnosed in 78% of cases in the population-based sample and in 75% of cases in the clinical sample. In the population-based sample, the prevalence of behavioral disorders (current/lifetime) was 39%/44%, that of anxiety disorders 39%/50% and that of tic disorders 44%/50%, while in the clinical sample, the corresponding figures were 48%/55%, 45%/58%, and 23%/35%.

In the clinical sample, current psychiatric disorders were more common in primary school-age (88%, n = 23/26) than in secondary school-age (50%, n = 7/14) participants (p = 0.018). Among these, statistical significance was reached as regards tic disorders (35%, n = 9/26 vs. 0%, n = 0/14; p = 0.016) and behavioral disorders (62%, n = 16/26 vs. 21%, n = 3/14; p = 0.015, df = 1).

5.4.3 Overall level of functioning in the combined population-based and clinical samples

The mean current CGAS score was 62 (SD 10.2; range 39–85), and the mean worst lifetime CGAS score was 58 (SD 9.6; range 35–79) in the combined sample (n = 50). The current CGAS score was below 70 in 80% (n = 40), and worst lifetime CGAS score was below 70 in 88% (n = 44) of the participants. The mean current CGAS score was significantly lower (p = 0.049, t = 2.021, df = 48) in females (57, SD 11.9; n = 12) compared with males (64, SD 9.2; n = 38), and the mean worst lifetime CGAS score was also significantly lower (p = 0.040, t = 2.116, df = 48)

in females (53, SD 12.0; n = 12) than in males (60, SD 8.3; n = 38). Mean CGAS scores did not differ significantly according to school level or as regards AS versus HFA. CGAS scores decreased significantly along with the number of comorbid psychiatric disorders (Table 11).

Comorbid psychiatric	n	Mean current CGAS score	SD	Range	p value	
disorder						
No	13	70.5	9.3	54-85		
Any	37	59.3	8.9	39–73	< 0.001	
One	16	63.1	5.7	55–73	0.014	
Two	10	58.5	9.1	45–73	0.006	
Three	7	55.4	11.2	39–68	0.005	
Four or more	4	52.5	10.0	39–61	0.005	

Table 11. Number of comorbid psychiatric disorders and mean current CGAS scores.

CGAS, Children's Global Assessment Scale; SD, Standard Deviation

Asperger syndrome/HFA associated with current anxiety disorders (p = 0.014, n = 21, SSq = 472.3, df = 1, MSSq = 472.3, F = 6.6), current mood disorders (p = 0.021, n = 3, SSq = 411.6, df = 1, MSSq = 411.6, F = 5.7) or current behavioral disorders (p = 0.038, n = 22, SSq = 330.4, df = 1, MSSq = 330.4, F = 4.6) decreased the current CGAS score significantly, and AS/HFA associated with two individual disorders, current ODD (p = 0.002, n = 8, SSq = 689.7, df = 1, MSSq = 689.7, F = 10.7), or current MDD (p = 0.009, n = 3, SSq = 478.7, df = 1, MSSq = 478.7, F = 7.4), also decreased the current CGAS score was found when AS/HFA was associated with current OCD (p = 0.085, n = 11, SSq = 200.8, df = 1, MSSq = 200.8, F = 3.1).

5.4.4 Overall level of functioning in the population-based sample and clinical sample

The mean current CGAS score was 62 (SD 10.5, range 39–79) and the worst lifetime CGAS score was 59 (SD 11.3, range 35–79) in the population-based sample (n = 18); the corresponding figures in the clinical sample (n = 40) were 62 (SD 10.4, range 39–85) and 58 (SD 9.0, range 39–77).

6 Discussion

6.1 Prevalence and diagnosis of autism spectrum disorders (I and II)

In the present study, we provide estimates of the prevalence of AS, autism and ASDs in an 8-year-old epidemiological cohort and clarify confusion as regards the diagnostic criteria of ASDs. We also evaluate DSM-5 draft criteria for ASD posted by the APA in February 2010 and suggest modifications regarding five details of the DSM-5 draft. Our study is the first epidemiological study in which the DSM-5 draft criteria for ASD have been evaluated.

On the basis of our results, the prevalence of AS depends on the diagnostic criteria, being 2.5 in 1,000 according to DSM-IV, 2.9 in 1,000 according to ICD-10, 2.7 in 1,000 according to Gillberg's criteria, and 1.6 in 1,000 according to the criteria of Szatmari et al.. The variation of the prevalence of AS across the four different sets of diagnostic criteria show problems in AS diagnostics because of the lack of consistent criteria. Two of the children who met the ICD-10 criteria of AS in our study had succeeded well enough and had not needed any outside help or guidance by the time of the study or no longer needed any help during the study. We interpreted this as indicating that these two children did not have clinically significant impairments in social or other important areas of functioning and thus did not meet the DSM-IV criteria of AS. Because of this conclusion the prevalences of AS according to DSM-IV and ICD-10 differ from each other. In addition, communication impairments are not stated in the criteria of AS according to DSM-IV and ICD-10. In our study, cases of communication impairment after 36 months of age in individuals with AS were counted in the prevalence of AS. yielding a prevalence of 2.5 in 1,000 according to DSM-IV. The prevalence of AS would have been as low as 0.5 in 1,000 according to DSM-IV if only the individuals with no communication impairments after 36 months had been counted in.

Concurrence across the four sets of AS diagnostic criteria in "impairment in social interaction" was complete in our study, but the strongest differences concerned "speech and language problems" according to Gillberg and "odd speech" according to Szatmari *et al.* plus "general delays" in childhood/under 3 years. "Misinterpretations of literal/implied meanings" in Gillberg's criteria proved to be difficult to uncover. The diagnostic picture often changes over time as regards peculiarities of intonation, rhythm, and tone of voice and they may be hard to recall later, e.g., intonation sounds more "autistic" in younger children. Phenotypes at school age corresponded to AS whether or not they had had "delay in early speech" or "lack of curiosity about the environment in childhood/under 3 years". Thus, six individuals with early developmental delay met Gillberg's criteria, but not the other three criteria for AS.

Of the 10 children with AS/AS traits in medical records, 40% were re-assigned as HFA in our epidemiological study following DSM-IV/ICD-10, revealing that clinical practices in our research area lead to diagnoses of AS rather than autism in high-functioning school-aged children. These children had delays in speech or curiosity about the environment before 3 years of age, but had clinical pictures of AS at school age. In one previous study, 23% of cases with AS would have been reassigned a diagnosis of autism by either DSM-IV or ICD-10, and 69% would have been diagnosed as AS when clinical diagnoses and those made according to DSM-IV and ICD-10 were compared (Woodbury-Smith *et al.* 2005). Our results were in concordance, but because of the low number of diagnosed cases in our study the percentage is only indicative of a trend.

The prevalence of autism was 4.1 in 1,000 in our study and that of ASDs was 8.4 in 1,000 according to DSM-IV. Although estimates in different studies vary, the prevalence of ASDs seems to have increased greatly since the 1960s and 1970s, when only AD with a prevalence about 0.5/1,000 was included, to 6–16/1,000 currently (Baird *et al.* 2006, Baron-Cohen *et al.* 2009, Davidovitch *et al.* 2013, Levy *et al.* 2009, Wingate *et al.* 2012). Recently, in a general-population sample of 7- to 12-year-old children in a South Korean community, a prevalence of ASDs as high as 26.4/1,000 was reported (Kim *et al.* 2011). If we are to understand these increases in prevalence, it is critical to know if the increase is a result of milder cases or increased numbers of all types of cases, and in addition, because there is confusion as to who has PDD-NOS versus who has autism or AS, patterns are difficult to discern (Bertrand *et al.* 2001). In addition, research results highlight differences in ascertainment among epidemiological studies performed decades ago (Miller *et al.* 2013).

Of the subjects with autism and ASDs in our study, 61% and 65% were high-functioning (FSIQ \geq 70), respectively. Recent epidemiological surveys of PDDs have yielded concordant results concerning the proportion of high-functioning subjects among cases of ASDs; nine of 14 surveys reported 51% to 74% of subjects with normal IQ (Fombonne 2009).

According to a review article, the average male-to-female ratio as regards ASDs is 4.2:1 (Fombonne 2009). In our study, the male-to-female ratio was 0.8:1 in cases of AS, 2:1 in cases of autism, 1.8:1 in subjects with ASDs, 1.7:1 in high-functioning subjects with ASDs, and 2.3:1 in subjects with ASDs and mental retardation when
using the DSM-IV criteria. The results concerning the male-to-female ratios, with more females than expected in our study, were somewhat surprising. Coincidence may play a part when the number of cases is small, as in our study, but females with ASDs may not have been recognized in many studies. However, in a South Korean epidemiological study of a general population sample of 7- to 12-year-old children, a concordant result, with a male-to-female ratio of 2.5:1 in cases of ASDs was shown (Kim *et al.* 2011). When using Gillberg's criteria for AS, the male-to-female ratio rose to 2:1 in our study, being in concordance with the results of other epidemiological studies (1.6–4:1) based on Gillberg's criteria (Ehlers & Gillberg 1993, Lesinskiene 2000).

Almost half of the higher-functioning (FSIQ \geq 50) children with ASDs according to DSM-IV in our study, 42% of them males and 58% females, were not diagnosed or suspected as ASD cases before our diagnostic evaluations. However, most of them had been examined and followed at hospital for developmental or behavioral reasons. The diagnosis (e.g., ADHD versus ASD) may have been dependent on the behavior traits that had been dominant at the time the diagnosis was given. An even higher proportion of undiagnosed and untreated ASD cases, two-thirds of the mainstream school population, was revealed in a study of a South Korean community sample (Kim et al. 2011). Additionally, Wing (1981) reported that girls with AS appeared to be superficially more sociable than boys, but closer observation showed the same problems in two-way social interaction. Later, in a Swedish thesis (Kopp 2010), based on one of the most comprehensive and timeconsuming studies of girls with neuropsychiatric disorders ever performed, it was shown that most female ASD cases had not been recognized correctly among preschool-age, school-age and teenage girls. In conclusion, continuing education of professionals is needed, aimed at recognizing individuals with ASD, especially girls. Clinicians are also reminded to use screening and diagnostic instruments and multi-informant sources in order to better identify ASD.

A lack of agreement between diagnostic labeling used by clinicians and diagnosis based on DSM-IV criteria has been shown, suggesting a lack of consistency in diagnostic communication, which is necessary to provide the best clinical care, appropriate services, and relevant information to parents and caregivers (Happe 2011, Williams *et al.* 2008). Confusion regarding the diagnostic criteria of ASDs in DSM-IV has yielded different solutions. The choice between a diagnosis of AS versus PDD-NOS is open to interpretation. In many studies, the prevalences of PDD-NOS/atypical autism and AS have been estimated together (e.g., Montiel-Nava & Peña 2008). In turn, some researchers have solved the

problem by publishing the prevalences of Kanner's autism and AS separately and other ASDs as "other forms" (e.g., Latif & Williams 2007). All cases of AS in our study could also have been labeled PDD-NOS/atypical autism (late onset/late onset plus sub-threshold symptomatology). The definition of age of manifestation beyond 36 months in PDD-NOS/atypical autism leads to overlap between the diagnostic criteria of AS and PDD-NOS/atypical autism. In addition, with regard to the criteria of PDD-NOS, the most important source of difficulty arises in connection with how many items of the symptomatology domains of autism need to be met. For these reasons, the prevalence of PDD-NOS was not estimated in our study. Based on our clinical insight during the diagnostic process, seven subjects could have been mildly affected ASD cases, e.g., PDD-NOS/atypical autism with subthreshold symptomatology/late onset plus subthreshold symptomatology, but did not meet any specific ASD diagnosis. If the seven cases had been included in ASDs using the diagnosis of PDD-NOS, the prevalence of ASDs according to DSM-IV would have risen to 10.0 in 1,000 in our study.

