SCREENING AND DIAGNOSIS OF AUTISM SPECTRUM DISORDERS

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ABSTRACT

Objectives: Develop and examine a new screening and diagnostic framework for autism spectrum disorders (ASD), and study the prevalence of ASD in 2-year-old children in Gothenburg. **Methods:** Psychometric properties of the Swedish version of the Diagnostic Interview for Social and COmmunication disorders (DISCO) were examined in 91 patients aged 2-40 years referred for assessment of ASD. Twenty-one children screening positive for language delay at the Child Health Centres (CHCs) at 2.5 years were followed up with comprehensive neuropsychiatric assessments at 7.5 years. Another CHC general population sample of several thousand 2.5-year-olds was screened for ASD using the Modified Checklist for Autism in Toddlers (M-CHAT) and a new joint attention observation measure, the JA-OBS. Children screening positive for ASD were given very comprehensive ASD diagnostic assessments (including the DISCO) in a specialised centre. Prevalence rates for ASD in one age cohort were estimated. Some psychometric properties of the CHC screening instruments were examined. **Results:** The psychometric properties of the DISCO were found to be good to excellent. In the "language cohort" 13/21children had a neuropsychiatric disorder at the age of 7 years (of whom several had ASD). The prevalence of ASD in 2-year-olds in 2010 was 0.80%. Corresponding rates for 2-year-olds referred to the specialised centre in 2000 and 2005 (when no population screening had occurred) were 0.18% and 0.04%. The Positive Predictive Value (PPV) for the combination of M-CHAT (+ M-CHAT interview) and the JA-OBS was 90%, and the sensitivity 96%. **Discussion:** ASD is a relatively common neurodevelopmental disorder that can be detected at high rates already at child age 2 years (prevalence 0.80%). The DISCO appears to be a good instrument in diagnostic assessment both for clinical use and in research. A positive language screen at age 2.5 years should be regarded as an indicator of other possible neurodevelopmental problems, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE), including ASD. The combination of instruments, M-CHAT and JA-OBS, has excellent PPV and sensitivity and the new screening programme shows promise for early detection of ASD as a routine in the developmental program at CHCs. Trained medical staff is a basic requirement and enables earlier detection and the use of screening tools also beyond routine population screening regardless of the age at which a suspicion of autism is raised. Crucial for screening are effective routines for further diagnostic assessments and interventions without delay.

Keywords: autism spectrum disorder (ASD), prevalence, early symptoms, screening, diagnostic assessment, M-CHAT, JA-OBS, DISCO, ESSENCE

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SAMMANFATTNING PÅ SVENSKA

Under det senaste årtiondet har kunskapen om autism ökat inom vården och i samhället i stort. Aktuella studier från Europa och USA visar en prevalens kring 0.6-1.1% för autismspektrumstörning (ASD), vilket innebär en stark ökning av den rapporterade prevalensnivån jämfört med den som angivits för cirka tjugo år sedan. Det finns en större medvetenhet både bland professionella och hos allmänheten om att svårigheter inom autismspektrum kan yttra sig mycket varierande och i olika grad. Det gemensamma är betydande funktions-nedsättningar i förmåga till socialt samspel och kommunikation samtidigt med begränsningar och avvikelser i beteende och intressen. Den biologiska bakgrunden är komplex och olika från individ till individ.

Under de senaste åren har internationell autismforskning i ökande grad fokuserats på symptom under de första levnadsåren och på studier av tidiga behandlingsinsatser. Vissa studier har givit stöd för betydelsen av tidiga behandlingsinsatser när det gäller symptombild och för barnets fortsatta utveckling. Detta är en viktig utgångspunkt för den fortsatta strävan att finna metoder för tidig upptäckt av autism.

Kunskapen om tidiga symptom bygger fram för allt på uppföljningsstudier av s.k. högrisk-barn (syskon till barn med autism) vilka senare bekräftats ha autism, på beskrivningar från föräldrar och på jämförande studier av filmer av barn med typisk utveckling och barn som senare konstaterats ha autism. Olika symptom kan noteras, bl.a. avvikelser i rörelsemönster och reaktioner på sinnesintryck. Centralt i symptombilden är en avvikande utveckling i förmågan till delad uppmärksamhet (”joint attention”), d.v.s. förmågan till ömsesidighet i samspelet med andra. En sådan avvikelse kan noteras tidigt hos ett barn och innebär ett hinder i den fortsatta utvecklingen av kommunikation och socialt samspel. Olika metoder för screening har prövats och i olika åldrar. Fortsatt är det vetenskapliga underlaget svagt när det gäller screening före 2-års ålder. Valet av tidpunkt och metod för screening är relaterat till kunskapen om diagnostik vid ASD. Det finns ett litet antal studier som visar att en ASD-diagnos som ställs då barnet är i 2-3-års-åldern oftast är stabil.

I det första delarbetet (Studie I) behandlas ämnet diagnostik vid autism. Mera specifikt studeras egenskaperna hos det diagnostiska instrumentet ”the Diagnostic Interview for Social and COmmunication Disorders” (DISCO) för svenska förhållanden. Instrumentet är en strukturerad intervju, som genomförs under 2-4 timmar med föräldrar. DISCO kan användas för alla åldrar och fångar in symptom i det breda autismspektrumet. En datorversion med algoritmer för olika ASD diagnoser ger stora fördelar både för kliniskt

bruk och för forskning jämfört med traditionell ”papper-och-penna”-version. De psykometriska egenskaperna, interbedömarreliabiliteten och validiteten för instrumentet, visade sig vara goda till utmärkta. DISCO utgör ett viktigt komplement i den diagnostiska processen, men den kliniska diagnosen är fortsatt ”gold standard”. Denna bygger på den kliniska observationen och bedömningen av barnet och all tillgänglig information där symptombilden värderas enligt diagnoskriterier i DSM. I den diagnostiska processen kan även andra diagnostiska instrument såsom en strukturerad observation av barnet, Autism Diagnostic Observation Schedule (ADOS), vara viktiga redskap.

