ASPERGER SYNDROME IN MALES OVER TWO DECADES

Adam Helles

UNIVERSITY OF GOTHENBURG

Gillberg Neuropsychiatry Centre

Institute of Neuroscience and Physiology at Sahlgrenska Academy

University of Gothenburg

Gothenburg 2016

Cover illustration: Copyright shutterstock.com; edited by Adam Helles

Asperger syndrome in males over two decades

adam.helles@gnc.gu.se

ISBN: 978-91-628-9778-9 (Print)
ISBN: 978-91-628-9779-6 (PDF)
URL: http://hdl.handle.net/2077/42343

Printed in Gothenburg, Sweden 2016
Ineko AB

To Nadja, Olle

&

Ronja

Asperger syndrome in males over two decades

Adam Helles

Gillberg Neuropsychiatry Centre, Institute of Neuroscience and Physiology at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

ABSTRACT

● BACKGROUND: Not much is known about the long-term outcome of Asperger syndrome (AS). The first set of diagnostic criteria was published in the late 1980's. Research on other normal range IQ Autism Spectrum Disorders (ASD) has shown great variability in terms of outcome. ● AIMS: The purpose of the present study was to study the naturalistic course of AS into adulthood in a clinical cohort of 100 males with AS diagnosed in childhood and to examine (1) stability of the diagnosis, (2) psychiatric comorbidity, (3) objective and subjective quality of life (QoL) and (4) examine Temperament and Character Inventory (TCI) traits in relation to aforementioned factors. ● METHODS: A cohort of 100 males diagnosed with AS at a mean age of 11 years has been followed from diagnosis (T0) over a period of 19 years in two follow-up studies. In the first follow-up (T1) at a mean age of 20 years, 76 of the 100 males participated and at the second follow-up (T2) at a mean age of 30 years, 50 individuals took part. A number of relevant and psychometrically established instruments were used at both time points. ● RESULTS: At T2, 78% still fulfilled criteria for an ASD diagnosis, compared to T1 when 90% still fulfilled an ASD. Almost all participants (94%) had at least one comorbid psychiatric or neurodevelopmental disorder during their lifetime and 54% had at least one current comorbid disorder. The 22 % (n=11) who no longer met criteria for ASD after nineteen years, had better objective QoL and average to high subjective QoL. Forty-four percent (n=22) of the men had a stable ASD and at least one current comorbid psychiatric disorder ("ASD Plus") and this group had extremely varied objective QoL (with many having low independence) and low subjective QoL. Lastly, there was a group of individuals (34% of those who participated) with a stable ASD diagnosis but no current comorbidity (n=15, "ASD Only") who also had extremely varied objective QoL (with many having low independence) and reporting average range subjective QoL. The three outcome groups (No-longer-ASD, ASD Plus and ASD Only) had significantly different profiles on the TCI. Background factors associated with negative outcome were ASD symptom load at T1 (but not T0) and degree of lifetime comorbidity. ● CONCLUSION: AS in males, when considered as an ASD was a relatively stable diagnosis over almost two decades. A majority met criteria of at least one other current comorbid disorder. No longer meeting criteria for an ASD was associated with better objective QoL, while having comorbidity was associated with lower subjective QoL. Personality traits were associated with different outcomes.

Keywords: Asperger syndrome; Autism Spectrum Disorder; Psychiatric comorbidity; Longitudinal study; Quality of Life; Diagnosis; Personality; Outcome

ISBN: 978-91-628-9778-9 (Print) **ISBN:** 978-91-628-9779-6 (PDF) **URL:** http://hdl.handle.net/2077/42343

SAMMANFATTNING PÅ SVENSKA

Asperger syndrom (AS) är en neuropsykiatrisk funktionsnedsättning inom autismspektrum. Diagnosen karakteriseras av svårigheter i socialt samspel och ömsesidighet samt en benägenhet att fastna i beteenden, rutiner eller intressen. Personer med AS har svag, genomsnittlig eller hög intelligens och den tidiga språkutvecklingen är sällan allvarligt försenad. Relativt lite är känt om långtidsprognosen, bland annat beroende på att de första kriterierna för diagnosen kom först under slutet av 1980-talet. I denna avhandling rapporteras resultaten från den första långtidsstudien av en relativt stor grupp med diagnosen AS. Hundra pojkar som fick diagnosen AS på 80- och 90-talet i Göteborg har följts under en period av i genomsnitt 19 år. Två uppföljningar har gjorts av gruppen, den första 2002-2003 (då deltog 76 personer) och den andra 2011-2013 (då deltog 50 personer). Resultaten i denna avhandling har främst fokuserat på den andra uppföljningen, men jämförelser mellan uppföljningsresultaten vid de två tillfällena har också gjorts. Avhandlingen är baserad på fyra delarbeten, en om diagnostisk stabilitet, en om psykiatrisk och neuropsykiatrisk komorbiditet, en om livskvalitet (både gällande hur man klarar sig i vardagen och hur man upplever sin livskvalitet) och en om personlighetens relation till vardagsfunktion för personer med AS.

Resultaten visade att efter 19 år uppfyllde 39 av 50 deltagare (78%) fortfarande en diagnos inom autismspektrum (men inte nödvändigtvis AS då flera hade bytt diagnos inom autismspektrumområdet). Detta kan jämföras med den första uppföljningen då 90% fortfarande uppfyllde kriterier för en autismspektrumdiagnos. Vidare visade resultaten att den nya autism-diagnosen i DSM-5 medförde att vissa som uppfyllde en autismspektrum-diagnos enligt DSM-IV inte längre kom att uppfylla en autismdiagnos i vuxen ålder trots klara samspelssvårigheter och begränsningar i vardagen. De 11 personer som inte längre uppfyllde någon autismspektrumdiagnos kallas framöver för *Ej längre autismspektrumdiagnos*-gruppen.

Nästan samtliga (47 av 50) deltagare i studien hade uppfyllt kriterier för minst en annan psykiatrisk eller neuropsykiatrisk diagnos under sin livstid (de vanligaste diagnoserna var depression, motorisk koordinationsstörning och Tourette syndrom). En majoritet (53 %) uppfyllde kriterier för minst en annan psykiatrisk diagnos (de vanligaste diagnoserna var ADHD och depression) vid uppföljning två. De personer som uppfyllde kriterier för en autismspektrumdiagnos och minst annan psykiatrisk diagnos vid uppföljning

två kallas framöver för *Autismspektrumdiagnos plus*-gruppen (*n*=24). De 15 individer som uppfyllde en autismspektrumdiagnos, men ingen annan psykiatrisk diagnos kallas framöver för *Endast autismspektrumdiagnos*-gruppen.

De tre grupperna visade både likheter och olikheter gällande livskvalitet, både gällande så kallad objektiv livskvalitet (det vill säga hur man har det) och subjektiv livskvalitet (det vill säga hur man uppfattar sitt liv). *Ej längre autismspektrumdiagnos*-gruppen hade signifikant bättre objektiv livskvalitet gällande boende, arbete och vänner och i princip alla individer i den gruppen hade arbete, eget boende och flera vänner. De hade dock inte studerat mer på universitet/högskolan och hade inte kärleksrelationer oftare än de två andra grupperna. De två andra grupperna (*Autismspektrumdiagnos plus* och *Endast autismspektrumdiagnos*) liknande varandra mycket gällande objektiv livskvalitet, då båda grupperna visade stor variation i fungerande. Ungefär hälften hade inte eget boende, cirka en tredjedel var helt arbetslösa och ungefär en fjärdedel hade inga vänner. Å andra sidan hade ungefär en fjärdedel en anställning utan extra stöd och strax under hälften hade någon annan form av anställning (daglig verksamhet eller anställning med lönebidrag), cirka hälften hade eget boende utan behov av stöd i vardagen och tre fjärde delar hade minst en vän. Gällande subjektiv livskvalitet så var det *Autismspektrumdiagnos plus*-gruppen som skiljde sig från de övriga två grupperna och hade signifikant lägre upplevd livskvalitet. Aningen överaskande så hade *Endast autismspektrumdiagnos*-gruppen inte lägre upplevd livskvalitet än *Ej längre autismspektrumdiagnos*-gruppen trots avsevärt lägre objektiv livskvalitet. Intelligens var positivt associerat till akademisk framgång, medan grad av autismsymtom var negativt associerat till självständighet i anställning och boende samt gällande vänskaps- och kärleksrelationer.

De tre grupperna jämfördes också utifrån personlighetstestet Temperament and Character Inventory (TCI), ett test som avser mätta fyra typer av temperament (medfödda personlighetsdrag som anses vara stabila över tid) och tre karaktärsmått (personlighetsdrag som utvecklas över tid och påverkas av omgivningsfaktorer). De tre grupperna beskrivna ovan skiljde sig åt i sina TCI-profiler. *Ej längre autismspektrumdiagnos*-gruppen hade i högre grad personlighetsdrag som kännetecknas av att man har stort behov av uppmuntran och stöd från andra människor och att man lättare knyter an till andra människor känslomässigt (högt Reward Dependence). *Endast autismspektrumdiagnos*-gruppen hade i högre grad personlighetsdrag som kännetecknas av man är försiktig, ordningssam och reserverad (lågt Novelty Seeking) och att man är aningen ängslig, blyg och oenergisk (aningen högt

Harm Avoidance). *Autismspektrumdiagnos plus*-gruppen hade i högre grad personlighetsdrag som kännetecknas av klar ängslighet, blyghet och brist på energi (mycket högt Harm Avoidance) och även låg självbild, svårigheter att ta ansvar och svårigheter att finna mål och mening i livet (lågt Self-Directedness) och svårigheter med att samarbeta, aggressivt beteende och svårigheter att behålla sociala relationer (lågt Cooperativeness) samt mer udda personlighetsdrag (hög andel ovanliga svar).

När de tre grupperna undersöktes med avseende på intelligensnivå, tidig utveckling, grad av autismsymtom då AS-diagnosen ställdes, ålder då AS-diagnos ställdes och ålder vid andra uppföljning fanns inga skillnader mellan grupperna. Däremot hade *Ej längre autismspektrumdiagnos*-gruppen lägre grad av autismsymtom vid den första uppföljningen när de var runt 20 år, även om majoriteten (8 av 11) då fortfarande uppfyllde kriterier för en autismspektrumdiagnos. *Autismspektrumdiagnos plus*-gruppen hade haft fler antal komorbida diagnoser genom livet.

Sammantaget så visar avhandlingen på vikten av regelbundna uppföljningar av personer med AS, för att eventuellt kunna stödja positiv utveckling och vända negativ utveckling. Det visar också på vikten av att göra regelbundna psykiatriska bedömningar av personer med AS då deltagarna i denna studie dels har haft hög grad av komorbiditet och dels haft relativt låg grad av psykiatrisk/psykologisk behandling för dessa svårigheter. Att hjälpa personer med AS med deras psykiatriska tillstånd bör kunna höja deras upplevda livskvalitet avsevärt. En delförklaring till den stora variationen i långtidsprognos hos personer med AS kan vara personlighetsdrag. Det skulle kunna vara så att prosociala personlighetsdrag är en del i positiv utveckling medan ängsliga personlighetsdrag bidrar till utvecklingen av psykiatrisk komorbiditet. Denna ängslighet verkar dock inte leda till utveckling av komorbiditet när den kombineras med att vara försiktig och ordningssam.

LIST OF PAPERS

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

I

Helles, A, Gillberg, I C, Gillberg, C & Billstedt, E. Asperger syndrome in males over two decades: stability and predictors of diagnosis. *Journal of Child Psychology and Psychiatry* 2015; 56(6): 711-8.

II

Gillberg, I C, Helles, A, Billstedt, E & Gillberg, C. Boys with Asperger Syndrome Grow Up: Psychiatric and Neurodevelopmental Disorders 20 Years After Initial Diagnosis. *Journal of Autism and Developmental Disorders* 2016; 46(1): 74-82.

III

Helles, A, Gillberg I C, Gillberg, C & Billstedt E. Asperger syndrome in males over two decades: Quality of life in relation to diagnostic stability and psychiatric comorbidity. *Autism*. Accepted.

IV

Helles, A, Wallinius, M, Gillberg I C, Gillberg, C & Billstedt E. Asperger syndrome in childhood – personality dimensions in adult life: Temperament, character and outcome trajectories. *Submitted*.

CONTENT

ABBREVIATIONS

AD	Autistic Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
ANOVA	Analysis of Variance
AS	Asperger Syndrome/Asperger's Disorder
ASD	Autism Spectrum Disorder/Pervasive Developmental Disorder
ASDI	Autism Spectrum Diagnostic Interview
ASRS	ADHD Self Rating Scale
ASSQ	Autism Spectrum Screening Questionnaire
BDI	Beck Depression Inventory
CNC	Child Neuropsychiatric Clinic
DCD	Developmental Coordination Disorder
DISCO	Diagnostic Interview of Social and Communication Disorders
DSM-IV	Diagnostic and Statistical Manual – 4th edition
DSM-5	Diagnostic and Statistical Manual – 5th edition
FSIQ	Full Scale Intelligence Quotient
GAF	General Ability of Functioning
GNC	Gillberg Neuropsychiatry Centre
HRQoL	Health-Related Quality of Life
ICD-10	International Classification of Disease – 10th edition
IQ	Intelligence Quotient
M.I.N.I.	Mini International Neuropsychiatric Interview
OCD	Obsessive Compulsive Disorder
PDD-NOS	Pervasive Developmental Disorder - Not Otherwise Specified
PIQ	Performance Intelligence Quotient
QoL	Quality of Life
SF-36	Short Form Health Survey – version 2.0
SoC	Sense of Coherence
T0	Time of diagnosis
T1	Time of first follow-up
T2	Time of second follow-up
TCI	Temperament and Character Inventory
VIQ	Verbal Intelligence Quotient
WAIS-III	Wechsler Adult Intelligence Scale – 3rd edition

TERMINOLOGY

Asperger Syndrome vs Asperger's Disorder

The diagnosis of Asperger Syndrome is named Asperger's Disorder in the DSM-IV/ICD-10. In this thesis, the term Asperger Syndrome will be used throughout, even when referring to Asperger's Disorder according to the DSM-IV/ICD-10.

Pervasive Developmental Disorder vs Autism Spectrum Disorder

In the DSM-IV/ICD-10 the term Pervasive Developmental Disorder is used as a general term to describe the collection of diagnoses; Autistic Disorder, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified, Atypical autism, Disintegrative Disorder and Rett Syndrome. This term has been replaced by Autism Spectrum Disorder in the DSM-5 and this term is today synonymous with Pervasive Developmental Disorder. The term Autism Spectrum Disorder will be used throughout this thesis, even when referring to Pervasive Developmental Disorders in the DSM-IV/ICD-10.

INTRODUCTION

Asperger syndrome (AS) is a neurodevelopmental disorder first described in 1944 by the Austrian physician Hans Asperger (Asperger, 1944). Asperger described a group of boys with "autistic psychopathy" (later named AS after the author), characterised by deficiencies in social interaction (e.g. difficulties making friends and deficits in interpreting others emotions and intentions), a tendency to have narrow interests (a.k.a. special interests), extreme adherence to routines, speech difficulties (often late speech debut, pedantic speech, and often misinterprets literal sayings), non-verbal communication deficits (e.g. lack of nuanced body language and prosody) and motor clumsiness. All of the boys were of normal to high intelligence and their difficulties could not be better explained by other difficulties.

Asperger's description of AS did not have any greater impact until his work was rediscovered in the 1980's. Particularly the account from Lorna Wing in 1981 (Wing, 1981a) had a huge impact in the scientific and clinical community. Wing was also the one who coined the phrase "autism spectrum disorders" (ASD), a notion that there was a wide range of diagnoses (including autistic disorder (AD), AS and Atypical Autism/Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS)) and functioning (ranging from well-adjusted members of society with milder social deficits to severely disabled individuals with almost no autonomy) that fit under the same umbrella and show the same core difficulties. There were diagnostic criteria for AD in earlier diagnostic manuals but there were no official diagnosis of AS until the publications of International Classification of Disease - 10th edition (ICD-10) (WHO, 1992) and Diagnostic and Statistical Manual – 4th edition (DSM-IV) (APA, 1994). There were however a few diagnostic criteria used in research, e.g. the Gillberg and Gillberg criteria published in 1989 (but used in clinical work several years earlier) that were based on Asperger's original description of the diagnosis.

The DSM-IV/ICD-10 diagnosis known as AS, differs somewhat from Hans Asperger's own description as well as the Gillberg and Gillberg criteria of AS (Table 1). The DSM-IV/ICD-10 diagnosis Asperger's Disorder (also referred to as AS) is characterised by social deficits and one or more stereotyped or repetitive behaviour (special interests, ritualised behaviours, unusual body movements and/or unusual sensory interests) and requires normal general development and normal language development before the

age of three and normal range intelligence. The DSM-IV Pervasive Developmental Disorder (also referred to as ASD) diagnoses of AD and AS are fairly similar, except regarding early development and communication, and the diagnosis of PDD-NOS is a more non-specific ASD diagnoses for individuals that almost meet criteria of AS and AD (table 2). When the Gillberg and Gillberg criteria of AS was compared to ICD-10 criteria of ASD it was found that the Gillberg and Gillberg criteria were most closely related to the ICD-10 diagnosis of AD and not AS (Leekam, Libby, Wing, Gould, & Gillberg, 2000).