DSM-5 criteria eliminate the concern about the prevalence of NOS diagnoses and the confusion that surrounds the distinction between AS, PDD-NOS and autism without intellectual disability or language delay by subsuming all ASDs within an umbrella category (Happe 2011, Lord & Jones 2012). By using such an approach the new system should clarify the unreliable, highly varied approaches that clinicians have used to differentiate milder cases of autism from AS and PDD-NOS (Lord et al. 2012), avoiding the phenomenon of the same individual receiving serial or sometimes even concurrent diagnoses of PDD-NOS, autism and AS, depending on the knowledge and biases of the diagnostician (Klin et al. 2007, Miller & Ozonoff 2000, Sharma et al. 2012). In a recent American report (Prevention CfDCa 2012), approximately one quarter of children with ASD had received at least two different ASD-subtype diagnoses by age 8 (Mahjouri & Lord 2012). Also, the results of a multisite study of the clinical diagnoses of different ASDs support the move from existing sub-groupings of ASDs to dimensional descriptions of core features of social affect and fixated, repetitive behaviors, together with characteristics such as language level and cognitive function (Lord et al. 2012). The overall goal for the new DSM-5 criteria is to increase equity across the subcategories of ASDs, *i.e.*, autism, AS, and PDD-NOS (Lord & Jones 2012).

The framework of the proposed DSM-5 criteria for ASD seemed excellent. Therefore, we wanted to evaluate the proposed DSM-5 draft criteria that were posted by the APA in February 2010 in connection with the thoroughly detailed results obtained according to DSM-IV in our epidemiological study. Surprisingly, only 46%

of the children with ASDs (FSIQ \geq 50; DSM-IV) and none of the children with AS (DSM-IV) met the DSM-5 draft criteria for ASD. The more severe the ASD and the lower the FSIQ, the more likely were the DSM-5 draft criteria met in our study. As regards poor sensitivity of the proposed criteria, concordant results with those in our study have been published (Frazier et al. 2012, Gibbs et al. 2012, McPartland et al. 2012, Taheri & Perry 2012, Turygin et al. 2013, Wilson et al. 2013). In the study by McPartland et al. (2012), sensitivity varied according to the diagnostic subgroup (AD = 76%, AS = 25% and PDD-NOS = 28%) and cognitive ability (IQ < 70 = 70%); $IQ \ge 70 = 46\%$). It was also demonstrated that children and adolescents meeting the proposed DSM-5 criteria tended to have more severe impairments than those meeting DSM-IV-TR criteria (Worley & Matson 2012). In a large sample of toddlers, 48% of them who met DSM-IV-TR ASD criteria did not meet DSM-5 draft criteria (Matson et al. 2012a), and in a sample of developmentally disabled adults with ASD, 36.5% of individuals failed to meet the proposed DSM-5 criteria (Matson et al. 2012b). In a validity study of the proposed DSM-5 criteria for ASD, DSM-5 draft criteria yielded superior specificity of 97% relative to DSM-IV criteria (86%); however, it was at the detriment of sensitivity (81% and 95%, respectively) (Frazier et al. 2012).

Consequently, the proposed DSM-5 criteria for ASD have not escaped controversy and debate. A major concern and subsequent media response arising from our study, the study by McPartland et al. (2012) and from the autism community was whether or not the new criteria are too restrictive to identify AS and PDD-NOS (e.g. interviews in Scientific American of author Mattila from our study, author Volkmar from the study by McPartland et al., and Professor Lord). Based on the results of our study as well as those of many other studies (Frazier et al. 2012, Gibbs et al. 2012, Matson et al. 2012a, 2012b, McPartland et al. 2012, Taheri & Perry 2012, Turygin et al. 2012, Worley & Matson 2012), the proposed criteria would have excluded a substantial proportion of cognitively able individuals with ASDs, and a more stringent diagnostic rubric holds significant public health ramifications regarding service eligibility and compatibility of historical and future research (Frazier et al. 2012, McPartland et al. 2012). Our publication and the study by McPartland et al. (2012) concerning the DSM-5 draft criteria have been discussed as regards matching existing DSM-IV data (in our study) and existing DSM-III data (in the study by McPartland et al. 2012) from other frameworks to the DSM-5 draft criteria (Lord & Jones 2012). According to the critics, many examples that would be needed in diagnostics were perhaps not available.

Greater sensitivity of the proposed DSM-5 criteria has also been reported. One study encompassing a sample of 4,453 children with PDD revealed the sensitivity

of the proposed DSM-5 criteria to be high (91%), with an overall specificity of 53% (Huerta *et al.* 2012). In that study, sensitivity remained high in specific subgroups of PDDs, including girls and children under four. Notably, the APA has publicly stated that there has been no reduction in the number of people receiving an ASD diagnosis during the APA's field trials of the DSM-5 draft (APA 2012).

In summary, the prevailing trend of opinion among published studies is that DSM-5 draft criteria offer greater specificity, *i.e.*, a decrease in false-positive diagnoses, but reduced sensitivity, *i.e.*, increased failure to detect true positive diagnoses. These studies all have notable limitations, including reliance on older datasets, use of outdated versions of the proposed DSM-5 criteria, or exclusive reliance on clinicians' observations or parental reports. Most importantly, none of these studies have involved comparison of diagnostic rubrics in a prospective manner. Concurrently evaluating children by using both sets of criteria (DSM-IV and DSM-5) is the only way to assess any true change in prevalence associated with alteration in diagnostic rubric. (Volkmar *et al.* 2012.)

The subsequent version of the proposed DSM-5 draft that was posted in January 2011 elected to deal with the need for breadth by describing principles that define each sub-domain (e.g., nonverbal/integration of verbal and nonverbal communication, social reciprocity, relationships and adjusting to social contexts) and then providing non-exhaustive examples that represent different ages and levels of development to represent these principles. We did not have access to the extra text that was included in the DSM draft published in January 2011 when making our assessment, because we conducted our study and the reviews were processed during the previous months before the release of the DSM-5 draft in January 2011. The extra text would have helped us in comparison of the criteria and might have altered some of the codings in our sample (personal communication with Professor Happe, one of the reviewers and a member of the DSM-5 workgroup, in January 2011).

On the basis of our results, we proposed five detailed modifications (see Table 7) to relax the DSM-5 draft criteria for ASD posted in February 2010 to improve agreement between DSM-IV and DSM-5. Of these, two were implemented in the proposed DSM-5 in January 2011: 1) "hyper- or hypo-reactivity to sensory input" (*i.e.*, "idiosyncratic sensory behavior" in our modification) was included in the sensory domain, and 2) "routines AND rituals" was changed to "routines OR rituals".

In the finally completed DSM-5 criteria, all five of our modifications were considered (see Table 7): the first two as above, plus 3) "symptoms must be

present in early childhood" was changed to "symptoms must be present in the early developmental period" (*i.e.*, "symptoms must be present in childhood" in our modification). 4) "Social interaction and social communication manifest by at least two of three areas" in our modification instead of "social interaction and social communication manifest by all areas" in DSM-5 draft criteria, and 5) "marked deficits in nonverbal AND/OR verbal communication used for social interaction" in our modification instead of "marked deficits in nonverbal and verbal communication used for social interaction" in DSM-5 draft criteria were considered – lowering the criteria in the domain of social communication and social interaction by defining the manifestation of symptoms "currently or by history". In addition, DSM-5 allows any co-occurring psychiatric disorder with ASD (APA 2013), as we had suggested in our publication.

Promisingly, the new DSM-5 criteria seem to provide a more specific framework to guide diagnosis, prevalence, psychiatric comorbidity, treatment and research, while continuing to acknowledge the heterogeneity of this disorder both across individuals and within individuals over time (Mahjouri & Lord 2012). On the other hand, the severity specifiers based on the degree of impairment in cases of ASD fail to determine quantitative methods or recommendations for differentiating between levels. This leaves the field vulnerable to potential discrepancies between severity categorizations (Weitlauf *et al.* 2013). Only future research will reveal whether individuals with ASD will be recognized or missed and how the severity specifiers work as regards the finally settled DSM-5 criteria. It also remains to be seen whether the next version of ICD, ICD-11, will consider the changes made to DSM-5.

6.2 The Finnish Autism Spectrum Screening Questionnaire (III)

Screening instruments belong to the current clinical practices when identifying the features of ASD. In the present study, we provide optimal cut-off scores for the Finnish ASSQ in high-/medium-risk settings and population-based screening among Finnish primary school-aged 7- to 12-year-old children with normal intelligence or mild mental retardation (FSIQ \geq 50). Previous studies (e.g. Mattila *et al.* 2009, Posserud *et al.* 2006, 2009, Szatmari *et al.* 1994) have shown low agreement between informants regarding children's autistic features, and this is partly explained by real differences in children's behavior at school and at home. Compared with home, school requires more social skills of children, which is one of the defining symptom domains of ASD. Based on the low agreement rates in previous studies as well as our own clinical experience, we sought to establish an

alternative method to screen cases with ASD more effectively. Thus, we combined information from different surroundings (*i.e.*, school and home) by using summed parent-rated and teacher-rated ASSQ scores. ROC analysis indicated the best statistical values for summed parent-rated and teacher-rated ASSQ scores, with almost perfect AUC in the total population validation sample and with very high AUC in the high-/medium-risk sample, yielding optimal cut-off scores with high sensitivity and specificity. Thus, the optimal cut-off score for a high-/medium-risk sample, comparable with a clinical sample, is 30 using summed parent-rated and teacher-rated ASSQ scores; correspondingly, in total population screening it is 28.

In clinical work, an excellent instrument provides high sensitivity (the proportion of subjects who have the disorder who test positive for it, *i.e.*, true positives) and specificity (the proportion of subjects who do not have the disorder who test negative for it, *i.e.*, true negatives). In primary screening units, such as health centers, child health clinics and school health care settings, the primary task is to identify possible ASD cases, whereas in child psychiatric, neurological and neuropsychiatric units, it is important to identify possible ASD cases, as well as to distinguish possible ASD from other types of behavioral problems with social impairment (e.g. ADHD, social anxiety, CD).

In the high-/medium-risk sample, which is very similar to a clinical sample, the summed cut-off value of 30 allowed us to identify all hospital-registered outpatients with ASDs and 89% of the subjects diagnosed as having ASDs according to DSM-IV in our study (*i.e.*, with or without previous hospital-registered diagnoses of ASDs), with 82% specificity. In cases in which only the teacher's ASSQ rating is available, the cut-off score of 22 can be used as an indication for more careful examination in a clinical setting. Importantly, using the high-/medium-risk sample, an optimal cut-off score with high sensitivity and high specificity for parents' ASSQ ratings alone could not be established. When sensitivity was high in parents' ratings, specificity was low, and vice versa. Also, a low AUC (70%) demonstrated that parents' ratings alone do not work well.

In our total population validation sample of 4,408 children, using ROC curve criteria, the best summed cut-off score was 28, which identified all subjects with ASDs with very high specificity (99%), AUC value (99.8%) and LR (125), but with low PPV (50%). To achieve similar levels of sensitivity and specificity, the cut-off score for teachers' ratings alone (sensitivity of 100%, specificity of 94% and LR 18) or parents' ratings alone (sensitivity of 96%, specificity of 93% and LR 14) should be as low as seven (see Table 9), and then the PPV would be very low (10%). Therefore, in total population screening, we recommend using the summed

cut-off score of 28, because it is laborious to examine many false-positive cases. However, if only parents' ratings are available, a cut-off score of 7 and below can be used in more specific settings, such as when recruiting control cases without ASD in a general population (e.g., school classes) for research projects, and if only teachers' ratings are available, a cut-off score of 7 and below can also be used. As a remark, predictive values depend strongly on the prevalence of a disorder in the sample under study because they are calculated using both affected and unaffected individuals. Therefore, PPV and NPV are only weakly generalizable. A low PPV is to be expected in a screening instrument used to assess a disorder with a low prevalence, such as an ASD.