Trots ökad kunskap om ASD ställs diagnosen ofta med flera års fördröjning. Utifrån denna bakgrund togs initiativ till ett samverkansprojekt i Göteborg. Projektet har pågått i full skala från 2010 med målsättningen att tidigt upptäcka symptom hos barn inom barnhälsovård och vid misstanke om ASD ha fungerande metoder och rutiner i vårdkedjan för utredning och diagnostik samt möjligheter för individuellt planerade insatser för de barn som är i behov av dessa. En samverkan har byggts upp mellan barnhälsovård, enheten för barnneuropsykiatri vid Drottning Silvias barn- och ungdomssjukhus och barnhabiliteringen.

Forskningsarbetet har inriktats på att finna metoder för tidig upptäckt av autism och utvärdering av dessa. Språkscreening har tidigare införts på barnavårdscentralerna (BVC) som rutin. En tidig språkavvikelse kan ses som en indikator på möjliga andra utvecklingsavvikelser (såsom generella inlärningssvårigheter, ASD, ADHD, motoriska svårigheter) och detta behöver beaktas vid uppföljning och varje barn bedömas individuellt. Språkscreeningen är alltså inte specifik för vare sig språkstörning eller autism (Studie II), utan har visat sig identifiera en stor grupp barn som har komplexa problembilder där språket bara är en av flera drabbade funktioner.

Efter omfattande utbildningsinsatser för all BVC-personal introducerades successivt ett nytt program för autismscreening inom Göteborgs barnhälsovård från år 2008. Från januari 2010 genomförs denna 2.5-års-screening på alla BVC i Göteborg. En kombination av två metoder användes. The Modified Checklist for Autism in Toddlers (M-CHAT) är ett fråge-formulär (23 frågor) till föräldrar, vilket tidigare har utvärderats i USA. Det finns tydliga kriterier för utfall. M-CHAT omfattar även en intervjudel som används för att säkra utfall (utesluta falskt positiva fall). Instrumentet finns tillgängligt på många språk och har översatts till svenska av vår grupp 2008. Det andra instrumentet är en observation på BVC av barnets förmåga till ”joint attention” (JA-OBS). Detta instrument har framtagits i avsikt att ta vara på BVC sjuksköterskornas kunskap och erfarenhet. JA-OBS innehåller fem delmoment där barnets förmåga till ömsesidigt samspel vid besöket bedöms. Med stöd av erfarenheter från en pilotstudie har ”cut-off gränser” (gränser för

utfall) för instrumenten fastställts. Utfall i autismscreening kan således vara antingen utfall i föräldraformuläret M-CHAT (och bekräftat vid intervju), eller utfall i JA-OBS, eller utfall i båda (Studie IV). Metoderna för autismscreening kan användas på BVC när helst misstanke om svårigheter i barnets förmåga till kontakt och kommunikation uppstår.

Under studieåret 2010 beräknades ca 5000 barn ha screenats i samband med 2.5-års-undersökningen på BVC. I 3999 fall (där föräldramedgivande inlämnats) kunde resultaten från screeningen analyseras. Femtiofyra barn genomgick fortsatt utredning på enheten för barnneuropsykiatri utifrån den misstanke om ASD som väckts på BVC. Majoriteten av barnen var 2.5 år. Av de 54 barnen konstaterades 48 ha ASD (40 pojkar och 8 flickor). Tre barn fick vid utredning diagnosen generell språkstörning och de övriga tre barnen bedömdes ha en utveckling inom normalvariationen. Det positivt predicerande värdet (PPV) och sensitiviteten för kombinationen M-CHAT och JA-OBS var 90% respektive 96%, d.v.s. utmärkta egenskaper för screening.

Parallellt med utvecklingen och introduktionen av metoder för autismscreening inom barnhälsovården undersöktes prevalensen av autism hos små barn i Göteborg 2010 (Studie III). Prevalensen för autism hos 2-åringar år 2010 jämfördes även med den registrerade prevalensen för 2-åringar år 2000 och 2005 i Göteborg. Prevalensen för ASD hos 2-åringar 2010 var 0.64% beräknad för hela populationen och 0.80% hos de screenade 5000 barnen. Detta kan jämföras med åren 2000 och 2005 då den registrerade prevalensen för 2-åringar var 0.18% respektive 0.04%.

Ökad kunskap hos BVC-personal och användning av den beskrivna kombinationen av instrument för autismscreening ger uppenbarligen möjlighet till tidig upptäckt av autism och därmed möjlighet till tidiga insatser. En viktig förutsättning för populationsscreening är effektiva rutiner för fortsatta utredningar och hjälpinsatser för barn med ASD och deras familjer.

