AUTISM SPECTRUM DISORDERS – FIRST INDICATORS AND SCHOOL AGE OUTCOME

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ABSTRACT

Background: Studies of early indicators, diagnostic stability and outcome at mid-school age in children referred early in life for a suspected autism spectrum disorder (ASD) have been few. ▸ Aims: To examine early indicators of ASD and eight-year stability of ASD diagnoses, comorbidity, cognitive levels and overall clinical profiles, in children diagnosed with ASD in preschool age after receiving early intervention. ▸ Methods: A community-based cohort of 208 preschool children with ASD were followed prospectively. Records from Child Healthcare Centers were reviewed regarding regulatory problems (RP) during infancy. When the children were about 11 years, parents of 128 of the children participated in the Autism-Tics, AD/HD and other Comorbidities (A-TAC) Telephone Interview. A subgroup of 50 children with ASD who had had borderline intellectual functioning (BIF) – were targeted for a new cognitive test. Another subgroup of 17 children who had "grown out of autism" (i.e. had no longer met diagnostic criteria for ASD at a previous follow-up) were separately targeted for follow-up. Parental telephone interviews in these subgroups also included the Vineland Adaptive Behavior Scales and a semi-structured interview regarding the child's daily functioning. ▸ Results: Early RP had been significantly more common in children later diagnosed with ASD. Approximately 90% of children with an early diagnosis of ASD still met criteria for ASD at mid-school age. A similar rate also had combinations of other developmental/neuropsychiatric disorders; attention problems, speech-/language difficulties and/or learning problems. Co-occurring disorders were particularly prevalent in children with ASD and intellectual disability. Half of the children in the group still met criteria for BIF, 20% had mild ID (intellectual disorder), while 30% had cognitive results in the average IQ range. The vast majority of the children who had "grown out of autism" still had major problems at follow-up, and some of them had indications of again meeting full criteria for a diagnosis of ASD. ▸ Conclusion: Early RP should be considered a possible marker for ASD. Almost all children with a preschool diagnosis of ASD had remaining neurodevelopmental problems eight years later, findings that support the concepts of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) and Autism Plus. The results underscore the need for follow-up assessments, educational adaptations and longer-term parental support targeted to this patient group.

Keywords: Autism spectrum disorder, autistic traits, neurodevelopmental disorders, attention-deficit/hyperactivity disorder, language impairment, regulatory problems, A-TAC, adaptive behavior, borderline intellectual functioning, intellectual disability, outcome, ESSENCE, Autism Plus.

SAMMANFATTNING PÅ SVENSKA

Syftet med avhandlingen var att över tid, upp till 9-13 års ålder, följa en populationsbaserad grupp barn som i förskoleåldern fått diagnos inom autismspektrum (Autism Spectrum Disorder, ASD). Barnen erhöll tidiga insatser under en tvåårsperiod från ett habiliteringscenter i Stockholm, specialiserat på autism hos förskolebarn. I den totala gruppen ingick initialt 208 barn. Gruppen var representativ för små barn i länet, som utretts och fått diagnos ASD mellan 2 och 4,5 års ålder.

I den första studien undersöktes så kallade regleringssvårigheter (problem med ätande, sömn och skrikighet) från barnens två första levnadsår. Kompletta BVC-journaler fanns för 190 av barnen. Dessa granskades och svårigheter med ätande, sömn samt skrikighet hos barnen kartlades utifrån sköterskans anteckningar och jämfördes med en grupp barn av samma ålder, kön och från samma geografiska områden. Det visade sig vara signifikant skillnad mellan grupperna avseende antalet gånger föräldrar sökt för regleringssvårigheter hos barnen. I studiegruppen hade föräldrar till 44% av barnen sökt minst två gånger för något problem med mat, sömn eller skrikighet medan endast 16% i jämförelsegruppen gjort det. Även om tidiga regleringssvårigheter således inte alls behöver innebära autism, bedöms det viktigt att uppmärksamma dessa problem på BVC för att stötta familjerna och följa barnens utveckling, då sådana problem *kan* vara en indikator för senare utvecklingsavvikelse.

I den andra studien erbjöds föräldrarna till samtliga 198 barn som deltagit i den första uppföljningen, två år efter inskrivning på centret, att delta i en andra uppföljning. Denna bestod av en telefonintervju enligt A-TAC (Autism-Tics, AD/HD and other Comorbidities) när barnen var 9-13 år. Intervjun utfördes av utbildade lekmän/intervjuare. Intervjun fångar, utöver ovan nämnda diagnoser, även problem med motorik, inlärning och beteende. Föräldrar till 128 barn av 198 tillfrågade (65%) deltog och barnen delades upp i tre grupper efter kognitiv nivå enligt resultat från tvåårsuppföljningen; 34 barn med genomsnittlig begåvning (Average Intellectual Function) (AIF), 36 med ”svagbegåvning” (Borderline Intellectual Function) (BIF) och 58 med intellektuell funk-

tionsnedsättning/utvecklingsstörning (Intellectual Disability) (ID). Utifrån intervjuresultaten hade 71% av de genomsnittligt begåvade A-TAC-poäng motsvarande klinisk ASD, liksom 89% av de svagbegåvade barnen och 95% av barnen med intellektuell funktionsnedsättning. De sistnämnda hade också högst grad av samsjuklighet i andra funktionsnedsättningar. Studien visade sammantaget att en stor majoritet av barn som fått autismspektrumdiagnos i förskoleåldern åtta år senare hade tecken på kvarstående diagnos inom autismspektrum och också andra utvecklingsneurologiska svårigheter, i enlighet med begreppet ”Autism Plus”, även när som här alla ingående barn fått ta del av vad som bedömts vara adekvata tidiga insatser.

I den tredje studien erbjöds de barn som vid den första uppföljningen, före skolstart, uppvisade begåvningsnivå mellan IK 70 och 84, förnyad kognitiv testning i 9-13 års åldern. Denna grupp barn benämns ofta ”högfungerande” (trots att begåvningsnivån är relativt låg) och man talar allmänt om ”högfungerande autism” eller HFA. Cirka 20% hade då, enligt testerna, sjunkit till en nivå motsvarande lindrig intellektuell funktionsnedsättning (IK<70), medan 30% hade höjt sin nivå till genomsnittlig (IK>84) och övriga uppvisade samma nivå som tidigare. Utöver A-TAC intervjun (se studie II) gjordes även Vineland Adaptive Behavior Scales (VABS-II) intervju med föräldrar på telefon, liksom en halvstrukturerad intervju rörande barnens vardagliga fungerande i hem och skola. Intervjuerna visade att barnen på gruppnivå sjunkit signifikant i sitt adaptiva fungerande, jämfört med jämnåriga, och att flertalet utöver autismspektrumproblematik även hade svårigheter med bland annat uppmärksamhet och aktivitetsreglering, med tal- och språk och utagerande beteenden. En majoritet hade otillräckliga stödinsatser i skolan, enligt föräldrarna. Studien visar på behovet att följa upp begåvningsnivån särskilt för barn med svag teoretisk begåvning.

Den fjärde studien fokuserade på den grupp barn från ursprungskohorten, som vid den första uppföljningen inför skolstart inte helt uppfyllde kriterier för autismspektrumtillstånd, och som inte hade intellektuell funktionsnedsättning (totalt 17 barn). Denna barngrupp uppgavs inte sällan i den tidiga autismforskningen vara ”botade” eller beskrevs som om ”autismen vuxit bort”. Föräldrar till 16 av de 17 barnen kunde nås för telefonintervju rörande barnens adaptiva

funktionsnivå (VABS-II), där en majoritet av barnen sjunkit, samt en halvstrukturerad intervju rörande vardagligt fungerande hos barnet (se även studie III). Föräldrar till 14 barn deltog i A-TAC intervju (se studie II och III). Sammantaget kunde konstateras att flertalet barn hade svårigheter med uppmärksamhet/aktivitetsreglering, tal- och språk, socialt samspel och utagerande beteende. Av de 17 barnen hade 3 (21%) åter en symtomnivå avseende ASD som motsvarade en klinisk diagnos och 4 barn (29%) hade symtomnivåer i A-TAC motsvarande klinisk diagnos av ASD, AD/HD eller både och. Ytterligare 50% uppnådde gränsvärden för dessa diagnoser. Studien visar att även barn som, under uppväxten inte längre helt bedöms uppfylla kriterier för ASD, bör få fortsatt uppföljning över lång tid. Flertalet hade kvarstående svårigheter som stämmer med begreppet "ESSENCE" (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations), och hade fortsatt stort behov av stödinsatser.

LIST OF PAPERS

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

I

Barnevik Olsson M, Höglund Carlsson L, Westerlund J, Gillberg C, Fernell E. Autism before diagnosis: crying, feeding and sleeping problems in the first two years of life. *Acta Paediatrica* 2013; 102: 635–39

II

Barnevik Olsson M, Lundström S, Westerlund J, Giacobini MB, Gillberg C, Fernell. Preschool to school in autism: neuropsychiatric problems 8 years after diagnosis at 3 years of age. *Manuscript.*

III

Barnevik Olsson M, Holm A, Westerlund J, Hedvall Å, Gillberg C, Fernell E. Children with Autism Spectrum Disorder of below average IQ: developmental trajectories from 3 to 11 years of age. *Submitted.*

IV

Barnevik Olsson M, Westerlund J, Lundström S, Giacobini MB, Fernell E, Gillberg C. "Recovery" from the diagnosis of autism – and then? *Neuropsychiatric Disease and Treatment* 2015; 11: 999-1005.

CONTENT

ABBREVIATIONS

ABA	Applied Behavior Analysis
ABAS	Adaptive Behavior Assessment System
ACYC	Autism Center for Young Children
AD	Autistic Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview – Revised
AIF	Average Intellectual Functioning
APA	American Psychiatric Association
ASD	Autism Spectrum Disorder
A-TAC	The Autism-Tics, AD/HD and other Comorbidities Interview
BIF	Borderline Intellectual Functioning
BVC	Barnavårdscentral (Swedish)
CAMHS	Child and Adolescent Mental Health Service
CHC	Child Healthcare Center
CI	Confidence Interval
DCD	Developmental Coordination Disorder
DISCO	The Diagnostic Interview for Social and Communication Disorders
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	4th Edition
DSM-5	5th Edition
DQ	Developmental Quotient
EIBI	Early Intensive Behavioral Intervention
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
FS IQ	Full Scale Intelligence Quotient
FTT	Failure to Thrive
HFA	High Functioning Autism

ICD-10	International Classification of Diseases, 10th Edition
ID	Intellectual Disability
IQ	Intelligence Quotient
LD	Learning Disorder
LSS	Lagen om Stöd och Service till vissa funktionshindrade (see SSF)
ODD	Oppositional Defiant Disorder
OR	Odds Ratio
PDD NOS	Pervasive Developmental Disorders – Not Otherwise Specified
RP	Regulatory Problems
SSF	Support and Services for Persons with Certain Functional Impairments (see LSS)
T1	Time 1
T2	Time 2
T3	Time 3
TEACCH	Treatment and Education of Autistic and related Communication handicapped CHildren
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
WHO	The World Health Organization
WISC-IV	Wechsler Intelligence Scales for Children, 4th Edition

INTRODUCTION 1

Autism Spectrum Disorder (ASD) is a group of neurodevelopmental conditions characterized by impaired social communication and restricted behaviors and interests. The clinical presentations are very heterogeneous, depending on the severity of the ASD *per se,* on associated neuropsychiatric/neurodevelopmental disorders and on the underlying medical disorder (Waterhouse et al. 1996, Coleman and Gillberg 2012). In addition to the core symptoms, most individuals with ASD also display other impairments, such as intellectual/learning problems, attention and activity regulation deficits, language impairments, motor coordination disorders, tics, emotional regulation and mood disorders. Many children with "neurological disorders", including some with epilepsy, infantile hydrocephalus and cerebral palsy meet full diagnostic criteria for ASD. Thus, clinical presentations vary from severe multi-impairments with intellectual disability, severe communication disorders and behavioral problems, including stereotyped, repetitive behaviors to high-functioning individuals with IQs within the "normal distribution" and with moderate deficits with regard to social communication/interaction, and behavioral restrictions (Coleman and Gillberg 2012).

Indications of ASD may present at different ages. Some children display symptoms already during infancy; regulatory problems, deviant reactions to sensory stimuli, insistence on sameness, "autistic aloneness" and abnormal play activities (Dahlgren and Gillberg 1989, Gillberg 1990). The most severely disabled children usually exhibit symptoms in their first years of life and are delayed in their general development and have communication/speech and language problems (Miniscalco et al. 2006). On the other hand, children with average or borderline intellectual function may not present severely impairing symptoms until school age. There is a significant overlap across other neurodevelopmental disorders, such as Intellectual disability (ID), Speech and Language Impairment (SLI), Attention-Deficit/Hyperactivity Disorder (AD/HD) and epilepsy, and co-existence of disorders, comorbidities, is the rule rather than the exception.

1.1 SOME HISTORICAL NOTES, TERMINOLOGY AND DEFINITIONS

The American psychiatrist Leo Kanner (1943) and the Austrian pediatrician Hans Asperger (1944) described children with symptom constellations that later were referred to as "the autistic continuum" or the "autism spectrum" (Gillberg 1983, Wing 1993). Kanner coined the term "early infantile autism", and Asperger called it "autistic psychopathy", a clinical presentation later referred to as Asperger syndrome (Wing 1981, Gillberg and Gillberg 1989).

In the first and second Diagnostic Manual of Mental Disorders, DSM-I and DSM-II, autism or any equivalent term was not described. Instead, autism was considered within the concept of childhood onset schizophrenia. It was not until 1980, that the term Infantile Autism (Rutter 1978 a,b) was introduced in the DSM-III.

In the following DSM-III-R and DSM-IV (APA 1994), the term was changed to Autistic Disorder, and recently, in the DSM-5 (APA 2013) to Autism Spectrum Disorder.

The DSM is the standard classification of mental disorders used by mental health professionals in the United States and many other countries around the world. It is applied in clinical settings as well as in research on clinical and community populations, and it is also used for collecting public-health statistics.

In the fifth edition of DSM, the subcategories of ASD have been collected under one umbrella. According to this manual, ASD (previously referred to as Pervasive Developmental Disorders, PDD) now covers, as one category, the various subgroups (except Rett syndrome) that were included as separate entities under the DSM-IV, viz. *autistic disorder, Asperger syndrome* and *Pervasive Developmental Disorder Not Otherwise Specified* (PDD NOS).

The autism criterion set in the *DSM-5* has several changes compared to the DSM-IV. Instead of a triad, there is a symptom dyad including A) Deficits in social communication/social interaction and B) Restricted, repetitive patterns of behavior, interests or activities.