Table 1. *Diagnostic criteria of AS according to Gillberg and Gillberg*

Asperger Syndrome according to Gillberg and Gillberg (1989)
1.Severe impairment in reciprocal social interaction (at least two of the following)
(a) inability to interact with peers
(b) lack of desire to interact with peers
(c) lack of appreciation of social cues
(d) socially and emotionally inappropriate behaviour
2.All-absorbing narrow interest (at least one of the following)
(a) exclusion of other activities
(b) repetitive adherence
(c) more rote than meaning
3.Imposition of routines and interests (at least one of the following)
(a) on self, in aspects of life
(b) on others
4.Speech and language problems (at least three of the following)
(a) delayed development
(b) superficially perfect expressive language
(c) formal, pedantic language
(d) odd prosody, peculiar voice characteristics
(e) impairment of comprehension including misinterpretations of literal/implied meanings
5.Non-verbal communication problems (at least one of the following)
(a) limited use of gestures
(b) clumsy/gauche body language
(c) limited facial expression
(d) inappropriate expression
(e) peculiar, stiff gaze
6.Motor clumsiness: poor performance on neurodevelopmental examination

The DSM-IV/ICD-10 concept of AS has been criticised (Mayes, Calhoun, & Crites, 2001), mostly because almost all who meet criteria of AS also meet criteria of AD. When the new Diagnostic and Statistical Manual –

5th edition (DSM-5) (APA, 2013) was published in 2013, the all subdiagnoses, including AS, had been removed and there is now just one general ASD diagnosis (Table 3). In the current beta draft of the International Classification of Disease – 11th edition planned to be published in 2018 (WHO, 2015), AS is also removed in favour of a more general ASD diagnosis.

Table 2. *Diagnostic criteria of AD, AS and PDD-NOS according to DSM-IV*

Autistic Disorder according to DSM-IV 299.00
A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3): 1. Qualitative impairment in social interaction, as manifested by at least two of the following: (a) marked impairment in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction (b) failure to develop peer relationships appropriate to developmental level (c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest) (d) lack of social or emotional reciprocity 2. Qualitative impairments in communication as manifested by at least one of the following: (a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime) (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others (c) stereotyped and repetitive use of language or idiosyncratic language (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level 3. Restricted repetitive and stereotyped patterns of behaviour, interests and activities, as manifested by at least one of the following: (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus (b) apparently inflexible adherence to specific, non-functional routines or rituals (c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole body movements) (d) persistent preoccupation with parts of objects B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age three years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play. C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Asperger's Disorder according to DSM-IV 299.80

1. Qualitative impairment in social interaction, as manifested by at least two of the following:
   (a) marked impairments in the use of multiple nonverbal behaviours such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
   (b) failure to develop peer relationships appropriate to developmental level
   (c) a lack of spontaneous seeking to share enjoyment, interest or achievements with other people, (e.g.. by a lack of showing, bringing, or pointing out objects of interest to other people)
   (d) lack of social or emotional reciprocity
2. Restricted repetitive & stereotyped patterns of behaviour, interests and activities, as manifested by at least one of the following:
   (a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
   (b) apparently inflexible adherence to specific, non-functional routines or rituals
   (c) stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting, or complex whole-body movements)
   (d) persistent preoccupation with parts of objects
3. The disturbance causes clinically significant impairments in social, occupational, or other important areas of functioning.
4. There is no clinically significant general delay in language (e.g. single words used by age 2 years, communicative phrases used by age 3 years)
5. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behaviour (other than in social interaction) and curiosity about the environment in childhood.
6. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia

Pervasive Developmental Disorder – Not Other Specified according to the DSM-IV 299.80

This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behaviour, interests, and activities are present, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant Personality Disorder. For example, this category includes "atypical autism"—presentations that do not meet the criteria for Autistic Disorder because of late age at onset, atypical symptomatology, or subthreshold symptomatology, or all of these.

Table 3. *Diagnostic criteria of ASD according to DSM-5*

Autism Spectrum Disorder according to DSM-5 (2013)
A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text): (1) Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions. (2) Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication. (3) Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.
B. Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text): (1) Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases). (2) Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behaviour (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day). (3) Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest). (4) Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
C. Symptoms must be present in the 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).
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
E. These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Prevalence of AS and other ASDs

There are few studies on the prevalence of AS according to the Gillberg and Gillberg criteria. Mattila et al (2007) found that the Gillberg and Gillberg AS had a prevalence of about .29 % and a male to female ratio of 2:1. Kadesjo et al (1999) found a prevalence of the Gillberg and Gillberg AS of .48% with a male to female ratio of 4:1. Extremely low prevalence rates of .06% have been found in one study of AS according to the DSM-IV (Fombonne, 2009).

There is an abundance of studies on the prevalence of ASDs according to the DSM-IV. Rates vary from different studies: from .6% up to 1.5% (Fombonne, 2005; Baron-Cohen et al., 2009; Fombonne, 2009; Kim et al., 2011; CDC, 2014). Male to female ratios also vary, ranging from 2.5:1 to 4.5:1.

Longitudinal studies of AS and other ASDs

Prospective longitudinal studies are an excellent approach to understand more about the natural development of a disorder. By following a group of individuals with the same baseline you are able to examine the cases with better or worse outcome than expected as well as those in-between. Cross-sectional or clinical studies usually only examine individuals that currently have contact with health-care services and there is a risk that with this approach only individuals with the worst possible outcome are examined.

Longitudinal studies on cohorts with AS show great variability in functioning, ranging from having a low degree of independence to being well-adjusted members of society (Szatmari, Bartolucci, Bremner, Bond, & Rich, 1989; Larsen & Mouridsen, 1997; Cederlund, 2007; Cederlund, Hagberg, Billstedt, Gillberg, & Gillberg, 2008; Cederlund, Hagberg, & Gillberg, 2010; Hagberg, Nyden, Cederlund, & Gillberg, 2013). Longitudinal studies on cohorts with AD and other ASDs with average range intelligence show similar results as studies on AS (Howlin, Goode, Hutton, & Rutter, 2004; Howlin & Moss, 2012; Howlin, Moss, Savage, & Rutter, 2013; Howlin, Savage, Moss, Tempier, & Rutter, 2014). The findings show great variability in functioning with many having severe difficulties in everyday life, but clearly functioning much better than individuals with ASDs and intellectual disabilities.

Diagnostic stability in AS and other ASDs

The only published study on diagnostic stability in AS (Cederlund et al., 2008) found that approximately 10 years after original diagnosis 70 % still fulfilled the diagnosis AS and 88% still fulfilled either AS or one other ASD diagnosis.

There are studies made on the diagnostic stability of other ASD diagnoses (i.e. AD and PDD-NOS). According to these studies AD is a very stable diagnosis when combined with an intellectual disability (Howlin et al., 2004; Billstedt, Gillberg, & Gillberg, 2005; Gillespie-Lynch et al., 2012; Howlin et al., 2012; Kocovska et al., 2013) but results are much more varied when intelligence is above Intelligence Quotient (IQ) 70. Systematic reviews and meta-analysis show that between 3 and 25% will no longer fulfil an ASD in follow-ups made on children and that AS and PDD-NOS are less stable than AD (Helt et al., 2008; Rondeau et al., 2011; Woolfenden, Sarkozy, Ridley, & Williams, 2012).

Psychiatric comorbidity and ASD

AS and other ASDs have been proven to also feature comorbid psychiatric and/or neurodevelopmental disorders. The first study of AS comorbidity was published in 1998 and reported a 65% rate of other psychiatric disorders in a sample of 35 children and adolescents (a few adults were also included) with a "primary" diagnosis of AS (Ghaziuddin, Weidmer-Mikhail, & Ghaziuddin, 1998). Mattila et al. (2010) found that 37 of 50 school age children with AS or "high-functioning autism" had at least one other (usually two or more) psychiatric disorders. Some of these associated disorders (including depression) were associated with considerably poorer adaptive functioning. A controlled study of depressive symptoms in children and adolescents with (and without) AS or "high functioning autism" revealed such symptoms to be associated with poorer global functioning (Mazzone, Ruta, & Reale, 2012). There is conflicting evidence or complete lack of systematic studies regarding the association, if any, of AS with psychosis and suicidal behaviour in children and adolescents (Skokauskas & Gallagher, 2010). In a systematic study of well-defined psychiatric disorders in adults with AS with a mean age of about 30 years (Lugnegard, Unenge Hallerback, & Gillberg, 2011) it was shown that very high rates of a number of associated psychiatric disorders were found, and especially rates of depression were extremely elevated with a lifetime prevalence of 80%.

Quality of Life and ASD

Quality of Life (QoL) has become an important measure in somatic and psychiatric medicine in later years. QoL has been defined as 'personal well-being or satisfaction with life, as well as physical and material well-being, relations with other people, social, communal, civic activities, personal development and fulfilment, positive mental health, a degree of goodness, and is related to health' (Eriksson & Lindström, 2007, p. 939). This indicates that QoL is relating to both more of an objective measure (relating to, among other things, income, employment, leisure time, education and social belonging) and subjective QoL (i.e. the individuals own perception of QoL). Studies have shown that adults with AS or ASD with normal range intelligence have a wide range of outcome with regard to the objective QoL factors mentioned above. Many have higher education, but few have meaningful employment or independent living and most do not have a social belonging (Szatmari et al., 1989; Engstrom, Ekstrom, & Emilsson, 2003; Howlin et al., 2004; Cederlund et al., 2008; Eaves & Ho, 2008). There is also evidence that a minority of the group function quite well with regard to objective QoL. The studies on subjective QoL are mainly focusing on the subjective QoL in family members of someone with ASD (Marciano & Scheuer, 2005; Shu, 2009; Dardas & Ahmad, 2014). There are, however, studies that show that adults with ASD report lower QoL (Saldana et al., 2009; van Heijst & Geurts, 2015).

The concept of Sense of Coherence (SoC) was developed according to Antonovsky's salutogenic model (Antonovsky, 1979) which implicates that SoC is needed in order to successfully cope with stressors and thus promote health and well-being. The concept of SoC has been shown to affect differing aspects of the individual's well-being and is closely related to the concept of QoL. Studies of SoC in relation to ASD have mostly focused on the parents of individuals with ASD, showing that parents of children with ASDs have lower SoC than parents of normally developing children (Pisula & Kossakowska, 2010) and very little is known regarding to SoC in individuals with an ASD.

Health-related QoL (HRQoL) is an area that is receiving increased focus in both general medicine and in psychiatry. HRQoL is a multi-dimensional measure of the individual's perception regarding differing aspects of mental/emotional and physical health and well-being, as well as relationships and participation in society. Individuals with ASD have been shown to

report lower ratings of HRQoL than healthy controls (Kamp-Becker, Schroder, Remschmidt, & Bachmann, 2010).

Personality and ASD

In Hans Asperger's original account of AS (Asperger, 1944), he referred to the disorder as a personality disorder. Even though the disorder is not considered as a personality disorder today, there have been several attempts to assess if personality subtypes can explain the variability in outcome and functioning in individuals with ASDs (Eaves, Ho, & Eaves, 1994; Wing, 1997; Schwartz et al., 2009).

Personality traits are enduring patterns of thinking, feeling and behaviour, and are commonly assessed with personality questionnaires (Roberts, Walton, & Viechtbauer, 2006). There are two personality-descriptive dimensional models that have been proposed in the past years. The five factor model (the Big Five) is one of the most dominant theories describing personality in five dimensions (openness to experience, conscientiousness, extraversion, agreeableness and neuroticism) (Costa & McCrae, 1985). The other theory that has gained a large interest is the psycho-biological theory of Temperament and Character (Cloninger, Svrakic, & Przybeck, 1993), a theory that every person shows different amounts of four traits called temperaments: Harm Avoidance, Novelty Seeking, Persistence and Reward Dependence, and three traits called characters: Self-Dependence, Cooperativeness and Self-Transcendence (table 1). Cloninger´s temperament and character has been reported to be strongly heritable and to have strong relationships with neurological findings. Few studies have made comparisons between the two models. Capanna et al. (2012) reported that the Big Five and Cloninger's temperament and characters are moderately correlated (except for Self-Transcendence), however, the authors stated that the conceptualisations and measures of personality are not totally consistent with each other.

Cloninger's model (Cloninger et al., 1993; Cloninger, 1994) of different temperaments and characters has been shown to be associated with a variety of outcome, both in general populations (Josefsson et al., 2011) and in a number of clinical populations, e.g. depression (Cloninger, Svrakic, & Przybeck, 2006), schizophrenia (Eklund, Hansson, & Bengtsson-Tops, 2004). Studies on temperament and character in adult populations with ASD have shown that high scores on Harm Avoidance and Self-Transcendence and low scores on Self-Directedness, Reward Dependence Novelty Seeking

and Cooperativeness have been associated with ASD, but not all studies have shown the same profiles (Soderstrom, Rastam, & Gillberg, 2002; Anckarsater et al., 2006; Sizoo, van den Brink, Gorissen van Eenige, & van der Gaag, 2009; Sizoo, van der Gaag, & van den Brink, 2015).

Table 4. *Description of traits associated with high and low levels of specific temperament and character dimensions*

	High score	Low score
Novelty Seeking	excitable	stoic
	impulsive	reflective
	extravagant	reserved
	disorderly	orderly
Harm Avoidance	worried	optimistic
	fearful	calm
	shy	outgoing
	fatigable	vigorous
Reward Dependence	sentimental	practical
	attached	detached
	dependent	independent
Persistence	persistent/hard-working	inactive/unreliable
Self-Directedness	responsible	blaming
	purposeful	lacking goal direction
	resourceful	inert
	self-accepting	self-striving
	good habits	bad habits
Cooperativeness	accepting	intolerant
	empathic	disinterested
	helpful	unhelpful
	compassionate	revengeful
	conscientious	self-serving
Self-Transcendence	self-forgetful	self-conscious
	identifying with nature	individualistic
	spiritual	rational

AIMS

The purpose of the study was to study the natural development of AS into adulthood in a clinical cohort of 100 males with AS and assess outcome trajectories and analyse possible factors that affect these trajectories. More specifically, the aims were:

1. To investigate stability and change in AS diagnosis and ASD symptoms and examine factors predicting stability

2. To examine the lifetime neurodevelopmental and psychiatric comorbidity in males with AS

3. To investigate general psycho-social life outcome and QoL in males with AS and examine the association with long-term diagnostic stability and psychiatric comorbidity

4. To examine the temperament and character in males with AS in relation to long-term diagnostic stability and psychiatric comorbidity

METHODS

This thesis is based on quantitative and semi-qualitative questionnaire and interview data and the design of the study was prospective longitudinal and involved a clinical cohort. The scientific approach has been inductive rather than deductive. The only hypothesis at the launch of the study was that outcome in AS would be extremely varied, ranging from very poor to superior. Other hypotheses have been added organically based on the results of the study.

Participants

In 2002, a project was started with the overarching aim to assess the long-term outcome of AS in males, defined by the Gillberg and Gillberg (1989) criteria. It was decided to target males who had been diagnosed with AS at the Child Neuropsychiatric Clinic (CNC) in Gothenburg during the years 1985 to 1999. During this time, all children in the Gothenburg region with a clinically suspected autism-related neurodevelopmental disorder were referred to the CNC for assessment. It was decided that 100 boys and 30 girls who had been consecutively diagnosed with AS at the CNC from 1985 (when the first clinical diagnoses of the Gillberg and Gillberg AS were made) through 1999 were to be included in the project. Further inclusion criteria were: a) over 16 years of age at follow-up, b) at least five years between time of diagnosis and time of follow-up and c) Full Scale IQ (FSIQ) over 70. One hundred boys were found who met inclusion criteria. Only seven girls were found who fulfilled inclusion criteria during the time period and because of the very low number a decision was then made to exclude them from the project. All one hundred males were analysed regarding a number of factors from childhood and time of diagnosis (T0). They were considered to be representative of all males diagnosed with AS in Gothenburg during the 1980s and 90s (Cederlund & Gillberg, 2004; Gillberg & Cederlund, 2005).

All individuals had been assessed by experienced clinicians working at the CNC at T0. Diagnosis of AS had been made using the Gillberg and Gillberg criteria for AS. All individuals had been tested with the Wechsler Scales of Intelligence for Children – Revised (Wechsler, 1974) or Wechsler Scales of Intelligence for Children – 3rd edition (Wechsler, 1991) at T0. Diagnostic assessment of AS was based partly on clinical judgement and partly based on state-of-the-art instruments at the time (DSM checklists, Autistic Behavior

Checklist (Krug, Arick, & Almond, 1980), Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers, Gillberg, & Wing, 1999)).

Out of the 100 males, 76 agreed to participate in a follow-up in 2002-2003, (either on their own, together with their parent, or only their parent participated) (T1). Seven individuals declined to participate and did not want to be contacted again, whereas 17 declined participation but did not refuse further contact.

This means that ninety-three out of the 100 males in the original selection group were contacted with a view to participating in a second follow-up (T2) in 2011–2013. Fifty men agreed to participate in the study (47 of whom had participated at T1 and 3 who had not) (Figure 1).