In the Norwegian Bergen Child Study, an optimal cut-off score of 17 with a sensitivity of 91% and a specificity of 86% was indicated in a total population sample when using the higher of either parent-rated or teacher-rated ASSQ scores (Posserud *et al.* 2009). We tested the "Norwegian model" in our total population validation sample, and a cut-off score of 19, for either the parent-rated or teacher-rated ASSQ scores, identified all subjects with ASDs with a high specificity of 98%. However, we achieved higher validity in our total population validation sample using our "summed score model" with the cut-off score of 28. As our validation data in the total population validation sample of 4,408 children is comparable with that in the Norwegian Bergen Child Study (Posserud *et al.* 2009), it would be interesting to see how our "summed score model" would work in the Norwegian population.

Our high-/medium-risk sample is very similar to a clinical child-psychiatric sample and our results are therefore more comparable with those of clinical sample studies conducted in Sweden (Ehlers *et al.* 1999) and in China (Guo *et al.* 2011) than the study conducted in Norway (Posserud *et al.* 2009). However, our cut-off score recommendation (summed score of 30) differs from the Swedish and Mandarin Chinese recommendations. Similarly to us, both parents' and teachers' ratings were also acquired in Sweden and a teacher-rated ASSQ cut-off score of 22 was suggested for use in clinical settings, but different from us, a parent-rated ASSQ cut-off score of 19 was established for use in clinical settings (Ehlers *et al.* 1999). In turn, only parents' ratings were acquired in China and the Mandarin Chinese ASSQ distinguished clinically diagnosed ASD patients from unaffected controls using a parent-rated cutoff score of 12 (Guo *et al.* 2011).

The broad variation of ASSQ cut-off scores could be partly explained by different methods (e.g. population-based vs. clinical-based, parent- and teacher-rated ASSQs vs. parent-rated ASSQs alone), but the variation also shows the importance

of determining valid cut-off scores when importing screening questionnaires from other languages and cultures. Merely translating the questionnaires is not enough; proper evaluation and validation are of utmost importance. Although Sweden, Norway and Finland are neighbors, the origins of Finnish differ from Swedish and Norwegian, and this may have affected the translations. For example, the rating "2" in the ASSQ 3-point Likert-type scale differs in Finland, Norway and Sweden. The Swedish ASSQ rating "2" indicates "stämmer absolut", meaning "fits definitely". In the Norwegian ASSQ, the same rating is translated as "stemmer helt" meaning "fits well" (personal communication with Dr. Posserud). Further, the translation in the Finnish ASSQ means "fits". Thus, interpretations of the items in different cultures may lead to different cut-off score recommendations.

It would be intriguing to gather a prospective genuine clinical sample in Finland in which validation of the Finnish ASSQ could be re-considered and the results compared with ours. It would also be interesting to define cut-offs separately for mothers' and fathers' ratings. The ASSQ-REV (Kopp & Gillberg 2011) would also merit translation and validation to see whether it is better able to detect the female phenotype of ASD.

6.3 Psychiatric comorbidity (IV)

To our knowledge, the present study is the first study involving population-based and clinical data sets and a standardized interview instrument to determine the prevalence of comorbid psychiatric disorders in high-functioning subjects with AS/ autism.

Comorbid psychiatric disorders seemed to be common and often multiple in cases of AS/HFA, decreasing the level of functioning significantly. The prevalence of current psychiatric disorders (74%) in children and adolescents with AS/HFA in our study was in concordance with the prevalence of psychiatric disorders (70%) in children with ASDs in a population-derived sample in the U.K. (Simonoff *et al.* 2008). In a Norwegian study, 72% of a special school population of children and adolescents with ASD were also diagnosed with at least one comorbid psychiatric disorder, using the same standardized tool as was used by ourselves, the K-SADS-PL (Gjevik *et al.* 2011). The present study was carried out in a democratic Western country that provides free primary education and nearly free healthcare for all inhabitants. Therefore, the present results concerning psychiatric comorbid disorders are most probably generalizable to developed countries that have a cultural context similar to that in Finland.

Behavioral disorders, specifically ODD, co-occurred with anxiety disorders, specifically with OCD. Current psychiatric comorbidity was more common in primary school-age than in secondary school-age participants. In particular, the prevalences of tic disorders and behavioral disorders decreased with age; as a consequence, no tic disorders were diagnosed in secondary school-age participants. The high number of tic disorders in primary school-age participants and non-existence in secondary school-age participants led to the somewhat surprising result of more psychiatric disorders (78% with a disorder) in the primary school-age population-based sample than in the clinical sample (75% with a disorder) with primary- and secondary school-age participants. However, the presence of tic disorders did not decrease the CGAS scores significantly and might not be considered to be very impairing psychiatrically.

In Finnish population-based studies, the prevalence of ADHD has been reported to be 7.1% according to DSM-III-R criteria in 8-year-old children, based on parental interviews (Almqvist *et al.* 1999) and 8.5% according to DSM-IV criteria in adolescents, based on both parental and adolescents' interviews (Smalley *et al.* 2007), whereas in our study, the prevalence of current ADHD was much higher (38%). Parallel with our study, the prevalence of ADHD was 28% in a population-derived sample of children with ASD in the U.K. (Simonoff *et al.* 2008), and 31% in the special school population of children and adolescents with ASD in Norway (Gjevik *et al.* 2011). Many investigators have demonstrated even higher prevalences of ADHD associated with ASDs (Gadow *et al.* 2004, Goldstein & Schwebach 2004, Lee & Ousley 2006). Because of the high prevalence of ADHD in order to target treatment, e.g., using psycho-stimulants, if needed (Posey *et al.* 2007).

None of the subjects in our study were reported as having recovered from ODD and no ODD diagnosis had changed to CD over the years, even if recovery from other comorbid psychiatric disorders, e.g. ADHD and tic disorders, had taken place. However, recall bias may be possible in ODD past diagnoses. The prevalence of ODD in otherwise typically developing children usually decreases with age, or the condition changes to CD, but on the basis of our results, the symptoms of ODD seem to be permanent during childhood in subjects with AS/HFA. The symptoms of ODD might partly be a manifestation of the stubbornness and difficulties in compliance that are often typical in ASDs, described as "insistence on sameness" in DSM-5. Based on our observation of co-occurrence of ODD and anxiety disorders, ODD may also be a behavioral manifestation of anxiety. In situations of social expectations becoming too high, the child or adolescent may feel anxiety without being able to express it verbally, thus leading to obstinate opposition. In a recent study, social anxiety in high-functioning children with ASD was demonstrated to predict aggression at levels commensurate with ODD/CD (Pugliese *et al.* 2013). In another recent study, social anxiety was found to partially mediate the relationship between ASD features and self-reported hostility in young adults (White *et al.* 2012). Importantly, AS/HFA associated with ODD was also reflected in significantly decreased CGAS scores in our study.

In the light of the results of our study, children and adolescents with AS/ HFA are at greater risk of anxiety disorders than the general child and adolescent population. The prevalence of current anxiety disorders was 39% in our populationbased sample, while in a Finnish national study of 8- to 9-year-old children based on diagnostic interviews with the parents the corresponding prevalence (according to DSM-III-R) was 5.2% (Almqvist *et al.* 1999). In concordance with our results, the prevalence of anxiety disorders in a special school population of children and adolescents with ASD was 41% in the previously mentioned Norwegian study (Gjevik *et al.* 2011). Moreover, in the Finnish national study (Almqvist *et al.* 1999) the prevalence of specific fears was 2.4%, while in our population-based sample, 33% suffered from current specific phobia.

Meta-analysis concerning studies of Gilles de la Tourette syndrome in children yielded a prevalence of 0.77% (95% CI 0.39–1.51%) (Knight *et al.* 2012). A minimum prevalence of 8.1% for Tourette's syndrome in children and adolescents with autism has been shown (Baron-Cohen *et al.* 1999), and in a study of children and adolescents with ASDs, 11% presented with Tourette's disorder (Canitano & Vivanti 2007). In our clinical sample, a concordant prevalence of 13% for Tourette's syndrome was assigned, but in our population-based sample the prevalence was more than twice as high (28%). Coincidence may also play a part when the number of cases is small.

A high prevalence of depression problems has been demonstrated in adolescents and adults with AS (Ghaziuddin *et al.* 1998) and a raised prevalence in children and adolescents with AS/HFA (Kim *et al.* 2000). Among young adults with AS, 70% had experienced at least one episode of major depression, and 50% of them had suffered from recurrent depressive episodes (Lugnegård *et al.* 2011). However, the prevalence of a current MDD in our study was low (6%), being at the same level as depressive disorder (6.2%) according to DSM-III-R in the Finnish national study of 8- to 9-year-old children (Almqvist *et al.* 1999). Observed within our examinations, the participants seemed to have good and close relationships with their parents, which may have prevented the development of depression and contributed to recovery from it. In adolescence in some cases, separation from primary family may also increase loneliness, leading to depression. However, the presence of MDD was associated with significantly lower CGAS scores in our study, although the number of MDD cases was low. Nevertheless, depression associated with AS/ HFA has to be taken seriously by professionals.

In the light of a few existing studies, the co-occurrence of schizophrenia does not appear to be common in subjects with AS (Asperger 1944, Ghaziuddin *et al.* 1998). However, a relatively high prevalence of schizophrenia has been determined in the relatives of subjects with AS (Ghaziuddin 2005). Schizophrenia usually becomes manifest after 15 years of age, at the age of 15–25 years in males and 20–30 years in females. In turn, ASDs have been reported to be overrepresented in subjects who have suffered from anorexia nervosa in their youth (Nilsson *et al.* 1999), and autistic traits overrepresented in female adolescents with anorexia (Baron-Cohen *et al.* 2013). Anorexia nervosa most often becomes manifest in youth or early adulthood. Therefore, the participants in our study were mostly too young to allow assessment of the prevalence of schizophrenia or anorexia nervosa. Additionally, the number of secondary school-age participants may have been too low to find them, owing to the fact of low prevalence in the general population.

Experiments with smoking are more obvious at secondary school age. In a Finnish questionnaire survey among 14- to 16-year-old teenagers, 48% had never smoked (Statistics Finland Website 2006a), whereas there had been no smoking among the subjects with AS/HFA in our study. This may partly be due to lack of social contacts, because the first experiments often take place with peers. In the K-SADS-PL interviews, the subjects with AS/HFA also seemed to have a negative attitude towards smoking. It remains to be seen in follow-up whether a comorbid diagnosis of ADHD might increase the incidence of smoking in subjects with AS/HFA.

Insomnia is a common and worsening problem. In a Finnish questionnaire survey among 14- to 16-year-old teenagers, the prevalence of almost daily initial and middle insomnia was 11% (Statistics Finland Website 2006b). Based on our results, the prevalence of initial insomnia was 34% in subjects with AS/HFA, being in concordance with the results of a previous study in school-age children with AS or HFA (Allik *et al.* 2006a). Therefore, identification of sleep disturbances and their treatment with melatonin, if needed, should be a routine part of the treatment plan of children/adolescents with AS/HFA (Rossignol & Frye 2011).

The CGAS scores reflected dysfunction in domains such as social interaction, but there was also a linear relationship between the number of comorbid psychiatric disorders and lower CGAS scores. AS/HFA associated with anxiety disorders or behavioral disorders, and with ODD or MDD, was reflected in significantly lowered CGAS scores. Anxiety disorders and behavioral disorders were more common in the clinical sample than in the population-based sample, possibly indicating that the subjects with a lower level of functioning had more often been referred to hospital or had been more carefully examined. The level of functioning (mean CGAS score) among girls was significantly lower than among boys, while mean CGAS scores did not differ significantly between primary- and secondary school-age participants or between participants with AS versus HFA. However, larger research groups might be needed to study CGAS score differences between younger and older subjects and between those with AS and HFA to establish or disprove these results.