The items under B include hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment, which was not there in the previous DSM-versions.

Current severity of the disorder must be specified, as must intellectual and language levels. ASD severity is based both on social communication impairments and restricted, repetitive patterns of behavior.

Comorbidity is possible according to DSM-5; for instance an individual may receive both a diagnosis of ASD and AD/HD, and associated medical conditions should be specified.

Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should, according to the DSM-5, be given the diagnosis of ASD.

The other widely used manual for ASD classification is the International Classification of Diseases, ICD, published by the World Health Organization (WHO). Currently the ICD-10 (International Classification of Diseases, ICD-10, 1992) is in use, with ASD subcategories resembling those of the DSM-IV. The release date for ICD-11 is scheduled for 2018.

In the studies presented in this thesis, the DSM-IV has been used, comprising deficits in three domains; A) Reciprocal social interaction, B) Communication and language and C) Behavior and interests (see diagnostic criteria).

Diagnostic criteria for 299.00 autistic disorder (DSM-IV)

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 behaviors 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 behavior, 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, nonfunctional routines or rituals
      c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex wholebody 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.

Diagnostic criteria for 299.80 Asperger's disorder (DSM-IV)

A. Qualitative impairment in social interaction, as manifested by at least two of the following:

   1. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
   2. failure to develop peer relationships appropriate to developmental level
   3. 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 to other people)
   4. lack of social or emotional reciprocity

B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

   1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
   2. apparently inflexible adherence to specific, nonfunctional routines or rituals
   3. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
   4. persistent preoccupation with parts of objects

C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

D. There is no clinically significant general delay in language (e.g., single words used by age two years, communicative phrases used by age 3 years).

E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

299.80 Pervasive Developmental Disorder Not Otherwise Specified (Including Atypical Autism) (DSM-IV)

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 behavior, 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.

1.2 PREVALENCE

The prevalence of ASD is currently reported to be around 1% in the general population (in preschool children slightly lower; about 0.6%-0,8%) (Fombonne 2005, Fernell and Gillberg, 2010, Nygren et al. 2012).

The first prevalence studies of autism were performed in the UK in the 1960's. The study by Lotter, supervised by Lorna and John Wing, demonstrated a prevalence of autism of 4,5/10,000 in school-age children (Lotter 1966). In the later Camberwell study in the UK, including also the broader autism spectrum, the prevalence was found to be 20/10,000 (0.2%) (Wing and Gould 1979). Prevalence studies from the 1980's in Gothenburg, Sweden, also reported low prevalences for severe autism, 0.02% and 0.07%, respectively (Gillberg 1984, Steffenburg and Gillberg 1986).

However, already in the 1970's, Gillberg, in a large general population study, had found 0.7% of seven-year-olds had marked autistic features (i.e. the triad of social, communication, and behavioral impairments typical of autism according to the DSM-III-R and the DSM-IV) in the city of Gothenburg (published in Gillberg 1981).

During the last decades increased ASD prevalence rates have been reported. There are probably several reasons for this (increased awareness among professionals, widening of criteria with milder cases also included, and availability of specific services offered to children with ASD). A recent Swedish study found that the autism symptom phenotype had remained stable in Sweden over many years at the same time as the official prevalence of autism spectrum diagnoses has increased. The authors suggest that the causes of this seem to be administrative rather than anything to do with a change in the pathogenesis of ASD (Lundström et al. 2015).

Rates of ASD are generally reported to be higher in males than in females; about 3-4:1 in population cohorts, and about 5-14:1 in clinical settings. The highest sex-ratios have been reported in so called high-functioning (without ID) children with ASD (Baron-Cohen et al. 2009, Gillberg et al. 2006) compared to a ratio of about 2:1 in those with ID (Fombonne 1999, 2005, 2009 and Volkmar et al. 1993).

It was suggested already in the 1990's that the phenotype of autism might be different in girls as compared to boys (Kopp and Gillberg 1992). To further study these observed gender differences among girls and boys with ASD, Kopp and Gillberg (2011) developed a questionnaire with a view to specifically address symptoms of ASD typically seen in girls. Their study demonstrated the importance of investigating such symptoms on an individual item level, and recommended further studies to confirm gender differences among individuals with ASD.

BACKGROUND FACTORS 1.3

With regard to origin, a classification into a prenatal, a perinatal or a postnatal period, as used for other neurodevelopmental disorders, can be applied. Prenatal factors dominate and consist on the one hand of 1) chromosomal abnormalities (numerical and structural), and monogenic disorders, and on the other hand of 2) acquired conditions; including infections (pre- or postnatally) and toxic influences (such as those of fetal alcohol and drug exposure). There are also many cases of ASD that are the result of a combination of factors, i.e., there are multi-factorial causes.

The genetic heritability of autism spectrum disorder is high compared with other factors. Several studies have found that 60-95 percent of the effect is estimated to be genetic (Freitag 2010). There are several genetic/chromosomal syndromes associated with autism; 22q11 deletion syndrome, Fragile X syndrome, Rett syndrome, Angelman syndrome, Smith-Lemli-Opitz syndrome, and many more (for an overview, see Coleman and Gillberg 2012). Several hundred different genetic variations and abnormalities have been documented to be statistically associated with a diagnosis of ASD, and it is likely that in "genetic cases" of ASD, several combinations of several different groups of genes act in concert to produce the clinical syndrome.

Genetic studies have revealed involvement of several synaptic cell adhesion molecules, the neuroligines in postsynaptic neurons, NLGN3 and NLGN4, and the neurexins, expressed in presynaptic neurons; by the NLGN1 gene, and a postsynaptic scaffolding protein encoded

by SHANK3 in the SHANK-family. This protein complex is crucial for the maintenance of functional synapses as well as the adequate balance between neuronal excitation and inhibition (Bourgeron 2009, Coleman and Gillberg 2012).

Pharmacological teratogens studied and found to be associated with autism are thalidomide and valproate (Geschwind 2008, Strömland et al. 1994, Coleman and Gillberg 2012, Ornoy et al. 2015). Another prenatal, acquired underlying condition found in children with ASD is the fetal alcohol spectrum disorder (Stevens et al. 2013). Some studies have also looked into the influence of insufficiency of vitamin D during pregnancy as a possible cause, but the evidence, so far, can only be said to be limited (McGrath 2010, Keen et al. 2010).

With regard to perinatally acquired conditions, extremely preterm born children constitute a group with increased risk of developing cognitive impairments, including autism (Verhaeghe et al. 2015), findings that support the need to include all kinds of cognitive functions in the follow-up of this group. A postnatal cause of autism, herpes encephalitis, was reported by Gillberg (1991).

Although an identified medical disorder/diagnosis can be recognized in an increasing number of children with ASD, there are still many children for whom the exact underlying medical condition cannot be identified (Eriksson et al. 2013).

1.4 COMORBIDITIES AND ESSENCE

Five years ago, the term ESSENCE (Early Symptomatic Syndromes Eliciting Neuropsychiatric/Neurodevelopmental Clinical Examinations) was launched by Gillberg (2010). Examples of such early symptomatic syndromes are AD/HD (Attention-Deficit/Hyperactivity Disorder) with or without ODD/CD (Oppositional Defiant Disorder/Conduct Disorder), ASD, SLI/LI ("Specific" Language Impairment), ID/IDD (Intellectual Disability/Intellectual Developmental Disorder), Tic Disorders/Tourettes syndrome), DCD (Developmental Coordination Disorder) and epilepsy. Gillberg pointed out that all of these disorders

overlap or co-exist (often in complex patterns), and there is *always* a need for a broad clinical assessment and follow up of children with symptoms within the ESSENCE area. In clinical practice this means that any child diagnosed with e.g. ASD would have to be assessed with an open mind as to the possibility of a whole host of other diagnosable conditions and problems, including ID, language disorder, ADHD, epilepsy, DCD etc. The same would hold for a child primarily diagnosed with e.g. ADHD.

In children who gradually develop all the symptoms of any one of these conditions there are almost always some symptoms from one or more domains to be seen before the age of four years. These are, for instance, global developmental delay (often with lower adaptive functioning), motor or perceptual deviations, speech and language problems, difficulties regulating activity level or controlling impulses, attention deficits, problems with social interaction, behavior or mood swings and also, in many children, problems with regulating food or sleep.

EARLY REGULATORY PROBLEMS 1.5

Regulatory problems (RP) are common in infancy. Feeding problems may occur in as many as 25-35% in typically developing children (Kodak et al. 2008) and up to 80% in children with developmental delay. The prevalence of sleep disorders in typically developing children has been estimated to be approximately 25%-40% (Tunström 1999, Hodge et al. 2014). Excessive crying in infancy usually referred to as infantile colic, is reported to occur in approximately 10-40% in children (Lucassen et al. 2001).

RP in early childhood may be associated with adverse behavioral outcomes (Hemmi et al. 2011) – particularly externalizing and ADHD-problems. Persistent RP in general and infancy feeding problems in particular have been found to predict deficits in social skills and in adaptive behavior in preschool age (Schmid et al. 2010). Excessive crying during the first months in life has not generally been found to be associated with any long-term behavioral consequences.

However, in a substantial proportion of children with persistent crying, this may be associated with multiple RP (von Kries et al. 2006). Persistent excessive crying after three months of age has been reported to be predictive of hyperactivity, and later discipline and cognitive problems.

In a Dutch study, a group of young children with ASD were frequently presented as crybabies to their GP (general practitioner) and often showed feeding problems compared to a control group. More than 25% of the children with ASD had sleeping disorders while no such problems were registered in the controls (van Tongerloo et al. 2011). In a study from 2015 dysregulated breastfeeding behaviors were found in children later diagnosed with autism (Lucas et al. 2015).

Östberg and Hagelin (2011) pointed out that early RP concerning sleeping and feeding generally tend to be less frequent when the children grow older (but they still tend to remain albeit at less severe levels.) They also reported that feeding and sleeping problems were associated with more externalizing and internalizing problems.

1.6 INTELLECTUAL DEFICITS

Matson and Shoemaker (2009) pointed out that ID and ASD co-vary at high rates and that a greater severity of one of these two disorders appears to have effects on the other disorder. The rate of ID in cohorts of individuals with ASD will differ with regard to population under study; i.e., age groups and types of ASDs included. In the 1980's the percentage of ID in children with ASD was estimated to be about 70-90% (Steffenburg and Gillberg 1986).

Today, considering the total ASD spectrum, including an increasing number of "high-functioning" children with ASD, the rate of ID in children with diagnosed ASD can be estimated to about 15-25% at school age. However, at preschool age the corresponding rate would probably be about 50% (Fernell et al. 2011).

There are few studies that have targeted the combination of ASD and Borderline Intellectual Functioning (slow learners), i.e., an intelligence

quotient (IQ) in the range between 70 and 84, i.e. between -2 and -1 standard deviations (SD) (Fernell et al 2011, Kantzer et al. 2013). This intellectual level is part of the normal distribution, but in our time's complex society, individuals with BIF and especially when combined with ASD, run the risk of shortcomings at the mainstream school of today.

ADAPTIVE BEHAVIOR 1.7

Adaptive function includes communication, daily living skills, social and motor skills necessary for everyday function. The instrument Vineland Adaptive Behavior Scales (VABS) is often used to measure these skills (Sparrow et al 2005). Another instrument for evaluating adaptive behavior is the Adaptive Behavior Assessment System (ABAS) (Oakland et al. 2008).

A measurement of adaptive functioning is an important complement to cognitive testing when to determine a person's all-around functioning in everyday life. In the general population adaptive behavior and IQ are highly correlated (Liss et al. 2001). Individuals with ASD, however, are not acquiring skills in these areas at a pace consistent with chronological development or intellectual growth. IQ has been found to be a strong predictor of adaptive behavior, although the gap between IQ and adaptive ability has been observed to decrease in the more cognitively impaired individuals compared to otherwise "high functioning" individuals with ASD (Kanne et al. 2010, Lopata et al. 2013).

INSTRUMENTS USED AND DIAGNOSTIC PROCEDURES 1.8

The assessment and diagnostics of neurodevelopmental disorders in the clinical setting or for the purpose of clinical research rely on gathering and clinical compilation of information, usually from two settings, family and preschool/school. This information should be partly based on structured instruments; questionnaires and rating scales for interviews and clinical observation schedules and specific tests. Instruments and rating scales in neurodevelopmental/neuropsychiatric diagnostics have to yield reproducible and consistent results between

raters and over time; i.e., exhibit reliability, and produce results that correspond to a clinical diagnosis, i.e., show validity.

Neurodevelopmental diagnoses per se are not based on medical investigations or imaging results but a medical/etiological disorder should always be considered. In an increasing number of children, both a neurodevelopmental/neuropsychiatric diagnosis and a medical diagnosis can be identified (Eriksson et al. 2013).

Structured interviews developed to improve reliability and validity in the diagnostic process of developmental disorders are The Vineland Adaptive Behavior Scale (Sparrrow et al. 2005), the ADI-R (Autism Diagnostic Interview-Revised) (Lord et al. 1993) or the DISCO (Diagnostic Interview for Social and Communication Disorders) (Wing et al. 2002), which focuses on neuropsychiatric/neurodevelopmental symptoms or behaviors. The ADOS (Autism Diagnostic Observation Schedule) (Lord et al. 2000) is a frequently used observational instrument to complete the assessment.

The A-TAC (Autism-Tics, ADHD and other Comorbidities Inventory has shown excellent inter-rater reliability and validity in identifying ASDs, ADHD and other common comorbid disorders (Hansson Halleröd 2016).

The most used tests of general intelligence in children are the Wechsler scales; in preschool children the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and in school children the Wechsler Intelligence Scale for Children (WISC) (Wechsler 2003).

1.9 INTERVENTION AND SUPPORT

Parents of children with ASD are in Sweden usually offered parental education and support from a local habilitation center. These measures include information about ASD and advice on how to cope with different behavioral problems in the child. Many children take part in a training/treatment program, such as early intensive behavioral intervention (EIBI) (Maglione 2012, Rogers et al. 2012). EIBI is one

of the more well-established treatments for ASD; a treatment based on the principles of applied behavior analysis starting at an early age and delivered for a period of some years, often at an intensity of 20 to 40 hours per week, to reinforce skills and desirable behaviors. It initially most often includes one-to-one teaching and is considered more effective if performed both at preschool and at home. A Cochrane systematic review calculated a beneficial effect of EIBI treatment for *some* children regarding adaptive behavior, intelligence, and communication and language skills (Reichow 2012). Another review (Warren 2011) found EIBI helpful *in the short term* for language function, cognitive skills, and some challenging behaviors.