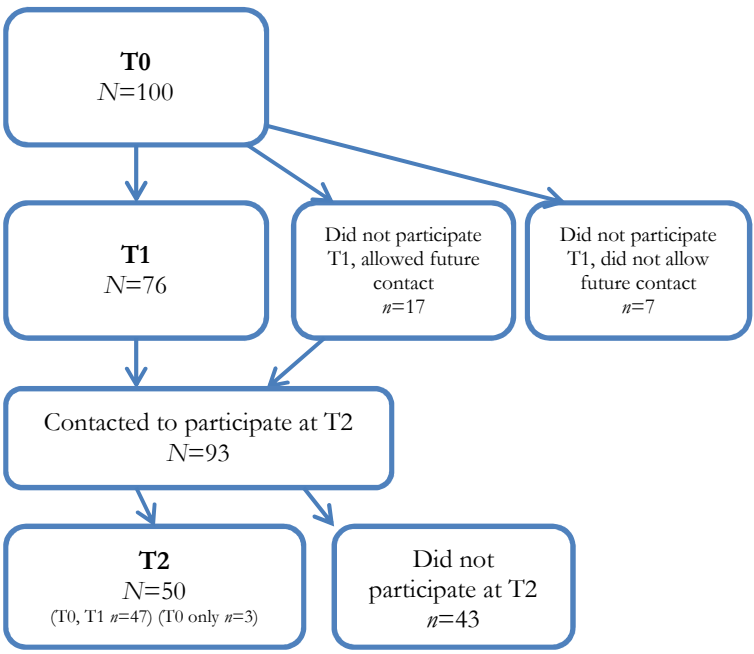

Figure 1. *Participants through the different stages of the follow-up studies*

The mean age at T0 (*N*= 100) was 11.4 years (*SD* 3.8 years, range 5.0 – 24.5 years), at T1 (*N*=76) 21.8 years (*SD* 4.5 years, range 16.0 – 36.5 years) and at T2 (*N*=50) 30.3 years (*SD* 5.0 years, range 23.7 – 43.9 years), respectively. The mean FSIQ at T0 (*N*=98) was 101.4 (*SD*=18.3, range 70 – 148), at T1 (*N*=71) 103.9 (*SD*=15.4, range 66 – 143) and at T2 (*N*=46) 109.1 (*SD*=15.3, range 78 – 140).

Procedure

At T2, study invitation letters were sent to 93 men. They were then personally invited over the phone to take part. One man had died since T1 (cause unknown), 35 declined to participate in the study, and seven were unreachable. All participants at T2 gave written consent to participate in the study.

The 35 males who declined participation cited the following reasons: (a) no specific reason (n = 16), (b) felt they had no difficulties and did not want to be reminded of the diagnosis (n = 5), (c) felt misunderstood by society because of their diagnosis and were reluctant to talk about AS (n = 5), and (d) first agreed to participate in the study but missed/postponed their appointments on several occasions, and finally decided not to participate, because (a) it would be too stressful (n = 5), (b) they had changed their mind (n = 2), or (c) they had wanted to say no directly but had difficulties in doing so (n = 2). The seven participants who were unreachable had a home address (but not a telephone number) listed in official records, and did not reply to our several mail requests.

A research team comprising a psychiatrist and a clinical psychologist, both with extensive experience in the field of ASD and other developmental disorders, met and observed, interviewed, tested and assessed the participants during a 4–6 hour visit to the Gillberg Neuropsychiatry Centre (GNC). The majority of the group (n = 46) were assessed at the GNC, one was assessed at home, two were interviewed over the phone, and one participant did not agree to be interviewed but allowed us to interview his parents.

Diagnostic assessment

ASD diagnostic assessment

To assess ASD diagnosis a combination of the Asperger Syndrome Diagnostic Interview (ASDI) results and clinical assessment based on all available data was used. Non-diagnosis was confirmed by the parent interview Diagnostic Interview for Social and Communication Disorders (DISCO). The Gillberg and Gillberg criteria of AS, DSM-IV criteria of AD, AS and PDD-NOS, and DSM-5 criteria of ASD were used (Table 5).

Table 5. *Study group and methods used in study I-IV*

Study Object of study	I Diagnostic stability	II Comorbidity	III Quality of Life	IV Temperament and character
Target group n	100	100	100	100
Group examined n	50	50	50	40
Attrition n	50	50	50	60
Male:female	50:0	50:0	50:0	40:0
DSM-IV ASD diagnosis	*T1 diagnosis* AD= 4; AS= 37 PDD-NOS= 2 No ASD= 4 DNP at T1=3	*T2 diagnosis* AD= 9 AS= 22 PDD-NOS= 8 No ASD= 11	*T2 diagnosis* AD= 9 AS = 22 PDD-NOS= 8 No ASD= 11	*T2 diagnosis* AD= 6 AS= 19 PDD-NOS= 7, No ASD= 8
Diagnostic criteria	Gillberg and Gillberg AS, DSM-IV, DSM-5	DSM-IV, DSM-5	DSM-IV	DSM-IV
Measurements	WAIS-III, DISCO, ASDI, GAF, Lotter	WAIS-III, DISCO, ASDI, M.I.N.I., BDI, GAF, Lotter, ASRS	SoC, SF-36v2, Psychosocial interview form	TCI, WAIS-III, ASDI, GAF, ASRS

DNP=Did not participate

Psychiatric and neurodevelopmental assessment

Lifetime prevalence of comorbid psychiatric and neurodevelopmental disorders was assessed with a wide approach. Current depression was assessed at T2 with both Mini International Neuropsychiatric Interview (M.I.N.I) and Beck Depression Inventory (BDI), and BDI had been used at T1 to assess depression in adolescence. A diagnosis of depression was considered to be fulfilled if the participant either scored above cut-off score on the BDI or met criteria for depression according to M.I.N.I. Anxiety disorders, psychotic disorders, Obsessive Compulsive Disorder (OCD), alcohol and drug dependency, eating disorders and bipolar disorder were assessed with the M.I.N.I. Tic disorders and DCD were assessed with DISCO. Attention-Deficit/Hyperactivity Disorder (ADHD) was diagnosed if one of two conditions were met. First condition was if the participant had been given a clinical diagnosis and prescribed central stimulant treatment for ADHD by an independent clinician. The second condition was if the participant scored above cut-off score on the Adult ADHD Self-Report Scale (ASRS) and the diagnosis was supported by the examining psychiatrist at assessment.

Instruments

The Asperger Syndrome Diagnostic Interview (ASDI) (I, II, IV)

The ASDI (Gillberg, Gillberg, Rastam, & Wentz, 2001), is a semi-structured clinical interview for use with an adolescent or adult with suspected AS relating to symptoms of the disorder, with scores ranging from 20-60 (20 = no indication of AS). It was used at both T1 and T2.

The Diagnostic Interview for Social and Communication Disorders (DISCO) (I, II)

The DISCO (Leekam, Libby, Wing, Gould, & Taylor, 2002), is a semi-structured interview for use with a parent/other close informant of a person with a suspected ASD. It was used at both T1 and T2. It yields diagnostic algorithm scores for a number of socio-communicative disorders, including the Gillberg and Gillberg AS and ICD-10 criteria of AD, AS and Atypical autism. Parents of 21 participants were interviewed at T2. The reasons that the parents of the remaining 29 participants were not interviewed were; (a) that the participant did not allow an interview with their parent (14 cases), (b) did not have a parent alive to interview (5 cases) or (c) the parent did not agree to or could not participate in the interview for other reasons (10 cases). At T1, the DISCO had been used in most cases. DISCO scores from T1 were also used to assess childhood/adolescent Developmental Coordination Disorder (DCD) and Tic disorder.

Global Assessment of Functioning (GAF) (I, II, IV)

The Global Assessment of Functioning (GAF) scale (APA, 1994) was used to measure general adaptive function. The scale ranges between 0-100 and scores below 70 indicate functioning that indicated need of care or support. GAF was used at both T1 and T2.

Lotter modified outcome criteria (I, II)

Lotter modified outcome criteria were used for categorical classification of outcomes (Lotter, 1974; Gillberg & Steffenburg, 1987). The outcome criteria were: *Good outcome*: (a) being employed or in higher education/vocational training, and, (b) living independently; *Fair outcome*: either (a) or (b) under good outcome; *Restricted but acceptable outcome*: neither (a) nor (b) under good outcome; *Poor outcome*: apparent and severe disability, no independent social progress, some clear verbal or non-verbal communicative skills; *Very poor outcome*: apparent and very severe disability, unable to lead any kind of

independent existence, no clear verbal or non-verbal communication. Lotter modified outcome criteria were used at both T1 and T2.

Psychosocial interview form (III)

Information regarding objective QoL was collected using a structured interview form that covered friendship (how many friends did they have, defined as a person they considered a friend but who was not a sibling, romantic partner, parent or personal assistant), romantic relationships (if they were married, lived with a partner, had a girl-/boyfriend or if they had ever experienced a romantic relationship), occupation (if they were employed or not, and if they were employed did they have a regular employment, a wage-subsided employment or a specialised employment), educational history (did they have a high school degree, did they have a college/university degree, did they currently study at college/university, and had they dropped out of college/university without taking a degree), living situation (did they live with parents, live alone, at a group home, and did they receive support from the municipality), and support from health care services (if they currently or previously had contact with a psychiatric or habilitation clinic or had undergone psychotherapy). A similar interview form was used in the Cederlund et al. (2008) study. The interview form was only used at T2.

Wechsler Adult Intelligence Scale 3rd edition (WAIS-III) (I, II, IV)

The Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III) (Wechsler, 2002), was used to assess FSIQ, Verbal IQ (VIQ), and Performance IQ (PIQ) at both T1 and T2. The test also gives results regarding Verbal Function, Perceptual Organisation, Processing Speed and Working Memory. FSIQ 70-79 = Borderline intellectual functioning; FSIQ 80-89 = Low average intelligence; FSIQ 90-109 = Average intelligence; FSIQ 110-119 High average intelligence; FSIQ 120-129 Superior intelligence; FSIQ 130+ = Very superior intelligence.

Mini International Neuropsychiatric Interview (M.I.N.I.) (II)

The M.I.N.I. (Sheehan et al., 1998), a widely used psychiatric structured diagnostic interview instrument for psychiatric diagnosis according to the DSM, was used at T2. The version consistent with the criteria of DSM-IV (APA, 1994) was used. The M.I.N.I. does not yield diagnostic information relating to neurodevelopmental disorders such as ADHD, ASD, or Tourette syndrome.

Adult ADHD Self-Report Scale (ASRS) (II, IV)

The ASRS (Kessler et al., 2007), is a self-report questionnaire that measures ADHD symptoms and was used at T2. Scores of 4 and above indicate ADHD.

Beck Depression Inventory (BDI) (II, IV)

The BDI (Beck & Steer, 1996), a self-report questionnaire that measures depression symptoms was used at T1 and T2. Scores of 0-9 indicate minimal depression, 10-18 indicate mild depression, 19-29 indicate moderate depression and 30-63 indicate severe depression.

Sense of coherence (SoC) (III)

The SoC (Bowman, 1996) is a self-rating questionnaire that assesses perceived quality of life and particularly focuses on people´s health-promoting and health-protecting characteristics. According to the theory a higher SoC score predicts lower stress and tension and better coping strategies. SoC yields a total SoC score and subscale scores for Manageability (believing you have the capacity to manage things and feel control), Comprehensibility (believing that things will happen in a predictable fashion that you can understand), and Meaningfulness (believing that things in life are meaningful and worthwhile). Total scores below 120 indicate low SoC, scores between 120 and 159 are considered average SoC and scores above 160 are considered high SoC. Scores below 35 on the Manageability and Comprehensibility subscales and below 30 on the Meaningfulness subscale indicate low scores on these scales.

Short form health survey version 2.0 (SF-36) (III)

The Short Form health survey version 2.0 (SF-36) (Sullivan, Karlsson, Taft, & Ware, 2002) was used to assess HRQoL at T2. The SF-36 includes two composite scores, the Physical Composite Score and Mental Composite Score, global measures of HRQoL regarding physical and mental health. There are also 8 subscales in the SF-36: Physical Functioning; Role-Physical (inability to perform important roles due to physical health); Bodily Pain; General Health; Vitality (perceived vitality and energy); Social Functioning; Role-Emotional (inability to perform important roles due to emotional problems); and Mental Health. All scores are presented as norm based T-scores with a mean of 50 and a standard deviation of 10. All scores are presented as norm based T-scores (calculated from Swedish norm data via www.sf-36.org) with a mean of 50 and a standard deviation of 10, i.e. 68% of

the population will score between 40 and 60. A higher score indicates better functioning with regard to HRQoL.

The Temperament and Character Inventory (TCI) (IV)

The Temperament and Character Inventory (TCI) (Cloninger et al., 1993) is a self-rating questionnaire assessing different personality dimensions: four temperament dimensions ("Harm Avoidance", "Novelty Seeking", "Reward Dependence" & "Persistence") and three character dimensions ("Self-Directedness", "Cooperativeness" & "Self-Transcendence") (Table 4). "Rare Answers" is a separate scale and is a collection of unusual answers that are associated with low social skills and odd or bizarre personality traits. All scores are presented as T-scores based on Swedish norm samples (Brändström, Sigvardsson, Nylander, & Richter, 2008) with a mean of 50 and a standard deviation of 10. Higher scores indicate higher levels of the temperament or character trait. The TCI has been proven to have good test–retest reliability, consistency with interview ratings, and have high internal consistency. The TCI original version with dichotomous answers (true/false) was used and scored using the TCI software.

Statistical methods

All data analyses were made with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA). Non-parametric statistics were used in most calculations and all significance tests were two-tailed. Means are presented even in cases where the statistical analysis was made based on medians or ranks, and proportions are sometimes presented when statistical analysis was made with ranks. This is done to enhance readability/comparability. A decision was made to not use corrections in any of the studies. This decision was made to keep a fair balance between type I and type II errors. Statistical significance level was set at $p<.05$ in study I, II and IV and in the unpublished data. To enhance comparability with similar studies a more restrictive significance level of $p<.01$ was used in study III.

Study I

Differences in proportions were assessed with Fisher exact χ^2 test and change of proportions was assessed with McNemar and McNemar-Bowker test. Stability of specific diagnosis was analysed with Cohen's kappa. Wilcoxon Signed Rank Test was used to analyse group change and Mann–Whitney U and Kruskal–Wallis H test were used to analyse group

differences. Post hoc analysis after Kruskal–Wallis H test was made with the Mann–Whitney U test. Binary logistic regression was used to assess factors predicting diagnostic stability with a forwards stepwise model, collinearity was analysed with Spearman's rho and goodness of fit was analysed with Hosmer–Lemeshow test. Repeated-measure Analysis of Variance (ANOVA) was made to assess change in symptoms and the effect of diagnostic stability on this change.

Study II

Between-group comparisons were made with the Mann–Whitney U test. Spearman's rho was used to assess correlation.

Study III

Group comparisons were made with the Kruskal Wallis H-test and post hoc analyses were made with the Mann-Whitney U test. Scores were compared with norm data using one-sample t-test. Linear regression models were used to assess factors affecting subjective QoL, while also controlling for intelligence and age. Due to the small sample size and limited power of the regression model, five theoretically important measures were chosen (friendship, living situation, occupation, comorbidity and ASD diagnostic stability). Friendship, occupation and living situation were ranked on an ordinal scale with higher scores indicating better functioning. Standardised beta-coefficients are presented to enhance comparability. Spearman's rho was used to assess correlation.

Study IV

Comparisons with norm data were made a one sample t-test. Group comparisons were made with the Kruskal-Wallis H test and post hoc analysis was made with Dunn's post hoc test. Correlation analyses were made with Spearman's rho. To minimise the risk of type I errors in the correlation, an automated bootstrapping technique in the SPSS software was used with 1000 samples and simple sampling. To be considered statistically significant both the p-value were <.05 and the bootstrap 95 % confidence interval did not overlap 0 (Haukoos & Lewis, 2005).

Unpublished data not presented in any of the four studies

Mann-Whitney U test was used to assess between group differences. Repeated-measure ANOVA was made to assess change in symptoms and the effect of outcome group on this change.

Ethics

Ethical approval was obtained from the Regional Ethical Review Board in Gothenburg (reference: 508-10). All participants signed an informed consent form. Information regarding the study was given both orally and in writing and all participants were asked if they needed any further explanations before signing the consent form.