LIST OF PAPERS

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

I. Nygren, G., Hagberg, B., Billstedt, E., Skoglund, Å., Gillberg, C., Johansson, M. (2009). The Swedish version of the Diagnostic Interview for Social and Communication Disorders (DISCO-10). Psychometric properties. *Journal of Autism and Developmental Disorders, 39, 730-741.*

II. Miniscalco, C., Nygren, G., Hagberg, B., Kadesjö, B., Gillberg, C. (2006). Neuropsychiatric and neurodevelopmental outcome of children at age 6 and 7 years who screened positive for language problems at 30 months. *Developmental Medicine and Child Neurology, 48, 361-366.*

III. Nygren, G., Cederlund, M., Sandberg, E., Gillstedt, F., Arvidsson, T., Gillberg, I.C., Westman Andersson, G., Gillberg, C. (2011). The prevalence of autism in toddlers: A population study of 2-year-old Swedish children. *Journal of Autism and Developmental Disorders, Nov 3. 2011. Epub ahead of print*

IV. Nygren, G., Sandberg, E., Gillstedt, F., Ekeroth, G., Arvidsson, T., Gillberg, C. (2011). A new screening programme for autism in a general population of Swedish toddlers (submitted)

CONTENT

ABBREVIATIONS

A	Average intellectual/developmental level
AA	Above Average intellectual/developmental level
ABA	Applied Behaviour Analysis
ADHD	Attention-Deficit/Hyperactivity Disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
APA	American Psychiatric Association
AS	Asperger Syndrome
ASD	Autism Spectrum Disorder
ASDI	Autism Syndrome Diagnostic Interview
ASC	Autism Spectrum Condition
ASSQ	Autism Spectrum Screening Questionnaire
BISCUIT	Baby and Infant Screen for Children with aUtIsm Traits
CARS	Childhood Autism Rating Scale
CDD	Childhood Disintegrative Disorder
C-GAS	Children´s Global Assessment Scale
CHC	Child Health Centre
CHAT	Checklist for Autism in Toddlers
CI	Confidence Interval
CNC	Child Neuropsychiatry Clinic
DISCO	Diagnostic Interview for Social and COmmunication disorders
DQ	Developmental Quotient
DSM	Diagnostic and Statistical Manual of Mental Disorders

DZ	Dizygotic
ESSENCE	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations
FTF	Five To Fifteen questionnaire
GAF	Global Assessment of Functioning scale
ICD	International Classification of Diseases
IQ	Intelligence Quotient
JA-OBS	Joint Attention OBservation Schedule
LD	Language Disorder
M-CHAT	Modified Checklist for Autism in Toddlers
MMR	Mild Mental Retardation
MR	Mental Retardation
MZ	Monozygotic
NA	Near Average intelligence/developmental level
NEPSY	A developmental NEuro PSYchological assessment
NPV	Negative Predictive Value
NOS	Not Otherwise Specified
PPD	Pervasive Developmental Disorder
PPV	Positive Predictive Value
RAN	Rapid Automatized Naming test
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-II	Structured Clinical Interview for DSM-IV Personality Disorders
SMR	Severe Mental Retardation
SLP	Speech and Language Pathologist
TD	Typical Development

VABS	Vineland Adaptive Behavior Scales
WHO	World Health Organization

1 INTRODUCTION

1.1 Autism spectrum disorders: the current scene

Autism spectrum disorders (ASD) are severely disabling neurodevelopmental conditions with a complex biological etiology. It has been around for centuries, and very good descriptions of what we currently would refer to as autism were published more than two hundred years ago (Haslam 1799, Itard 1801).

Our understanding of children with autism has changed dramatically since Kanner and Asperger described the condition in the 1940s, and, particularly, since autism was introduced as a childhood diagnosis in the international classifications of psychiatric disorders (ICD-8) in the 1960s. In the current editions of the diagnostic classification systems, ICD-10 (WHO 2004) and DSM-IV (American Psychiatric Association 2000), the criteria for autism (childhood autism ICD-10 and autistic disorder DSM-IV) are almost identical and both emphasise unusual development in social interaction, communication and in narrow, repetitive activities. Symptoms are also required before the age of three years for a diagnosis of "core" autism.

During the last decades there has been a reconceptualisation of autism as a spectrum condition (Wing 1996). Autism is considered to be the core and generally the most severe disorder in a broader autism spectrum. In the following text the spectrum includes autism (autistic disorder/childhood autism), Asperger´s syndrome and atypical autism (also referred to as pervasive developmental disorder not otherwise specified/PDDNOS). In clinical practice, professionals may use different diagnostic terms to refer to children with similar presentations. In the literature the different diagnostic categories are often referred to as ASD or autism spectrum conditions (ASC). The symptoms can be manifested in a wide variety of ways and at different developmental levels. The cognitive levels range from nonverbal severe mental retardation/learning disability to IQ levels above average. In addition to the core features of autism a range of coexisting problems are common, such as epilepsy, behavioural phenotype syndromes, motor control problems, hearing deficits, tic disorders, attention deficits (including attention-deficit/hyperactivity disorder (ADHD), anxiety, depression, sleep and eating disturbances. This whole group of "disorders" (including autism) are now increasingly referred to as ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) (Gillberg 2010).

The current DSM-IV and ICD-10 systems have deficits. The systems mix categorical definition with the severity of the disorder, and they do not take varying presentations in toddlers or adults into account. The upcoming DSM-5, which is expected to be published in 2013, will introduce changes which will probably correspond better to clinical practice. There is expected to be one major overarching diagnosis Autism Spectrum Disorder in the new diagnostic system. The criteria will include two domains; 1) social/communication deficits and 2) fixated interests and repetitive behaviours. Three different levels of severity of ASD according to severity of symptoms have been proposed. "Unusual sensory behaviours" which is proposed to be included within a subdomain of stereotyped motor and verbal behaviours will be particularly relevant for younger children (*DSM-5 Development* 2011). However, even before it has been published, deficits in the DSM-5 have been highlighted (Wing, Gould & Gillberg 2011).