In a review by Zwaigenbaum et al. (2015) the central role of parents was emphasized, and that interventions for the child should be designed to incorporate learning opportunities into everyday activities, capitalize on "teachable moments," and facilitate the generalization of skills beyond the familiar home setting.

There is now clinical agreement that autism should be diagnosed early in order to start intervention at the youngest possible age (Zwaigenbaum et al. 2015). Although EIBI has been found to be effective for some children with ASD, the heterogeneity between individual children with ASD entails a wide variability in response to treatment (Howlin et al. 2009). Evidence about exact type of method and the extent to which it should be delivered is still limited. Some individuals with ASD are probably more likely than others to benefit from EIBI and some children would possibly benefit from other types of targeted interventions (Howlin et al. 2009, Fernell et al. 2011).

A study from Stockholm, encompassing about 200 children, followed in a naturalistic setting in which about half the group received EIBI and the other half non-intensive, targeted interventions, could not demonstrate more improvement among children receiving intensive interventions as compared to children receiving targeted non-intensive interventions. However, all interventions were based upon ABA techniques and all parents and preschool staff were offered an educational program when the child was registered at the autism center (Fernell et al. 2011). Treatment and Education of Autistic and related

Communication handicapped CHildren (TEACCH) (Welterlin et al. 2012) is another method that has been widely used, as has Picture Exchange Communication System (PECS) (Charlop-Christy et al. 2002), and Social Stories (Swaggart et al. 1995).

1.10 PHARMACOLOGICAL TREATMENT

There is no pharmacological treatment for autism *per se*. However, specific symptoms, coexisting with ASD can be targeted for treatment; i.e., epilepsy, AD/HD and sleeping problems.

However, several pharmacological studies, with different drugs, have been performed with the aim of alleviating symptoms of ASD and associated behavioral problems. Evidence is limited regarding the use of Tricyclic Antidepressants (TCAs) for ASD in children and adolescents (Hurwitz et al. 2012). Other studied drugs are Fenfluramine (Leventhal et al. 1993), omega-3 fatty acids (James et al. 2011), risperidon (Luby et al. 2006), secretin (Krishnaswami et al. 2011), and selective serotonin reuptake inhibitors (SSRI) (Williams et al. 2013) but according to results virtually none of these have had any effect on core symptoms. There are some studies evaluating treatment with the hormone oxytocin in children with ASD. The background is that oxytocin may optimize the social circuits in the brain and enhance reward, motivation and learning. However, the current evidence of therapeutic benefit from extended oxytocin treatment remains limited (Guastella and Hickie 2016).

The observation that GABA-acting benzodiazepines exert paradoxical excitatory effects in autism has been shown to result from elevated intracellular chloride ([Cl–]i) that shifts the polarity of GABA from excitation to inhibition. The diuretic bumetanide, that decreases (Cl–)i and reinforces GABAergic inhibition, has been reported to reduce the severity of autism symptoms (Lemonnier et al. 2012, Hadjikhani et al. 2015). This pharmacological agent is now undergoing randomized trials.

OUTCOME AND STABILITY OF DIAGNOSIS 1.11

A higher cognitive level and acquisition of speech before age five to six years have been found to be associated with better outcomes in children with ASD, for example regarding adaptive skills (Billstedt et al. 2007, Kanne et al. 2010, Fernell et al. 2011 and Howlin et al. 2014). Factors associated with negative outcome include comorbid conditions such as ID, language impairment, AD/HD, epilepsy and suboptimal cognitive factors, such as executive dysfunctions and slow processing (Hagberg et al. 2013, Hedvall et al. 2014, Gillberg and Fernell 2014).

There are distinct subpopulations within the Autism Spectrum Disorder, needing better description in terms of their outcomes, predictors of outcomes and possible etiologies (Woolfenden et al. 2012).

Diagnostic stability has been studied in children with developmental disorders, with special regard to ASD. It has been reported that some diagnostic categories are more stable, i.e., autism/autistic disorder and some are more likely to change over time, e.g., atypical autism/PDD-NOS (Daniels 2011, Hedvall et al. 2014).

CHILD HEALTHCARE CENTERS 1.12

Child Healthcare Centers (CHCs) are an important part of child healthcare in Sweden and reach about 95-99% (Child Health Services, Stockholm County Council, 2010, Årsrapport 2010 in Swedish) of all children during the first two years of life. Developmental surveillances are performed by nurses as well as physicians during infancy and preschool ages. Apart from examinations, vaccinations, measurements of height and weight, screening of vision and hearing are performed. Parents also have the possibility to contact the CHC-nurse if having any other problems or worries about the child's development or behavior, and further contact with a physician, a psychologist and/or a speech and language pathologist can be arranged (www.rikshandboken-bhv.se in Swedish, Höglund Carlsson et al. 2016).

2 AIMS

The overall aim of the thesis was to examine early indicators of autism, stability of ASD diagnosis, comorbidities and cognitive and adaptive trajectories during the childhood years.

More specifically, the aims were to;

1. explore whether or not regulatory problems during the first two years of life were overrepresented in children who received an ASD diagnosis after age two;

2. analyze A-TAC results in children aged 9-13 years, who were diagnosed with ASD at ages 2-4 years, and relate outcome to cognitive function at follow-up around 5-6 years of age;

3. reexamine cognitive levels in a subgroup of preschool children with ASD and borderline intellectual functioning, when at mid-school age;

4. explore stability in ASD diagnosis in preschool children without ID at a mid-school age follow-up, as well as presence of non-ASD ESSENCE diagnoses.

PARTICIPANTS AND METHODS 3

PARTICIPANTS 3.1

The thesis is based on results obtained in the study of one and the same ASD cohort – including four different sets of data, from Stockholm County. Targeted subgroups of the cohort and flow charts are presented in figures below.

1. In Study I – *The Regulatory Study,* 190 children from the total preschool cohort of 208 children with ASD, see below, had complete CHC records which were scrutinized for reference to early regulatory problems.

2. In Study II – *The Preschool to School Study,* those 198 of the 208 children with ASD, who had attended the two-year follow-up after an intervention period, were targeted for investigation, using the parental Autism- AD/HD-Tics and other Comorbidities (A-TAC) Telephone Interview at around 11 years of age, with regard to ASD and other co-occurring disorders.

3. In Study III – *The Borderline Intellectual Functioning Group Study,* the group of 50 children with ASD who had had borderline intellectual functioning (BIF) at the two-year follow-up, were targeted for another follow-up around age 11 years, using cognitive testing and parental interviews.

4. In Study IV – *The Growing Out Of Autism Study,* the group of 17 children with ASD who, at the two-year follow-up after intervention, no longer met criteria for ASD and did not have ID (intellectual disability) were targeted for a second follow-up at mid-school age using parental interviews.

3.1.1 Study I – The Regulatory Study

The ASD child preschool cohort was recruited within a representative community sample of 313 children, born in the years 2002-2006, who had been diagnosed with ASD in Stockholm County 2005-2008. Of these, 288 children had been referred to the Autism Center for Young Children (ACYC) for intervention, and 25 admitted to a regular habilitation center in the area, due to multi-impairments. Of the 288 children, 24 had been referred to the ACYC before start of the project and were for this reason not included. Parents of the remaining 264 were offered to take part in the study with their children. In 15 families, neither Swedish nor English was spoken and parents of 37 other children declined participation. Two children were transferred to a general habilitation center because of specific medical needs and two families had moved abroad. Thus the original study cohort consisted of 208 children. Of the remaining 208 children, 198 came to follow-up after two years *(Figure 1)*.

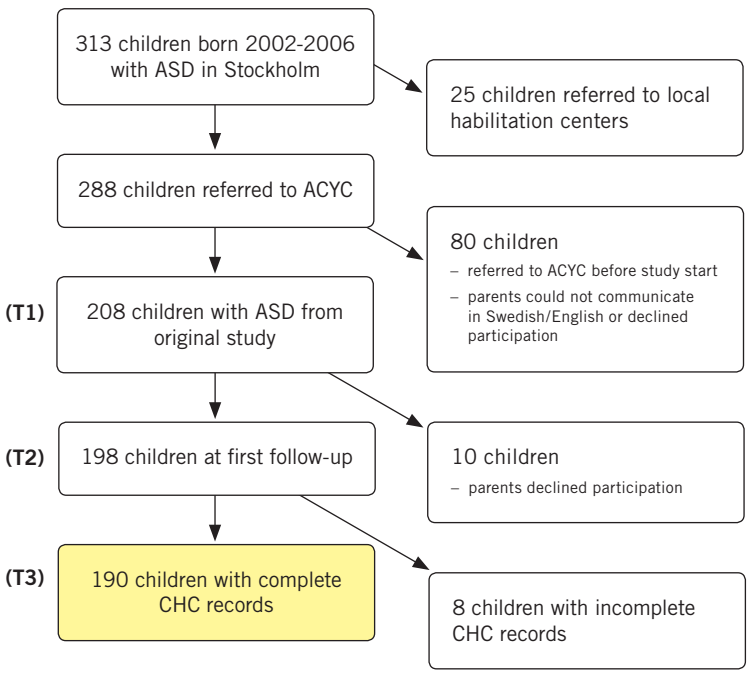

Figure 1 *Study I. Flowchart demonstrating the inclusion procedure*

Study II – The Preschool to School Study 3.1.2

Of the cohort of 208 children, 198 (168 boys, 30 girls) came to the first follow up Time 2 (T2) at 4-6 years of age, after two years of intervention. The children were then tested with regard to cognitive functions and on the basis of these results, divided into three cognitive groups: average intellectual functioning (AIF) with IQ/Developmental Quotient (DQ)⩾85 (n=51), borderline intellectual functioning (BIF) with IQ/DQ 70-84 (n=50) and intellectual disability (ID) with IQ/DQ<70 (n=95). Parents were again contacted by letter when the children were 9-13 years of age (median 11 years), offering participation in a second follow-up Time 3 (T3) *(Figure 2).* Parents of 128 children (110 boys, 18 girls) accepted participation in the new follow-up, while parents of 70 children declined (n=29) or could not be reached (n=41).

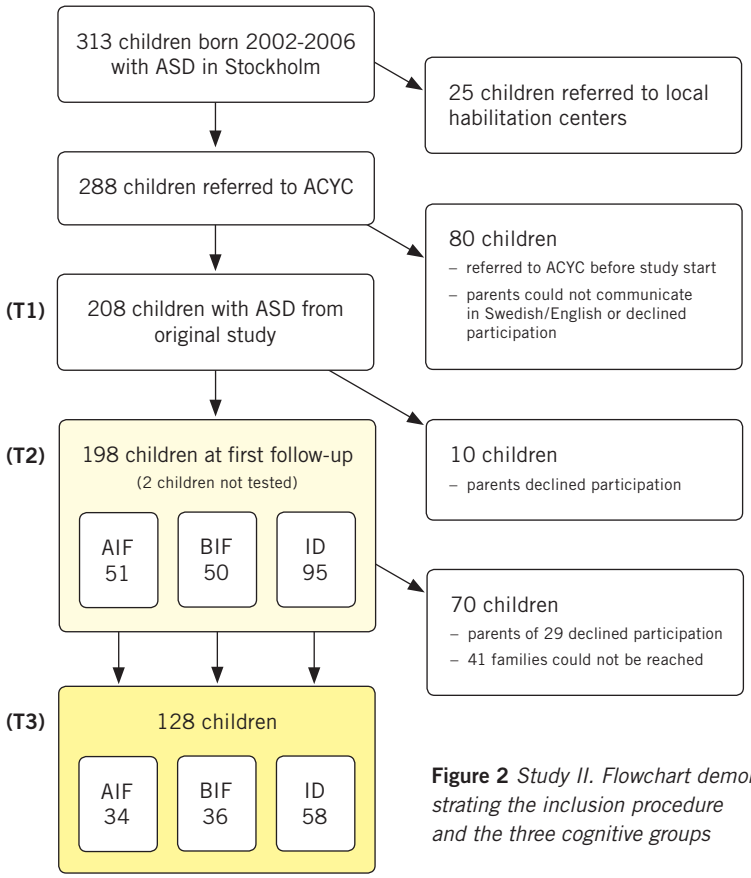

Figure 2 *Study II. Flowchart demonstrating the inclusion procedure and the three cognitive groups*

3.1.3 Study III – The Borderline Intellectual Functioning Group Study

At the two year follow-up (T2), cognitive testing had been performed in the children at ages 4-6 years. 50 children (46 boys and 4 girls) had IQ-levels between 70 and 84, considered as borderline intellectual functioning (BIF). 51 children had average intellectual functioning (AIF), 95 had ID and two children had not had an IQ test at the T2 assessment. The 50 children with BIF were chosen as target group for this study *(Figure 3)*.

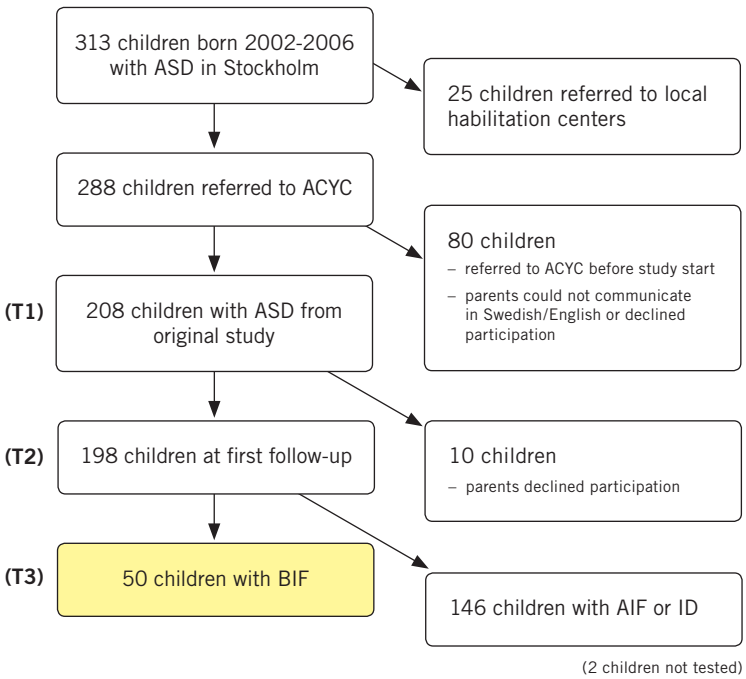

Figure 3 *Flowchart demonstrating the inclusion procedure and study group in Study III*

Study IV – The Growing Out Of Autism Study 3.1.4

From the original cohort of 208 children with ASD, 198 were followed up at T2 with regard to persisting ASD two years after ABA intervention. 21 children did not fully meet criteria for ASD. 17 of these hade average (AIF) (n=13) or borderline intellectual function (BIF) (n=4) and were chosen as target group for the last study *(Figure 4)*.