Subjects with ASD are considered to differ from each other and each of them is taken to be an individual with a variety of symptoms and traits. Importantly, our study raised a comment caused by individually variable comorbid psychiatric disorders: comorbidity influenced the clinical picture of the subjects with AS/HFA and the severity of the level of their functioning. Longitudinal studies are needed to show the trajectories of the comorbid psychiatric disorder spectrum and the level of functioning.

A major challenge for clinicians is to determine if psychiatric symptoms observed in cases of AS/HFA are part of the same dimension, *i.e.*, the autism spectrum itself, or rather whether they represent different categorical factors, *i.e.*, a comorbid psychiatric disorder. The core symptoms of ASD may also mask the symptoms of a comorbid psychiatric condition. For instance, a sudden decrease in forms of repetitive and obsessive behavior in individuals with AS may represent a manifestation of depressive symptoms, but could also be mistakenly ascribed to an improvement in one of the diagnostic dimensions of ASD itself (Stewart *et al.* 2006). Therefore, longitudinal studies are needed to assess the changes in developmental trajectories of AS/HFA to discriminate between those symptoms that are part of the AS/HFA clinical phenotype from those that are the expression of a comorbid psychiatric disorder (Mazzone *et al.* 2012).

6.4 Limitations

1. Possible bias in screening. The ASSQ as a screening instrument in our study could have biased the prevalence of AS according to the criteria of Szatmari *et al.* In the validation study of the original Swedish ASSQ, all of the individuals with AS met Gillberg's criteria as well as DSM-IV/ICD-10 criteria, except the one related to completely normal development in the first 3 years of life, but the AS diagnoses according to the criteria of Szatmari *et al.* usere not determined (Ehlers *et al.* 1999).

2. Refusal of screened children. Of the 125 screened children, 15 (12%) refused to participate in the diagnostic examinations, two of them having a diagnosis of AS/AS traits in their medical records. Some of these 15 might also have been diagnosed as having ASDs in our study, which would have had something of an impact on the prevalence figures. In our university hospital at the time of our study, all high-functioning (FSIQ \geq 70) children and adolescents with ASDs had been diagnosed as having AS or AS traits according to prevailing behavior. Developmental history before 36 months had not been considered in diagnostics, and, thus, differential diagnosis between AS and autism had not been performed. Therefore, the two children with diagnoses of AS/AS traits in their medical records were included in the data on the prevalence of ASDs, but not in the data on the prevalence of AS.

3. Challenges in diagnosis. Difficulties in uncovering "language problems"/"odd speech" (Gillberg's criteria/Szatmari *et al.*'s criteria) may also have influenced the prevalence figures and male-to-female ratios somewhat.

4. Possible bias in the prevalences of autism and ASDs in lower-functioning subjects. The participation percentage of the children with FSIQ scores of < 50 (0.27%) was a little lower in the final sample of the epidemiological population (n = 4,422) than the estimated prevalence of moderate, severe, and profound mental retardation in northern Finland (0.38%) (Heikura *et al.* 2003). There might have been more drop-outs among the lower-functioning subjects than among the higher-functioning subjects, which may have biased the prevalences of autism and ASDs among the lower-functioning subjects. The diagnoses of ASDs in the children with FSIQ scores < 50 were drawn from the medical records, which could also have biased the prevalence figures compared with the subjects with FSIQ scores of \geq 50, whose diagnoses of ASDs were based on screening and consensus in our study. On the other hand, the children with severe mental retardation (FSIQ < 50) had regularly been followed up and, thus, were likely to have been recognized as ASD cases.

5. No randomized subsample in the low-risk sample. Concerning the validation of the Finnish ASSQ, children in the low-risk sample were neither clinically followed up in our study, nor was a subsample randomly selected from them, which could be considered as a limitation. However, one of our previous studies (Mattila *et al.* 2009) showed that all medically-registered ASD cases in the study met the inclusion criteria of the high-/medium-risk sample that we used in the present

study. In addition, on the basis of previous results (Ehlers et al. 1999, Mattila et al. 2009) and the prevalence figures of ASDs (Fombonne 2009, Levy et al. 2009), we gave up random selection of subjects at low risk because the probability of detecting ASD cases in that group was minimal in relation to the time-consuming effort and cost. In connection with this, in the previously mentioned Norwegian population-based study (n = 9,430), only two children with ASDs who were scored below 19 in parent-rated ASSQs and below 16 in teacher-rated ASSQs were detected (Posserud et al. 2009). Our medical register search also showed that all subjects with medically-registered ASDs met our inclusion criteria for diagnostic examinations, *i.e.*, all subjects with medically-registered ASDs were recognized in our screening. Marked similarity between the questions in psychiatric screening tests and diagnostic interviews supports the decision not to examine children in the low-risk sample. Furthermore, individual data (Table 1 of Publication III) in our study demonstrate well that the lower the ASSQ score, the more unlikely it was to have an ASD diagnosis. Based on these findings, generalization of the validity findings concerning the ASSQ can be applied to clinical settings as well as to total population screening.

6. Recall bias. In K-SADS-PL past diagnosis, the retrospective assessment by the parents and children/adolescents may have resulted in some recall bias. Because of the possible recall bias, we mainly reported current diagnoses.

7. Modified instruments were not available. Recently, a modification of K-SADS-PL (Autism Comorbidity Interview–Present and Lifetime Version, ACI-PL; Leyfer *et al.* 2006) for children and adolescents with autism, and a CGAS modification (Developmental Disability–Child Global Assessment Scale, DD-CGAS; Wagner *et al.* 2007) for children with ASDs have been developed. However, our study was drawn up and performed before these modified instruments were available. In addition, the K-SADS-PL schedule and CGAS can be used in all children irrespective of diagnosis. Our results with the original K-SADS-PL and CGAS may thus be more comparable with the results of non-ASD studies.

8. Possible bias in the prevalence of ADHD and anxiety disorders. Familiarity with the etiology of ADHD may also result in bias if parents with ADHD symptoms either under- or over-report these symptoms in their offspring. However, it has been reported that parental ADHD symptoms do not bias maternal reports of ADHD symptoms in their children (Faraone *et al.* 2003). Also, it might be possible that

parental anxiety may influence parental reporting trends and/or biases (Bernstein *et al.* 2005). However, the diagnosis was based on both parents' and children's/ adolescents' interviews and most children/adolescents with a specific phobia in our study seemed to be very stuck in their phobias.

9. Possible bias in comparison between younger and older participants. Comparison between primary- and secondary school-age participants in order to find out whether the comorbid psychiatric disorder spectra and CGAS scores change along with age involves a risk of bias. In this kind of comparison, we assume that the current primary school-age participants will turn into the same kind of secondary school-age adolescents as the current secondary school-age participants. Longitudinal studies are needed to show the trajectory of the comorbid psychiatric disorder spectrum and the trajectory of the impairment based on CGAS scores.

7 Conclusions

The present study provides novel data and information on epidemiological and diagnostic aspects of ASDs.

1. The prevalence of ASDs in our study is in concordance with recent international prevalence figures. The diagnostic manuals of DSM-IV and ICD-10 help with the definition of ASDs only up to a point. Our results indicate the need to standardize the diagnostic criteria of ASDs in order to better compare research studies and to avoid diagnostic confusion in clinical work and research.

2. From the point of view of clinical practice and reliably comparable research, it is crucial to avoid two competing diagnostic frameworks for ASD. The forthcoming ICD-11 criteria should be uniform and harmonize with DSM-5 criteria for ASD.

3. The Finnish ASSQ is an appropriate screening instrument. Validation of imported ASD screening instruments and determination of cut-off scores in different languages and cultures are of utmost importance. Clinicians are reminded that the ASSQ is not a diagnostic instrument. For children rated at or above the cut-off scores in the ASSQ, comprehensive examinations are needed, using diagnostic instruments and multi-informant sources, in order to establish ASD or to exclude it. 4. The significant number of cases of ADHD and OCD in children/adolescents with AS/HFA indicates that the exclusionary ICD-10 criteria concerning comorbid psychiatric diagnoses should be re-considered. Clinicians are reminded not to forget ASD when evaluating children/adolescents with psychiatric diagnoses and neuropsychiatric disorders (e.g., ADHD, Tourette's syndrome). We also emphasize the importance of comorbid psychiatric evaluation in cases of ASD in order to target treatment and rehabilitation precisely.

References

- Adams C, Green J, Gilchrist A & Cox A (2002) Conversational behaviour of children with Asperger syndrome and conduct disorder. J Child Psychol Psychiatry 43(5): 679–690.
- Allik H, Larsson JO & Smedje H (2006a) Insomnia in school-age children with Asperger syndrome or high-functioning autism. BMC Psychiatry 6: 18.
- Allik H, Larsson JO & Smedje H (2006b) Sleep patterns of school-age children with Asperger syndrome or high-functioning autism. J Autism Dev Disord 36(5): 585–595.
- Allik H, Larsson JO & Smedje H (2008) Sleep patterns in school-age children with Asperger syndrome or high-functioning autism: a follow-up study. J Autism Dev Disord 38(9): 1625–1633.
- Almqvist F, Puura K, Kumpulainen K, Tuompo-Johansson E, Henttonen I, Huikko E, Linna S, Ikäheimo K, Aronen E, Katainen S, Piha J, Moilanen I, Räsänen E & Tamminen T (1999) Psychiatric disorders in 8–9-year-old children based on a diagnostic interview with the parents. Eur Child Adolesc Psychiatry 8(Suppl 4): 17–28.
- American Psychiatric Association (APA) (1952) Diagnostic and Statistical Manual of Mental Disorders–1st ed. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (APA) (1968) Diagnostic and Statistical Manual of Mental Disorders–2nd ed. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (APA) (1980) Diagnostic and Statistical Manual of Mental Disorders–3rd ed. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (APA) (1987) Diagnostic and Statistical Manual of Mental Disorders–3rd ed., Text rev. Washington, DC, American Psychiatric Association.
- American Psychiatric Association (APA) (1994) Diagnostic and Statistical Manual of Mental Disorders–4th ed. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (APA) (2000) Diagnostic and Statistical Manual of Mental Disorders–4th ed., Text rev. Washington, DC: American Psychiatric Association.
- American Psychiatric Association (APA) (2012) DSM-5 proposed criteria for autism spectrum disorder designed to provide more accurate diagnosis and treatment, Press release.
 American Psychiatric Association, http://www.dsm5.org/Documents/12–03%20
 Autism%20Spectrum%20Disorders%20-%20DSM5.pdf. Accessed 14 October 2012.
- American Psychiatric Association (APA) (2013) Diagnostic and Statistical Manual of Mental Disorders–5th ed. Washington, DC: American Psychiatric Association.
- Amr M, Raddad D, El-Mehesh F, Bakr A, Sallam K & Amin T (2012) Comorbid psychiatric disorders in Arab children with autism spectrum disorders. Res Autism Spectr Disord 6(1): 240–248.
- Andersen LM, Näswall K, Manouilenko I, Nylander L, Edgar J, Ritvo RA, Ritvo E & Bejerot S (2011) The Swedish version of the Ritvo autism and asperger diagnostic scale: revised (RAADS–R). A validation study of a rating scale for adults. J Autism Dev Disord 41(12): 1635–1645.
- Asperger H (1938) Das psychisch abnorme Kinde. Wien Klin Wochenschr 51: 1314–1317.
- Asperger H (1944) Die "Autistischen Psychopathen" im Kindesalter. Archiv für Psyciatrie und Nervenkrankheiten 117: 76–136.

Asperger H (1979) Problems of infantile autism. Communication 13: 45-52.