Table 6. *Attrition analysis*

	Participated T2 Data from T0 *N*=50 Data from T1 *N*=47	Did not participate T2 Data from T0 *N*=50 Data from T1 *N*=29	Group comparison
	Mean (SD)	Mean (SD)	*Z* (*p*)
FSIQ T0	103.7 (17.3)	99.1 (19.3)	1.6 (.11)
FSIQ T1	107.6 (15.1)	97.0 (13.7)	2.8 (<.01)
VIQ T0	107.8 (17.4)	106.3 (19.9)	.5 (.64)
VIQ T1	107.7 (16.7)	100.5 (13.8)	1.5 (.14)
PIQ T0	98.1 (18.1)	91.1 (18.9)	2.2 (.03)
PIQ T1	106.3 (15.0)	92.4 (14.2)	3.5 (<.01)
ASSQ T0	22.8 (8.4)	23.1 (9.3)	-.1 (.93)
ASSQ T1	17.2 (11.2)	19.3 (9.8)	-.9 (.37)
ASDI T1	42.1 (8.8)	40.3 (8.5)	.6 (.52)
Age T0	11.5 (4.4)	11.2 (3.2)	.3 (.78)
Age T1	22.0 (4.9)	21.4 (3.8)	.3 (.78)
GAF T1	59.6 (9.2)	58.0 (9.4)	.8 (.43)
BDI T1	8.0 (8.0)	6.1 (5.0)	.5 (.62)

Attrition

The 50 participants at T2 did not differ from the 50 individuals who did not participate regarding T0 ASSQ scores, age, FSIQ or VIQ or regarding age at walking onset, parent education level or early language development (study

I). They did, however, differ regarding PIQ at T0, with T2 participants having had a significantly higher PIQ at T0. Participants at T2 also did not differ regarding T1 ASDI score, GAF score, Lotter outcome score, age, type of ASD diagnosis or VIQ (study I) or regarding BDI or ADHD symptoms at T1 (study II). They did, however, differ regarding FSIQ and PIQ at T1 with T2 participants having had higher FSIQ and PIQ scores at T1 than non-participants at T2 (Table 6).

The TCI was only completed by 40 participants, but the 40 who completed the form did not differ from the 10 that did not complete the form regarding age, FSIQ, ASDI scores, ASRS score, GAF score, BDI score or ASD diagnosis at T2 (study IV).

RESULTS

Stability of diagnosis of AS over 20 years

The results from study I showed that 39 out of 50 men (78%) still fulfilled criteria for an ASD diagnosis according to the DSM-IV, DSM-5 or the Gillberg and Gillberg criteria twenty years after being diagnosed with AS according to the Gillberg and Gillberg criteria. At T1 90% still fulfilled criteria of an ASD according to DSM-IV or the Gillberg and Gillberg criteria. Not fulfilling an ASD diagnosis at T2 was confirmed in most cases (8 out of 11) by a DISCO interview with a parent. The eleven individuals not fulfilling any ASD (any ASD diagnosis according to either DSM-IV or DSM-5 or AS according to Gillberg and Gillberg) are henceforth known as the **No-longer-ASD group**.

The stability of the diagnosis of AS according to Gillberg and Gillberg was lower, with 44% still fulfilling criteria of their original diagnosis, a significant decrease compared to T1 when 83% had met the criteria of the Gillberg and Gillberg AS ($p<.001$).

The stability of specific DSM-IV ASD diagnosis from T1 to T2 was low (*kappa*=.21, *p*=.01) with 22 out of 47 (47%) having changed DSM-IV ASD diagnosis from T1 to T2 or having changed from meeting criteria of ASD at T1 to not meeting criteria at T2 or vice versa (Table 7).

Table 7. *DSM-IV ASD diagnosis at T1 and T2*

	DSM-IV Diagnosis at T2				
DSM-IV Diagnosis at T1	No diagnosis	PDD-NOS	AS	AD	Total T1
No diagnosis	**3**	0	1	0	4
PDD-NOS	1	**1**	0	0	2
AS	7	4	**19**	7	37
AD	0	0	2	**2**	4
Total T2	11	5	22	9	47

Numbers in bold indicate number of individuals with the same DSM-IV ASD diagnosis at T1 and T2.

Factors associated with diagnostic stability

In a logistic regression, including possible predictors for ASD diagnostic stability at T2, the only significant factor found was ASDI score at T1. ASDI at T1 as a single factor predicted the ASD diagnostic stability in 84% of the cases (94% of cases with a stable diagnosis and 50% of cases no longer fulfilling a diagnosis).

There was a general decrease in ASDI scores from T1 to T2. The decrease trajectory did not differ between the No-longer-ASD group and the other participants, but the No-longer-ASD group had lower ASDI scores at both T1 and T2 (Figure 2).

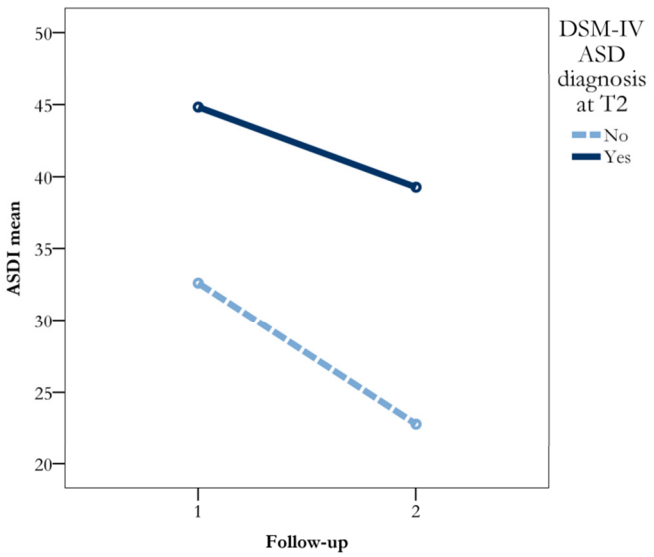

Figure 2. *Changes in ASDI mean score from T1 to T2 based on ASD diagnostic stability at T2. Published in study I. Reprinted with permission. Copyright John Wiley & Sons Inc.*

Comorbid diagnoses current and over 20 years

The results from study II showed that 94% of the study group fulfilled or had fulfilled criteria for at least one other psychiatric or neurodevelopmental disorder at either T0, T1 or T2 and that 54% fulfilled at least one other psychiatric or neurodevelopmental currently (Table 8). The majority fulfilled

several comorbid diagnoses (72% have fulfilled two or more diagnoses during their lifetime and 30% currently fulfilled two or more diagnoses).

The most common comorbid diagnoses in lifetime (ever) were DCD (77%), depression (58%) and Tic disorder (50%) and the most common current comorbid diagnoses were depression (28%), ADHD (28%) and anxiety disorders (22%) (Table 9). ADHD was associated with lower GAF scores as mean GAF score for participants with ADHD were 55.6 (*SD*=14.7) and for participants with no ADHD were 64.9 (*SD*=17.4), $p<.05$. No other specific comorbid diagnosis was associated with general functioning, but fulfilling any comorbid diagnosis was also associated with lower GAF scores (current comorbidity *M*=56.8, *SD*=15.3, no current comorbidity *M*=68.8, *SD*=17.0, $p=.02$)

Table 8. *Number of comorbid diagnosis ever and currently*

Number of comorbid psychiatric/developmental disorder	N	%
None ever	3	6
One ever	11	22
Two ever	15	30
Three ever	10	20
Four ever	6	12
Five or more ever	5	10
None current	23	46
One current	12	24
Two current	10	20
Three or more current	5	10

Table 9. *Specific comorbid diagnosis ranked based on commonality*

Diagnosis	N	%
Developmental Coordination Disorder ever [a]	34	77
Depressive Disorders ever	29	58
Any Tic Disorder ever [a]	22	50
Any Psychotic Disorder ever	2	4
Bipolar Disorder ever	2	4
Depressive Disorders current	14	28
Attention-Deficit/Hyperactivity Disorder current	14	28
Any Anxiety Disorder current	11	22
Obsessive Compulsive Disorder current	4	8
Alcohol Dependency current	2	4

a) Percentages out of N=44

The No-longer-ASD group differed somewhat from participants with a stable ASD regarding comorbidity. In the No-longer-ASD group 27% met criteria of at least on other current comorbid diagnosis at T2 and 82% had met criteria of at least one comorbid diagnosis during their lifetime compared to 62% current and 97% lifetime among participants who still met criteria of an ASD at T2. There was, however, a group of 15 participants with a stable ASD diagnosis and no current comorbid diagnosis. This group, henceforth known as the **ASD Only group**, had significantly lower average number of comorbid lifetime (ever) diagnoses than those with a stable ASD and current comorbidity, henceforth known as the **ASD Plus group** (ASD Only M=1.47, SD=.92 vs ASD Plus M=3.5, SD=1.4, Z=-4.3, p<.001[1]). In study III and IV analyses were made based on the subgroup division of **No-longer-ASD**, **ASD Only** and **ASD Plus** and this division will also be used in the remainder of the thesis. The three groups did not differ regarding age, FSIQ or ASSQ scores at T0 or FSIQ or age at T2, but the No-longer-ASD group differed from the two other groups regarding ASDI scores at T2 (study III).

Current subjective QoL

In study III, subjective QoL/HRQoL was assessed using the SoC and SF-36. The mean total SoC score for the total study group was 129.0 (SD=22.2), a result in the average range on the SoC (average range on SoC is considered to be between 120 and 159). Fourteen participants (28%) had SoC scores below 120, indicating low SoC (13 out of the 14 were in the ASD Plus group) and six participants (12%) had SoC scores of 160 and above, indicating high SoC (five out of the six were in the No-longer-ASD group). In a regression model the only significant factor predicting SoC was having a current comorbid diagnosis. The ASD Only group did not differ from the No-longer-ASD group on the SoC, but had higher scores than the ASD Plus group on most parts of the test.

The SF-36 was used to assess HRQoL. The participants scored significantly higher on the Physical Composite Score and significantly lower on the Mental Composite Score compared to norms for the Swedish population. There were no significant predictors of either Composite Scores, but on the subscales General Health, Social Functioning and Mental Health (all associated with the Mental Composite Score) the ASD Plus group scored

[1] Mann-Whitney U test, unpublished data not presented in any of the four studies.

significantly lower, indicating an association between current comorbidity and perceived mental HRQoL.

General functioning, outcome and objective QoL

There was great variability with regard to general functioning, overall outcome and objective QoL in the total study group. In study I and II, GAF scores were presented in relation to ASD diagnostic stability and current psychiatric comorbidity. The mean GAF score was significantly higher in the No-longer-ASD group and this subgroup also had a significantly larger increase in GAF score from T1 to T2 (Figure 3) than the combined group of ASD Only and ASD Plus. Lotter outcome scores, presented in study I, were also significantly higher in the No-longer-ASD group compared to the combined group of ASD Only and ASD Plus.

Having one or more current comorbid diagnosis was also associated with lower GAF scores, those with a comorbid diagnosis scored significantly lower (M=56.8, SD=15.3 for those with comorbidity and M=68.8, SD=17.0 for those without, p=.02) than those without. Fulfilling criteria for a comorbid diagnosis of ADHD was associated with lower GAF scores (ADHD M=55.6, SD=14.7 compared to no ADHD M=64.9, SD=17.4, p<.05), but no other specific comorbid diagnosis was associated with GAF scores (study II).

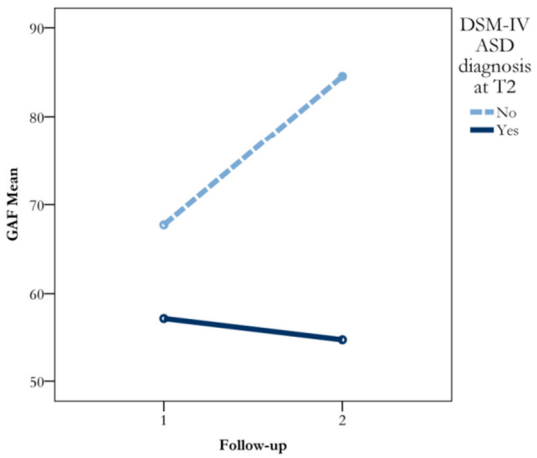

Figure 3. *Changes in mean GAF score based on DSM-IV ASD diagnostic stability at T2. Published in study I. Reprinted with permission. Copyright John Wiley & Sons Inc.*

Table 10. *Objective QoL in relation to ASD diagnostic stability and current comorbidity*

	Subgroups				
	1) No-longer-ASD *n*=11	2) ASD Only *n*=15	3) ASD Plus *n*=24		
	N (%)	*N* (%)	*N* (%)	Kruskal Wallis	Mann-Whitney U post-hoc analysis
Current employment					
Employment (wage)/ student (student loan)	10 (91)	5 (33)	5 (21)	χ^2=10.5 (p<.01)	1 vs 2: Z=-2.6 (p<.01) 1 vs 3: Z=-3.2 (p<.01)
Wage-subsidised employment	0 (0)	1 (7)	5 (21)		2 vs 3: ns
Specialised employment[a]	0 (0)	4 (27)	7 (29)		
Unemployed	1 (9)	5 (33)	7 (29)		
Highest academic level achieved					
University degree or currently student	2 (18)	2 (13)	3 (13)	ns	1 vs 2: ns 1 vs 3: ns
University drop-out	1 (9)	4 (27)	7 (29)		2 vs 3: ns
High school degree	8 (73)	8 (62)	10 (42)		
No high school degree	0 (0)	1 (7)	4 (17)		
Current living situation					
Independent living	11 (100)	7 (47)	13 (54)	χ^2=8.1	1 vs 2: Z=-2.8 (p<.01)
Lives with parent	0 (0)	4 (27)	3 (13)	(p=.02)	1 vs 3: Z=-2.6 (p<.01)
Lives with support or in group home	0 (0)	3 (20)	8 (33)		2 vs 3: ns
Friendship					
Two or more friends[b]	11 (100)	5 (33)	8 (33)	χ^2=13.3	1 vs 2: Z=-3.3 (p<.01)
One friend[b] or only acquaintances	0 (0)	6 (40)	11 (46)	(p<.01)	1 vs 3: Z=-3.5 (p<.001) 2 vs 3: ns
No friends	0 (0)	4 (27)	5 (21)		
Marital status					
Married or lives with partner[c]	1 (9)	3 (20)	3 (13)	ns	1 vs 2: ns
Currently has a partner[c] (do not live together)	3 (27)	0 (0)	5 (21)		1 vs 3: ns 2 vs 3: ns
Currently single, have had a partner[c]	4 (36)	3 (20)	4 (17)		
Currently single, never had a partner[c]	3 (27)	9 (60)	12 (50)		

a) Specialised employment= unskilled labor for individuals with disabilities provided by the municipality; b) Friend= Defined by the person himself as a friend that they see regularly and could not be a family member, partner or personal assistant; c) Partner= girl- or boyfriend or fiancé; ns=non-significant, p>.01. Published in study III.

In study III, objective measures of QoL were presented. The No-longer-ASD group had significantly higher degree of independent employment and

living conditions and had significantly more friends, but did not differ regarding academic achievements or romantic relationships (Table 10) from the other two groups. The ASD Only group did not differ from the ASD Plus group regarding any measure of objective QoL.

The objective measures of QoL in Table 10 were correlated with FSIQ and ASDI total scores and the results showed a positive association between intelligence and academic success on the one hand, and a negative association between ASD symptoms and the other factors on the other hand (Table 11).

Table 11. *Spearman's rho correlation between FSIQ and ASDI Total scores and objective QoL factors ranked on an ordinal scale in the order presented in table 10*

	FSIQ	ASDI Total
Employment	ns	-.36 **
Highest academic level achieved	.58 ***	ns
Living situation	ns	-.61 ***
Friendship	ns	-.51 ***
Marital status	ns	-.42 **

ns= p>.01; **= p<.01; ***=p<.001. Published in study III.

Factors associated with outcome trajectories

Across the first three studies, as mentioned above, three different outcome trajectories emerged: 1) the No-longer-ASD group, individuals who no longer fulfil an ASD after twenty years and function quite well with regard to general functioning, QoL and overall outcome, 2) the ASD plus group, individuals with a stable ASD and at least one other current comorbid diagnosis, that have had a higher amount of comorbid diagnoses in life, function poorly in general functioning while also having a low QoL and finally 3) the ASD Only group, individuals with a stable ASD and no current comorbid diagnosis, who have had fewer comorbid diagnoses in life than the ASD Plus group, that function just as poorly in general life as the ASD Plus group but score about the same as the No-longer-ASD group on measures of subjective QoL.

In the following sections data will be presented from all of the four studies relating to factors that have been examined and could be associated with the differing trajectories.

Background variables

As described above, background variables were assessed in relation to ASD diagnostic stability in study I and the only significant factor found was ASDI score at T1. The factors that yielded non-significant results were age at diagnosis, delayed speech development (no sentences before the age of 3 years), age at walking onset, parents' educational level, FSIQ, and ASSQ scores at T0.

In study I, repeated measure ANOVA analyses were made to assess differing trajectories on GAF and ASDI based on ASD diagnostic stability (Figure 2 and 3). To further examine the differences in trajectory on GAF and ASDI a new repeated measure ANOVA was made for this thesis, based on the three subgroups: No-longer-ASD, ASD Only and ASD Plus. There was a significant increase in GAF scores from T1 to T2 ($F(1,44)=8.1$, $p<.01$) and this increase was significantly affected by subgroup at T2 ($F(2,44)=17.0$, $p<.001$). Post-hoc analysis showed that the No-longer-ASD group had a significantly different trajectory of symptoms than both the ASD Only and ASD Plus groups but the ASD Only and ASD Plus did not differ significantly (Figure 4)[2]. There was a significant decrease in ASDI scores from T1 to T2 ($F(1, 44)=38.1$, $p<.001$), but this decrease was not significantly affected by subgroup at T2 ($F(2, 44)=3.1$, $p=.06$) (Figure 4)[3].