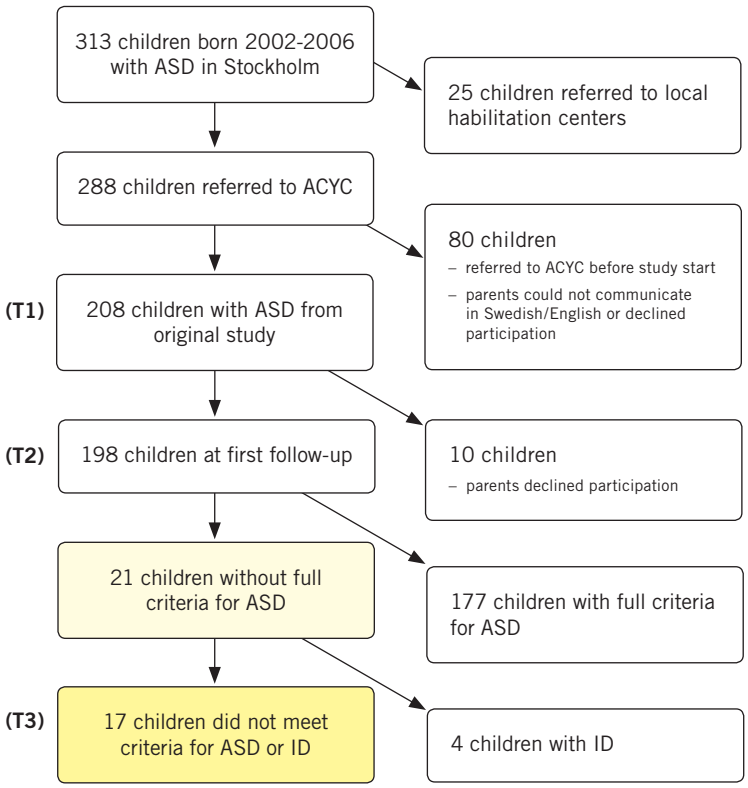

Figure 4 *Flowchart demonstrating the inclusion procedure and study group in Study IV*

3.2 METHODS

3.2.1 Study I – The Regulatory Study

Of the 208 children with ASD, 190 children (161 boys, 29 girls) had complete Child Health Centers (CHC) records available and could be included in the study.

3.2.1.1 CHC records

The files were sent for with parents' consent and reviewed with regard to regulatory problems (RP) (excessive crying, feeding and sleeping), occurring in the child's first two years of life. In order to obtain a representative comparison group, nurses at the same CHC (or at the same school healthcare unit areas as the index children) were asked to pick the record of a child of the same sex immediately before and after the project child in the archives. In this way, the comparison children were as close in age as possible compared to the project children, and from the same areas.

The comparison group consisted initially of 185 children, and after correction for gender (by randomly excluding 24 girls), 161 children remained in the comparison group, with the rate of boys 84,5%, as compared to 84,7% in the project group. RP noted in the records were counted and registered from the second month of life and onwards, until two years of age.

3.2.1.2 The DISCO Interview (Diagnostic Interview for Social and Communication Disorders)

The DISCO Interview had been performed at the two-year follow-up (T2) with parents of 105 project children, as part of the total study. No DISCO interviews could be carried out with parents of children in the comparison group. The DISCO is a standardized, semi-structured and investigator based schedule for diagnosing autism spectrum disorders. The purpose of including the DISCO in the current study was to see any possible correlation between the health records and the parental interview.

The same areas, excessive crying, feeding and sleeping problems, were rated with two questions for each domain, with a sum 0-2.

The questions were, regarding *crying;*

1. Was A a quiet baby or did he/she cry a lot?
2. When A cried was it easy to know why?

Regarding *feeding;*

1. Did A feed well as a baby?
2. Did A need any treatment for excessive vomiting?

Regarding *sleeping;*

1. Did A tend to wake up screaming from sleep?
2. Did A sleep well, after the first few weeks?

Study II – The Preschool to School Study 3.2.2

At T3, parents were again contacted by letter of information and by telephone regarding participation in a telephone interview; The Autism-Tics, AD/HD and other comorbidities (A-TAC) (Hansson et al. 2005). The interview was performed by an experienced layperson from a market research center.

The A-TAC Interview (see Appendix) *3.2.2.1*

The interview has been shown to have excellent psychometric properties and has been used in many clinical research studies (Halleröd et al. 2010, Larsson et al. 2014). It is a screening interview focusing on child and adolescent psychiatric problems and designed to be used by laymen over the phone. The A-TAC has been validated against comprehensive multidisciplinary clinical diagnoses cross-sectionally (Hansson et al. 2005, Larson et al. 2010) and longitudinally (Larson et al. 2013) and has been found to be a sensitive tool to screen for ASD, AD/HD, tics, learning disorder/ID and developmental coordination disorder (DCD), with good to excellent test-retest properties (Larson et al. 2014). For ASD, AD/HD, learning disorder/ID and DCD, two cut-offs exist (1) "high" which is a *proxy for a clinical diagnosis* with moderate sensitivity and high specificity, and (2) "low" which is a broad screening level with high sensitivity but moderate specificity for subthreshold traits and can be taken as a *proxy for a subclinical disorder* (Larson et al. 2010; Larson et al. 2013). In the current study, oppositional defiant disorder (ODD) was also studied. For this disorder, there is only one cut-off, corresponding to "high" (Kerekes et al. 2014).

3.2.3 Study III – The Borderline Intellectual Functioning Group Study + Study IV – The Growing Out Of Autism Study

The parents of the children were once again contacted by letter and telephone for different telephone interviews; one clinical semi-structured interview and a Vineland Interview (Sparrow, Cicchetti, and Balla, 2005) both performed by MBO. A third interview, the Autism-Tics, AD/HD and other Comorbidities (A-TAC) (Hansson et al. 2005; Larson et al. 2010; Halleröd et al. 2010; Larson et al. 2013) was performed by an experienced layperson from a market research center. In addition, for the group of children with BIF at the T2 follow-up, a cognitive test was included in this second follow-up (T3).

3.2.3.1 *Parental semi-structured interview*

A semi-structured telephone interview was performed with one of each child's parents, to obtain information about the child's current situation both in school and at home. Questions on type of school and school support were raised, as were questions pertaining to different developmental domains; speech and language, social abilities, activity and impulsivity regulation, attention span and externalizing behavior. Parents were also asked if the child had had any new clinical assessments at a Child and Adolescent Mental Health Service (CAMHS) and/or a pediatric department since the research follow-up at the ACYC (T2), if the family had any ongoing contacts with a pediatrician/neuropediatrician, child psychiatrist or habilitation center and if the parents found that the services they received met their needs.

- How is your child's current school form/curriculum?
- Does your child have any specific support at school (type and extent)?
- Do you think your child gets support according to his/her needs?
- Has your child had any new assessments?
- Does your child have any ongoing medical, psychiatric or habilitation contacts? Medication?
- How do you perceive your child's speech and language?
- Does your child have attention deficits?
- Does your child have difficulties regulating activity or impulsivity?
- Does your child have any specific behavioral problems (like tantrums)?
- Does your child have problems interacting with peers? – with adults?
- Does your child have any support outside school? After school care?
- Do you as parents have any specific support due to your child´s impairment?
- How would you rate your overall situation and the development of your child?

A-TAC Interview 3.2.3.2

See Study II

Vineland Adaptive Behavior Scales (VABS-II) Interview 3.2.3.3

An interview was also performed at this second follow-up (T3) according to the Vineland Adaptive Behavior Scales (Sparrow et al. 2005), with one of the child's parents. This interview includes Communication, Daily Living Skills and Social domains and a Composite score. The interview is administered to a parent or caregiver using a semi-structured interview format, which provides a targeted assessment of adaptive behavior. In this study, the interview was given on the telephone, taking approximately 45-60 minutes. The children in these groups had complete VABS-II results, also at both the first (T1) and second (T2) period of measurement.

Testing with Wechsler Intelligence Scale for Children (WISC-IV) 3.2.3.4

Parents of the 50 children who at the T2 follow-up in addition to ASD had BIF, were offered a new cognitive test of their child according to WISC-IV (Wechsler, 2003). WISC-IV includes Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index. The WISC-IV test was performed by one of the two earlier project psychologists (AH) and took place at Karolinska University Hospital in Stockholm. Test duration was about half a day per child.

STATISTICS 3.3

Due to highly skewed number of consultations for regulatory problems in the first study, the nonparametric Mann-Whitney test, Pearson's chi-square and ODDs ratio (OR) with 95% confidence interval (CI) were used to compare the two groups. An alpha level of .05 was used for all statistical tests.

All statistical analysis in the second study were made using IBM Statistical Package for the Social Sciences (SPSS) version 23. A-TAC participating vs non-participating groups were compared regarding distribution of cognitive levels, ASD type and parental ethnicity using

Pearson's chi-square with SPSS exact sig. The A-TAC results (ASD, ADHD, Learning/ID and ODD scores) were compared for the three cognitive groups using one-way analysis of variance (ANOVA) with post hoc tests (Fishers LSD, Least Significant Difference). An alpha significance level of .05 was used for all tests.

Differences between the three time points with regard to mean Vineland composite scores were analyzed in study three and four, with a repeated measures analysis of variances (ANOVA). In this analysis, partial etasquared *(η2partial)* was used as a measure of effect size. The ANOVA was followed up by post hoc analysis (Bonferroni) in order to study differences between specific time points. An alpha level of .05 was used for all statistical analyses.

3.4 ETHICS

Study I was approved by the regional medical ethical board at Karolinska Institute: 2010/1675-32 and Study II, III and IV at Karolinska Institute: 2012/734-32.

RESULTS 4

STUDY I – THE REGULATORY STUDY 4.1

Overall findings 4.1.1

Regulatory problems (RP) were much more common in children who later received an autism spectrum diagnosis as compared to the comparison group.

Regulatory domains 4.1.2

Analyses were performed separately for each domain (crying, feeding, sleeping) and for the domains when merged. The number of consultations was significantly higher in the ASD group, in each of the three studied domains, compared to the comparison group, and even more so when domains were merged.

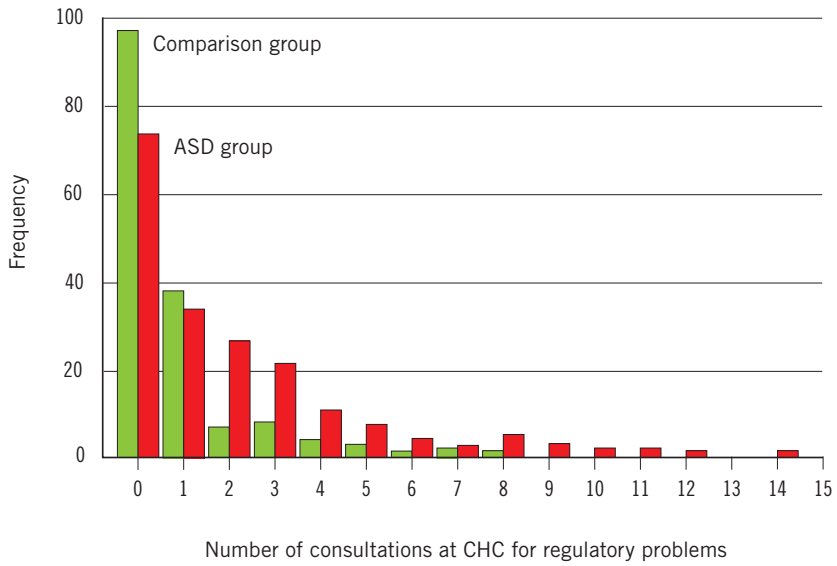

Figure 5 *Number of consultations for regulatory problems (RP) in children with autism spectrum disorder (ASD) and in the comparison group*

4.1.3 DISCO Interview

In the DISCO Interview performed with parents of just over half of the children in the project group (n=105), there was a significant correlation between sleeping problems and feeding problems reported to the CHC nurse during infancy, as compared to parents' answers in the interview regarding the same problems during the same time period. The correlation between total number of RP reported at the CHC and at DISCO interview was significant.

4.2 STUDY II – THE PRESCHOOL TO SCHOOL STUDY

Parents of 128 children (110 boys, 18 girls) accepted participation in the new follow-up, while parents of 70 children declined (n=29) or could not be reached (n=41). In this group, 34 children had, at the cognitive testing at T2, performed at a level corresponding to AIF, 36 had performed corresponding to a level of BIF, and 58 were regarded as having ID.

4.2.1 Overall findings

More than 90% of the children who at preschool age were diagnosed with ASD, had remaining neuropsychiatric problems ("Autism Plus") at age 11.

4.2.2 A-TAC

All A-TAC results were subdivided according to the three cognitive groups; AIF, BIF and ID. Five modules were targeted; ASD, AD/HD, learning disorder/ID, DCD and ODD. A majority of the 128 children presented problems within several areas. There were no significant differences regarding child characteristics or parental ethnicity between the A-TAC-participating (n=128) and A-TAC-non-participating (n=70) groups.

Proxies for clinical disorders related to cognitive groups 4.2.3

Criteria for a clinical or subclinical proxy of ASD were met by 71%, 89% and 95% respectively in the AIF, BIF and ID-groups. Children with ASD and ID at T2 presented the overall highest symptom levels at T3, apart from ASD symptoms, 79% in this cognitive group had criteria for a clinical or subclinical proxy of AD/HD, and 48% had symptoms corresponding to clinical ID. ASD and AD/HD-rates were lower in the AIF group, and ODD-rates lower in the BIF-group. DCD-rates were similar across groups (detailed rates are presented in *Table 1*).

Table 1 *Clinical and subclinical disorders according to A-TAC high and low level related to cognitive groups*

		Total n=128	AIF n=34	BIF n=36	ID n=58
ASD	clinical disorder	16 (47%)	16 (47%)	21 (58%)	44 (76%)
	subclinical disorder	8	8	11	11
	Total	24 (71%)	24 (71%)	32 (89%)	55 (95%)
ADHD	clinical disorder	10 (29%)	10 (29%)	11 (31%)	27 (47%)
	subclinical disorder	10	10	13	19
	Total	20 (59%)	20 (59%)	24 (67%)	46 (79%)
LD/ID	clinical disorder	–	–	5 (14%)	28 (48%)
	subclinical disorder	11	11	15	26
	Total	11 (32%)	11 (32%)	20 (56%)	54 (93%)
ODD	cut-off level	12 (35%)	12 (35%)	8 (22%)	26 (45%)
DCD	clinical disorder	9 (26%)	9 (26%)	9 (26%)	7 (12%)
	subclinical disorder	8	8	14	18
	Total	17 (50%)	17 (50%)	20 (56%)	25 (43%)
	Any clinical or subclinical disorder	28 (82%)	28 (82%)	34 (94%)	56 (97%)

AIF = average intellectual function,
BIF = borderline intellectual function,
ID = intellectual disability

4.2.4 Total scores in the different disorders related to cognitive group

ASD, AD/HD, learning disorder/ID and ODD scores in relation to the three cognitive groups are presented in *Figure 6 a, b, c* and *d*. The group with ID had significantly higher scores compared to the BIF and AIF groups with regard to ASD, AD/HD and learning disorder/ID. ASD and AD/HD scores correlated in the total group and in the three cognitive groups. The distribution of ODD problems did not differ significantly between the groups.