- Autismi- ja Aspergerliitto ry (2012) Available at http://www.autismiliitto.fi/files/1046/ ASSQ-lomake_virallinen_kaannos_v._2000_5_8_2012.pdf.
- Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E & Rutter M (1995) Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med 25(1): 63–77.
- Baird G, Charman T, Baron-Cohen S, Cox A, Swettenham J, Wheelwright S & Drew A (2000) A screening instrument for autism at 18 months of age: a 6-year follow-up study. J Am Acad Child Adolesc Psychiatry 39(6): 694–702.
- Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D & Charman T (2006) Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet 368(9531): 210– 215.
- Baron-Cohen S, Allen J & Gillberg C (1992) Can autism be detected at 18 months? The needle, the haystack, and the CHAT. Br J Psychiatry 161: 839–843.
- Baron-Cohen S, Jaffa T, Davies S, Auyeung B, Allison C & Wheelwright S (2013) Do girls with anorexia nervosa have elevated autistic traits? Mol Autism 4(1): 24.
- Baron-Cohen S, Mortimore C, Moriarty J, Izaguirre J & Robertson M (1999) The prevalence of Gilles de la Tourette's syndrome in children and adolescents with autism. J Child Psychol Psychiatry 40(2): 213–218.
- Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE & Brayne C (2009) Prevalence of autism-spectrum conditions: UK school-based population study. Br J Psychiatry 194(6): 500–509.
- Beglinger LJ & Smith TH (2001) A review of subtyping in autism and proposed dimensional classification model. J Autism Dev Disord 31(4): 411–422.
- Bejerot S & Humble M (1999) Low prevalence of smoking among patients with obsessivecompulsive disorder. Compr Psychiatry 40(4): 268–272.
- Bejerot S & Nylander L (2003) Low prevalence of smoking in patients with autism spectrum disorders. Psychiatry Res 119(1–2): 177–182.
- Beratis S, Katrivanou A & Gourzis P (2001) Factors affecting smoking in schizophrenia. Compr Psychiatry 42(5): 393–402.
- Bernstein GA, Layne AE, Egan EA & Nelson LP (2005) Maternal phobic anxiety and child anxiety. J Anxiety Disord 19(6): 658–672.
- 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. Pediatrics 108(5): 1155–1161.
- Berument SK, Rutter M, Lord C, Pickles A & Bailey A (1999) Autism screening questionnaire: diagnostic validity. Br J Psychiatry 175: 444–451.
- Bleuler E (1911) Dementia Praecox oder Gruppe der Schizophrenien. In: Aschaffenburg G, editor. Handbuch der Psychiatrie. Leipzig: Deuticke; (Ger).
- Bleuler EP (1983, original 1916) Lehrbuch der Psychiatrie/Textbook of Psychiatry. Berlin Heidelberg: Springer-Verlag.

- Booth T, Murray AL, McKenzie K, Kuenssberg R, O'Donnell M & Burnett H (2013) Brief report: an evaluation of the AQ–10 as a brief screening instrument for ASD in adults. J Autism Dev Disord 43(12): 2997–3000.
- Canitano R & Vivanti G (2007) Tics and Tourette syndrome in autism spectrum disorders. Autism 11(1): 19–28.
- Carrey NJ (1995) Itard's 1828 mémoire on "Mutism caused by a lesion of the intellectual functions": a historical analysis. J Am Acad Child Adolesc Psychiatry 34(12): 1655–1661.
- Chakrabarti S & Fombonne E (2001) Pervasive developmental disorders in preschool children. JAMA 285(24): 3093–3099.
- Chakrabarti S & Fombonne E (2005) Pervasive developmental disorders in preschool children: confirmation of high prevalence. Am J Psychiatry 162(6): 1133–1141.
- Charman T & Baird G (2002) Practitioner review: Diagnosis of autism spectrum disorder in 2- and 3-year-old children. J Child Psychol Psychiatry 43(3): 289–305.
- Charman T, Jones CR, Pickles A, Simonoff E, Baird G & Happé F (2011) Defining the cognitive phenotype of autism. Brain Res 1380: 10–21.
- Chevallier C, Noveck I, Happé F & Wilson D (2011) What's in a voice? Prosody as a test case for the Theory of Mind account of autism. Neuropsychologia 49(3): 507–517.
- Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, Metzger LM, Shoushtari CS, Splinter R & Reich W (2003) Validation of a brief quantitative measure of autistic traits: comparison of the social responsiveness scale with the autism diagnostic interview-revised. J Autism Dev Disord 33(4): 427–433.
- Cox A, Klein K, Charman T, Baird G, Baron-Cohen S, Swettenham J, Drew A & Wheelwright S (1999) Autism spectrum disorders at 20 and 42 months of age: stability of clinical and ADI-R diagnosis. J Child Psychol Psychiatry 40(5): 719–732.
- Davidovitch M, Hemo B, Manning-Courtney P & Fombonne E (2013) Prevalence and incidence of autism spectrum disorder in an Israeli population. J Autism Dev Disord 43(4): 785–793.
- Dennis M, Lazenby AL & Lockyer L (2001) Inferential language in high-function children with autism. J Autism Dev Disord 31(1): 47–54.
- Ecker C, Marquand A, Mourao-Miranda J, Johnston P, Daly EM, Brammer MJ, Maltezos S, Murphy CM, Robertson D, Williams SC & Murphy DG (2010) Describing the brain in autism in five dimensions-magnetic resonance imaging- assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. J Neurosci 30(32): 10612–10623.
- Ehlers S & Gillberg C (1993) The epidemiology of Asperger syndrome. A total population study. J Child Psychol Psychiatry 34(8): 1327–1350.
- Ehlers S, Gillberg C & Wing L (1999) A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. J Autism Dev Disord 29(2): 129–141.
- Faraone SV, Monuteaux MC, Biederman J, Cohan SL & Mick E (2003) Does parental ADHD bias maternal reports of ADHD symptoms in children? J Consult Clin Psychol 71(1): 168–175.

- Feinstein A (2010) A History of Autism: Conversations with the Pioneers. Wiley-Blackwell, pp 175–176.
- Fernell E & Gillberg C (2010) Autism spectrum disorder diagnoses in Stockholm preschoolers. Res Dev Disabil 31(3): 680–685.
- Fombonne E (2001) What is the prevalence of Asperger disorder? J Autism Dev Disord 31(3): 363–364.
- Fombonne E (2009) Epidemiology of pervasive developmental disorders. Pediatr Res 65(6): 591–598.
- Frazier TW, Youngstrom EA, Speer L, Embacher R, Law P, Constantino J, Findling RL, Hardan AY & Eng C (2012) Validation of proposed DSM-5 criteria for autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 51(1): 28–40.
- Frith U (1991) Asperger and his syndrome. In Autism and Asperger syndrome, Frith U, ed. Cambridge: Cambridge University Press, pp 1–36.
- Frith U (2004) Emmanuel Miller lecture: confusions and controversies about Asperger syndrome. J Child Psychol Psychiatry 45(4): 672–686.
- Gadow KD & DeVincent CJ (2012) Comparison of children with autism spectrum disorder with and without schizophrenia spectrum traits: gender, season of birth, and mental health risk factors. J Autism Dev Disord 42(11): 2285–2296.
- Gadow KD, DeVincent CJ & Pomeroy J (2006) ADHD symptom subtypes in children with pervasive developmental disorder. J Autism Dev Disord 36(2): 271–283.
- Gadow KD, DeVincent CJ, Pomeroy J & Azizian A (2004) Psychiatric symptoms in preschool children with PDD and clinic and comparison samples. J Autism Dev Disord 34(4): 379–393.
- Georgsdottir I, Haraldsson A & Dagbjartsson A (2013) Behavior and well-being of extremely low birth weight teenagers in Iceland. Early Hum Dev 89(12): 999-1003.
- Geschwind DH (2008) Autism: many genes, common pathways? Cell 135(3): 391-395.
- Geschwind DH (2011) Genetics of autism spectrum disorders. Trends Cogn Sci 15(9): 409–416.
- Ghaziuddin M (2005) A family history study of Asperger syndrome. J Autism Dev Disord 35(2): 177–182.
- Ghaziuddin M, Weidmer-Mikhail E & Ghaziuddin N (1998) Comorbidity of Asperger syndrome: a preliminary report. J Intellect Disabil Res 42(Pt 4): 279–283.
- Gibbs V, Aldridge F, Chandler F, Witzlsperger E & Smith K (2012) Brief report: an exploratory study comparing diagnostic outcomes for autism spectrum disorders under DSM-IV-TR with the proposed DSM-5 revision. J Autism Dev Disord 42(8): 1750–1756.
- Gillberg C (1991) Clinical and neurobiological aspects of Asperger syndrome in six family studies. In Autism and Asperger Syndrome, Frith U, ed. Cambridge: Cambridge University Press, pp 122–146.
- Gillberg C, Gillberg C, Råstam M & Wentz E (2001) The Asperger Syndrome (and highfunctioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. Autism 5(1): 57–66.
- Gillberg IC & Gillberg C (1989) Asperger syndrome some epidemiological considerations: a research note. J Child Psychol Psychiatry 30(4): 631–638.

- Gillott A, Furniss F & Walter A (2001) Anxiety in high-functioning children with autism. Autism 5(3): 277–286.
- Gjevik E, Eldevik S, Fjæran-Granum T & Sponheim E (2011) Kiddie-SADS reveals high rates of DSM-IV disorders in children and adolescents with autism spectrum disorders. J Autism Dev Disord 41(6): 761–769.
- Goin-Kochel RP, Mackintosh VH & Myers BJ (2006) How many doctors does it take to make an autism spectrum diagnosis? Autism 10(5): 439–451.
- Goldstein S & Schwebach AJ (2004) The comorbidity of pervasive developmental disorder and attention deficit hyperactivity disorder: results of a retrospective chart review. J Autism Dev Disord 34(3): 329–339.
- Gotham K, Risi S, Dawson G, Tager-Flusberg H, Joseph R, Carter A, Hepburn S, McMahon W, Rodier P, Hyman SL, Sigman M, Rogers S, Landa R, Spence MA, Osann K, Flodman P, Volkmar F, Hollander E, Buxbaum J, Pickles A & Lord C (2008) A replication of the Autism Diagnostic Observation Schedule (ADOS) revised algorithms. J Am Acad Child Adolesc Psychiatry 47(6): 642–651.
- Gotham K, Risi S, Pickles A & Lord C (2007) The Autism Diagnostic Observation Schedule: revised algorithms for improved diagnostic validity. J Autism Dev Disord 37(4): 613– 627.
- Guo YQ, Tang Y, Rice C, Lee LC, Wang Y F & Cubells JF (2011) Validation of the Autism Spectrum Screening Questionnaire, Mandarin Chinese Version (CH-ASSQ) in Beijing, China. Autism 15(6): 713–727.
- Guttmann-Steinmetz S, Gadow KD & Devincent CJ (2009) Oppositional defiant and conduct disorder behaviors in boys with autism spectrum disorder with and without attentiondeficit hyperactivity disorder versus several comparison samples. J Autism Dev Disord 39(7): 976–985.
- Hallerbäck MU, Lugnegård T & Gillberg C (2012) ADHD and nicotine use in schizophrenia and Asperger syndrome: a controlled study. J Atten Disord 2012 Apr 12. [Epub ahead of print].
- Happe F (2011) Why fold Asperger syndrome into autism spectrum disorder in the DSM-5? Simons Foundation Autism Research Initiative News and Opinion. Available at http:// sfari.org/news-and-opinion/viewpoint/2011/ why-fold-asperger-syndrome-into-autismspectrum-disorder-in-the-dsm-5.
- Heikura U, Taanila A, Olsén P, Hartikainen AL, von Wendt L & Järvelin MR (2003) Temporal changes in incidence and prevalence of intellectual disability between two birth cohorts in Northern Finland. Am J Ment Retard 108(1): 19–31.
- Hogrefe Psykologisk Forlag (2009) Available at http://www.hogrefe.dk.
- Howlin P & Asgharian A (1999) The diagnosis of autism and Asperger syndrome: findings from a survey of 770 families. Dev Med Child Neurol 41(12): 834–839.
- Huerta M, Bishop SL, Duncan A, Hus V & Lord C (2012) Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. Am J Psychiatry 169(10): 1056–1064.