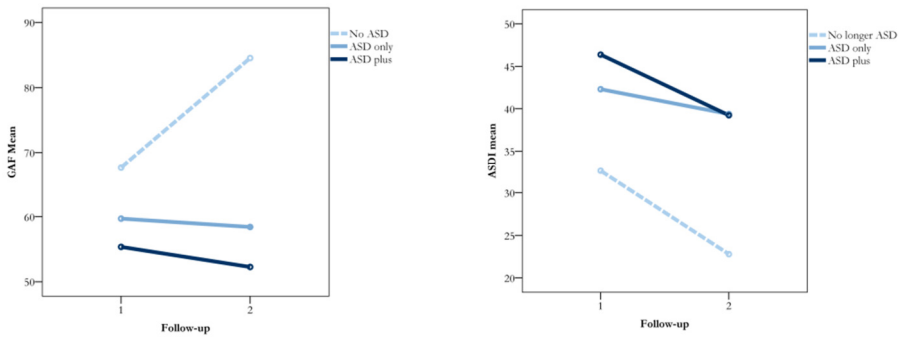

Figure 4. *Changes in GAF and ASDI mean score from T1 to T2 based on the groups No-longer-ASD, ASD Only and ASD Plus. Unpublished data not presented in any of the four studies.*

In study II, comorbid diagnoses were assessed. The No-longer-ASD group had lower degree of comorbid ADHD, Tic disorder, DCD and

[2] Unpublished data not presented in any of the four studies

[3] Unpublished data not presented in any of the four studies

depression than those with a stable ASD. None in the No-longer-ASD group had ever had any psychosis or bipolar disorder. None in the ASD Only group had ever had ADHD, bipolar disorder, psychosis or OCD and they had lower degree of DCD and depression ever than the ASD Plus group (Figure 5). As presented above, the ASD Only group also had significantly fewer comorbid diagnoses ever than the ASD Plus group.

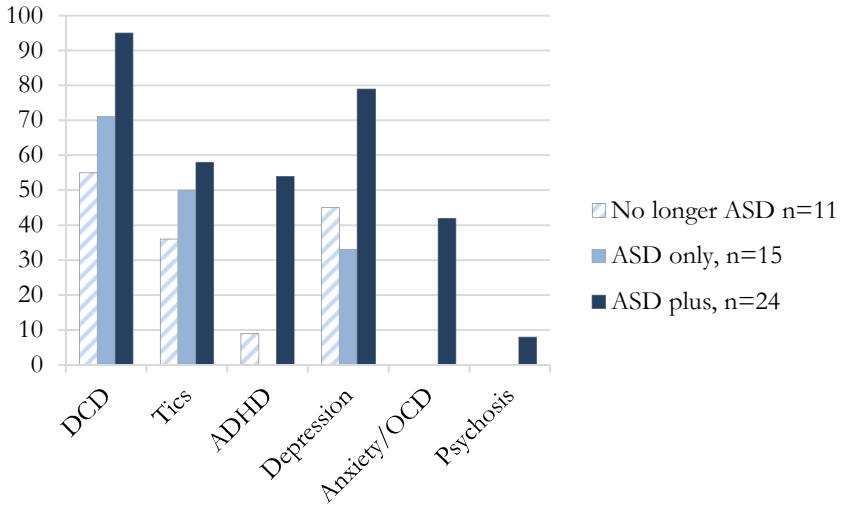

Figure 5. *Percentage of participants in the different outcome groups having met criteria of another specific comorbid diagnosis in lifetime (ever)* [4]

In study III, data showed that there were no differences between the three subgroups regarding the age when they moved away from home. The ASD Plus group had a higher proportion that left high school without a degree than the other two groups (17% in the ASD Plus group, 7% in the ASD Only group and 0% in the No-longer-ASD group), several because they had attended schools for children with learning disabilities[5], a school form which does not give a regular high school degree.

[4] Unpublished data not presented in any of the four studies

[5] Today only children with a learning disability can attend school for children with learning disabilities in Sweden, but previously children with autism, even when intelligence was in the average range, were allowed to attend

Intelligence

In the four studies, intelligence was assessed in relation to outcome. We found that FSIQ at T0 or T1 could not predict stability of ASD diagnosis (study I). No difference in FSIQ at T0 and T2 was found between the No-longer-ASD, ASD Only and ASD Plus groups (study III). In study II, FSIQ and PIQ at T2 were negatively associated with ADHD symptoms at T2, but no other association between intelligence and comorbidity was found. FSIQ intelligence at T2 was not associated with subjective QoL or employment, but was positively associated with academic success (study III). Intelligence was not associated with temperament or character dimensions (study IV). For this thesis, analysis of subscale differences on the WAIS-III in relation to the three outcome groups was performed. There were no significant differences regarding PIQ, VIQ, Verbal Comprehension, Perceptual Organisation, Working Memory or Processing Speed between the three outcome groups[6]. Analysis of IQ range in relation to outcome group was also made and no clear differences were found. In the ASD Only group there were 6 men (40%) with superior or very superior intelligence, compared to 4 men (36%) in the No-longer-ASD group and 5 men (21%) in the ASD Plus group.

Personality

In study IV, temperament and character were analysed, comparing the results of the three subgroups. The No-longer-ASD group was characterised by average scores regarding Novelty Seeking, Harm Avoidance, Persistence, Self-Directedness, Cooperativeness and Self-Transcendence and above average regarding Reward Dependence (also scoring significantly higher than both other groups on this temperament dimension) (Figure 6).

The ASD Only group was characterised by lower than average Novelty Seeking (also scoring significantly lower than the No-longer-ASD group but not the ASD Plus group), higher than average Harm Avoidance (but scoring lower than the ASD Plus group) and average scores on all other temperament and character dimensions (Figure 6).

[6] Unpublished data not presented in any of the four studies

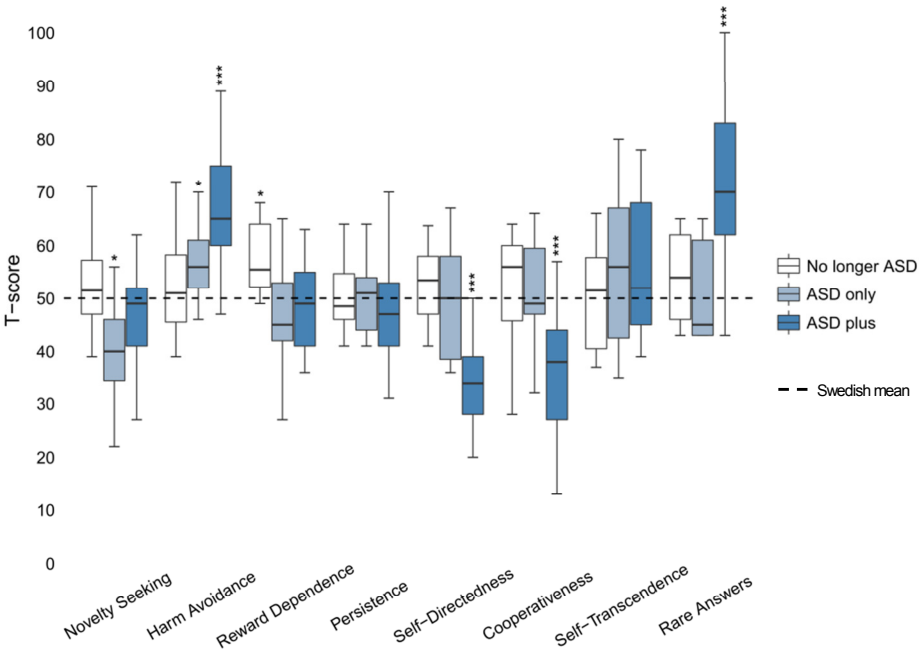

Figure 6. *Temperament and character dimensions comparing subgroups to norm data with a single sample T-test (Swedish mean T-score=50, SD=10), presented in a Tukey boxplot. Statistical analyses were based on means, but medians and quartiles are presented to better represent the distribution of the data. *=p<.05; **=p<.01; ***=p<.001. Published in study IV.*

The ASD Plus group was characterised by high Harm Avoidance (scoring higher than norm data and the No-longer-ASD and ASD Only groups), low Self-Directedness and Cooperativeness (scoring lower than norm data and the No-longer-ASD and ASD Only groups on both dimensions), and high degree of Rare Answers (scoring higher than norm data and the No-longer-ASD and ASD Only groups), while scoring average regarding Novelty Seeking, Reward Dependence, Persistence and Self-Transcendence (Figure 5).

Support

There were a few questions asked regarding degree of support from health care services, family and society, that have not been previously published. All

the data presented in this section have not been published previously in any of the four studies.

Ten out of 50 participants had received support from a habilitation clinic either currently or previously as far as they could remember (7 in the ASD Plus group and three in the ASD Only group), 8 out of 50 participants had contact with a psychiatric clinic (excluding the contact they had when they received their diagnosis) either currently or previously as far as they could remember (4 in the ASD Plus group, 2 in the ASD Only group and 2 in the No-longer-ASD group) and 10 participants had gone to some form of psychotherapy (4 in the ASD Plus group, 4 in the ASD Only group and 2 in the No-longer-ASD group), either currently or previously. Twenty-six out of 50 participants had, as far as they could remember, never had contact with a psychiatric or habiliation clinic or undergone psychotherapy (6 or 55% in the No-longer-ASD group, 9 or 60 % in the ASD Only group and 11 or 46% in the ASD Plus group).

Six out of the participants had a trustee that took care of all their finances (2 in the ASD Only group and 4 in the ASD Plus group) and 14 (1 in the No-longer-ASD group, 4 in the ASD Plus group and 9 in the ASD Plus group) had support from their parents regarding their finances (ranging from getting help paying bills to having full support regarding all their financial transactions). Nineteen of the participants (10 or 91% in the No-longer-ASD group, 4 or 27 % in the ASD Only group and 5 or 36% in the ASD Plus group) did not receive any added support regarding finances (receiving economic compensation and/or help with taking financial decisions), living situation or work, either from their parents or society. Reversely 31 participants received support from either the government or from their parents regarding finances, living or work and several had support regarding several aspects of their adult life.

DSM-5 ASD

Diagnostic assessment was also made using DSM-5 criteria for ASD. Thirty-one participants in the group (62%) fulfilled criteria for ASD according to the DSM-5, compared to 78% who fulfilled criteria of one of the ASD diagnoses in the DSM-IV. Of the 19 not meeting the criteria of a DSM-5 ASD diagnosis, eight fulfilled an ASD diagnosis according to DSM-IV (AS = 2 and PDD-NOS=6). The eleven participants that did not meet criteria of any DSM-IV ASD diagnosis also did not meet criteria of DSM-5 ASD (Figure 7).

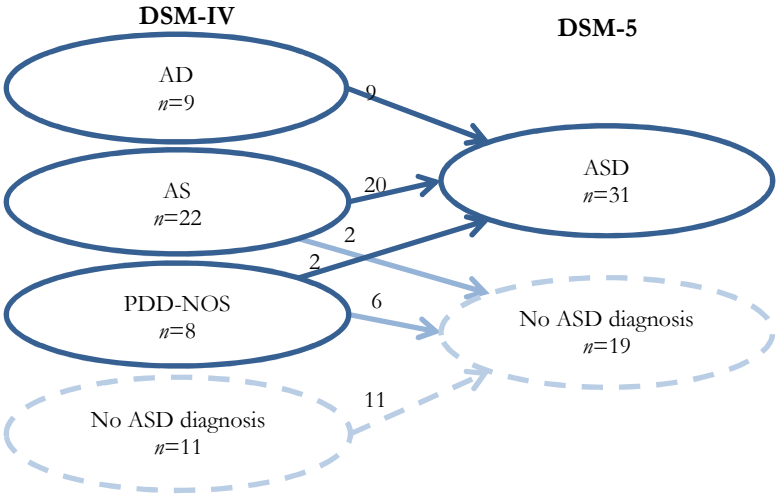

Figure 7. *Comparison between DSM-IV and DSM-5 criteria of ASD diagnoses*

The eight participants not fulfilling full DSM-5 criteria but fulfilling criteria for an ASD according to the DSM-IV scored significantly lower than the No-longer-ASD group on GAF, Lotter and ASDI scores but significantly higher than those fulfilling both DSM-5 and DSM-IV criteria of an ASD (study I) (Table 12).

Table 12. *Comparison of GAF and ASDI scores based on DSM-5 and DSM-IV ASD diagnosis.*

	a) DSM-IV and DSM-5 ASD *n*=26	b) DSM-IV not DSM-5 ASD *n*=13	c) No-longer-ASD *n*=11	Post hoc analysis
	Mean (SD)	Mean (SD)	Mean (SD)	
GAF, mean (SD)	51.9 (11.1)	64.5 (11.8)	84.6 (10.2)	a<b<c (p<.05)
ASDI, mean (SD)	41.4 (6.6)	32.6 (4.9)	22.6 (2.3)	a<b<c (p<.05)

The DSM-IV not DSM-5 ASD group was also as likely to have a current comorbid diagnosis as the DSM-IV and DSM-5 ASD group and was also more likely to have a comorbid depression (Figure 8). These results were presented in study II. Five out of eight in the DSM-IV not DSM-5 group were categorised in the ASD Plus group.

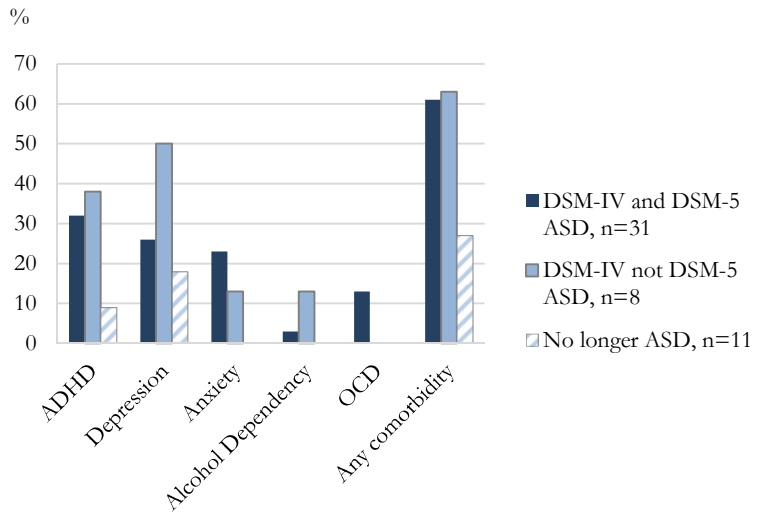

Figure 8. *Degree of current comorbidity based on DSM-IV vs DSM-5 criteria of ASD diagnoses. Published in study II. Reprinted with permission. Copyright Springer Science and Business Media.*

DISCUSSION

General findings

This thesis is based on a prospective longitudinal study of males diagnosed with AS in childhood and followed up for a mean period of nineteen years. The results clearly showed that the long-term outcome of AS is very varied. The vast majority (78 %) of individuals with AS diagnosed in childhood still met criteria for an ASD diagnosis according to the DSM-IV 19 years after original diagnosis, compared to 90% in the first follow-up 10 years earlier. The specific AS diagnosis was not as stable (44 % met the Gillberg and Gillberg criteria of AS at T2, a significant decrease from T1). Compared to other studies on populations of ASDs (AS and other ASD) the results of this thesis are fairly similar. Diagnostic stability of ASDs have been shown to vary down to 75% even though most studies report diagnostic stability in the 85-95% range (Helt et al., 2008; Rondeau et al., 2011; Woolfenden et al., 2012). It is important to note that very few studies have examined diagnostic stability in cohorts consisting of only individuals without intellectual disability. ASD diagnoses are generally more stable when combined with intellectual disability. There is also clear evidence from other studies that the specific ASD diagnosis is not very stable (Rondeau et al., 2011).

Almost all of the participants (94 %) had had at least one other comorbid neurodevelopmental or psychiatric disorder during their lifetime. The most common diagnoses over time were DCD, tic disorders and depression (more than half of the participants had had depression during their lifetime). More than half of the participants (54 %) had at least one other current comorbid psychiatric diagnosis in adult life (most commonly ADHD or depression). These findings are similar to results of other studies, with numerous authors reporting high rates of comorbidity in populations with average range intelligence and ASD (Mattila et al., 2010; Lugnegard et al., 2011; Mazzone et al., 2012; Buck et al., 2014).

Not fulfilling criteria for ASD was associated with better general functioning and high objective QoL. Having a current comorbid psychiatric disorder was associated with low subjective QoL, but not with general functioning or objective QoL. These results are perhaps surprising given that ASD per se may be associated with both poor objective and subjective QoL according to Barnevald and co-workers (2014). These could be related to methodological issues, as the subjective measures of QoL in this study, SF-

36 and SoC, are more focused on general well-being and physical and psychological distress and in the Barnevald study mentioned above subjective QoL was more focused on satisfaction regarding the different objective QoL aspects. Intelligence was positively associated with academic success and ASD symptom severity was negatively associated with independent living, employment and relationships (both romantic relationships and friendship.

Factors associated with different outcome trajectories were ASD symptom load at T1 (in adolescence/young adulthood) – but not T0 – and degree of lifetime comorbidity and degree of serious psychiatric comorbidity such as psychosis, alcohol dependency, OCD or bipolar disorder. Personality traits were also associated with variability in outcome trajectories.