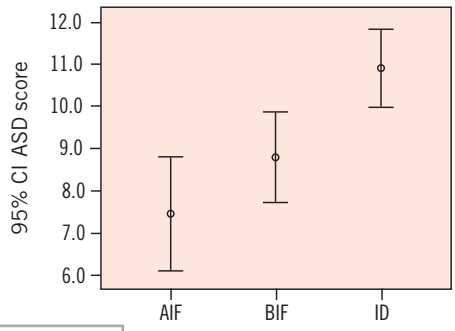

Figure 6a

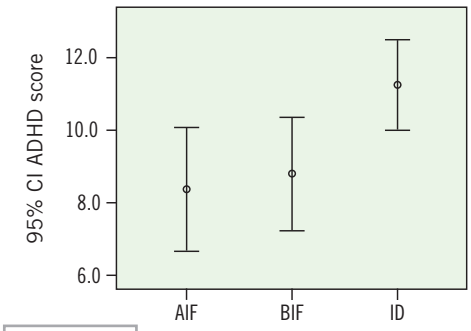

Figure 6b

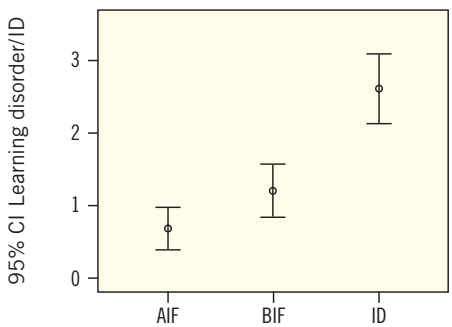

Figure 6c

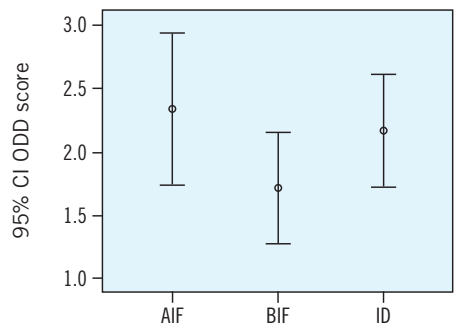

Figure 6d

Figure 6 a – d *Different A-TAC results in relation to cognitive groups*

STUDY III – THE BORDERLINE INTELLECTUAL FUNCTIONING GROUP STUDY 4.3

Of the 50 children, parents of 49 (45 boys and 4 girls, age range 9-13 years, mean age 10,4 years) could be reached. Six families declined participation and one had left the area, leaving parents of 43 children, who took part in all or parts of the follow-up. Parents of 41 children participated in the semi-structured interview and in the Vineland Interview, parents of 36 children participated in the A-TAC Interview and 30 children had a cognitive test according to WISC-IV.

Overall findings 4.3.1

The majority of children diagnosed at preschool age as suffering from ASD with borderline intellectual functioning still show behavioral and cognitive problems several years later.

Semi-structured interview 4.3.2

The majority of the children had moderate-severe problems with attention/activity, speech and language, behavior and/or social interaction, according to parents' report. Parents of 24 children reported that their child had AD/HD or severe problems regulating activity and/or attention deficits, 21 children had major difficulties interacting with peers according to parents, while parents of 18 children reported disabling problems with speech and language in their child. Parents of 10 children reported major learning disabilities at school, four children had reported tics and five had severe coordination problems.

In spite of this, 10 of the 41 parents clearly expressed that their children did not at all have enough support in school.

A-TAC 4.3.3

Of the 36 children, 21 had symptom levels corresponding to a clinical proxy of ASD and another 11 reached the cut-off for the broad screening diagnosis. 10 children had symptom levels corresponding to a clinical proxy of AD/HD, and another 15 encompassed the broad screening cut-off. 13 children had symptom levels corresponding to tic disorder and

6 had DCD (clinical proxy). Five had symptom levels corresponding to learning disorder (clinical proxy), while 18 reached cut-off for the broad screening diagnosis.

4.3.4 Vineland Adaptive Behavior Scales

A repeated measures ANOVA with Time (1, 2, 3) as the within-subject factor and rating on the Vineland Behavior Adaption Scales as the dependent variable showed a significant effect of Time ($F2, 80 = 28.24$, $p<.001$, $\eta 2 = .414$) *see Figure 7.*

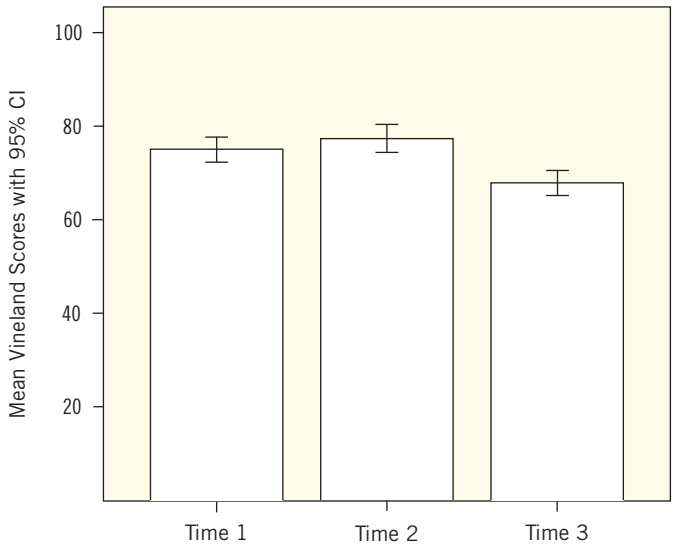

Figure 7 *Mean Vineland scores with 95% confidence intervals for the three assessment times*

Post-hoc tests (Bonferroni) showed that the children had a significantly lower mean rating at T3 as compared to both T1 ($p<.001$) and T2 ($p<.001$). The difference between T1 and T2 was however not significant ($p = .155$).

Cognitive testing 4.3.5

Of the total of 50 children with BIF at T2, 30 children had a cognitive test according to WISC-IV (of which two were outside the study but copies of tests were obtained). In total, six children received a result of FS IQ (Full Scale Intelligence Quotient) below 70, nine had FS IQ above or equivalent to 85 and 15 children had results between 70 and 84. These 15 children had not changed their IQ scores and could thus still be considered as having a cognitive level corresponding to BIF.

Of the six children who had an IQ below 70 at T3, one had an identified medical disorder. Five had A-TAC levels corresponding to a clinical proxy of ASD in the A-TAC Interview. All six children also had a decrease of their total VABS scores.

Nine children had improved their IQ and scored at average level at T3. None of these children had an identified medical disorder. Two of the nine children had levels corresponding to a clinical proxy of ASD in the A-TAC Interview. Two of the nine children had increased their total VABS-scores.

STUDY IV – THE GROWING OUT OF AUTISM STUDY 4.4

Of the 17 children, parents of 16 (12 boys and four girls [age range, 7-11 years; mean age 9 years]) could be reached. Parents of all 16 children participated in the semistructured interview and in the Vineland Interview. Parents of 14 children participated in the A-TAC Interview.

Overall findings 4.4.1

Children diagnosed at 2-4 years of age as suffering from ASD and who, after appropriate intervention for two years, no longer met diagnostic criteria for the disorder, clearly needed to be followed up longer. About 3-4 years later, they still had major problems diagnosable under the umbrella term of ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations).

4.4.2 Semi-structured interview

The vast majority of the children had moderate-to-severe problems with attention/activity regulation, speech and language, behavior and/or social interaction. Parents of 13 of the 16 children reported various difficulties with social interaction. Parents of 13 of the 16 children reported problems regarding attention, and nine children also had problems with hyperactivity and/or impulsivity. Of the 16 children, parents of 12 reported that their children had problems with speech and language and parents of 15 children reported behavioral problems.

4.4.3 A-TAC

Most children presented problems within several areas *(Table 2)*. Five modules were targeted: ASD, AD/HD, tic disorder, DCD, and learning disorder. Three children had symptom levels corresponding to a

Table 2 *Screening diagnoses in individual children according to A-TAC*

	Screening diagnoses								
Child nr	ASD High	ASD Low	ADHD High	ADHD Low	TDs	DCD	LD/ID High	LD/ID Low	No of screening diagnosis
1	0	1	0	1	1	0	1	*	*4*
2	1	*	1	*	1	0	0	1	*4*
3	1	*	1	*	1	1	0	0	*4*
4	1	*	0	1	0	0	0	0	*2*
5	0	1	1	*	1	0	0	0	*3*
6	0	1	0	1	0	0	0	0	*2*
7	0	1	0	0	1	0	0	1	*3*
8	0	1	0	1	0	0	0	1	*3*
9	0	0	0	0	0	0	0	1	*1*
10	0	1	0	0	0	0	0	0	*1*
11	0	0	0	0	0	0	0	0	*0*
12	0	0	0	0	0	0	0	0	*0*
13	0	0	0	1	0	0	0	0	*1*
14	0	0	0	1	0	0	0	0	*1*

*If one of the "high" diagnoses are ascribed the threshold for the corresponding "low" diagnosis is automatically met.

clinical proxy of ASD and six reached the cut-off for the broad screening diagnosis. Three children had symptom levels corresponding to a clinical proxy of AD/HD, and another six encompassed the broad screening cut-off. Five children had symptom levels corresponding to tic disorder, one had DCD, and one had symptom levels corresponding to learning disorder or ID.

Vineland Adaptive Behavior Scales 4.4.4

A 3 × 3 repeated measures ANOVA with T1, T2 and T3 and Subscale (Communication, Daily Living Skills, Social Domains) as within-subject factors and VABS score as the dependent variable showed a significant main effect of Time ($F2, 60=7.36$, $p=0.003$, $\eta 2$ partial $=0.33$). As can be seen in *Figure 8,* mean VABS-scores increased between T1 and T2, but then decreased between T2 and T3. Post hoc analysis (Bonferroni) showed that the overall increase between T1 and T2 was significant ($p=0.036$), as was the decrease between T2 and T3 ($p=0.005$). The difference between T1 and T3 was not significant ($p=0.879$).

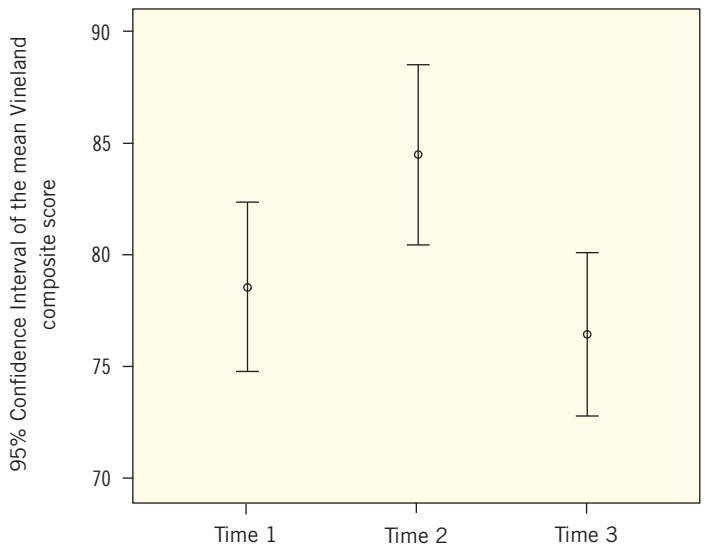

Figure 8 *Mean VABS scores with 95% confidence intervals for the three assessment times*

5 DISCUSSION

5.1 GENERAL FINDINGS

This thesis reports data from a naturalistic longitudinal, prospective study of initially 208 preschool children with ASD, representing a community-based cohort. The children were followed up after a two year intervention period before start of school, and again at ages 9-13. It is one of the largest and most detailed follow-up studies ever published on the outcome of young children with ASD. In general terms, the outcomes varied widely, but overall, marked and pervasive impairments persisted in the majority of the total group.

Long-term studies of ASD outcome in mid-school children are rare (Elmose et al. 2014). Previous studies have usually followed children for no more than 1-3 years. However, longer follow-up have been shown to provide more definitive information on disorder outcome.

Together, the studies clearly show that ASD is a heterogeneous condition with a high degree of comorbidity, and there are always many aspects other than ASD "per se" to consider. In accordance with the DSM-5, it is important to specify not only ASD severity and functional impairment, but also coexisting conditions, intellectual and language levels as well as medical aspects, as these vary widely.

Many studies focus only on ASD diagnostic outcome even though this limits full understanding of prognosis (Towle et al. 2014, Waterhouse 2013). The presentation of symptoms and problems changes over time but it is apparent that major difficulties and impairments remain in the majority of children.

In this thesis, different longer-term outcome aspects have been studied longitudinally in the community based preschool child cohort with ASD; regulatory problems in infancy, neuropsychiatric problems from pre-school to school age as measured by A-TAC interview results, developmental trajectories of children of "non-retarded but below average IQ" (i.e. those often referred to as having "high-functioning

autism" in earlier publications), and finally stability of diagnosis and outcome at mid-school age in the (relatively small) subgroup with ASD, who no longer met full criteria for ASD at start of school (i.e. those often referred to as having "grown out of autism" or "being cured of autism" in early publications).

DISCUSSION OF STUDY RESULTS 5.2

Study I – The Regulatory Study 5.2.1

This study focused on three domains of early RP: excessive crying, eating/feeding and sleeping problems both in the representative group of children with ASD and in a representative comparison group. The measure used to assess such problems was the number of registered consultations at the CHC concerning problems in these domains during the child's first two years.

Children with ASD had had significantly more consultations for crying, feeding and sleeping problems at the CHC than the children in the comparison group.

Many studies have found that autism appears to be associated with feeding problems and abnormal food behavior. It is common that children with developmental abnormalities are, already at an early stage extra sensitive regarding their perceptual and sensory functioning and this could in turn, augment reactions in terms of more frequent or severe RP. The presence of severe and persistent feeding problems, or atypical patterns of "failure to thrive" (FTT) should alert clinicians to the possibility of an ASD (or other developmental disorder). Conversely, in the clinical evaluation of children presenting with ASD, it is essential to obtain a detailed history of feeding behavior and to evaluate the child's growth (Keen 2008).