- Hughes V (2010) Kevin Pelphrey: Charting the course of the social brain. Simons Foundation Autism Research Initiative, News and Opinion. Available at http://sfari.org/news-andopinion/investigator-profiles/2010/kevin-pelphrey-charting-the-course-of-the-socialbrain [last accessed 5 December 2012].
- Hurtig T, Ebeling, H, Taanila A, Miettunen J, Smalley S, McGough J, Loo S, Järvelin MR
 & Moilanen I (2007) ADHD and comorbid disorders in relation to family environment and symptom severity. Eur Child Adolesc Psychiatry 16(6): 362–369.
- Itard JMG (1962, original 1894) The wild boy of Aveyron, Humphrey G & Humphrey M, trans. New York: Appleton-Century-Crofts.
- Jacob S, Landeros-Weisenberger A & Leckman JF (2009) Autism spectrum and obsessivecompulsive disorders: OC behaviors, phenotypes and genetics. Autism Res 2(6): 293– 311.
- Jakab A, Emri M, Spisak T, Szeman-Nagy A, Beres M, Kis SA, Molnar P & Berenyi E (2013) Autistic traits in neurotypical adults: correlates of graph theoretical functional network topology and white matter anisotropy patterns. PLoS One 8(4): e60982.
- James SJ, Melnyk S, Jenigan S, Pavliv O, Trusty T, Lehman S, Seidel L, Gaylor DW & Cleves MA (2010) A functional polymorphism in the reduced folate carrier gene and DNA hypomethylation in mothers of children with autism. Am J Med Genet B Neuropsychiatr Genet 153B(6): 1209–1220.
- Jansson-Verkasalo E, Kujala T, Jussila K, Mattila ML, Moilanen I, Näätänen R, Suominen K & Korpilahti P (2005) Similarities in the phenotype of the auditory neural substrate in children with Asperger syndrome and their parents. Eur J Neurosci 22(4): 986–990.
- Jasmin E, Couture M, McKinley P, Reid G, Fombonne E & Gisel E (2009) Sensori-motor and daily living skills of preschool children with autism spectrum disorders. J Autism Dev Disord 39(2): 231–241.
- Johnson CR, Turner KS, Foldes EL, Malow BA & Wiggs L (2012) Comparison of sleep questionnaires in the assessment of sleep disturbances in children with autism spectrum disorders. Sleep Med 13(7): 795–801.
- Jolliffe T & Baron-Cohen S (1999) A test of central coherence theory: linguistic processing in high-functioning adults with autism or Asperger syndrome: Is local coherence impaired? Cognition 71(2): 149–185.
- Joshi G, Wozniak J, Petty C, Martelon MK, Fried R, Bolfek A, Kotte A, Stevens J, Furtak SL, Bourgeois M, Caruso J, Caron A & Biederman J (2013) Psychiatric comorbidity and functioning in a clinically referred population of adults with autism spectrum disorders: a comparative study. J Autism Dev Disord 43(6): 1314–1325.
- Kadesjö B, Gillberg C & Hagberg B (1999) Brief report: autism and Asperger syndrome in seven-year-old children: a total population study. J Autism Dev Disord 29(4): 327–331.
- Kanner L (1943) Autistic disturbances of affective contact. Nervous Child 2: 217–250.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D & Ryan N (1997) Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36(7): 980–988.

- Keehn B, Lincoln AJ, Muller RA & Townsend J (2010) Attentional networks in children and adolescents with autism spectrum disorder. J Child Psychol Psychiatry 51(11): 1251– 1259.
- Kielinen M, Linna SL & Moilanen I (2000) Autism in Northern Finland. Eur Child Adolesc Psychiatry 9(3): 162–167.
- Kim JA, Szatmari P, Bryson SE, Streiner DL & Wilson FJ (2000) The prevalence of anxiety and mood problems among children with autism and Asperger syndrome. Autism 4(2): 117–132.
- Kim SH & Lord C (2012) Combining information from multiple sources for the diagnosis of autism spectrum disorders for toddlers and young preschoolers from 12 to 47 months of age. J Child Psychol Psychiatry 53(2): 143–151.
- Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, Cheon KA, Kim SJ, Kim YK, Lee H, Song DH & Grinker RR (2011) Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry 168(9): 904–912.
- King BH & Lord C (2011) Is schizophrenia on the autism spectrum? Brain Res 1380: 34-41.
- Klin A, Saulnier CA, Sparrow SS, Cicchetti DV, Volkmar FR & Lord C (2007) Social and communication abilities and disabilities in higher functioning individuals with autism spectrum disorders: The Vineland and the ADOS. J Autism Dev Disord 37(4): 748–759.
- Knight T, Steeves T, Day L, Lowerison M, Jette N & Pringsheim T (2012) Prevalence of tic disorders: a systematic review and meta-analysis. Pediatr Neurol 47(2): 77–90.
- Kobayashi K, Endoh F, Ogino T, Oka M, Morooka T, Yoshinaga H & Ohtsuka Y (2013) Questionnaire-based assessment of behavioral problems in Japanese children with epilepsy. Epilepsy Behav 27(1): 238–242.
- Kochhar P, Batty MJ, Liddle EB, Groom MJ, Scerif G, Liddle PF & Hollis CP (2011) Autistic spectrum disorder traits in children with attention deficit hyperactivity disorder. Child Care Health Dev 37(1): 103–110.
- Kopp S (2010) Girls with social and/or attention impairments. Institute of Neuroscience and Physiology Child and Adolescent Psychiatry University of Gothenburg Sweden. Göteborg: Intellecta Infolog AB.
- Kopp S & Gillberg C (2011) The Autism Spectrum Screening Questionnaire (ASSQ)revised extended version (ASSQ-REV): An instrument for better capturing the autism phenotype in girls? A preliminary study involving 191 clinical cases and community controls. Res Dev Disabil 32(6): 2875–2888.
- Korpilahti P, Jansson-Verkasalo E, Mattila ML, Kuusikko S, Suominen K, Rytky S, Pauls DL & Moilanen I (2007) Processing of affective speech prosody is impaired in Asperger syndrome. J Autism Dev Disord 37(8): 1539–1549.
- Krakowiak P, Goodlin-Jones B, Hertz-Picciotto I, Croen LA & Hansen RL (2008) Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: A population-based study. J Sleep Res 17(2): 197–206.
- Krug DA, Arick J & Almond P (1980) Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. J Child Psychol Psychiatry 21(3): 221–229.

- Kujala T, Aho E, Lepistö T, Jansson-Verkasalo E, Nieminen-von Wendt T, von Wendt L & Näätänen R (2007) Atypical pattern of discriminating sound features in adults with Asperger syndrome as reflected by the mismatch negativity. Biol Psychol 75(1): 109– 114.
- Kujala T, Kuuluvainen S, Saalasti S, Jansson-Verkasalo E, von Wendt L & Lepisto T (2010) Speech-feature discrimination in children with Asperger syndrome as determined with the multi feature mismatch negativity paradigm. Clin Neurophysiol 121(9): 1410–1419.
- Kujala T, Lepistö T, Nieminen-von Wendt T, Näätänen P & Näätänen R (2005) Neurophysiological evidence for cortical discrimination impairment of prosody in Asperger syndrome. Neurosci Lett 383(3): 260–265.
- Kuusikko S, Haapsamo H, Jansson-Verkasalo E, Hurtig T, Mattila ML, Ebeling H, Jussila K, Bölte S & Moilanen I (2009) Emotion recognition in children and adolescents with autism spectrum disorders. J Autism Dev Disord 39(6): 938–945.
- Kuusikko S, Pollock-Wurman R, Jussila K, Carter AS, Mattila ML, Ebeling H, Pauls DL & Moilanen I (2008) Social anxiety in high-functioning children and adolescents with autism and Asperger syndrome. J Autism Dev Disord 38(9): 1697–1709.
- Lam Y & Yeung S (2012) Towards a convergent account of pragmatic language deficits in children with high-functioning autism: depicting the phenotype using the Pragmatic Rating Scale. Res Autism Spectr Disord 6: 792–797.
- Lampi KM, Lehtonen L, Tran PL, Suominen A, Lehti VP, Banerjee N, Gissler M, Brown AS & Sourander A (2012) Risk of autism spectrum disorders in low birth weight and small for gestational age infants. J Pediatr 161(5): 830–836.
- Landa R (2000) Social language use in Asperger syndrome and high-functioning autism. In Asperger Syndrome, Klin A, Volkmar FR & Sparrow SS, eds. New York: Guilford, pp 125–155.
- Latif AH & Williams WR (2007) Diagnostic trends in autistic spectrum disorders in the South Wales valleys. Autism 11(6): 479–487.
- Le Couteur A, Lord C & Rutter M (2003) Autism Diagnostic Interview—Revised (ADI-R). Los Angeles, California: Western Psychological Services.
- Leckman JF, Sholomskas D, Thompson WD, Belanger A & Weissman MM (1982) Best estimate of lifetime psychiatric diagnosis: a methodological study. Arch Gen Psychiatry 39(8): 879–883.
- Lee DO & Ousley OY (2006) Attention-deficit hyperactivity disorder symptoms in a clinic sample of children and adolescents with pervasive developmental disorders. J Child Adolesc Psychopharmacol 16(6): 737–746.
- Leekam SR, Libby SJ, Wing L, Gould J & Taylor C (2002) The Diagnostic Interview for Social and Communication Disorders: algorithms for ICD-10 childhood autism and Wing and Gould autistic spectrum disorder. J Child Psychol Psychiatry 43(3): 327–342.
- Lepistö T, Kajander M, Vanhala R, Alku P, Huotilainen M, Näätänen R & Kujala T (2008) The perception of invariant speech features in children with autism. Biol Psychol 77(1): 25–31.

- Lepistö T, Nieminen-von Wendt T, von Wendt L, Näätänen R & Kujala T (2007) Auditory cortical change detection in adults with Asperger syndrome. Neurosci Lett 414(2): 136–140.
- Lepistö T, Silokallio S, Nieminen-von Wendt T, Alku P, Näätänen R & Kujala A (2006) Auditory perception and attention as reflected by the brain event-related potentials in children with Asperger syndrome. Clin Neurophysiol 117(10): 2161–2171.
- Lesinskiene S (2000) Vilniaus miesto vaiku autizmas, Vilniaus Universitetas, Daktaro disetacijos santrauka, Biomedicinos mokslai, medicina 07B, psichiatrija B650. Vilnius: Lithuania.
- Lesinskiene S & Puras D (2001) Prevalence of Asperger syndrome among children of Vilnius. Int J Circumpolar Health 60: 13.
- Levy SE, Mandell DS & Schultz RT (2009) Autism. Lancet 374(9701): 1627–1638. Erratum in Lancet (2011) 378(9802): 1546.
- Leyfer OT, Folstein SE, Bacalman S, Davis NO, Dinh E, Morgan J, Tager-Flusberg H & Lainhart JE (2006) Comorbid psychiatric disorders in children with autism: interview development and rates of disorders. J Autism Dev Disord 36(7): 849–861.
- Lord C & Jones RM (2012) Annual research review: re-thinking the classification of autism spectrum disorders. J Child Psychol Psychiatry 53(5): 490–509.
- Lord C, Luyster RJ, Gotham K & Guthrie W (2012) Autism Diagnostic Observation Schedule, 2nd ed. (ADOS-2), Toddler Module. Los Angeles, California: Western Psychological Services.
- Lord C, Petkova E, Hus V, Gan W, Lu F, Martin DM & Risi S (2012) A multisite study of the clinical diagnosis of different autism spectrum disorders. Arch Gen Psychiatry 69(3): 306–313.
- Lord C, Risi S, DiLavore PS, Shulman C, Thurm A & Pickles A (2006) Autism from 2 to 9 years of age. Arch Gen Psychiatry 63(6): 694–701.
- Lord C, Rutter M, DiLavore PC & Risi S (2000) Autism Diagnostic Observation Schedule (ADOS). Los Angeles, California: Western Psychological Services.
- Lord C, Rutter M & Le Couteur A (1995) Autism Diagnostic Interview—Revised (ADI-R), 3rd ed. Los Angeles, California: Western Psychological Services.
- Losh M & Capps L (2003) Narrative ability in high-functioning children with autism or Asperger syndrome. J Autism Dev Disord 33(3): 239–251.
- Losh M, Sullivan PF, Trembath D & Piven J (2008) Current developments in the genetics of autism: from phenome to genome. J Neuropathol Exp Neurol 67(9): 829–837.
- Lotspeich LJ, Kwon H, Schumann CM, Fryer SL, Goodlin-Jones BL, Buonocore MH, Lammers CR, Amaral DG & Reiss AL (2004) Investigation of neuroanatomical differences between autism and Asperger syndrome. Arch Gen Psychiatry 61(3): 291– 298.
- Loukusa S, Leinonen E, Kuusikko S, Jussila K, Mattila ML, Ryder N, Ebeling H & Moilanen I (2007) Use of context in pragmatic language comprehension by children with Asperger syndrome or high-functioning autism. J Autism Dev Disord 37(6): 1049–1059.