No-longer-ASD/Optimal outcome

In study I it was shown that 22% of the males diagnosed with AS in childhood did not meet criteria for an ASD diagnosis in adult life. They all functioned within the average range on scales measuring everyday activities and objective QoL. This No-longer-ASD group could be considered to fit within the concept of optimal outcome, a term used by several researchers to describe the phenomenon of not only no longer fulfilling criteria for an ASD diagnosis at follow-up but also being fairly well-adjusted and not needing support in everyday life. Optimal outcome has received interest in the scientific community during the last few years but still there is very little that is known about why some individuals with ASD have "optimal" outcome (Fein et al., 2013; Anderson, Liang, & Lord, 2014; Orinstein et al., 2015).

This thesis has produced some clues as to why some males with AS have an optimal outcome. The positive trend had been gradual with lower ASD symptom load already at T1, *but not at T0*, paralleled with a significantly greater increase in functioning from T1 to T2 than for the other participants. This indicates that, perhaps, individuals with optimal outcome start by showing a decrease in ASD symptoms in adolescence and thereafter start to show a clear improvement in overall functioning during the time period from their late teens/early twenties to their thirties. Anecdotally several of the participants in the No-longer-ASD group described that they actively started to engage in social interaction and really tried to fit in during their late teens. They did not differ regarding intelligence, which is somewhat surprising as intelligence is usually reported to be associated with better outcome in individuals with ASD. In the study, all except one of the

participants had intelligence in the low average to superior range, perhaps, indicating that when intelligence is within this range other factors are more important. On a number of other background variables reported to be associated with better outcome, such as age at original diagnosis or early speech development, there were no significant differences between the groups.

The No-longer-ASD group clearly had better outcome than the other participants and functioned similarly to the typical Swedish male regarding most parts in life. One area that still was still a problem however was romantic relationships, with about half the group being single and three out of eleven never having had a romantic relationship and only one out of the eleven living with their partner. This indicates that even though the No-longer-ASD group had improved in most social relationships they still had some difficulties. Another area where the No-longer-ASD group did not have as much success as would have been expected was academic success. The group had a mean FSIQ of 110 (i.e. high average intelligence) and only three out of eleven (27%) had studied at university compared to 41% of the Swedish average males age 25-34 years (according to Statistics Sweden[7]). Given the high intelligence in the group and the overall positive development, one could have expected a higher degree of academic success, perhaps indicating that the No-longer-ASD group had had a good outcome but perhaps not "optimal".

The added effect of psychiatric comorbidity

In study II it was clearly shown that almost all of the participants (94%) had had at least one other comorbid psychiatric or neurodevelopmental disorder during their lifetime and 72% had met criteria for at least two other diagnoses. The most common lifetime diagnosis was DCD, which is perhaps not that surprising given that some degree of motor clumsiness is a core feature of the Gillberg and Gillberg AS diagnostic algorithm and there is evidence of high comorbidity of DCD in AS (Gillberg & Kadesjo, 2003). Depression was another major comorbid diagnosis, which has been shown to be the case in numerous studies on comorbidity in ASDs (Lugnegard et al., 2011). There were low rates of psychosis reported in study II, only two participants reported previous psychosis and none reported schizophrenia.

[7] Statistics accessed at http://www.scb.se/sv_/Hitta-statistik/Statistik-efter-amne/Utbildning-och-forskning/Befolkningens-utbildning/Befolkningens-utbildning/9568/9575/36661/

These results are in line with previous studies on adults with AS (Unenge Hallerback, Lugnegard, & Gillberg, 2012).

It was also shown that slightly more than half (54%) of the participants suffered from at least one other psychiatric disorder (including ADHD) at T2. The most common current comorbid diagnoses were depression (28%) and ADHD (28%). ADHD was the only specific comorbid diagnosis that was associated with worse general functioning.

The group with a stable ASD and current comorbidity, referred to as ASD Plus, has throughout the study (T0, T1 and T2) had substantially more comorbidity during their lifetime (an average of 3.5 comorbid diagnoses in the ASD Plus group versus 1.6 diagnoses in the No-longer-ASD group and 1.5 in the ASD Only group). The ASD Plus group did not have more difficulties in functioning (neither globally or specifically regarding work, independent living, education, friendship or romantic relationships) than the ASD Only group, but they reported lower SoC and HRQoL, indicating a higher degree of subjective suffering. The ASD Plus group also reported higher degrees of more severe psychiatric diagnoses (i.e. psychosis, OCD, bipolar disorder, alcohol dependency) than the other two groups. The results from this thesis adds some support to the notion put forth by Gillberg and Fernell (2014), that the comorbid diagnoses (the "Plusses") are at least as important to outcome in ASD as ASD "per se", at least in relation to subjective QoL.

Close to half of the ASD Plus group reported that they had not received any support from a psychiatric or habilitation clinic since the contact they had had in relation to the diagnostic assessment in childhood. There was no possibility to cross-check these rates against medical records and there might be a recollection bias regarding these numbers. We also do not know if the participants' parents had received support from a psychiatric habilitation clinic. Still, it is noteworthy that almost half of a group with clear psychiatric comorbidity did not receive current support for their mental health issues. As the two most common psychiatric disorders reported were ADHD and depression, disorders with widely available treatments and with high scientific support (i.e. central stimulants for ADHD (Bitter, Angyalosi, & Czobor, 2012) and anti-depressants (Undurraga & Baldessarini, 2012) or psychotherapy (Spielmans, Berman, & Usitalo, 2011) for depression) these are somewhat surprising results. This indicates that men with normal range IQ ASD and comorbid psychiatric disorders do not seek and/or receive enough support from the healthcare system.

Personality and outcome trajectories in ASD

In this thesis and in study IV it has been shown that personality traits differ between the three subgroups analysed: the No-longer-ASD, ASD Plus and ASD Only groups. The ASD Plus group clearly had the most distinctive personality profile, with extremely elevated Harm Avoidance (associated with being worried, fearful, shy and fatigable) and Rare Answers (associated with odd personality traits) and low scores on Self-Directedness (associated with lacking goal direction, being inert and self-striving, blaming others and having bad habits) and Cooperativeness (associated with being intolerant, disinterested, unhelpful, revengeful and self-serving). These results are very similar to other studies on adult ASD populations, with the exception of Novelty Seeking (for which scores tend to be low in ASD populations and were average in the ASD Plus group) (Soderstrom et al., 2002; Anckarsater et al., 2006; Sizoo et al., 2009; Sizoo et al., 2015).

The ASD Only group showed similar temperament patterns as previous studies have found, i.e. low Novelty Seeking (associated with being stoic, reflective, reserved and orderly) and high Harm Avoidance (associated with being worried, fearful, shy and fatigable), but clearly differed when it came to the character traits, where the mean score was average for all three traits, even though they were expected to be low. There is some evidence that indicates that having ASD and comorbidity is associated with different personality profiles than not having another comorbid disorder (Anckarsater et al., 2006; Sizoo et al., 2015). On the other hand no other study has shown average character traits in an ASD population.

The No-longer-ASD group differed from both the other groups and results from other studies regarding temperament and character with high scores regarding the pro-social trait Reward Dependence (associated with being sentimental, dependent and attached) and average scores regarding all other traits. Perhaps these results indicate that one aspect of having optimal outcome when having been diagnosed with AS in childhood is having high Reward Dependence and average regarding other traits.

The different diagnostic criteria of AS/ASD

In this thesis, three different sets of diagnostic criteria for AS/ASD have been used. All participants were diagnosed on the basis of the Gillberg and Gillberg AS criteria in childhood. The Gillberg and Gillberg criteria of AS are fairly specific and you need a distinct presentation of your autistic

symptoms to meet criteria for this diagnosis. Many of the specific criteria are also based on childhood behaviours. The specific diagnosis of the Gillberg and Gillberg AS was not very stable into adult life (44% still met all the diagnostic criteria for AS twenty years after original diagnosis). In study II, it was shown that ASD symptoms decreased over time (a result previously shown in a number of studies, e.g. (Shattuck et al., 2007)) and this fact might be the main reason more than half of the participants no longer fulfilled the Gillberg and Gillberg AS. However, many met several, but not all of the criteria of the diagnosis.

The second set of criteria used was the DSM-IV criteria of AD, AS and PDD-NOS. The overarching criteria for ASD clearly had the highest stability, with 78% still meeting criteria for ASD at T2 compared to 90% at T1. On the other hand, the specific ASD diagnosis was not stable at all with a kappa of .21, indicating that even though the general concept of DSM-IV ASD was stable, the specific diagnostic constructs were not. Other studies have shown almost an identical pattern, that up to 25% will no longer fulfil an ASD according to the DSM-IV at follow-up and the specific ASD diagnosis is very likely to change between follow-ups (Rondeau et al., 2011; Woolfenden et al., 2012).

The third set of criteria used at T2 was the DSM-5 ASD criteria. Even though a clear majority (79%) of individuals with a DSM-IV ASD also fulfilled a DSM-5 ASD there were a few individuals with clear difficulties in everyday life who would not be considered as having an ASD in the DSM-5. In a number of studies it has been shown that almost all with AD according to the DSM-IV will fall within the category of ASD according to the DSM-5, whereas AS and PDD-NOS have much lower agreement with the DSM-5 ASD category (Mattila et al., 2011; Kulage, Smaldone, & Cohn, 2014).

The results of the study indicated that in the long-term the ASD concept as a whole was stable, but the specific ASD diagnosis was not. This adds support to the rationale behind the DSM-5 definition of ASD, i.e. foregoing the specific subdiagnoses with a general ASD diagnosis. On the other hand the results also indicate that some individuals with milder ASD symptoms, but clear difficulties in everyday life no longer fit within the ASD concept as adults.

Intelligence

Throughout the studies that constitute the basis of this thesis intelligence has been assessed in relation to diagnostic stability, comorbidity, QoL, and

overall outcome. A positive association was found between intelligence and academic success and a negative association was found between intelligence and ADHD symptom severity. Diagnostic stability, overall functioning, friendship, employment and living situation were mainly associated with ASD symptom severity and were not associated with intelligence. Subjective QoL was mainly associated with psychiatric comorbidity and also was not associated with intelligence. In many other studies, intelligence has been found to be a strong predictor of outcome (Howlin et al., 2004; Anderson et al., 2014), but this relationship mainly seems to be associated with being over or under FSIQ of 70. Individuals with ASD and FSIQ over 70 generally have clearly better overall outcome than individuals with IQ below 70. The participants in this thesis have all had FSIQ over 70 and almost all had a FSIQ over 85 (i.e. in the average range) and several had FSIQ above average. Being in the superior or very superior range (i.e. FSIQ over 120) was not associated with better functioning. This might indicate that there is no added effect of having high intelligence compared to average intelligence for individuals with ASD with regard to long-term outcome, except when it comes to academic success.

Gender aspects of AS

During the 1980's and 1990's relatively few individuals with suspected AS were actually discovered and even fewer females with AS and other "normal IQ" ASDs were diagnosed during this time. Currently there are considerably more females who are diagnosed with ASD but the male:female ratio is still uneven with ratios of 2.5: to 4.5:1 (Fombonne, 2005, 2009; Kim et al., 2011). There are numerous theories as to why these differences exist, including the female camouflage effect, i.e. females are better at hiding their socio-communicative difficulties (Wing, 1981b; Gould & Ashton-Smith, 2011), that there is a diagnostic bias against females with suspected ASD (Kreiser & White, 2014), and that ASD is an extreme manifestation of the male brain (Baron-Cohen et al., 2011) which might be explained by the effect of prenatal hormone exposure on the brain (Auyeung, Lombardo, & Baron-Cohen, 2013).

According to the research literature fairly little is known about the long-term outcome into adulthood of ASD in females within the average intelligence range. There is some evidence that indicates that females have similar adult functioning as males (Baldwin & Costley, 2016; Rubenstein, Wiggins, & Lee, 2015), but with slightly better social functioning and less

repetitive behaviours (Mandy et al., 2012), that they receive their ASD diagnosis later (Lai et al., 2011) or are being undiagnosed (Kirkovski, Enticott, & Fitzgerald, 2013) and that a higher proportion of women than men report clinical mental health conditions (Baldwin et al., 2016). Even though these differences are small it does make the results of this thesis hard to generalise to a female population of AS.

Methodological discussion

This thesis has used a slightly more inductive than deductive approach, i.e. there were no clear hypotheses at the beginning of the study, except that outcome would be very varied. The specific hypotheses in this thesis have arisen organically from the observed results in the studies. This method is somewhat more speculative than a strictly deductive approach with hypothesis testing, but it gives new information that could never be examined with a purely deductive approach. The results of this thesis have to be replicated in order to make clear conclusions of the results. Worth noting is that most of the results in this thesis are in line with results from other studies, but some results such as the results regarding temperament and character are fairly unique and need to be replicated.

The statistical analyses in this thesis are all made on the same sample, meaning that there is a problem with multiple testing and a high risk of type I errors. One way of solving this would have been using some type of correction for multiple testing. After much consideration it was decided to not use corrections as that would increase the risk of type II errors. In study III we decided to use a significance level of .01 (as several other studies on objective QoL used that significance level) and in study IV we used a bootstrapping technique to somewhat address the issue. This issue does shed some doubt on the results of this thesis as there is a chance of type I errors. The descriptive results, e.g. diagnostic stability, psychiatric comorbidity and objective QoL, were not based on statistical analysis and should not be as affected by this issue.

As mentioned, this thesis has been based on prospective, longitudinal data. One area that has not been analysed prospectively is personality and the analysis regarding personality was strictly cross-sectional. This means that the direction of causation is hard to assume. It could be hypothesised that the personality traits found at T2 were present earlier in life, i.e. the temperament and character traits predicted the three outcome groups. On the other hand it could also be hypothesised that because of different outcome, i.e.

developing comorbidity or improving their socio-communicative skills, the participants have developed different traits. There is some evidence indicating that personality traits are fairly stable in adulthood (Caspi, Roberts, & Shiner, 2005), thus adding some support to the notion that personality traits partially predicted outcome.

Strengths and limitations

This thesis has some clear strengths but also some limitations. Many of the strengths of the thesis are also closely related to its limitations. The approach of the thesis was an observational prospective longitudinal study of a clinical well-defined cohort, an excellent method for learning more regarding the natural development of a condition, but the method comes with some limitations that are difficult to deal with.

One of the main strengths of this thesis is that the cohort was representative of males with AS diagnosed during the 1980's and 90's in Sweden and that the follow-up period was long. To our knowledge there have not been any studies on a well-defined clinical cohort of individuals with normal range IQ ASD or AS with a follow-up period of over 19 years. On the other hand it is important to note that the results in this thesis cannot be generalised to the total ASD population, but only individuals with an IQ over 85 (only one participant had an IQ between 70 and 85).

A major limitation of almost all prospective longitudinal studies is attrition and this has been the case in the studies in this thesis as well. Only 50 of the original 100 cases participated in the second follow-up 19 years after their original diagnosis and there were further attrition on specific tests, most notably on the TCI that was answered by 40 participants. Extensive attrition analysis has been made and in most areas (functioning, ASD symptoms, early development, comorbidity) there were no differences between participants and non-participants. The one area where there were differences was regarding intelligence. Non-participants had significantly lower PIQ at T0 and T1 and lower FSIQ at T1. As intelligence has been shown to be only associated with academic success and ADHD symptoms in this thesis, it is hard to analyse the effect of this attrition. It might indicate that the results of this thesis are less generalisable regarding individuals with a childhood diagnosis of AS and lower PIQ. It also might indicate that the numbers regarding university studies perhaps were slightly exaggerated compared to if all 100 in the selection group had participated and that the numbers regarding ADHD might have been a bit low.

A strength of the study (that some might argue is a limitation) was using a clinical assessment approach when diagnosing ASD. The clinicians making the assessments were experienced clinical psychiatrists and psychologists with extensive training and experience (including considerable research experience) in the field of ASD. The assessment was based on a combination of self-report of ASD symptoms in the ASDI interview, participants functioning during all of the stages of the assessment and the parental interview DISCO. Using a clinical diagnostic approach instead of using cut-off scores on a specific instrument does give some reliability issues, but on the other hand gives a much more valid diagnosis and mimics the results one would find in a clinical setting. The diagnosis should preferably have been confirmed by the parental interview DISCO in all cases, but unfortunately attrition regarding the DISCO was high. No longer fulfilling an ASD was confirmed in most cases (8 out of 11) with the DISCO interview.

Another major limitation of this thesis is that all participants in the study were male. The complete lack of females in this thesis is not only a problem for generalisability to all individuals with ASDs but also because it could have given important information in a highly understudied area.

Another strength of the thesis is that data regarding comorbidity have been collected from several time-points. Lifetime comorbidity was analysed by a combination of parental interview of DCD and tics in childhood at T1, self-report of depressive symptoms at T1 and T2, self-report of ADHD-symptoms at T2 and a clinical interview regarding current and previous psychiatric symptoms at T2. This approach means that there is reliable information regarding mental health at several points in the person's life and not only recollection of previous mental health issues. The assessment of psychiatric symptoms at T1 was not a complete assessment of the mental health at the time, for instance there were no diagnostic assessment of ADHD and no assessment of anxiety. This means that the scores regarding lifetime comorbidity in this thesis could be a bit on the low side. The lack of ADHD diagnosis from T0 and T1 is also a limitation because it could have given important information regarding the long-term outcome of individuals with combined AS+ADHD. There are historical reasons for this, as a combination of AS and ADHD was not allowed in the DSM-IV.