1.1.1 Genetic and other biological risk factors

The biological etiology in ASD is complex. There are possibly almost as many causes as there are cases. It is likely that autism can result from genes alone, biological environmental factors alone, and, perhaps in many cases, a combination of genetic and environmental factors. Autism is one of the most strongly heritable of all psychiatric conditions with concordance rates of 60-92% for monozygotic twins (MZ) and 0-10% for dizygotic twins (DZ) (Steffenburg, Gillberg, Hellgren et al. 1989; Muhle, Trentacoste & Rapin 2004; Veenstra-Vanderweele, Christian & Cook 2004). The disparity in some MZ twin pairs who share 100% of their genes indicates that other factors can modify the phenotypes.

There are important environmental, prenatal, epigenetic factors that may trigger and modify the genetic expression (e.g. infections, alcohol, valproate and various toxins and poisons, possibly also vitamin D). Genes and environment operate in concert altering the developmental program. In clinical ASD practice there are currently known "etiologies", including single gene diseases, and other diagnosable medical conditions (tuberous sclerosis, fragile X syndrome) in about 20% of cases (Coleman & Gillberg 2011).

Complex neuronal networks underlie social and communication functions. The prefrontal, temporal, brainstem and cerebellar regions are usually affected in ASD. There are alterations in brain architecture, due to excess neuron and microglia numbers and altered neuronal connectivity in the networks which may explain early clinical manifestations in ASD (Coleman & Gillberg 2011). Several neuropathological features have been reported, e.g., Purkinje cell loss in the cerebellar cortex (Bauman & Kemper 2005), alterations in amygdala (Mosconi, Cody-Hazlett, Poe et al. 2009) and narrower cortical minicolumns in the brain (Casanova, Buxhoeveden & Brown 2002). There is also evidence of altered connectivity in the brain´s

default network. This network contains a set of interacting brain areas, that are functionally connected, and parts of the system are seen in the medial temporal lobes, the medial prefrontal lobes, the cerebellum and the brainstem. It is at its most active in the resting state, when a person is not interacting or being tested by other people. Studies suggest that the network's main functions may be to allow flexible mental explorations, to plan for the future, and to navigate social interactions. In ASD the default network seems to be critically differently functioning (Buckner, Andrews-Hanna & Schacter 2008; Coleman & Gillberg 2011).

The identification during the last decade of mirror neurons in the brain has, by some, been considered another important discovery for understanding many human behaviours, including some of the symptoms encountered in ASD (Rizzolatti & Craighero 2004; Rizzolatti & Fabbri-Destro 2008). The mirror neurons have been suggested to play a major role for imitation, for the understanding of action of others, for language learning, and for the development of empathy.

1.2 Prevalence

Prevalence surveys of ASD have been carried out in many countries over the past 45 years. Methodological differences in case definition and case finding make comparisons difficult. The reported prevalence rates have gone dramatically up over time, from about 4 in 10.000 children (Lotter 1966; Wing, Yeates, Brierley et al. 1976; Gillberg 1984) to recent estimates for ASD in Europe and the US around 0.6-1.1% of all school-age children (Baird, Simonoff, Pickles et al. 2006; Gillberg, Cederlund, Lamberg et al. 2006; Fombonne 2009). The increase, most likely, represents changes in the definitions, widening of diagnostic criteria and awareness both among professionals and the general public. However, it cannot be ruled out that other, as yet unknown, factors may contribute. Given the diversity of the etiology, it would be surprising if there was not some regional variation in the rate of autism. Boys are affected more often than girls, at a ratio of 2:1 to 6.5:1. The male to female ratio is even higher for ASD in the normal IQ range, such as in Asperger syndrome (Johnson & Myers 2007). A range of different hypothesis concerning possible etiological factors linked to the skewed sex ratio have been presented (Coleman & Gillberg 2011). It has also been pointed out that many girls might be missed because, as a group, they tend to be less disruptive, more (superficially) social and have better communicative language skills.

1.3 Screening for ASD and related conditions

Symptoms in autism are present from the first few years of life, but there is still often a considerable delay from the first symptoms, and the parents´ first concern, to diagnosis (Siegel, Pliner, Eschler et al. 1988; De Giacomo & Fombonne 1998; Robins, Fein, Barton et al. 2001).

In most western countries there are developmental surveillance programs for children from their first months of life. Standardised screening can increase the accuracy of detection of a developmental disorder. In Sweden, a language screening has been conducted at most Child Health Centres for many years at the age of 2.5-3 years (Mattsson, Marild & Pehrsson 2001). Several studies have shown a prevalence of major language disorder in 2-3% of children (Westerlund 2008).

There are specific screening criteria adopted in 1968 by the WHO. Autism is a disorder (or group of disorders) that accord with these criteria. Priority for population screening should be given to disabilities that have one or more of the following traits: high frequency of occurrence, improved outcome if detected early and efficient, low-cost screening methods available.

There is limited but growing evidence of the efficacy of early intervention for children with autism and this has led to increasing emphasis on the need for standardised ASD screening in addition to ongoing developmental surveillance. There is, internationally, a quest for very early screening, including during the first year, but there is still only limited evidence for population screening of children around the age of 2 years.

In Gothenburg 95-99% of children are reported to be followed up at the CHCs during their first years (Arvidsson, Holmberg, Reuter et al. 2010). Despite regular health check-ups, in recent years, the symptoms of autism have not been noticed, or if noticed, not led to referral for autism diagnostic assessment until several years later. The observed delay in diagnosis was the background for the development of a new screening programme for autism at the CHCs in Gothenburg (Study III-IV).