In a prospective study, the relation between crying in infants at the age of three months, defined as "crying more than others of the same age", and behavioral problems (according to the Child Behavior Checklist, CBCL) at the age of four years was analyzed. The authors reported that

excessive crying was a prevalent problem and that mothers of crying babies at the age of three months reported more problem behaviors when their children reached four years of age than mothers of non-crying babies. The study was carried out in a low income country but the correlation between crying and later behavioral problems was found to be in agreement with findings from high income countries. Implications with regard to maternal counselling on childcare were discussed (Santos et al. 2015).

In the Avon Longitudinal Study of Parents and Children (ALSPAC), parents had reported data on sleep duration at eight time points when the child was between six months and 11 years. When the children were 11 years old, sleeping data in children with ASD was compared to controls. The study revealed that children who had developed ASD had slept significantly less than controls from the age of 30 months, but no significant difference had been present during infancy (Humphreys et al. 2013).

However, it has also been reported that children and adolescents with ASD are particularly vulnerable to sleep difficulties, regardless of their age (Richdale and Schreck 2009).

A large study based on parental report estimated prevalence of sleep problems to be approximately 44-83% in children with autism (Richdale and Prior 1995). In contrast, only 20-30% of typically developing infants and preschool children presented had had sleep problems (Owens et al. 2000).

It has also been discussed that not only do children with autism demonstrate a higher rate of sleep disturbance than typically developing children, but prevalence is even higher than in children with other developmental disorders (Cotton and Richdale 2006, Owens et al. 2000).

Genetic and neurobiological findings have demonstrated the role of synaptic and clock genes and the circadian modulation of synaptic function in ASD (Bourgeron 2007).

Melatonin is necessary for promoting sleep and quite a few studies have described reduced melatonin levels in ASD, as well as an abnormal circadian rythm (Nir et al. 1995). Reduced serum levels of melatonin have been found in both children and adults with ASD compared to controls (Kulman et al. 2000).

Even though there are no medications approved specifically for treating insomnia in children, melatonin is frequently used together with behavioral intervention (Singh et al. 2015).

A recent study found that a combination of data, on RP and other developmental data, included in the 18-month routine check-up at the CHC would help identify children in need of further neurodevelopmental assessments (Höglund Carlsson et al. 2016).

The current thesis study does *not* indicate that regulatory problems in infancy are definite precursors of ASD (or any other developmental disorder) but results suggest that children with a high level of RP in infancy and many consultations at the CHC, should be closely followed. This is important with regard to the child's general development and possible need of interventions but also when it comes to the well-being of the whole family.

Limitations and strengths in The Regulatory Study 5.2.1.1

A limitation of the study was that no specific protocols were used at the CHC to structurally collect data on regulatory problems. However, strengths included that the study used a representative non-ASD comparison group, that it comprised almost 200 children from a representative, community-based cohort of children with ASD and that the data was gathered before the child had received a diagnosis of ASD, so that it was, in effect, a semi-prospective study.

Study II – The Preschool to School Study 5.2.2

The study reported on the neuropsychiatric symptom/problem profiles at about 11 years of age of the children who had been assessed and diagnosed with ASD – at different cognitive levels – at ages between 2,0 and 4,5 years and then again two years later after ABA interventions.

More than 90% of children with a preschool diagnosis of ASD had remaining neuropsychiatric problems at age 11.

Generally, besides ASD, there were indications of very high rates of associated disorders, such as AD/HD, ID, ODD and DCD, in accordance with the ESSENCE and Autism Plus concepts (Gillberg 2010, Gillberg and Fernell 2014). There was, however, considerable discrepancies across the different cognitive groups. The group with ID had significantly higher A-TAC scores compared to the BIF and AIF groups, with regard to persisting ASD and co-occurring AD/HD and Learning disorder/ID.

ODD and DCD symptoms did not differ significantly between the cognitive groups. In a recent study (Kerekes et al. 2014), autistic-like social interaction problems were implicated as among the strongest neurodevelopmental covariates of ODD- and CD-like problems in both genders, which could explain why also many children with average intellectual functioning (and diagnoses of Asperger's syndrome) had high ODD-scores. Concerning DCD, it is difficult to know the reasons why these symptoms do not seem correlated with the children's intellectual level. It is perhaps possible that parents of children with ID may underestimate motor problems in their children because of significant difficulties in many other areas (academic achievements, speech/language, social and adaptive abilities).

Follow-up studies of representative cohorts of children with ASD into school age have been few. However, in one study (Towle et al. 2014), the school age outcome of 80 children, diagnosed with ASD at a young age, was examined with regard to diagnostic stability, developmental and behavioral functioning, adaptive and social functioning, medication use and school placement. The utility of relatively indirect methods (chart review and parent questionnaire) in the information gathering process was also investigated. The authors discussed that the methods used provided support for using relatively indirect methods in these kinds of studies. The results from that study seem to accord well with our findings in terms of ASD diagnostic stability and outcome at school age. In the Towle et al. study, 20% no longer had ASD diagnoses.

Limitations and strengths of the Preschool to School Study 5.2.2.1

A limitation of the study was that results at the school-age follow-up were based only on parental interviews. No clinical evaluation in person had been possible to arrange and no information had been collected from teachers. However, the study group was community-based and several data on each child had been collected at the previous clinical follow-up (T2). Although the attrition rate was 35%, no systematic differences between the participating group and the group who declined participation – with regard to background data – was found. Moreover, the A-TAC interview has been thoroughly validated and results from the interview have been found to correlate to clinical diagnoses.

Study III – The Borderline Intellectual Functioning Group Study 5.2.3

There have been few studies targeting children – with or without ASD – in the intellectual range between 70 and 84 i.e., between 1.0 to 2.0 standard deviations below average (the level between average intelligence and intellectual disability). With regard to intellectual function, children testing in this area are usually referred to as having a borderline intellectual functioning (BIF). These children have been reported to be at increased risk of chronic educational failure, absence from school, repetition of grades and drop-out from school. They do not meet eligibility criteria for special education as a student with ID but have remarkably high failure rates in the general education setting (Shaw 2008 a,b, Jankowska et al. 2012).

Children with ASD combined with BIF are usually referred to as high-functioning children, although their cognitive level is not within the high, but the low "normal" variation. The term high-functioning may therefore, in this group, be somewhat misleading. The term, again, highlights the need for cognitive assessments in all children with ASD in order to provide best possible education and support (Steffenburg and Gillberg 1986).

In our community-based group of 198 children with ASD who participated in a follow-up assessment before school start (T2), 50 children had BIF (again, this combination of ASD with BIF is what has vague-

ly, in older literature, often been equated with HFA). At T1 when the original study group of 208 children participated, 78 (38%) were considered to have a developmental delay/BIF, based on collected information from their assessment at a Child and Adolescent Mental Health Service (CAHMS) or a neuropediatric clinic (Fernell et al. 2010). At their very first assessment at or before ages between 2 and 4,5 years, several of these children had been difficult to test and it remained uncertain whether they had a developmental delay, ID or whether they were "actually" in the average range.

In the follow-up study (T3) presented in this thesis, cognitive and adaptive outcome and current functioning in different developmental areas were analyzed in this group of children with BIF at T2. Of the eligible 50 children 30 could be assessed with a new cognitive test at the T3 follow-up at school-age. Between T1 and T2 the children had received intervention of different types based on ABA (Fernell et al. 2011). Between T1 and T2 it was demonstrated that the BIF group, in comparison with children with ID or AIF, was less stable in terms of "intellectual profile trajectory" (Hedvall et al. 2014).

It has been pointed out that longitudinal studies that have assessed cognitive performance in children with intellectual disability several times in the course of their development are practically non-existent (Jenni et al. 2015). Studies following children with ASD and their different intellectual levels at various time-points are also few. In one study, 36 children with borderline to mild intellectual disability of unknown origin were examined in a retrospective clinical case series with standardized intelligence tests (Jenni et al. 2015). The authors concluded that although ID during childhood is a relatively stable phenomenon, individual stability of IQ is only moderate and is likely to be affected by test-to-test reliability (e.g. level of child's cooperation, motivation, and attention). Therefore, clinical decisions and predictions should not rely on single IQ assessments, but should also consider adaptive functioning, previous developmental history, and follow-up changes over time.

Parents of 41 of the 50 children with BIF in the present study were also interviewed with the Vineland and a semi-structured interview, and 36 parents took part in the A-TAC Interview (Barnevik-Olsson

et al. submitted). The main finding was that a high rate (90%) still met criteria for a clinical proxy for ASD or had definite subthreshold symptoms of ASD, and a high percentage (70%) had symptoms corresponding to AD/HD or subthreshold AD/HD. There was also a high degree of co-existence between these two disorders. Other areas of high problem load were speech and language problems, reported in 75% and behavior problems in 80% of the children. A consistency was observed between A-TAC scores and reports from the semi-structured interview, i.e., results were in agreement.

In addition to these impairments, 50% still met criteria for BIF and 20% now had an IQ level below 70, corresponding to mild ID, while 30% had cognitive results in the average IQ area.

In a meta-analysis of the stability of low IQ (IQ < 80) stability coefficients of .77 and .78 were found for Verbal IQ and Performance IQ and .82 for Full-Scale IQ (FS IQ) during an interval of 2,8 years. The majority of FS IQs changed by less than 6 points but 14% changed by 10 points or more. It was recommended that results of IQ assessments should be treated with more caution than previously thought (Whitaker 2008).

There are many studies reporting strong relationships between ASD or social-communication dysfunction traits on the one hand, and AD/HD or hyperactive traits on the other, in children and adolescents, supporting the evidence for the co-existence of ASD and AD/HD (St Pourcain et al. 2011, van der Meer et al. 2012, Musser et al. 2014). Besides shared genetic factors, this co-occurrence may be due to pre- and perinatal risk factors (Oerlemans et al. 2015).

In the present study it was evident that adaptive functioning in the majority of the children with BIF (i.e. children who would up until recently have been considered under the label HFA) had deteriorated over time – co-occurring with a situation when general support from habilitation services had diminished and higher demands had been placed on the children at school.

Taken together, the children's developmental profiles were complex and changing over time, resulting in great needs of educational support at school, and parental support. The findings from the study strongly suggest the need for continuing support – educationally, psychologically, and medically – for several years during middle childhood. The study revealed that the group with ASD and BIF (i.e. children with HFA) run the risk of not getting appropriate support since current societal systems (not least as reflected in recent Swedish system/organizational changes), to a large extent, restricts services to certain *diagnoses,* such as ID +/- ASD. Many children with combinations of developmental problems; autistic features, hyperactivity/impulsivity, attention deficits, language and behavioral problems, borderline intellectual functioning (i.e. with functionally impairing ESSENCE) – but not a formal intellectual disability diagnosis – do not receive appropriate support from habilitation, education or society more generally.

5.2.3.1 *Limitations and strengths of the Borderline Intellectual Functioning Group Study*

In this study, only 30 of the 50 children who had BIF at T2 could be assessed with a new cognitive test at school age. However, 41 of the children had parents who took part in both the VABS and the semi-structured interview, which corresponded well to one another. An important strength is the focus on this exposed BIF (HFA) group, as very few studies have focused specifically on these children in the follow-up studies that have been performed to date.

5.2.4 Study IV – The Growing Out of Autism Study

Children who did not meet full criteria for ASD at school start followed for another four years

The main findings in this study was that 20% of the children with ASD combined with BIF or AIF, who at the T2 follow-up no longer met full criteria for ASD (i.e. those who were considered to have "grown out of autism"), again did so at around eleven years of age at the second follow-up (T3).

Although Autistic Disorder is a reasonably stable diagnosis, a significant minority of children will no longer meet diagnostic criteria after

a period of follow-up (Woolfenden et al. 2012). It has been pointed out that there is a need for longer term, population cohort studies measuring diagnostic stability, and that moving "off the spectrum" does not mean that children will not still have significant problems with communication and or behavior. This stance is well in line with the findings from Study IV where children – who at the first follow-up assessment before school start, no longer had fully met criteria for ASD – were targeted for a second follow-up. This subgroup accounted for about 10% of the total original child cohort, which is consistent with many other studies on diagnostic stability of an ASD diagnosis in young children (Charman et al. 2005, Lord et al. 2006).

At the second follow-up, at early mid-school age, it was evident that major problems in several "ESSENCE" areas remained. Parents reported in interviews on child problems with speech and language, attention and activity regulation, with social interaction and peer relationships, as well as with behavior more generally (including throwing tantrums). Despite the fact that these children at first follow-up were found to have average IQ or BIF, many now had major academic problems in school. Results from the A-TAC interviews showed that some children again met criteria for a clinical proxy for ASD, and also for AD/HD and tic disorder. Only parents of two children in total reported no major problems while half of the children had levels corresponding to at least two clinical disorders. In the VABS-II interview, a majority of the children had decreased scores, (i.e. deteriorated in adaptive functioning), a smaller group had stable results and very few had increased their adaptive scores.

At a group level, these children had lower rates of autism symptoms, but their adaptive functioning had not improved accordingly, as measured by the VABS. This finding may partly be explained by the children's co-occurring problems, i.e., with AD/HD, which in itself has a negative impact on adaptive functioning (Lindblad et al. 2013).

Few children had had any pediatric, neurological, or neuropsychiatric follow-up outside of the study. This group was not considered entitled to any type of individual support from a habilitation center but several parents reported that they would have needed such an individual con-

tact. Now, at school age, the children's developmental disorders and difficulties had a different character but it was evident that they were at least as challenging as those at preschool age.

Above all, the study indicates that most preschool children, once diagnosed with ASD – at further follow-up many years later, even after having received appropriate intervention for a few years in the preschool period – still have different combinations of neurodevelopmental/neuropsychiatric problems at school age, and that some again meet full criteria for ASD. The vast majority of children have a variety of impairing problems that accord with the umbrella term of ESSENCE.

5.2.4.1 Limitations and strengths in The Growing Out of Autism Study

Study limitations include the small number of cases and the fact that, at T3, information was based only on parent report in telephone interviews. The T2 assessment was considerably more extensive with visits to different members of the study team, including cognitive testing and a questionnaire completed by preschool staff, apart from parental interviews. Another limitation is the lack of a comparison group consisting of age- and IQ-matched children still meeting criteria for ASD (but this has, in effect, been accomplished through comparison with the findings obtained in Study II).