The instruments chosen in this thesis are all psychometrically sound, with good reliability and validity, and are widely used instruments in both clinical and scientific settings. However, all instruments come with their limitations and some of these limitations will be discussed here. As the study is a longitudinal study it is of importance to use the same instruments in all

follow-ups. This means that in some cases an older version of a test had to be used, most notably the BDI instead of the BDI-II and the WAIS-III instead of the WAIS-IV. The changes from BDI to BDI-II are minor and therefore should not have any major effect on the results. The changes from WAIS-III to WAIS-IV were major and also included new norms. This could be of importance as the Flynn effect (Flynn, 1987) has shown that IQ norms will become a bit lenient over time. This has also been shown to be true regarding the changes from WAIS-III to WAIS-IV (Flynn, 2009). On the other hand, the importance of using the same instruments at both follow-ups and thus being able to make reliable comparisons far outweigh the risks of norms being a bit too lenient at T2.

The two measures regarding subjective QoL, the SoC and SF-36, cover some parts of the notion of QoL, but are not a complete approach to understanding the person's full perception of the QoL. Both SoC and SF-36 measure a more general perception of QoL, but not regarding how satisfied the person is regarding specific things such as living, support and relationships. This could be one reason that there was a great difference between objective and subjective QoL in the ASD Only group, who reported average subjective QoL even though they had clear limitations regarding objective QoL. If there were more questions regarding satisfaction of different aspects of objective QoL perhaps individuals with no job and no friends in the ASD Only group might have reported lower subjective QoL. On the other hand it is possible that the ASD Only group was satisfied with their life, even though they had limited independence.

Clinical implications

There are some clear clinical implications of this thesis. First of all, it is important to note that the long-term prognosis of the specific AS diagnosis is fairly uncertain and a minority of individuals with AS will be functioning well at follow-up and no longer fulfil a diagnosis. One way of interpreting these results could be that one should be more restrictive diagnosing ASD. The results of this thesis do not give support to such an interpretation, as we only have results regarding the long-term outcome of individuals who received an AS diagnosis in childhood. In the studies in this thesis there are no data regarding what happens to individuals with ASD symptoms that do not receive an ASD diagnosis. In other studies there has been evidence indicating that individuals with undiagnosed ASD might have a higher risk of developing psychosis and that individuals who have received an ASD

diagnosis are less likely to develop psychosis (Unenge Hallerback et al., 2012). A more reasonable interpretation of the results regarding diagnostic stability in this thesis is therefor that it is important to follow-up individuals with a diagnosed ASD and average range intelligence and be aware that some adults (about as high as one out of five) might not need the diagnosis in adult life.

This thesis has shown that the changes in diagnostic criteria from the DSM-IV to the DSM-5 will affect a number of patients with normal IQ ASD. The results indicate that changing from several specific diagnoses to a general ASD concept is reasonable as the specific diagnosis was not stable. But as the new DSM-5 ASD is defined, a small, but substantial group will no longer fit within the ASD construct even though they have clear ASD symptoms, difficulties regarding general functioning and have a high degree of psychiatric comorbidity. This means that psychiatrists and psychologists will continue to treat this group for their comorbid disorders but can no longer call the group ASD even though they have clear autistic features.

The high rates of comorbidity are also an important clinical implication. Most individuals with ASD will develop several comorbid disorders in their lifetime and especially the diagnosis of ADHD had a negative relationship with outcome. A surprisingly high proportion of individuals in our study group had not received medical or psychological treatment for their comorbid psychiatric conditions, further emphasising the need for regular psychiatric evaluations of individuals with ASD.

Another salient issue is the importance of psychiatric comorbidity on subjective QoL. Treatment of the comorbid disorders of individuals with ASD will probably be important in attempts to increase the QoL of these individuals.

Personality factors have been shown to be closely related to both ASD diagnostic stability and psychiatric comorbidity in this thesis. Assessing personality factors in samples with AS might give early information if the individual is likely to have optimal outcome or psychiatric comorbidity. Prosocial traits, such as the temperament trait Reward Dependence, might be a factor that helps positive development, whereas worrying, such as Harm Avoidance, might be an indicator of comorbidity and being cautious, such as low Novelty Seeking, might somewhat mitigate the risk of developing comorbidity.

CONCLUSION

The long-term outcome of AS in males was very varied. On one end there were individuals who still met criteria of an ASD diagnosis and had high degree of ASD symptoms, who had high degree of support in everyday life and low objective QoL (i.e. employment, living, relationships) and reported low subjective (i.e. perceived) QoL while also having a high degree of psychiatric comorbidity. On the other end there were individuals who no longer met criteria of any ASD diagnosis and did not show major ASD symptoms, who functioned fairly well in society, had relatively high objective and subjective QoL, did not exhibit any psychiatric comorbidity and did not need support to function in everyday life. Most participants in the study had an outcome somewhere in between these two extremes, with difficulties in some parts of their life. No factors from childhood could predict outcome but ASD symptom severity in late adolescence/early adult life was associated with differing outcome. These results clearly indicate that it is hard to determine the long-term prognosis of a specific individual with AS when the diagnosis is made in early childhood. It also shows that regular follow-ups might be important in order to aid positive development or reverse negative development.

The specific diagnosis of AS was not particularly stable over time, but when considered as a part of the ASD construct the diagnosis was stable with almost four in five meeting full criteria of an ASD 19 years after their original AS diagnosis. The best predictor of a stable ASD at mean age 30 years was having high load of ASD symptoms at mean age 20 years. However, the degree of ASD symptoms at mean age 11 years did not predict diagnostic stability. Not fulfilling an ASD was associated with better general functioning. The changes from DSM-IV to DSM-5 meant that some individuals with ASD and lower degree of ASD symptoms no longer met criteria of an ASD according to the DSM-5 even though they had clear difficulties in everyday life. These results indicate that it is important to allow for re-evaluations of the diagnosis at the individuals request. The results also suggest that even though the DSM-5 concept of a single ASD diagnosis is more relevant than specific sub-diagnoses, the criteria will exclude some adults that need support and have previously been considered as ASD (Study I).

Most individuals (94%) with AS diagnosed in childhood fulfilled criteria for at least one other psychiatric or neurodevelopmental disorder during

their lifetime and more than half met criteria of at least one other psychiatric disorder (most commonly depression or ADHD) at 30 years. ADHD was the only specific comorbid diagnosis that was associated with worse general functioning. These results stress the importance of making assessments of comorbid conditions and to offer treatment for these conditions as they clearly affect the individuals QoL. Specifically, the diagnosis of ADHD is important to assess and treat to aid positive development in individuals with AS. (Study II).

Overall functioning and objective QoL (independent living, employment, friendship) were related to the stability of the ASD diagnosis: with individuals who no longer met criteria of an ASD diagnosis clearly functioning better regarding these measures than those with a stable ASD. Subjective QoL on the other hand was not related to ASD diagnostic stability or objective QoL, but had a clear association with current comorbidity. Individuals with ASD and comorbidity had both low objective and subjective QoL, while individuals with a stable ASD diagnosis and no comorbidity had low objective QoL but reported average subjective QoL. Academic success was positively associated with intelligence and employment, relationships and independent living were negatively associated with ASD symptom severity. What these results indicate is that ASD severity is associated with poorer outcome in many facets of life, but academic success is related more to one's intelligence. It also indicates that how one feels about one's life is mainly associated with comorbidity (Study III).

Temperament traits were associated with both ASD diagnostic stability and current psychiatric comorbidity and add another important piece to understanding the outcome of AS. Being sentimental, attached and dependent on others was associated with not fulfilling an ASD (High Reward Dependence). Worrying, being fearful, shy and fatigable was strongly associated with comorbidity (High Harm Avoidance) as were negative character features. Being stoic, reflective, reserved and orderly (low Novelty Seeking) and being somewhat worrying, shy and fatigable (slightly elevated Harm Avoidance) was associated with having a stable ASD and no current comorbidity. These results give support that temperament features are related to outcome, that perhaps prosocial temperament traits aids development and being cautious somewhat protects from developing comorbidity (Study IV).

Future perspectives for research

The results in this study further emphasises the importance of longitudinal studies with long follow-up periods. There was an increase in individuals no longer fulfilling an ASD and a general decrease in ASD symptoms over time. It would be interesting to learn if this trend continues over time and if even more individuals move off the autistic spectrum or if ASD traits become more stable or even worsen after 30 years of age. Furthermore, it would be useful to examine the stability of optimal outcome over time, i.e. if some with optimal outcome will move back into an ASD diagnosis if life becomes more demanding. One of the participants who had been assessed to not fit within any ASD diagnosis at T1 moved back into ASD at T2. This indicates that there might be some in the No-longer-ASD group that will move back into an ASD diagnosis at an older age.

This thesis has shown that temperament and character dimensions are related to ASD diagnostic stability and psychiatric comorbidity. All of the analyses regarding the TCI have been cross-sectional though and therefore it is hard to assess causality. It would be of great interest to see if temperament and character scores have predictive capabilities regarding outcome in ASD populations, e.g. using TCI at a younger age and then follow the participants longitudinally.

Another important area that needs to be examined further is the long-term outcome in females with ASD and average-range intelligence as this is an area that is extremely underexplored.

ACKNOWLEDGEMENTS

I would like to thank all the participants in this study for taking the time in participating and sharing their stories.

Eva Billstedt, my fantastic main supervisor. I would not have been able to complete this journey without you. Thank you for all our talks, for your support and encouragement and for all your advice. Thank you for pushing me when I needed it and giving me calming support when I needed it. Thank you for all your support in the data collection process. Living on the other side of the country when collecting data in Gothenburg has been incredibly difficult and without you helping me where I needed help, I probably would not have been able to do it. You have become such an important person in my life. Thank you for believing in me.

Christopher Gillberg, my co-supervisor. Thank you for all your insights in the field and for all your support in the writing process. I have learned so much from you. Thank you for believing in me and allowing me to be one of the first new PhD students when the Gillberg Neuropsychiatry Centre started.

Carina Gillberg, my partner throughout the data collection phase and co-author on all my papers. Thank you for a great working relationship and thank you for the many great talks through the years and for all your insights in the field.

Märta Wallinius, my closest and dearest friend. Thank you for all your support in helping me reaching this goal, all the way from first giving me the idea, to getting me an interview with Eva and Christopher, to pushing and supporting me through our many talks through the years, to finally being my collaborator on my final manuscript. Words cannot even begin to express how I feel.

Thank you to all my colleagues at the Gillberg Neuropsychiatry Centre. **Anna Spyrou**, and **Ingrid Vinsa**, thank you for all your help and support, and thank you **Elisabeth Wentz** for always making me feel at home when I come to Gothenburg. **Ida Lindblad**, **Sebastian Lundström**, **Gunilla**

Westman Andersson, **Nanna Gillberg**, **Jakob Åsberg Johnels** and so many more, thank you for great talks and inspiration through the years.
Mats Cederlund and Bibbi Hagberg. My thesis would not be what it is today without your work in the first follow-up on the participants in this study. Thank you.

Thank you to all my colleagues at the Centre for Research and Development in Gävleborg for support and for giving me a home during my PhD research. A special thanks to **Lennart Fredriksson** for your support and for many interesting talks regarding the nature of science and to **Per Liv** for helping me with my statistical questions.

Thank you to my former bosses **Marieann Högman** (at the Centre for Research and Development in Gävleborg) and **Pia Holmqvist** (at the Child and Adolescent Habilitation Clinic in Gävle) for believing in me and giving me the economic support needed to become a PhD student. Thank you to my current boss **Björn Augustsson** (at the Child and Adolescent Psychiatric Clinic in Gävle) for your support.

Olle and **Ronja**, my darling children, my memories of this thesis will always be linked to my first memories of you two. I love you both so much.

Finally, thank you to the love of my life, **Nadja**. Jag kan aldrig förklara hur mycket du betyder för mig. Den här resan har varit tuff för oss båda och jag skulle aldrig ha klarat det utan ditt stöd. Att skaffa två barn och kämpa på i en stad långt borta från våra nära och kära har varit utmanande, men också underbart. Jag älskar dig.

This thesis was financially supported by: grants to the author from the Centre for Research and Development in Region Gavleborg, Wilhelm and Martina Lundgren Foundation, the Jerring Fund, the Foundation for the sisters Greta Johansson and Brita Andersson's memory fund, the Swedish Child Neuropsychiatry Science Foundation, Petter Silfverskiold Foundation, and the Golje Foundation and also by economic support from the Child and Adolescent Habilitation Clinic in Gavle and the Gillberg Neuropsychiatry Centre. Grants from VG Region Scientific Fund (EB) and Annmarie and Per Ahlqvist's Foundation (CG) also supported this thesis financially.

REFERENCES

Anckarsater, H., Stahlberg, O., Larson, T., Hakansson, C., Jutblad, S. B., Niklasson, L., et al. (2006). The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *American Journal of Psychiatry, 163*(7), 1239-1244.

Anderson, D. K., Liang, J. W., & Lord, C. (2014). Predicting young adult outcome among more and less cognitively able individuals with autism spectrum disorders. *Journal of Child Psychology and Psychiatry, 55*(5), 485-494.

Antonovsky, A. (1979). *Health, Stress and Coping*. San Fransisco, CA: Jossey-Bass.

APA/American Psyciatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV* (4th ed.). Washington, DC: American Psychiatric Association.

APA/American Psyciatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders : DSM-5*. Arlington, Va.: American Psychiatric Association.

Asperger, H. (1944). Die autistischen Psychopathen im Kindesalter. *Archiv fur Psychiatrie und Nervenkrankheiten, 117*, 76-136.

Auyeung, B., Lombardo, M. V., & Baron-Cohen, S. (2013). Prenatal and postnatal hormone effects on the human brain and cognition. *Pflugers Archiv (European Journal of Physiology), 465*(5), 557-571.

Baldwin, S., & Costley, D. (2016). The experiences and needs of female adults with high-functioning autism spectrum disorder. *Autism, 20*(4), 483-495.

Barneveld, P. S., Swaab, H., Fagel, S., van Engeland, H., & de Sonneville, L. M. (2014). Quality of life: a case-controlled long-term follow-up study, comparing young high-functioning adults with autism spectrum disorders with adults with other psychiatric disorders diagnosed in childhood. *Comprehensive Psychiatry, 55*(2), 302-310.

Baron-Cohen, S., Lombardo, M. V., Auyeung, B., Ashwin, E., Chakrabarti, B., & Knickmeyer, R. (2011). Why are autism spectrum conditions more prevalent in males? *PLoS Biology, 9*(6), e1001081.

Baron-Cohen, S., Scott, F. J., Allison, C., Williams, J., Bolton, P., Matthews, F. E., et al. (2009). Prevalence of autism-spectrum conditions: UK school-based population study. *British Journal of Psychiatry, 194*(6), 500-509.

Beck, A., & Steer, R. (1996). *Beck Depression Inventory Manual - Swedish version*. Fagernes, Norway: Psykologiforlaget.

Billstedt, E., Gillberg, I. C., & Gillberg, C. (2005). Autism after adolescence: population-based 13- to 22-year follow-up study of 120 individuals with autism diagnosed in childhood. *Journal of Autism and Developmental Disorders, 35*(3), 351-360.

Bitter, I., Angyalosi, A., & Czobor, P. (2012). Pharmacological treatment of adult ADHD. *Current Opinion in Psychiatry, 25*(6), 529-534.

Bowman, B. J. (1996). Cross-cultural validation of Antonovsky's Sense Of Coherence Scale. *Journal of Clinical Psychology, 52*(5), 547-549.

Brändström, S., Sigvardsson, S., Nylander, P.-O., & Richter, J. (2008). The Swedish Version of the Temperament and Character Inventory (TCI). *European Journal of Psychological Assessment, 24*(1), 14-21.

Buck, T. R., Viskochil, J., Farley, M., Coon, H., McMahon, W. M., Morgan, J., et al. (2014). Psychiatric comorbidity and medication use in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 44*(12), 3063-3071.

Capanna, C., Struglia, F., Riccardi, I., Daneluzzo, E., Stratta, P., & Rossi, A. (2012). Temperament and Character Inventory-R (TCI-R) and Big Five Questionnaire (BFQ): convergence and divergence. *Psychological Reports, 110*(3), 1002-1006.

Caspi, A., Roberts, B. W., & Shiner, R. L. (2005). Personality development: stability and change. *Annual Review of Psychology, 56*, 453-484.

CDC/Centers for Disease Control and Prevention. (2014). Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *Morbidity and mortality weekly report. Surveillance summaries (Washington, D.C. : 2002), 63*(2), 1-21.

Cederlund, M. (2007). *Boys with Asperger syndrome grown up : a longitudinal follow-up study of 100 cases more than 5 years after original diagosis.* Institute of Neuroscience and Physiology, Child and Adolescent Psychiatry, Göteborg University, Göteborg.