1.3.1 Autism screening instruments

The development of screening instruments relies heavily on retrospective studies from children who got the diagnosis of ASD years after the first symptoms appeared. The identified symptoms that are most consistent include perceptual abnormalities, motor control problems, delay or absence in orienting to name, looking at others, pointing and showing objects (Gillberg, Ehlers, Schaumann et al. 1990; Osterling & Dawson 1994). Many of these

symptoms are related to lack or deficiency of the joint attention ability, which is believed to be crucial for development of social communication. Items concerning joint attention are key in most current screening instruments, which range from parent questionnaires to brief observations made by trained clinicians during examination.

Several autism screening instruments for young children have been studied and a number are under way. Level 1 screening tools are appropriate for low risk population screening, whereas Level 2 screening instruments are designed for use when screening children who have been identified to be at risk of the disorder. A Level 2 instrument might be used as part of the first diagnostic evaluation, e.g. the Baby and Infant Screen for Children with aUtIsm Traits (BISCUIT) (Matson, Wilkins, Sharp et al. 2009; Matson, Wilkins & Fodstad 2011).

Some general requirements in relation to primary care assessment tools are essential for population screening (Level 1). The assessment instrument must be brief and low cost and designed for easy use in primary care. Parent check-lists are easy to administer. Observations made by professionals, on the other hand, can be related to knowledge of typical child development and, thus, provide more objective information (Dumont-Mathieu & Fein 2005). Other demands made on instruments used for population screening are clear cut-off scores, and validation against clinical diagnosis and standard diagnostic tests. The tool must have cut-off scores and be validated against clinical diagnosis and standard diagnostic instruments. The Positive Predictive Value (PPV), (the proportion of children correctly identified from screening), the sensitivity and specificity should optimally have been demonstrated in population studies to have acceptable levels.

The British-Swedish instrument Checklist for Autism in Toddlers (CHAT) was a pioneer autism screening instrument for 18-month-old children (Baron-Cohen, Allen & Gillberg 1992; Baron-Cohen, Cox, Baird et al. 1996). For population screening, however, the sensitivity for the instrument proved to be too low. From the CHAT, the Modified Checklist for Autism in Toddlers (M-CHAT) was developed in 1999 in the US by Robins et al with a view to improving sensitivity. The M-CHAT, a 23-item yes/no parent report, has shown promising properties, also for Level 1 screening and has been used in studies of children aged 16-40 months (Robins et al. 2001; Ventola, Kleinman, Pandey et al. 2007; Kleinman, Robins, Ventola et al. 2008; Robins 2008; Yama, Freeman, Graves et al. 2012). The M-CHAT has been translated into many languages, including Swedish in 2008. In the following, the use of the parent questionnaire M-CHAT in combination with a nurse observation of the child's joint attention ability (JA-OBS) in a general screening of 2.5-year-old children at the CHCs will be described. The latter instrument, the JA-OBS, has been developed in the context of the present study.

1.4 Diagnosis of social and communication disorders and the concept of ESSENCE

The diagnosis of ASD is clinical and based on behavioural criteria. Retrospective studies suggest that despite early signs and early parental concern about developmental problems, there is still a considerable delay to ASD diagnosis (Siegel et al. 1988; De Giacomo & Fombonne 1998). Children with any kind of major social and communication, behavioural or learning problems should be considered for a possible diagnosis within the autism spectrum. The triad of impairments typical of all ASD affects *social, communicative and behavioural function*. In clinical practice children are diagnosed as having ASD if there are severe problems in at least two of the three domains or if there are mild-moderate problems in two domains and severe in a third domain. Subgrouping according to current ICD-10/DSM-IV can then be achieved for autism and atypical autism (PDD NOS). For the diagnosis of Asperger´s syndrome, the ICD-10/DSM-IV criteria are far from perfect. Asperger´s own cases do not meet criteria for this category (Miller & Ozonoff 1997), and the requirement that development in the first three years of life should have been normal for a diagnosis to be considered does not tally with clinical realities. The criteria for Asperger syndrome published by the Gillbergs in the 1980s were based on Asperger´s case descriptions, and are the ones currently most used in clinical practice (Gillberg & Gillberg 1989).

The diagnosis of ASD in childhood is based on a detailed symptom account, an in-depth perinatal and developmental history as documented during the interview with the parents and a clinical observation and examination of the child. Work-up in connection with diagnosis must include detailed medical assessment and examination, including for co-existing seizure disorders and behavioral phenotype syndromes such as fragile-X-syndrome and tuberous sclerosis. Psychological tests are not required for the diagnosis but are necessary parts of the evaluation and especially crucial for interpreting information for the diagnosis of ASD in very young children. Differential diagnosis varies depending on the age at which a child comes for an evaluation. Before the age of 3-4 years many children with ASD present with the suspicion of language delay, deafness, general delay, different kinds of behavioural problems or in some cases extreme hyperactivity (or extreme passivity). Already in early childhood there are often overlapping or "co-morbid" disorders (including ADHD, DCD and oppositional defiant disorder). Gillberg has suggested that such early symptomatic syndromes eliciting neurodevelopmental clinical examinations (ESSENCE) might best be considered as a group of disorders and that, at presentation, individual disorders may not be clearly separable from each other (Gillberg 2010). Throughout childhood and adolescence there will usually be need for regular

check-ups and, sometimes, renewed assessments regarding diagnosis, symptoms, problems, strengths and comorbidity.