- Loukusa S & Moilanen I (2009) Pragmatic inference abilities in individuals with Asperger syndrome or high-functioning autism. A review. Res Autism Spectr Disord 3(4): 890– 904.
- Lugnegård T (2012) Asperger syndrome and schizophrenia. Psychiatric and social cognitive aspects. Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology Sahlgrenska Academy at University of Gothenburg. Gothenburg: Ineko Ab.
- Lugnegård T, Hallerbäck MU & Gillberg C (2011) Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. Res Dev Disabil 32(5): 1910–1917.
- Mack H, Fullana MA, Russell AJ, Mataix-Cols D, Nakatani E & Heyman I (2010) Obsessions and compulsions in children with Asperger's syndrome or high-functioning autism: a case-control study. Aust N Z J Psychiatry 44(12): 1082–1088.
- Magnuson KM & Constantino JN (2011) Characterization of depression in children with autism spectrum disorders. J Dev Behav Pediatr 32(4): 332–340.
- Mahjouri S & Lord CE (2012) What the DSM-5 portends for research, diagnosis, and treatment of autism spectrum disorders. Curr Psychiatry Rep 14(6): 739–747.
- Mars AE, Mauk JE & Dowrick PW (1998) Symptoms of pervasive developmental disorders as observed in prediagnostic home videos of infants and toddlers. J Pediatr 132(3 Pt 1): 500–504.
- Matson J, Belva B, Horovitz M, Kozlowski A & Bamburg J (2012b) Comparing symptoms of autism spectrum disorders in a developmentally disabled adult population using the current DSM-IV-TR diagnostic criteria and the proposed DSM-5 diagnostic criteria. J Dev Phys Disabil 24(4): 403–414.
- Matson J, Kozlowski A, Hattier M, Horovitz M & Sipes M (2012a) DSM-IV vs DSM-5 diagnostic criteria for toddlers with autism. Dev Neurorehabil 15(3): 185–190.
- Mattila ML, Jussila K, Kuusikko S, Kielinen M, Linna SL, Ebeling H, Bloigu R, Joskitt L, Pauls D & Moilanen I (2009) When does the Autism Spectrum Screening Questionnaire (ASSQ) predict autism spectrum disorders in primary school-aged children? Eur Child Adolesc Psychiatry 18(8): 499–509.
- Mazzone L, Ruta L & Reale L (2012) Psychiatric comorbidities in asperger syndrome and high functioning autism: diagnostic challenges. Ann Gen Psychiatry 11(1): 16.
- McPartland JC, Reichow B & Volkmar FR (2012) Sensitivity and specificity of proposed DSM-5 diagnostic criteria for autism spectrum disorder. J Am Acad Child Adolesc Psychiatry 51(4): 368–583.
- Miller JN & Ozonoff S (1997) Did Asperger's cases have Asperger disorder? A research note. J Child Psychol Psychiatry 38(2): 247–251.
- Miller JN & Ozonoff S (2000) The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology. J Abnorm Psychol 109(2): 227–238.
- Miller JS, Bilder D, Farley M, Coon H, Pinborough-Zimmerman J, Jenson W, Rice CE, Fombonne E, Pingree CB, Ritvo E, Ritvo RA & McMahon WM (2013) Autism spectrum disorder reclassified: a second look at the 1980s Utah/UCLA autism epidemiologic study. J Autism Dev Disord 43(1): 200–210.
- Montiel-Nava C & Peña JA (2008) Epidemiological findings of pervasive developmental disorders in a Venezuelan study. Autism 12(2): 191–202.

- Mukaddes NM & Fateh R (2010) High rates of psychiatric co-morbidity in individuals with Asperger's disorder. World J Biol Psychiatry 11(2 Pt 2): 486–492.
- Mukaddes NM, Hergüner S & Tanidir C (2010) Psychiatric disorders in individuals with high-functioning autism and Asperger's disorder: similarities and differences. World J Biol Psychiatry 11(8): 964–971.
- Mulvihill B *et al.*; Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators; Centers for Disease Control and Prevention (CDC) (2009) Prevalence of autism spectrum disorders – Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill Summ 58(10): 1–20. Erratum in: MMWR Surveill Summ (2010) 59(30): 956.
- Murphy D (2006) Theory of mind in Asperger's syndrome, schizophrenia and personality disordered forensic patients. Cogn Neuropsychiatry 11(2): 99–111.
- Nieminen-von Wendt T, Paavonen JE, Ylisaukko-oja T, Sarenius S, Källman T, Järvelä I & von Wendt L (2005) Subjective face recognition difficulties, aberrant sensibility, sleeping disturbances and aberrant eating habits in families with Asperger syndrome. BMC Psychiatry 5: 20.
- Nilsson EW, Gillberg C, Gillberg IC & Råstam M (1999) Ten-year follow-up of adolescentonset anorexia nervosa: personality disorders. J Am Acad Child Adolesc Psychiatry 38(11): 1389–1395.
- O'Connor K (2012) Auditory processing in autism spectrum disorder: a review. Neurosci Biobehav Rev 36(2): 836–854.
- Osterling J & Dawson G (1994) Early recognition of children with autism: a study of first birthday home videotapes. J Autism Dev Disord 24(3): 247–257.
- Osterling JA, Dawson G & Munson JA (2002) Early recognition of 1-year-old infants with autism spectrum disorder versus mental retardation. Dev Psychopathol 14(2): 239–251.
- Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L, Bryson S, Carver LJ, Constantino JN, Dobkins K, Hutman T, Iverson JM, Landa R, Rogers SJ, Sigman M & Stone WL (2011) Recurrence risk for autism spectrum disorders: a baby siblings research consortium study. Pediatrics 128(3): e488–495.
- Paavonen EJ, Vehkalahti K, Vanhala R, von Wendt L, Nieminen-von Wendt T & Aronen ET (2008) Sleep in children with Asperger syndrome. J Autism Dev Disord 38(1): 41–51.
- Paul R, Augustyn A, Klin A & Volkmar FR (2005) Perception and production of prosody by speakers with autism spectrum disorders. J Autism Dev Disord 35: 205–220.
- Petersen DJ, Bilenberg N, Hoerder K & Gillberg C (2006) The population prevalence of child psychiatric disorders in Danish 8- to 9-year-old children. Eur Child Adolesc Psychiatry 15(2): 71–78.
- Poirier MF, Canceil O, Bayle F, Millet B, Bourdel MC, Moatti C, Olié JP & Attar-Lévy D (2002) Prevalence of smoking in psychiatric patients. Prog Neuropsychopharmacol Biol Psychiatry 26(3): 529–537.

- Posey DJ, Aman MG, McCracken JT, Scahill L, Tierney E, Arnold LE, Vitiello B, Chuang SZ, Davies M, Ramadan Y, Witwer AN, Swiezy NB, Cronin P, Shah B, Carroll DH, Young C, Wheeler C & McDougle CJ (2007) Positive effects of methylphenidate on inattention and hyperactivity in pervasive developmental disorders: an analysis of secondary measures. Biol Psychiatry 61(4): 538–544.
- Posserud MB, Lundervold AJ & Gillberg C (2006) Autistic features in a total population of 7–9-year-old children assessed by the ASSQ (Autism Spectrum Screening Questionnaire). J Child Psychol Psychiatry 47(2): 167–175.
- Posserud MB, Lundervold AJ & Gillberg C (2009) Validation of the autism spectrum screening questionnaire in a total population sample. J Autism Dev Disord 39(1): 126–134.
- Posserud B, Lundervold AJ, Steijnen MC, Verhoeven S, Stormark KM & Gillberg C (2008) Factor analysis of the Autism Spectrum Screening Questionnaire. Autism 12(1): 99– 112.
- Prevention CfDCa. Autism Spectrum Disorders. 2012 March 29, 2012 [cited 2012 July 8, 2012]; Available from: http://www.cdc.gov/ncbddd/autism/data.html.
- Pugliese CE, White BA, White SW & Ollendick TH (2013) Social anxiety predicts aggression in children with ASD: clinical comparisons with socially anxious and oppositional youth. J Autism Dev Disord 43(5): 1205–1213.
- Raja M & Azzoni A (2010) Autistic spectrum disorders and schizophrenia in the adult psychiatric setting: diagnosis and comorbidity. Psychiatr Danub 22(4): 514–521.
- Rapoport J, Chavez A, Greenstein D, Addington A & Gogtay N (2009) Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. J Am Acad Child Adolesc Psychiatry 48(1): 10–18.
- Ringman JM & Jankovic J (2000) Occurrence of tics in Asperger's syndrome and autistic disorder. J Child Neurol 15(6): 394–400.
- Risi S, Lord C, Gotham K, Corsello C, Chrysler C, Szatmari P, Cook EH Jr, Leventhal BL & Pickles A (2006) Combining information from multiple sources in the diagnosis of autism spectrum disorders. J Am Acad Child Adolesc Psychiatry 45(9): 1094–1103.
- Ronald A, Simonoff E, Kuntsi J, Asherson P & Plomin R (2008) Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. J Child Psychol Psychiatry 49(5): 535–542.
- Rossignol DA & Frye RE (2011) Melatonin in autism spectrum disorders: a systematic review and meta-analysis. Dev Med Child Neurol 53(9): 783–792.
- Rossignol DA & Frye RE (2013) Melatonin in autism spectrum disorders. Curr Clin Pharmacol 2013 Sep 20. [Epub ahead of print].
- Russell AJ, Mataix-Cols D, Anson M & Murphy DG (2005) Obsessions and compulsions in Asperger syndrome and high-functioning autism. Br J Psychiatry 186: 525–528.
- Rutter M, Bailey A & Lord C (2003) Social Communication Questionnaire (SCQ). Los Angeles, California: Western Psychological Services.
- Schopler E, Reichler RJ, DeVellis RF & Daly K (1980) Toward objective classification of childhood autism: Childhood Autism Rating Scale (CARS). J Autism Dev Disord 10(1): 91–103.