Cederlund, M., & Gillberg, C. (2004). One hundred males with Asperger syndrome: a clinical study of background and associated factors. *Developmental Medicine and Child Neurology, 46*(10), 652-660.

Cederlund, M., Hagberg, B., Billstedt, E., Gillberg, I. C., & Gillberg, C. (2008). Asperger syndrome and autism: a comparative longitudinal follow-up study more than 5 years after original diagnosis. *Journal of Autism and Developmental Disorders, 38*(1), 72-85.

Cederlund, M., Hagberg, B., & Gillberg, C. (2010). Asperger syndrome in adolescent and young adult males. Interview, self- and parent assessment of social, emotional, and cognitive problems. *Research in Developmental Disabilities, 31*(2), 287-298.

Cloninger, C. R. (1994). Temperament and personality. *Current Opinion in Neurobiology, 4*(2), 266-273.

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry, 50*(12), 975-990.

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (2006). Can personality assessment predict future depression? A twelve-month follow-up of 631 subjects. *Journal of Affective Disorders, 92*(1), 35-44.

Costa, P. T., & McCrae, R. R. (1985). *The NEO personality inventory: manual, form S and form R.* . Odessa: Psychological assessment resources.

Dardas, L. A., & Ahmad, M. M. (2014). Quality of life among parents of children with autistic disorder: a sample from the Arab world. *Research in Developmental Disabilities, 35*(2), 278-287.

Eaves, L. C., & Ho, H. H. (2008). Young adult outcome of autism spectrum disorders. *Journal of Autism and Developmental Disorders, 38*(4), 739-747.

Eaves, L. C., Ho, H. H., & Eaves, D. M. (1994). Subtypes of autism by cluster analysis. *Journal of Autism and Developmental Disorders, 24*(1), 3-22.

Ehlers, S., Gillberg, C., & Wing, L. (1999). A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. *Journal of Autism and Developmental Disorders, 29*(2), 129-141.

Eklund, M., Hansson, L., & Bengtsson-Tops, A. (2004). The influence of temperament and character on functioning and aspects of psychological health among people with schizophrenia. *European Psychiatry, 19*(1), 34-41.

Engstrom, I., Ekstrom, L., & Emilsson, B. (2003). Psychosocial functioning in a group of Swedish adults with Asperger syndrome or high-functioning autism. *Autism, 7*(1), 99-110.

Eriksson, M., & Lindström, B. (2007). Antonovsky's sense of coherence scale and its relation with quality of life: a systematic review. *Journal of Epidemiology and Community Health, 61*(11), 938-944.

Fein, D., Barton, M., Eigsti, I. M., Kelley, E., Naigles, L., Schultz, R. T., et al. (2013). Optimal outcome in individuals with a history of autism. *Journal of Child Psychology and Psychiatry, 54*(2), 195-205.

Flynn, J. R. (1987). Massive IQ gains in 14 nations: What IQ tests really measure. *Psychological Bulletin, 101*(2), 171-191.

Flynn, J. R. (2009). The WAIS-III and WAIS-IV: Daubert motions favor the certainly false over the approximately true. *Applied Neuropsychology, 16*(2), 98-104.

Fombonne, E. (2005). Epidemiology of autistic disorder and other pervasive developmental disorders. *Journal of Clinical Psychiatry, 66 Suppl 10*, 3-8.

Fombonne, E. (2009). Epidemiology of Pervasive Developmental Disorders. *Pediatric Research, 65*(6), 591-598.

Ghaziuddin, M., Weidmer-Mikhail, E., & Ghaziuddin, N. (1998). Comorbidity of Asperger syndrome: a preliminary report. *Journal of Intellectual Disability Research, 42 (Pt 4)*, 279-283.

Gillberg, C., & Cederlund, M. (2005). Asperger syndrome: familial and pre- and perinatal factors. *Journal of Autism and Developmental Disorders, 35*(2), 159-166.

Gillberg, C., & Fernell, E. (2014). Autism plus versus autism pure. *Journal of Autism and Developmental Disorders, 44*(12), 3274-3276.

Gillberg, C., Gillberg, I. C., Rastam, M., & Wentz, E. (2001). The Asperger Syndrome (and high-functioning autism) Diagnostic Interview (ASDI): a preliminary study of a new structured clinical interview. *Autism, 5*(1), 57-66.

Gillberg, C., & Kadesjo, B. (2003). Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). *Neural Plasticity, 10*(1-2), 59-68.

Gillberg, C., & Steffenburg, S. (1987). Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. *Journal of Autism and Developmental Disorders, 17*(2), 273-287.

Gillberg, I. C., & Gillberg, C. (1989). Asperger syndrome--some epidemiological considerations: a research note. *Journal of Child Psychology and Psychiatry, 30*(4), 631-638.

Gillespie-Lynch, K., Sepeta, L., Wang, Y., Marshall, S., Gomez, L., Sigman, M., et al. (2012). Early childhood predictors of the social competence of adults with autism. *Journal of Autism and Developmental Disorders, 42*(2), 161-174.

Gould, J., & Ashton-Smith, J. (2011). Missed diagnosis or misdiagnosis? Girls and women on the autism spectrum. *Good Autism Practice (GAP), 12*(1), 34-41.

Hagberg, B. S., Nyden, A., Cederlund, M., & Gillberg, C. (2013). Asperger syndrome and "non-verbal learning problems" in a longitudinal perspective: neuropsychological and social adaptive outcome in early adult life. *Psychiatry Research, 210*(2), 553-558.

Haukoos, J. S., & Lewis, R. J. (2005). Advanced Statistics: Bootstrapping Confidence Intervals for Statistics with "Difficult" Distributions. *Academic Emergency Medicine, 12*(4), 360-365.

Helt, M., Kelley, E., Kinsbourne, M., Pandey, J., Boorstein, H., Herbert, M., et al. (2008). Can children with autism recover? If so, how? *Neuropsychology Review, 18*(4), 339-366.

Howlin, P., Goode, S., Hutton, J., & Rutter, M. (2004). Adult outcome for children with autism. *Journal of Child Psychology and Psychiatry, 45*(2), 212-229.

Howlin, P., & Moss, P. (2012). Adults with autism spectrum disorders. *Canadian Journal of Psychiatry, 57*(5), 275-283.

Howlin, P., Moss, P., Savage, S., & Rutter, M. (2013). Social outcomes in mid- to later adulthood among individuals diagnosed with autism and average nonverbal IQ as children. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(6), 572-581.

Howlin, P., Savage, S., Moss, P., Tempier, A., & Rutter, M. (2014). Cognitive and language skills in adults with autism: a 40-year follow-up. *Journal of Child Psychology and Psychiatry, 55*(1), 49-58.

Josefsson, K., Cloninger, C. R., Hintsanen, M., Jokela, M., Pulkki-Raback, L., & Keltikangas-Jarvinen, L. (2011). Associations of personality profiles with various aspects of well-being: a population-based study. *Journal of Affective Disorders, 133*(1-2), 265-273.

Kadesjo, B., Gillberg, C., & Hagberg, B. (1999). Brief report: autism and Asperger syndrome in seven-year-old children: a total population study. *Journal of Autism and Developmental Disorders, 29*(4), 327-331.

Kamp-Becker, I., Schroder, J., Remschmidt, H., & Bachmann, C. J. (2010). Health-related quality of life in adolescents and young adults with high functioning autism-spectrum disorder. *GMS Psycho-Social-Medicine, 7*.

Kessler, R. C., Adler, L. A., Gruber, M. J., Sarawate, C. A., Spencer, T., & Van Brunt, D. L. (2007). Validity of the World Health Organization Adult ADHD Self-Report Scale (ASRS) Screener in a representative sample of health plan members. *International Journal of Methods in Psychiatric Research, 16*(2), 52-65.

Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., Lim, E. C., et al. (2011). Prevalence of autism spectrum disorders in a total population sample. *American Journal of Psychiatry, 168*(9), 904-912.

Kirkovski, M., Enticott, P. G., & Fitzgerald, P. B. (2013). A review of the role of female gender in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 43*(11), 2584-2603.

Kocovska, E., Billstedt, E., Ellefsen, A., Kampmann, H., Gillberg, I. C., Biskupsto, R., et al. (2013). Autism in the Faroe Islands: diagnostic stability from childhood to early adult life. *TheScientificWorldJournal, 2013*, 592371.

Kreiser, N. L., & White, S. W. (2014). ASD in females: are we overstating the gender difference in diagnosis? *Clinical Child and Family Psychology Review, 17*(1), 67-84.

Krug, D. A., Arick, J., & Almond, P. (1980). Behavior checklist for identifying severely handicapped individuals with high levels of autistic behavior. *Journal of Child Psychology and Psychiatry, 21*(3), 221-229.

Kulage, K. M., Smaldone, A. M., & Cohn, E. G. (2014). How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *Journal of Autism and Developmental Disorders, 44*(8), 1918-1932.

Lai, M. C., Lombardo, M. V., Pasco, G., Ruigrok, A. N., Wheelwright, S. J., Sadek, S. A., et al. (2011). A behavioral comparison of male and female adults with high functioning autism spectrum conditions. *PLoS One, 6*(6), e20835.

Larsen, F. W., & Mouridsen, S. E. (1997). The outcome in children with childhood autism and Asperger syndrome originally diagnosed as psychotic. A 30-year follow-up study of subjects hospitalized as children. *European Child & Adolescent Psychiatry, 6*(4), 181-190.

Leekam, S. R., Libby, S., Wing, L., Gould, J., & Gillberg, C. (2000). Comparison of ICD-10 and Gillberg's Criteria for Asperger Syndrome. *Autism, 4*(1), 11-28.

Leekam, S. R., Libby, S. J., 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. *Journal of Child Psychology and Psychiatry, 43*(3), 327-342.

Lotter, V. (1974). Factors related to outcome in autistic children. *Journal of Autism and Childhood Schizophrenia, 4*(3), 263-277.

Lugnegard, T., Unenge Hallerback, M., & Gillberg, C. (2011). Psychiatric comorbidity in young adults with a clinical diagnosis of Asperger syndrome. *Research in Developmental Disabilities, 32*(5), 1910-1917.

Mandy, W., Chilvers, R., Chowdhury, U., Salter, G., Seigal, A., & Skuse, D. (2012). Sex differences in autism spectrum disorder: evidence from a large sample of children and adolescents. *Journal of Autism and Developmental Disorders, 42*(7), 1304-1313.

Marciano, A. R., & Scheuer, C. I. (2005). Quality of Life in siblings of autistic patients. *Revista Brasileira de Psiquiatri, 27*(1), 67-69.

Mattila, M. L., Hurtig, T., Haapsamo, H., Jussila, K., Kuusikko-Gauffin, S., Kielinen, M., et al. (2010). Comorbid psychiatric disorders associated with Asperger syndrome/high-functioning autism: a community- and clinic-based study. *Journal of Autism and Developmental Disorders, 40*(9), 1080-1093.

Mattila, M. L., Kielinen, M., Jussila, K., Linna, S. L., Bloigu, R., Ebeling, H., et al. (2007). An epidemiological and diagnostic study of Asperger syndrome according to four sets of diagnostic criteria. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(5), 636-646.

Mattila, M. L., Kielinen, M., Linna, S. L., Jussila, K., Ebeling, H., Bloigu, R., et al. (2011). Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(6), 583-592 e511.

Mayes, S. D., Calhoun, S. L., & Crites, D. L. (2001). Does DSM-IV Asperger's disorder exist? *Journal of Abnormal Child Psychology, 29*(3), 263-271.

Mazzone, L., Ruta, L., & Reale, L. (2012). Psychiatric comorbidities in asperger syndrome and high functioning autism: diagnostic challenges. *Annals of General Psychiatry, 11*(1), 16.

Orinstein, A., Tyson, K. E., Suh, J., Troyb, E., Helt, M., Rosenthal, M., et al. (2015). Psychiatric Symptoms in Youth with a History of Autism and Optimal Outcome. *Journal of Autism and Developmental Disorders, 45*(11), 3703-3714.

Pisula, E., & Kossakowska, Z. (2010). Sense of coherence and coping with stress among mothers and fathers of children with autism. *Journal of Autism and Developmental Disorders, 40*(12), 1485-1494.

Roberts, B. W., Walton, K. E., & Viechtbauer, W. (2006). Patterns of mean-level change in personality traits across the life course: a meta-analysis of longitudinal studies. *Psychological Bulletin, 132*(1), 1-25.

Rondeau, E., Klein, L. S., Masse, A., Bodeau, N., Cohen, D., & Guile, J. M. (2011). Is pervasive developmental disorder not otherwise specified less stable than autistic disorder? A meta-analysis. *Journal of Autism and Developmental Disorders, 41*(9), 1267-1276.

Rubenstein, E., Wiggins, L. D., & Lee, L. C. (2015). A Review of the Differences in Developmental, Psychiatric, and Medical Endophenotypes Between Males and Females with Autism Spectrum Disorder. *Journal of Developmental and Physical Disabilities, 27*(1), 119-139.

Saldana, D., Alvarez, R. M., Lobaton, S., Lopez, A. M., Moreno, M., & Rojano, M. (2009). Objective and subjective quality of life in adults with autism spectrum disorders in southern Spain. *Autism, 13*(3), 303-316.

Schwartz, C. B., Henderson, H. A., Inge, A. P., Zahka, N. E., Coman, D. C., Kojkowski, N. M., et al. (2009). Temperament as a predictor of symptomotology and adaptive functioning in adolescents with high-functioning autism. *Journal of Autism and Developmental Disorders, 39*(6), 842-855.

Shattuck, P. T., Seltzer, M. M., Greenberg, J. S., Orsmond, G. I., Bolt, D., Kring, S., et al. (2007). Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. *Journal of Autism and Developmental Disorders, 37*(9), 1735-1747.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59 Suppl 20*, 22-33;quiz 34-57.

Shu, B. C. (2009). Quality of life of family caregivers of children with autism: The mother's perspective. *Autism, 13*(1), 81-91.

Sizoo, B. B., van den Brink, W., Gorissen van Eenige, M., & van der Gaag, R. J. (2009). Personality characteristics of adults with autism spectrum disorders or attention deficit hyperactivity disorder with and without substance use disorders. *Journal of Nervous and Mental Disease, 197*(6), 450-454.

Sizoo, B. B., van der Gaag, R. J., & van den Brink, W. (2015). Temperament and character as endophenotype in adults with autism spectrum disorders or attention deficit/hyperactivity disorder. *Autism, 19*(4), 400-408.

Skokauskas, N., & Gallagher, L. (2010). Psychosis, affective disorders and anxiety in autistic spectrum disorder: prevalence and nosological considerations. *Psychopathology, 43*(1), 8-16.

Soderstrom, H., Rastam, M., & Gillberg, C. (2002). Temperament and character in adults with Asperger syndrome. *Autism, 6*(3), 287-297.

Spielmans, G. I., Berman, M. I., & Usitalo, A. N. (2011). Psychotherapy versus second-generation antidepressants in the treatment of depression: a meta-analysis. *Journal of Nervous and Mental Disease, 199*(3), 142-149.

Sullivan, M., Karlsson, J., Taft, C., & Ware, J. E. (2002). *SF-36 Health Qustionnaire (Swedish manual and Interpretation Guide, 2nd edition)*. Gothenburg: Sahlgrenska University Hospital.

Szatmari, P., Bartolucci, G., Bremner, R., Bond, S., & Rich, S. (1989). A follow-up study of high-functioning autistic children. *Journal of Autism and Developmental Disorders, 19*(2), 213-225.

Undurraga, J., & Baldessarini, R. J. (2012). Randomized, placebo-controlled trials of antidepressants for acute major depression: thirty-year meta-analytic review. *Neuropsychopharmacology, 37*(4), 851-864.

Unenge Hallerback, M., Lugnegard, T., & Gillberg, C. (2012). Is autism spectrum disorder common in schizophrenia? *Psychiatry Research, 198*(1), 12-17.

van Heijst, B. F., & Geurts, H. M. (2015). Quality of life in autism across the lifespan: A meta-analysis. *Autism, 19*(2), 158-167.

Wechsler, D. (1974). *Manual for Wechsler Intelligence Scale for Children - Revised*. San Antonio, TX: Psychological Corp.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children - Third edition*. San Antonio, TX: Psychologiscal Corp.

Wechsler, D. (2002). *WAIS-III, Wechsler Adult Intelligence Scale, Third Edition: Technical Manual*. San Antonio, TX: Psychological Corporation.

WHO/World Health Organization. (1992). *International statistical classification of diseases and related health problems : ICD-10*. Geneva: World Health Organization.

WHO/World Health Organization. (2015). *ICD-11 Beta Draft*. Retrieved 27th of November, 2015, from www.who.int/classifications/icd11

Wing, L. (1981a). Asperger's syndrome: a clinical account. *Psychological Medicine, 11*(1), 115-129.

Wing, L. (1981b). Sex ratios in early childhood autism and related conditions. *Psychiatry Research, 5*(2), 129-137.

Wing, L. (1997). The autistic spectrum. *Lancet, 350*(9093), 1761-1766.

Woolfenden, S., Sarkozy, V., Ridley, G., & Williams, K. (2012). A systematic review of the diagnostic stability of Autism Spectrum Disorder. *Research in Autism Spectrum Disorders, 6*(1), 345-354.