There are several diagnostic instruments that can assist in the clinical diagnostic procedure. Standardised diagnostic instruments with proven good psychometric properties are of value for clinical evaluation and usually very important for research studies. The most important instruments in current use are the Childhood Autism Rating Scale (CARS), which is a combined carer interview-observation schedule, the collateral informant structured interviews, such as the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing, Leekam, Libby et al. 2002), Autism Diagnostic Interview (ADI-R) (Lord, Rutter & Le Couteur 1994) and the 3-di (Skuse, Warrington, Bishop et al. 2004), and the child observation schedules such as the Autism Diagnostic Observation Schedule (ADOS) (Lord, Risi, Lambrecht et al. 2000). Screening instruments, such as the parent and teacher versions of the Autism Spectrum Screening Questionnaire (ASSQ) (Ehlers, Gillberg & Wing 1999), and the brief "diagnostic screening" instrument Autism Spectrum Diagnostic Interview (ASDI) (Gillberg, Rastam & Wentz 2001) can also serve as effective aids in diagnosis. However, it is important to emphasize that none of the listed instruments are better than comprehensive clinical diagnosis formulated by a very experienced clinicians, and that they cannot serve as a substitute for such diagnosis.

Several longitudinal studies have shown that the diagnosis of autism made before the age of 3 years is relatively stable over time (Gillberg et al. 1990; Lord, Risi, DiLavore et al. 2006; Chawarska, Klin, Paul et al. 2009).

1.4.1 The relationship between language disorders and autism

Speech delay is a common symptom in ASD. Indeed, in many cases, it is the speech delay that prompts parents to raise concern about their child's development. A considerable delay in referral and diagnosis of ASD is common when a child is verbal and does not have intellectual disability. One study showed children with severe language deficits received a diagnosis of ASD 1.2 years earlier than children with less severe language deficits (Mandell, Novak & Zubritsky 2005).

Some children with ASD never babble and never start talking. Others start talking but speech may seem to regress during their second year of life, and some may even loose the words they have learnt. Children with Asperger syndrome often have a good vocabulary early on and may go unnoticed until later school age. Some individuals have good verbal fluency although verbal abilities may be accompanied by errors in word meaning and other different features in speech. Children with ASD compared to children with other

developmental disorders/language disorders use fewer conventional gestures such as nodding and shaking their head (Lord, Rutter & Le Couteur 1994), and, when speech is present, they have more echolalia and stereotyped phrases, and they are less likely to initiate or respond to verbal communication (Lord 1995; Trillingsgaard, Ulsted Sorensen, Nemec et al. 2005). The "language endophenotype" in ASD, thus, is very heterogeneous.

The willingness to engage in reciprocal communication (not only the formal language competence) is of utmost importance as regards social interaction. Lack of speech or other types of language impairments are common in children diagnosed with ASD, but there are often early pre-speech deficits important to detect for early diagnosis. These are often related to difficulties in *joint attention*. The deficits include: lack of appropriate gaze, lack of joyful expressions with gaze, lack of to-and-fro pattern of vocalisations between infant and parent, delayed onset of babbling and absent use of gestures such as pointing and showing.

Speech and language impairment is not only a common feature in ASD but in many other disorders as well (Westerlund 2008; Gillberg 2010).

1.5 Early screening – early diagnosis – and then what?

Early screening and diagnosis of ASD increase possibilities for interventions. The rationale for screening and early detection of symptoms is that early interventions, including psychoeducation, are helpful and can improve the outcome for the child (Ospina, Krebs Seida, Clark et al. 2008; Rogers & Vismara 2008; Dawson, Rogers, Munson et al. 2010).

There is still much controversy concerning early interventions and the research field is complex as regards e.g. intervention approaches, methodological issues and difficulties to perform long-term randomised control studies. Given the biological heterogeneity of the autism spectrum, this is not unexpected. Some research groups have reported findings supporting early intervention improving developmental functioning and decreasing maladaptive behaviours. This has usually been demonstrated at a group level, but which particular treatment is most effective for an individual child, we usually have no idea (Ospina et al. 2008; Rogers & Vismara 2008; Al-Qabandi, Gorter & Rosenbaum 2011). Some large scale, longer-term naturalistic studies have not found evidence that more intensive early intervention is better than less intensive intervention (Fernell, Hedvall, Westerlund et al. 2011).

There is no known general cure for autism. Studies during the last decade, not only of intervention, but reports from developmental neuroscience, neuro-biology and genetics contribute to a more optimistic view for outcome in the future (Dawson 2008; Coleman & Gillberg 2011). Also, there is growing evidence that general developmental delay and associated medical conditions may contribute more to restricted outcomes in autism than the autism "in itself" (Coleman & Gillberg 2011).

An ideal therapy would target the child´s social, communicative and behavioural difficulties. Generally there has been most support for manualised intervention programs based on methods of Applied Behaviour Analysis (ABA) and developmental strategies. Combinations of strategies have often been used. There is no universal treatment for all symptoms in all children. It is likely that with different biological background, different development profiles and symptoms, different parents and environment, children will benefit from different approaches and intensity of treatment. The individual tailoring of interventions to each child´s developmental profile as soon as the symptoms have been detected, and focusing on a broad range of learning targets in agreement with the parents, will be crucial for all interventions. Ongoing coaching of the parents in their use of strategies in close relationship with the child in everyday activities and routines is probably essential. An example of this type of intervention is the Early Start Denver Model (Dawson et al. 2010), which focuses on the individual child's development, quality of relationships, affect and adult sensitivity and feedback.

Early screening for autism in toddlers should be linked to possibilities for diagnostic assessments and also to individualised interventions for children with ASD without delay. This was the fundament for the introduction of the new screening programme for autism in Gothenburg presented in the following (Study IV).