6 CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

The major findings from the four studies of the present thesis were that children diagnosed with ASD at preschool age, and thereafter having received appropriate early intervention for two years: (1) had had very high rates of RP many months-years before being diagnosed, (2) still suffered from a wide variety of ASD/developmental/neuropsychiatric symptoms at mid-school age and were impaired in their adaptive functioning, and (3) that this was true whether or not the children had originally fallen into the HFA (BIF) group, or (4) that they had been considered having "out-grown autism" after intervention. A tiny minority (one to two per cent of the whole cohort) appeared to be "problem-free" in the middle school years. The longitudinal findings from this unique representative ASD study cohort clearly elucidate the clinical relevance of the ESSENCE concept.

The very early symptoms that may be recorded at CHCs also indicate that nurses and physicians seeing infants and young children, need to be attentive to signs that may be indicative of neurodevelopmental deviations. On the basis of the results obtained in the RP study, we would suggest that data on RP should be gathered in a structured way at CHCs since such information can help in the evaluation of children with developmental disorders.

An early diagnosis of ASD (and other developmental disorders) is important so as to provide a basis for information to parents, preschool teachers and others about the child's underlying cognitive impairment and the associated developmental and behavioral symptoms. Many parents of the children in the study expressed the value of participating in the parental education programs that the habilitation center offered. Information will also help to make adjustments and adaptations in the child's daily routines and environment. Interventions need to be individually and adequately adapted to enable the best possible

development for the child, positively influence the child's self-esteem and to reduce the risk of mental illness.

The school age follow-up revealed that the vast majority of children had difficulties within many developmental areas and that they were or appeared to be in need of specific educational measures and more support at school. Also the parents needed, or would have needed an individualized contact with a habilitation center, to meet their own and their child's needs. Children and parents had been part of specific and comprehensive intervention programs, based on ABA techniques, during the preschool period, but it was evident that this support, in the vast majority of children, had diminished considerably – or indeed disappeared completely – when the child had reached school age. Unfortunately, there are few schools providing adapted education and classes for children with ASD. Regular schools of today place high demands on their students, not least regarding requirements of well developed communication and executive functions, i.e., two of the core cognitive deficits in ASD.

A problem in many western society/habilitation care systems of today is that support is based on diagnostic categories and not on an assessment of what the child's difficulties entail in daily life. Cognitive/neurodevelopmental/neuropsychiatric diagnoses currently "entitling" to a guaranteed support from society are ID and ASD. In Sweden, individuals with these diagnoses can receive care from habilitation centers, are eligible for Support and Services for Persons with Certain Functional Impairments, SSF (see LSS in Swedish) and parents are entitled to apply for a monthly care allowance. Children with combinations of autistic features, BIF, ADHD, speech and language disorder and different types of behavioral problems are not given the same sort of support, in spite of the fact that the legislation, as such, does not put up a bar.

Children with ASD, and children with other developmental disorders, need multi-disciplinary assessments and follow-ups continuously throughout the school years. Such broad assessments should also include medical/etiological aspects. This thesis has not specifically analyzed underlying medical aspects in this cohort, but this has been the theme of another thesis from our group (Eriksson M.A. 2013).

The modern view of autism based on knowledge about its biological/neurological roots, expanded during the 1980's (Gillberg and Coleman 1985, Gillberg et al. 1987, Coleman and Gillberg 2012) and had an enormous impact in society in many parts of the world. The view considerably influenced treatment, intervention, habilitation and support to this patient group and their families. Even so, it is becoming clear that medical (including "simple" things such as testing of vision and hearing) and psychological (including repeated neuropsychological testing at various time-points during development) aspects of autism are again becoming neglected in the focus on "autism only" and "autism-specific interventions".

This thesis hopefully adds to the understanding of ASD in its different presentations from preschool to school, and as one of several groups of disorders/symptom complexes in the broad context of ESSENCE. Autism is one of the many "Plus Disorders" under the ESSENCE umbrella. Young children diagnosed with ASD usually have Autism Plus; they will have had "non-autism" *and* "autism" problems before diagnosis, and will continue to have such problems long after "autism interventions" have finished. The need for very long-term follow-up and support to all families of preschool children with Autism Plus (even when the children no longer meet criteria for ASD at a specific time point during development and even when they have received appropriate intervention in the early years) is evident.

With regard to continued research, there is a need for long-term follow-up studies, of at least ten years, to evaluate different types of early interventions. These follow-up studies should include repeated assessments covering different developmental/behavioral areas, and take place at defined time intervals over the study period. There is a need both for Randomized Control Trials, and of prospective studies planned in the child's naturalistic setting. Moreover and optimally, outcome studies should compare etiologically and cognitively similar groups, meaning that total numbers will have to be very large indeed.

Another expanding and very important research area is genetics in the field of ASD and other cognitive disorders. It is generally of great importance for parents if an etiological diagnosis can be established.

Such information will entail a better understanding of the child's overall clinical situation, help in genetic counseling and also involve possibilities to give more realistic perspectives on prognostic factors.

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APPENDIX

A-TAC: FV
Child and adolescent version

This questionnaire is in particular detail focused on a number of abilities and behaviours in children. All children are different from one another. This means that their abilities in various areas as well as their conduct and behaviour vary a great deal.

To gain as complete a picture as possible of your child, we ask you to answer a considerable number of questions.

Naturally, children function in different ways at different ages. State your perception of your child's functioning as compared to his or her peers. If your child has had a certain problem or specific characteristic during *any period of life*, answer the question with "yes" even if the problem or characteristic is no longer present.

Name of child/youth: _____

Date of birth/personal identity number: _____

Age: _____ **Sex:** _____

Date of interview: _____

Informant (the person answering the questions): _____

Informant's relationship to the child/youth (i.e. mother, father, etc): _____

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A. Motor control	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
1	Does he/she have problems coordinating movements smoothly?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to this question:			
A1	Is he/she clumsy?	☐	☐	☐
A2	Is he/she fumbling?	☐	☐	☐
A3	Does he/she have balance problems?	☐	☐	☐
A4	Does he/she easily stumble and fall?	☐	☐	☐
A5	Have the peculiarities or problems relating to motor control caused significant impairment in school, among peers or at home?	☐	☐	☐
A6	Do the peculiarities or problems relating to motor control cause him/her significant suffering?	☐	☐	☐
A7	At what age did the peculiarities or problems relating to motor control commence?	Age:		
A8	Are they still present?	Yes ☐	No ☐	

B. Perception	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
2	Does he/she seem disturbed by height differences such as in connection with climbing stairs etc.?	☐	☐	☐
3	Does he/she have difficulty judging distance or size?	☐	☐	☐
4	Is he/she oversensitive to touch or tight clothing?	☐	☐	☐
5	Is he/she particularly sensitive to certain sounds/noise?	☐	☐	☐
6	Is he/she particularly sensitive to certain flavours, smells, or consistencies?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
B1	Does he/she have difficulty comprehending orientation and spatial directions, e.g. puts clothes on backwards?	☐	☐	☐
B2	Does he/she often bump into other people?	☐	☐	☐
B3	Does he/she have poor concepts of time?	☐	☐	☐
B4	Does he/she have difficulty imitating other people's movements?	☐	☐	☐
B5	Does he/she have difficulty recognizing people?	☐	☐	☐
B6	Have the peculiarities or problems relating to perception caused significant impairment in school, among peers or at home?	☐	☐	☐
B7	Do the peculiarities or problems relating to perception cause him/her significant suffering?	☐	☐	☐
B8	At what age did the peculiarities or problems relating to perception commence?	Age:		
B9	Are they still present?	Yes ☐	No ☐	

C. Concentration and attention	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
7	Does he/she often fail to pay close attention to details or make careless mistakes in schoolwork, or other activities?	☐	☐	☐
8	Does he/she often have difficulty sustaining attention in tasks or play activities?	☐	☐	☐
9	Does he/she often seem not to listen when spoken to directly?	☐	☐	☐
10	Does he/she have difficulty following instructions and finishing tasks?	☐	☐	☐
11	Does he/she often have difficulty organizing tasks and activities?	☐	☐	☐
12	Does he/she often avoid tasks that require sustained mental effort (such as homework)?	☐	☐	☐
13	Does he/she often lose things?	☐	☐	☐
14	Is he/she easily distracted or disturbed?	☐	☐	☐
15	Is he/she often forgetful in daily activities?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
C1	Does he/she have difficulty getting started on tasks/activities?	☐	☐	☐
C2	Does he/she have difficulty completing tasks/activities?	☐	☐	☐
C3	Have the peculiarities or problems relating to concentration and attention caused significant impairment in school, among peers or at home?	☐	☐	☐
C4	Do the peculiarities or problems relating to concentration and attention cause him/her significant suffering?	☐	☐	☐
C5	At what age did the peculiarities or problems relating to concentration and attention commence?	Age:		
C6	Are they still present?	Yes ☐	No ☐	

D. Impulsiveness and activity	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
16	Does he/she have difficulties keeping his/her hands and feet still or can he/she not stay seated?	☐	☐	☐
17	Does he/she get up and move about in class or in other situations when he/she is supposed to remain seated?	☐	☐	☐
18	Does he/she often run around or climb excessively compared to peers?	☐	☐	☐
19	Does he/she have difficulty playing calmly and quietly?	☐	☐	☐
20	Does he/she often act as though he/she had "ants in his/her pants", i.e. being unable to stay still?	☐	☐	☐
21	Does he/she talk constantly?	☐	☐	☐
22	Does he/she often blurt out answers to questions before they are completed?	☐	☐	☐
23	Does he/she have difficulty waiting for his/her turn?	☐	☐	☐
24	Does he/she often interrupt, or intrude on, others?	☐	☐	☐
25	Does he/she easily get bored?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
D1	Is he/she unusually intrepid in physically dangerous situations?	☐	☐	☐
D2	Have the peculiarities or problems relating to impulsiveness and activity caused significant impairment in school, among peers or at home?	☐	☐	☐
D3	Do the peculiarities or problems impulsiveness and activity cause him/her significant suffering?	☐	☐	☐
D4	At what age did the peculiarities or problems relating to impulsiveness and activity commence?	Age:		
D5	Are they still present?	Yes ☐	No ☐	

E. Learning	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
26	Has he/she had more difficulties than expected acquiring reading skills?	☐	☐	☐
27	Is learning slow and laborious for him/her?	☐	☐	☐
28	Does he/she have difficulties with basic maths?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
E1	Is he/she a slow reader?	☐	☐	☐
E2	Does he/she dislike reading (e.g. does he/she avoid reading books)?	☐	☐	☐
E3	Does he/she have difficulties solving maths problems, which require him/her to read written material?	☐	☐	☐
E4	Does he/she have difficulties understanding or using abstract terms?	☐	☐	☐
E5	Does he/she have difficulties spelling?	☐	☐	☐
E6	Does he/she get special education in school?	☐	☐	☐
E7	Have peculiarities or problems relating to learning caused significant impairment in school, among peers or at home?	☐	☐	☐
E8	Do the peculiarities or problems relating to learning cause him/her significant suffering?	☐	☐	☐
E9	At what age did the peculiarities or problems relating to learning commence?	Age:		
E10	Are they still present?	Yes ☐ No ☐		

F. Planning and organizing tasks	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
29	Does he/she have difficulty shifting plan or strategy when this is required?	☐	☐	☐
30	Does he/she have difficulty keeping things in order around him/her?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
F1	Does he/she have difficulties understanding consequences of his/her own actions?	☐	☐	☐
F2	Is he/she dependent and very much in need of support?	☐	☐	☐
F3	Does he/she find it difficult to take care of his/her personal hygiene, his/her clothes, and the like?	☐	☐	☐
F4	Does he/she have difficulties in postponing rewards until later and finding the meaning in things that are not immediately rewarding?	☐	☐	☐
F5	Does he/she experience simple, everyday activities as tiring or energy consuming?	☐	☐	☐
F6	Have peculiarities or problems relating to planning and organizing tasks caused significant impairment in school, among peers or at home?	☐	☐	☐
F7	Do the peculiarities or problems relating to planning and organizing tasks cause him/her significant suffering?	☐	☐	☐
F8	At what age did the peculiarities or problems relating to planning and organizing tasks commence?	Age:		
F9	Are they still present?	Yes ☐ No ☐		

G. Memory	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
31	Does he/she have difficulties remembering where he/she put things?	☐	☐	☐
32	Does he/she have difficulties remembering long or multiple-step instructions?	☐	☐	☐
33	Does he/she have difficulties learning rhymes, songs, multiplication tables etc by heart?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
G1	Does he/she have difficulties remembering information about personal data, such as date of birth, home address etc.?	☐	☐	☐
G2	Does he/she have difficulties remembering the names of people around him?	☐	☐	☐
G3	Does he/she have difficulties remembering the names of weekdays, months and seasons?	☐	☐	☐
G4	Does he/she have difficulties remembering non-personal facts learned at school (e.g. historic events, chemical formulas etc.)?	☐	☐	☐
G5	Does he/she have difficulty remembering specific events that he/she recently experienced, e.g. what happened during the day or, what he/she ate a few hours ago etc.?	☐	☐	☐
G6	Does he/she have difficulties remembering events that occurred some time ago, such as what happened on a trip, what Christmas presents he/she got etc.?	☐	☐	☐
G7	Does he/she have difficulties remembering appointments with peers or what homework he/she has?	☐	☐	☐
G8	Does he/she have difficulties learning the rules of new games, sports etc.?	☐	☐	☐
G9	Have peculiarities or problems relating to memory caused significant impairment in school, among peers or at home?	☐	☐	☐
G10	Do the peculiarities or problems relating to memory cause him/her significant suffering?	☐	☐	☐
G11	At what age did the peculiarities or problems relating to memory commence?	Age:		
G12	Are they still present?	Yes ☐	No ☐	

H. Language	The essential aspect of each question is whether the problems/characteristics has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
34	Was his/her language development delayed or doesn't he/she speak at all?	☐	☐	☐
35	Does he/she have difficulties sustaining a conversation?	☐	☐	☐
36	Does he/she like to repeat words and expressions or does he/she use words in a way that other people find strange?	☐	☐	☐
37	Does he/she have difficulties with games of make-believe or does he/she imitate others considerably less than other children?	☐	☐	☐
38	Does he/she talk in too high a pitch or too quietly?	☐	☐	☐
39	Does he/she have difficulties keeping "on track" when telling other people something?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
H1	Does he/she have difficulties expressing him/herself in whole sentences?	☐	☐	☐
H2	Does he/she speak in a monotonous or strange voice?	☐	☐	☐
H3	Does he/she have difficulties explaining/recounting his/her experiences to other people?	☐	☐	☐
H4	Does he/she have difficulties explaining what he/she wants?	☐	☐	☐
H5	Does he/she have difficulties speaking fluently, without any pauses?	☐	☐	☐
H6	Does he/she have difficulties pronouncing complex words?	☐	☐	☐