- Scott FJ, 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. Autism 6(1): 9–31.
- Shaffer D, Gould MS, Brasic J, Ambrosini P, Fischer P, Bird H & Aluwahlia S (1983) A children's global assessment scale (CGAS). Arch Gen Psychiatry 40(11): 1228–1231.
- Sharma S, Woolfson LM & Hunter SC (2012) Confusion and inconsistency in diagnosis of Asperger syndrome: a review of studies from 1981 to 2010. Autism 16(5): 465–486.
- Shattuck PT, Durkin M, Maenner M, Newschaffer C, Mandell DS, Wiggins L, Lee LC, Rice C, Giarelli E, Kirby R, Baio J, Pinto-Martin J & Cuniff C (2009) Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. J Am Acad Child Adolesc Psychiatry 48(5): 474–483.
- Shriberg LD, Paul R, McSweeny JL, Klin A, Cohen DJ & Volkmar FR (2001) Speech and prosody characteristics of adolescents and adults with high-functioning autism and Asperger syndrome. J Speech Lang Hear Res 44(5): 1097–1115.
- Simonoff E, Pickles A, Charman T, Chandler S, Loucas T & Baird G (2008) Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 47(8): 921–929.
- Skuse D, Warrington R, Bishop D, Chowdhury U, Lau J, Mandy W & Place M (2004) The developmental, dimensional and diagnostic interview (3di): a novel computerized assessment for autism spectrum disorders. J Am Acad Child Adolesc Psychiatry 43(5): 548–558.
- Smalley SL, McGough JJ, Moilanen IK, Loo SK, Taanila A, Ebeling H, Hurtig T, Kaakinen M, Humphrey LA, McCracken JT, Varilo T, Yang MH, Nelson SF, Peltonen L & Järvelin MR (2007) Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent Finnish population. J Am Acad Child Adolesc Psychiatry 46(12): 1575–1583.
- Sponheim E & Skjeldal O (1998) Autism and related disorders: epidemiological findings in a Norwegian study using ICD-10 diagnostic criteria. J Autism Dev Disord 28(3): 217–227.
- Ssucharewa GE (1926) Die schizoiden Psychopathien im Kindesalter. (Part 2 of 2). Mschr Psychiat Neurol 60: 248–261.
- Statistics Finland (2000) Statistics Finland Web site. Available at http://www.stat.fi/ index_en.html.
- Statistics Finland Website (2006a) Available at http://info.stakes.fi/kouluterveyskysely/FI/ tulokset/taulukot2006/tupakointi06.htm.
- Statistics Finland Website (2006b) Available at http://info.stakes.fi/kouluterveyskysely/FI/ tulokset/taulukot2006/terveys06.htm.
- Stewart ME, Barnard L, Pearson J, Hasan R & O'Brien G (2006) Presentation of depression in autism and Asperger syndrome: a review. Autism 10(1): 103–116.
- Stone WL, Lee EB, Ashford L, Brissie J, Hepburn SL, Coonrod EE & Weiss BH (1999) Can autism be diagnosed accurately in children under 3 years? J Child Psychol Psychiatry 40(2): 219–226.

- Sukhodolsky DG, Scahill L, Gadow KD, Arnold LE, Aman MG, McDougle CJ, McCracken JT, Tierney E, Williams White S, Lecavalier L & Vitiello B (2008) Parent-rated anxiety symptoms in children with pervasive developmental disorders: frequency and association with core autism symptoms and cognitive functioning. J Abnorm Child Psychol 36(1): 117–128.
- Swinkels S, Dietz C, van Daalen E, Kerkhof I, Engeland H & Buitelaar J (2006) Screening for autistic spectrum in children aged 14 to 15 months. I: the development of the Early Screening of Autistic Traits Questionnaire (ESAT). J Autism Dev Disord 36(6): 723– 732.
- Szatmari P (1992) The validity of autistic spectrum disorders: a literature review. J Autism Dev Disord 22(4): 583–600.
- Szatmari P, Archer L, Fisman S & Streiner DL (1994) Parent and teacher agreement in the assessment of pervasive developmental disorders. J Autism Dev Disord 24(6): 703–717.
- Szatmari P, Bremner R & Nagy J (1989) Asperger's syndrome: a review of clinical features. Can J Psychiatry 34(6): 554–560.
- Taheri A & Perry A (2012) Exploring the proposed DSM-5 criteria in a clinical sample. J Autism Dev Disord 42(9): 1810–1817.
- Tani P, Lindberg N, Nieminen-von Wendt T, von Wendt L, Alanko L, Appelberg B & Porkka-Heiskanen T (2003) Insomnia is a frequent finding in adults with Asperger syndrome. BMC Psychiatry 3: 12.
- Tercyak KP, Lerman C & Audrain J (2002) Association of attention-deficit/hyperactivity disorder symptoms with levels of cigarette smoking in a community sample of adolescents. J Am Acad Child Adolesc Psychiatry 41(7): 799–805.
- Towbin KE (2005) Pervasive developmental disorder not otherwise specified. In Handbook of Autism and Pervasive Developmental Disorders, Volkmar FR, Paul R, Klin A & Cohen DJ, eds. Hoboken, NJ: Wiley, pp 165–200.
- Treffert DA (1970) Epidemiology of infantile autism. Arch Gen Psychiatry 22(5): 431-438.
- Turygin N, Matson JL, Beighley J & Adams H (2013) The effect of DSM-5 criteria on the developmental quotient in toddlers diagnosed with autism spectrum disorder. Dev Neurorehabil 16(1): 38–43.
- Unenge Hallerbäck M, Lugnegård T & Gillberg C (2012) Is autism spectrum disorder common in schizophrenia? Psychiatry Res 198(1): 12–17.
- Valkanova V, Rhodes F & Allan CL (2013) Diagnosis and management of autism in adults. Practitioner 257(1761): 13–16, 2–3.
- van Krevelen DA (1971) Early infantile autism and autistic psychopathy. J Autism Child Schizophr 1(1): 82–86.
- van Steensel FJ, Bögels SM & Perrin S (2011) Anxiety disorders in children and adolescents with autistic spectrum disorders: a meta-analysis. Clin Child Fam Psychol Rev 14(3): 302–317.
- Veenstra-Vanderweele J, Christian SL & Cook EH Jr (2004) Autism as a paradigmatic complex genetic disorder. Annu Rev Genomics Hum Genet 5: 379–405.
- Volden J (2004) Conversational repair in speakers with autism spectrum disorder. Int J Lang Commun Disord 39(2): 171–189.

- Volkmar F, Chawarska K & Klin A (2005) Autism in infancy and early childhood. Annu Rev Psychol 56: 315–336.
- Volkmar F, Cook E Jr, Pomeroy J, Realmuto G & Tanguay P (1999) Summary of the practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. American Academy of Child and Adolescent Psychiatry. J Am Acad Child Adolesc Psychiatry 38(12): 1611–1616.
- Volkmar FR, Reichow B & McPartland J (2012) Classification of autism and related conditions: progress, challenges, and opportunities. Dialogues Clin Neurosci 14(3): 229–237.
- Wagner A, Lecavalier L, Arnold LE, Aman MG, Scahill L, Stigler KA, Johnson CR, McDougle CJ & Vitiello B (2007) Developmental disabilities modification of the Children's Global Assessment Scale. Biol Psychiatry 61(4): 504–511.
- Wechsler D (1991) Wechsler Intelligence Scale for Children–3rd ed. San Antonio, Texas: The Psychological Corporation.
- Weiss LA *et al.*; Gene Discovery Project of Johns Hopkins & the Autism Consortium (2009) A genome-wide linkage and association scan reveals novel loci for autism. Nature, 461(7265): 802–808.
- Weitlauf AS, Gotham KO, Vehorn AC & Warren ZE (2013) Brief report: DSM-5 "levels of support:" a comment on discrepant conceptualizations of severity in ASD. J Autism Dev Disord 2013 Jun 28. [Epub ahead of print].
- White SW, Kreiser NL, Pugliese C & Scarpa A (2012) Social anxiety mediates the effect of autism spectrum disorder characteristics on hostility in young adults. Autism 16(5): 453–464.
- White SW, Oswald D, Ollendick T & Scahill L (2009) Anxiety in children and adolescents with autism spectrum disorders. Clin Psychol Rev 29(3): 216–229.
- White SW & Roberson-Nay R (2009) Anxiety, social deficits, and loneliness in youth with autism spectrum disorders. J Autism Dev Disord 39(7): 1006–1013.
- Williams J, Scott F, Stott C, Allison C, Bolton P, Baron-Cohen S & Brayne C (2005) The CAST (Childhood Asperger Syndrome Test): test accuracy. Autism 9(1): 45–68.
- Williams K, Tuck M, Helmer M, Bartak L, Mellis C & Peat JK; Autism Spectrum Disorder Steering Group (2008) Diagnostic labelling of autism spectrum disorders in NSW. J Paediatr Child Health 44(3): 108–113.
- Wilson CE, Gillan N, Spain D, Robertson D, Roberts G, Murphy, CM Maltezos S, Zinkstok J, Johnston K, Dardani C, Ohlsen C, Deeley PQ, Craig M, Mendez MA, Happé F & Murphy DGM (2013) Comparison of ICD-10R, DSM-IV-TR and DSM-5 in an adult autism spectrum disorder diagnostic clinic. Journal of Autism and Developmental Disorders 43(11): 2515–2525.
- Wing L (1981) Asperger's syndrome: a clinical account. Psychol Med 11(1): 115–129.
- Wing L, Leekam SR, Libby SJ, Gould J & Larcombe M (2002) The Diagnostic Interview for Social and Communication Disorders: background, inter-rater reliability and clinical use. J Child Psychol Psychiatry 43(3): 307–325.

- Wingate M *et al.*; 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. MMWR Surveill Summ 61(3): 1–19.
- Wolff S (1996) The first account of the syndrome Asperger described? Translation of a paper entitled "Die schizoiden Psychopathien im Kindesalter" by Dr. G.E. Ssucharewa; scientific assistant, which appeared in 1926 in the Monatsschrift fur Psychiatrie und Neurologie 60: 235–261. Eur Child Adolesc Psychiatry 5(3): 119–132.
- Woodbury-Smith M, Klin A & Volkmar F (2005) Asperger's syndrome: a comparison of clinical diagnoses and those made according to the ICD-10 and DSM-IV. J Autism Dev Disord 35(2): 235–240.
- Woodbury-Smith MR, 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. J Autism Dev Disord 35(3): 331–335.
- World Health Organization (1979) The ICD-9 International Classification of Mental and Behavioural Disorders. Geneva: World Health Organization.
- World Health Organization (1993) The ICD-10 International classification of Mental and Behavioural Disorders. Diagnostic Criteria for Research. Geneva: World Health Organization.
- Worley JA & Matson JL (2012) Comparing symptoms of autism spectrum disorders using the current DSM-IV-TR diagnostic criteria and the proposed DSM-V diagnostic criteria. Res Autism Spectr Disord 6(2): 965–970.
- Yerys BE, Wallace GL, Sokoloff JL, Shook DA, James JD & Kenworthy L (2009) Attention deficit/hyperactivity disorder symptoms moderate cognition and behavior in children with autism spectrum disorders. Autism Res 2(6): 322–333.
- Yoshida Y & Uchiyama T (2004) The clinical necessity for assessing attention deficit/ hyperactivity disorder (AD/HD) symptoms in children with high-functioning pervasive developmental disorder (PDD). Eur Child Adolesc Psychiatry 13(5): 307–314.

Original Publications

- I Mattila ML, Kielinen M, Jussila K, Linna SL, Bloigu R, Ebeling H & Moilanen I (2007) An epidemiological and diagnostic study of Asperger syndrome according to four sets of diagnostic criteria. J Am Acad Child Adolesc Psychiatry 46(5): 636–646.
- II Mattila ML, Kielinen M, Linna SL, Jussila K, Ebeling H, Bloigu R, Joseph RM & Moilanen I (2011) Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. J Am Acad Child Adolesc Psychiatry 50(6): 583–592.
- III Mattila ML, Jussila K, Linna SL, Kielinen M, Bloigu R, Kuusikko-Gauffin S, Joskitt L, Ebeling H, Hurtig T & Moilanen I (2012) Validation of the Finnish Autism Spectrum Screening Questionnaire (ASSQ) for clinical settings and total population screening. J Autism Dev Disord 42(10): 2162–2180.
- IV Mattila ML, Hurtig T, Haapsamo H, Jussila K, Kuusikko-Gauffin S, Kielinen M, Linna SL, Ebeling H, Bloigu R, Joskitt L, Pauls DL & Moilanen I (2010) Comorbid psychiatric disorders associated with Asperger syndrome/high-functioning autism: a community- and clinic-based study. J Autism Dev Disord 40(9): 1080–1093.

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