2 AIMS

The overall aim of this study was to develop a good new screening and diagnostic framework for ASD. The detailed aims were to

- establish the psychometric properties of the Swedish version of the DISCO, which would be used as a diagnostic instrument for ASD in the new screening and diagnostic programme;

- assess the extent to which children with ASD are missed in the general language screening at age 2.5 years;

- study the prevalence of ASD in 2-year old children in Gothenburg;

- examine the result of introducing autism screening at primary health care centres at age 2.5 years as regards clinical diagnoses of ASD;

- examine the PPV and the sensitivity of the combined use of two autism screening instruments, the M-CHAT and the JA-OBS.

3 MATERIAL AND METHODS

3.1 Subjects

The thesis is based on studies of several groups of children (and some adults): Study I) individuals coming for neuropsychiatric assessment and diagnosis to a specialised Child Neuropsychiatry Clinic (CNC) with the suspicion of ASD; Study II) a prospective cohort of children screened positive for language disorder at the age of 2.5 years and re-assessed in a comprehensive neuropsychiatric evaluation at the age of 7 years; Study III and IV) a general population cohort of 2-3-year-old children screened for and diagnosed with ASD in Gothenburg in 2010. An overview of all subjects participating in the studies is given in Table 1.

Study I (Diagnostic study): A total of 91 patients (66 males, 25 females) aged 2-40 years were included in the Diagnostic study of the DISCO-10. They had all been referred for neuropsychiatric evaluations with a suspicion of ASD or other neuropsychiatric disorders at the same clinic, the CNC at Sahlgrenska University Hospital in Gothenburg. At the time of the study there was an ongoing project at the same clinic for evaluations of adults with a suspicion of ASD.

Study II (Language disorder study): Twenty-one children (17 males, 4 females), from a prospective representative "language disorder cohort" of 25 children, identified after screening positive for language disorder at 2.5 years, were followed up neuropsychiatric assessments at the age of 7 years at the CNC.

Study III (Prevalence study): The study population consisted of all 2-year-olds, born in 2007 or 2008 (and living in the city of Gothenburg in 2010), referred to the CNC in 2010, at the age of 2 years ($\geq$24 months and <36 months), with a suspicion of ASD and diagnosed there with an ASD. The CNC serves the whole city with neuropsychiatric diagnostic work–up in young children. In Gothenburg the total population of 2.5-year-old children in 2010 (born in 2007 or in 2008) was estimated at 6220 based on the numbers of the two birth years 2007 (6022) and 2008 (6418) at the end of 2010. According to statistics from the CHC authority (Arvidsson et al. 2010) it was estimated that 5007 children (80%) were screened with the new routines for autism screening in 2010. Thus, the total 2-year-old population available for study consisted of these 5007 children who were actually screened.

Study IV ("Screening study"): The population consisted of the same population (as in study III) of 2-year-olds screened at the age of 2.5 years in 2010 but also a number of children in which suspicion of ASD had been raised at the CHC <24 months and >36 months during the same year.

Table 1. Study groups and methods used in study I-IV

Study	I Diagnostic	II Language	III Prevalence	IV Screening
Object of study	Psychometric properties of the Swedish version of the DISCO	ASD in relation to language screening	ASD prevalence in 2-year-olds	A new screening programme for ASD
Target group	91	25	6220 total (5007 screened)	3999
Group examined	91 (73 ASD)	21	40	54 (48 ASD)
Age range	2-40 years	7 years	2-3 years	1.6-3.9 years
Male:female	66:25	17:4	32:8	46:8
Mental develop-mental level	AA 1 A 28 NA 21 MMR 21 SMR 20	A 13 NA 6 MMR 2	A+NA 26 Developmental delay/MR 14	A+NA 38 Developmental delay/MR 16
Diagnostic criteria	ICD10/ DSM-IV/ Gillberg´s AS	ICD10/ DSM-IV/ Gillberg´s AS	ICD10/ DSM-IV Gillberg´s AS	ICD10/ DSM-IV Gillberg´s AS
Measurements	DISCO, ADI-R, Neuropsychiatric/ paediatric medical examination, Wechsler scales / Griffiths SCID I-II (adults), Preschool/school observation (children), ADOS (majority of children)	Neuropsychiatric/ paediatric examination, GAF, Wechsler scales, NEPSY (language functions), RAN test, DISCO, Examination of language domains	M-CHAT, JA-OBS, Language screen, Neuropsychiatric /paediatric examination, Griffiths, Vineland, Examination of language domains, ADOS, DISCO, Preschool observation	M-CHAT JA-OBS Language screen Neuropsychiatric /paediatric examination, Griffiths, Vineland, Examination of language domains, ADOS, DISCO, Preschool observation, C-GAS

3.2 Clinical methods and instrument used

The instruments used for screening and diagnostic assessment of ASD are presented in the following in some detail (3.2.1-3.2.5.), as is the new screening programme for the CHCs (3.2.6). The other instruments and methods used for the neuropsychiatric assessment are briefly reviewed here. (See Table 1 for an overview of all the instruments used).

The clinical evaluation included a thorough medical and psychiatric examination by a neuropediatrician/psychiatrist including checking for neuropsychiatric symptoms according to the criteria of the DSM-IV (APA 2000). The interview covered, among other things, family history, neuro-developmental and medical history, behavioural symptoms and problems. In study II, the Five To Fifteen (FTF) questionnaire for parents and teachers (Kadesjo, Janols, Korkman et al. 2004) was used to cover the range of issues that pertain to ESSENCE. The overall functioning of the individual was estimated according to the Global Assessment of Functioning scale (GAF) (APA 2000) in study II and according to the Children´s Global Assessment Scale (C-GAS) (Shaffer, Gould, Brasic et al. 1983) in study III-IV. In study III-IV the Vineland Adaptive Behaviour Scales (VABS) (Sparrow, Balla & Cicchetti 1984) instrument was used in interview with the parents.