H7	Does he/she explain emotions verbally so that other people have difficulty understanding what he/she means?	☐	☐	☐
H8	Does he/she use strange neologisms, old-fashioned words, or too elegant words?	☐	☐	☐
H9	Does he/she speak so rapidly that it is difficult to comprehend what he/she is saying?	☐	☐	☐
H10	Have peculiarities or problems relating to language caused significant impairment in school, among peers or at home?	☐	☐	☐
H11	Do the peculiarities or problems relating to language cause him/her significant suffering?	☐	☐	☐
H12	At what age did the peculiarities or problems relating to language commence?	Age:		
H13	Are they still present?	Yes ☐	No ☐	

I. Social interaction	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
40	Does he/she have difficulties expressing emotions and reactions with facial gestures, prosody, or body language?	☐	☐	☐
41	Does he/she exhibit considerable difficulties interacting with peers?	☐	☐	☐
42	Is he/she uninterested in sharing joy, interests, and activities with others?	☐	☐	☐
43	Can he/she only be with other people on his/her terms?	☐	☐	☐
44	Does he/she have difficulties behaving as expected by peers?	☐	☐	☐
45	Do other people easily influence him/her?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
I1	Is he/she self-centred?	☐	☐	☐
I2	Is he/she perceived as different, odd, or eccentric by peers?	☐	☐	☐
I3	Does he/she have difficulty understanding other people's social cues, e.g., facial expressions, gestures, tone of voice, or body language?	☐	☐	☐
I4	Does he/she have difficulty understanding the feelings of other people?	☐	☐	☐
I5	Does he/she have difficulty showing other people respect?	☐	☐	☐
I6	Does he/she get overly excited when there are a lot of people around?	☐	☐	☐
I7	Does he/she often leave in the middle of a conversation, or abruptly change the topic of a conversation?	☐	☐	☐
I8	Does he/she have difficulty realising how to behave in different social situations?	☐	☐	☐
I9	Does he/she inadvertently make a fool of him/herself or does he/she make embarrassing remarks?	☐	☐	☐
I10	Does he/she often seem to lack common sense?	☐	☐	☐
I11	Does he/she have difficulty with eye contact?	☐	☐	☐
I12	Does he/she think that relationships are not very important or does he/she prefer to be on his/her own?	☐	☐	☐
I13	Is his/her body language awkward, gauche, clumsy, strange or unusual?	☐	☐	☐
I14	Does he/she have difficulty interpreting what is conveyed through eye contact?	☐	☐	☐
I15	Is his/her gaze stiff, strange, peculiar, abnormal or odd?	☐	☐	☐
I16	Have peculiarities or problems relating to social interaction caused significant impairment in school, among peers or at home?	☐	☐	☐
I17	Do the peculiarities or problems relating to social interaction cause him/her significant suffering?	☐	☐	☐
I18	At what age did the peculiarities or problems relating to social interaction commence?	Age:		
I19	Are they still present?	Yes ☐	No ☐	

J. Flexibility		The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
46	Does he/she get absorbed by his/her interests in such a way as being repetitive or too intense?		☐	☐	☐
47	Does he/she get absorbed by routines in such a way as to produce problems for him/herself or others?		☐	☐	☐
48	Has he/she ever engaged in strange hand movements or toe-walking when he/she was happy or upset?		☐	☐	☐
49	Does he/she get obsessed with details?		☐	☐	☐
50	Does he/she dislike changes in daily routines?		☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:				
J1	Have peculiarities or problems relating to flexibility caused significant impairment in school, among peers or at home?		☐	☐	☐
J2	Do the peculiarities or problems relating to flexibility cause him/her significant suffering?		☐	☐	☐
J3	At what age did the peculiarities or problems relating to flexibility commence?		Age:		
J4	Are they still present?		Yes ☐ No ☐		

K. Tics		The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
51	Has he/she during any period of life made involuntary sounds such as throat clearing, sneezing, swallowing, barking, or shouting?		☐	☐	☐
52	Has he/she during any period of life made involuntary facial grimaces or body movements?		☐	☐	☐
53	Does he/she make a lot of noise, e.g. whistle, hum, mumble?		☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:				
K1	Does he/she curse or use dirty words in an exaggerated way?		☐	☐	☐
K2	Have peculiarities or problems relating to tics caused significant impairment in school, among peers or at home?		☐	☐	☐
K3	Do the peculiarities or problems relating to tics cause him/her significant suffering?		☐	☐	☐
K4	At what age did the peculiarities or problems relating to tics commence?		Age:		
K5	Are they still present?		Yes ☐ No ☐		

L. Compulsions		The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
54	Does he/she have obsessive thoughts, i.e. thoughts that recur over and over again and that he/she cannot stop, for example about dirt, contagion or that something terrible will happen?		☐	☐	☐
55	Does he/she have compulsive behaviours such as washing his/her hands, touching things, checking on things, repeating things or procedures, arranging or ordering things, or counting?		☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:				
L1	Have peculiarities or problems relating to compulsions caused significant impairment in school, among peers or at home?		☐	☐	☐

L2	Do the peculiarities or problems relating to compulsions cause him/her significant suffering?	☐	☐	☐
L3	At what age did the peculiarities or problems relating to compulsions commence?	Age:		
L4	Are they still present?	Yes ☐ No ☐		

M. Eating habits	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
56	Has he/she ever failed to gain enough weight for more than a year or been underweight?	☐	☐	☐
57	Has he/she appeared to be fearful of gaining weight or becoming fat?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
M1	Has he/she dieted hard enough to cause underweight or no weight gain for any length of time?	☐	☐	☐
M2	Has he/she exercised excessively or has he/she been overly interested in his/her physical appearance?	☐	☐	☐
M3	Females only: Has she failed to menstruate for at least 3 months due to weight loss?	☐	☐	☐
M4	Has he/she had periods of overeating followed by vomiting?	☐	☐	☐
M5	Has he/she ever tried to lose weight in spite of already being thin?	☐	☐	☐
M6	Has he/she ever had anorexia nervosa?	☐	☐	☐
M7	Have peculiarities or problems relating to eating caused significant impairment in school, among peers or at home?	☐	☐	☐
M8	Do the peculiarities or problems relating to eating cause him/her significant suffering?	☐	☐	☐
M9	At what age did the peculiarities or problems relating to eating commence?	Age:		
M10	Are they still present?	Yes ☐ No ☐		

N. Separations	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
58	Does he/she have difficulties functioning outside the family home?	☐	☐	☐
59	Does he/she often voice fears that family members may die or get hurt?	☐	☐	☐
60	Does he/she have an unreasonable fear of being alone or home alone?	☐	☐	☐
61	Does he/she have difficulty sleeping if family members are not around?	☐	☐	☐
62	Does he/she complain about recurring headaches, bellyaches, nausea or vomiting after being separated from loved ones?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
N1	Does he/she have difficulty leaving home to go to school for fear of being separated from his/her family?	☐	☐	☐
N2	Does he/she have recurring nightmares about being separated from the family?	☐	☐	☐
N3	Does he/she react unusually strongly when friendships or other close relationships come, or are about to come, to an end?	☐	☐	☐
N4	Have peculiarities or problems relating to separation caused significant impairment in school, among peers or at home?	☐	☐	☐
N5	Do the peculiarities or problems relating to separation cause him/her significant suffering?	☐	☐	☐
N6	At what age did the peculiarities or problems relating to separation commence?	Age:		
N7	Are they still present?	Yes ☐ No ☐		

O+P. Defiance/Conduct	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
63	Has there ever been a time when he/she was so angry that he/she could not be reached?	☐	☐	☐
64	Does he/she often argue with adults?	☐	☐	☐
65	Does he/she often tease others by deliberately doing things that are perceived as provocative?	☐	☐	☐
66	Is he/she easily offended, or disturbed by others?	☐	☐	☐
67	Is he/she easily teased?	☐	☐	☐
68	Does he/she often lie or cheat?	☐	☐	☐
69	Has he/she ever engaged in shoplifting?	☐	☐	☐
70	Has he/she ever deliberately been physically cruel to anybody?	☐	☐	☐
71	Does he/she often get into fights?	☐	☐	☐
72	Does he/she steal things at home or away from home?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
O1	Does he/she often lose his/her temper?	☐	☐	☐
O2	Does he/she often refuse to follow other directives from adults?	☐	☐	☐
O3	Is he/she often vindictive or cruel?	☐	☐	☐
O4	Does he/she often treat people close to him/her badly or without respect?	☐	☐	☐
O5	Does he/she often blame others for his/her own mistakes?	☐	☐	☐
P1	Does he/she often threaten, harass or humiliate others?	☐	☐	☐
P2	Is he/she cruel to bugs/insects?	☐	☐	☐
P3	Is he/she cruel to other animals?	☐	☐	☐
P4	Has he/she ever started a fire?	☐	☐	☐
P5	Has he/she ever sexually abused other children?	☐	☐	☐
P6	Has he/she ever been detained by the police?	☐	☐	☐
P7	Has he/she ever used a weapon that could cause serious physical harm?	☐	☐	☐
P8	Has he/she ever robbed anyone or else unlawfully acquired other people's property by means of direct threats?	☐	☐	☐
P9	Has he/she ever purposely attempted to destroy other people's property?	☐	☐	☐
P10	Has he/she ever broken into someone else's home, premises or car?	☐	☐	☐
P11	Is he/she often out late at night without consent (beginning before 13 years of age)?	☐	☐	☐
P12	Has he/she ever run away from home and spent the night elsewhere at least twice (or once if it was for an extended period of time)?	☐	☐	☐
P13	Is he/she often skipping school (beginning before 13 years of age)?	☐	☐	☐
OP14	Have peculiarities or problems relating to defiance/conduct caused significant impairment in school, among peers or at home?	☐	☐	☐
OP15	Do the peculiarities or problems relating to defiance/conduct cause him/her significant suffering?	☐	☐	☐
OP16	At what age did the peculiarities or problems relating to defiance/conduct commence?	Age:		
OP17	Are they still present?	Yes ☐	No ☐	

Q. Anxiety	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
73	Does he/she have panic attacks with sudden strong fear or anxiety?	☐	☐	☐
74	Does he/she fear leaving the house alone, being in crowds, waiting in line or going on a bus or train?	☐	☐	☐
75	Is he/she often particularly nervous or anxious?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
Q1	Is he/she extremely shy and reticent?	☐	☐	☐
Q2	Is he/she silent in situations where you are not expected to be silent?	☐	☐	☐
Q3	Is there anything he/she fears doing in front of other people, i.e. talking, eating or writing (excluding presentations of reports)?	☐	☐	☐
Q4	Have peculiarities or problems relating to anxiety caused significant impairment in school, among peers or at home?	☐	☐	☐
Q5	Do the peculiarities or problems relating to anxiety cause him/her significant suffering?	☐	☐	☐
Q6	At what age did the peculiarities or problems relating to anxiety commence?	Age:		
Q7	Are they still present?	Yes ☐ No ☐		

R. Mood	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
76	Does he/she have poor self-confidence?	☐	☐	☐
77	Does he/she often complain about bellyaches, headaches, breathing difficulties or other bodily symptoms?	☐	☐	☐
78	Has he/she had recurrent episodes with extremely high activity level, talkativeness and flight of ideas?	☐	☐	☐
79	Does he/she have recurrent periods of obvious irritability?	☐	☐	☐
80	Does his/her self-confidence vary considerably across different situations?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to any of these questions:			
R1	Does he/she often appear to be unhappy, sad, or depressed?	☐	☐	☐
R2	Does he/she often complain about a feeling of loneliness?	☐	☐	☐
R3	Does he/she often express a feeling of being worthless or inferior to peers?	☐	☐	☐
R4	Has there ever been a period when nothing could make him/her feel happy?	☐	☐	☐
R5	Has he/she been thinking of or talked about committing suicide?	☐	☐	☐
R6	Has he/she tried to commit suicide?	☐	☐	☐
R7	Has he/she often had a feeling of emptiness?	☐	☐	☐
R8	Does he/she feel that his/her qualities and talents are ignored by others?	☐	☐	☐
R9	Have peculiarities or problems relating to his/her mood caused significant impairment in school, among peers or at home?	☐	☐	☐
R10	Do the peculiarities or problems relating to his/her mood cause him/her significant suffering?	☐	☐	☐
R11	At what age did the peculiarities or problems relating to his/her mood commence?	Age:		
R12	Are they still present?	Yes ☐ No ☐		

S. Concept of reality	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
81	Has he/she ever had visions or seen things that no one else could see?	☐	☐	☐
	If "Yes" or "Yes, to some extent" to this question:			
S1	Has he/she ever perceived him/herself as being followed or haunted by others even though this has not actually been the case?	☐	☐	☐
S2	Has he/she ever heard voices or sounds, which no one else could hear?	☐	☐	☐
S3	Have peculiarities or problems relating to concept of reality caused significant impairment in school, among peers or at home?	☐	☐	☐
S4	Do the peculiarities or problems relating to concept of reality cause him/her significant suffering?	☐	☐	☐
S5	At what age did the peculiarities or problems relating to concept of reality commence?	Age:		
S6	Are they still present?	Yes ☐ No ☐		

T. Miscellaneous	The essential aspect of each question is whether the problem/peculiarity has been **pronounced compared to peers during any period of life**	Yes	Yes, to some extent	No
82	Does he/she stutter?	☐	☐	☐
83	Is he/she or has she/she ever been bullied by other children in school?	☐	☐	☐
84	Has he/she ever been severely overweight?	☐	☐	☐
85	Does he/she often have sleeping problems?	☐	☐	☐
86	Does he/she often have nightmares?	☐	☐	☐
87	Does he/she often walk in his/her sleep or have nocturnal attacks when he/she cannot be "reached" or comforted?	☐	☐	☐
88	Has he/she ever deliberately hurt him/herself?	☐	☐	☐
89	Has he/she repeatedly and purposely hurt him/herself?	☐	☐	☐
90	Is there anything he/she fears excessively, such as flying, see blood, have an injection, heights, cramped rooms, or certain kind of animals or insects?	☐	☐	☐
91	Has he/she wet him/herself during daytime on several occasions after the age of 5?	☐	☐	☐
92	Has he/she soiled him/herself on several occasions after the age of 4 except in connection with gastro-intestinal infection?	☐	☐	☐
93	Does he/she smoke?	☐	☐	☐
94	Does he/she use any other form of tobacco?	☐	☐	☐
95	Has he/she ever used alcohol?	☐	☐	☐
96	Has he/she ever had a period after age 5 when he/she only wanted to eat particular types of food?	☐	☐	☐