The adults included (Study I) were given the Structured Interview for Diagnosis according to the DSM-IV (SCID I-II) for psychiatric disorders and personality disorders, respectively (First, Gibbon, Spizer et al. 1997a; First, Gibbon, Spitzer et al. 1997b).

All patients and clinically assessed probands were examined by a neuropsychologist who used appropriate intelligence/developmental tests mostly one of the Wechsler Scales (Wechsler 1997, 1999a, 1999b). For children with mental ages too low for Wechsler Scale assessment, the Griffiths Scales (Norberg, Tingwall & Ahlin-Åkerman 1980) were used. In study I, III and IV all children under the age of 10 years were observed at preschool/school by a specially trained teacher. The ADOS (Lord et al. 2000) was performed by experienced clinicians in the vast majority of cases included in study III-IV. Language tests and assessments were done by an experienced speech and language therapist in all cases in study II-IV.

3.2.1 The ADI-R

The ADI-R covers in a systematic fashion the developmental and behavioural symptoms associated with autism and is well established as a diagnostic aid (Le Couteur, Rutter, Lord et al. 1989; Lord, Rutter & Le Couteur 1994; de Bildt, Sytema, Ketelaars et al. 2004; Lecavalier, Aman, Scahill et al. 2006). The instrument comprises 111 items, current and past behaviour, and the content closely mirrors the description of autism found in the DSM-IV and

the ICD-10. The instrument provides a diagnostic algorithm for childhood autism according to ICD-10/DSM-IV. The ADI-R does not provide standard cut-offs for ASDs other than autism, but thresholds for non autism-ASDs have been proposed (Risi, Lord, Gotham et al. 2006).

3.2.2 The DISCO-10

The DISCO is a 2-4-hour investigator based diagnostic instrument intended for use at interview with parents. The instrument was developed by Lorna Wing and Judith Gold and validated in the UK in 2002 (Wing et al. 2002).

The DISCO covers the broad autism spectrum, at all ages and different developmental levels. The instrument has a strong developmental focus and is structured to obtain information about the individual´s development in different areas from birth and to give historical information ("ever") and information about current symptoms ("current"). The interview comprises 362 items (cf. 111 in the ADI-R) and the rating of most of the items is by numerical codes arranged in a threefold hierarchy of severity. The instrument provides computerised algorithms for diagnoses of childhood autism/autistic disorder and for Asperger syndrome according to ICD-10 and DSM-IV. There are also algorithms for early infantile autism ("Kanner type"), for ASD (Wing & Gould 1979) and for Asperger syndrome according to Gillberg criteria. The DISCO collects extensive information beyond the core symptoms of autism and the broad autism spectrum about e.g. sensory symptoms, gross and fine motor skills, emotional symptoms psychiatric and forensic problems, maladaptive behaviours and sleep difficulties.

The psychometric properties of the Swedish version of the DISCO-10 (authorised Swedish translation by Johansson & Gillberg, 1999) were analysed in the Diagnostic study (Study I). In this study the DISCO-10 was validated in relation to clinical diagnosis but also in relation to the ADI-R. (A new version, including minor changes, the DISCO-11, is in use since 2007).

DISCO-10 inter-rater reliability
The study was conducted in parallel and independently of the clinical evaluation and was done by having every other patient interviewed by one clinical researcher and rated by her and one of two other clinical researchers, independently of each other, rating all DISCO-10 items at the time of the interview. For the remaining cases the order was reversed. The three investigators (two medical doctors and a clinical neuropsychologist) were all DISCO-10-licensed.

DISCO-10 validity
The DISCO-10 was given independently of the routine clinical work up by one of three different DISCO- and ADI-R licensed investigators. Fifty-seven of the 91 clinical probands in the Diagnostic study were included, 30 children

and 27 adults. This comprised three parts: (1) the *child one-rater part* (n=30), (2) the *adult one-rater part* (n=6), and (3) the *adult two-raters part* (n=21).

3.2.3 The M-CHAT

The M-CHAT was developed in the US on the basis of the pioneer (British-Swedish) screening tool, the Checklist for Autism in Toddlers (CHAT) (Baron-Cohen, Allen & Gillberg 1992). The M-CHAT comprises a 23 item yes/no parent report and a follow-up interview. The parent report was validated in the US in 2001 (Robins et al. 2001) and shown to have promising psychometric properties. Six of the 23 items (2, 7, 9, 13, 14, 15) pertaining to social relatedness and communication were found to have the best discriminating ability for ASD/non ASD ("critical items"). Failure on the screening was defined as "failure" on any three of the 23 items or on any two of the 6 critical items failed. The M-CHAT instrument has been used in a large number of studies and is currently the most respected instrument for early autism screening. The instrument was originally developed and used for children aged 18-30 months (Robins et al. 2001; Kleinman et al. 2008; Robins 2008) but a recently published study by Yama et al suggests that the instrument can be administered for low risk screening to the maximum age of 48 months (Yama et al. 2012). Earlier studies (Robins et al. 2001; Kleinman et al. 2008) have proved that, for population screening, the parental report in screen positive cases must be completed by an interview, developed for the instrument, to avoid too many false positive. This two-step procedure of M-CHAT was chosen for the present study. Translations into many languages have been performed according to the guidelines from the originators and rules for translations of instruments (Banville, Desrosiers & Genet-Volet 2000).The M-CHAT, including the follow-up interview, can be found in different languages on the website M-CHAT™ Information.

3.2.4 The JA-OBS

This instrument was developed by the author and the research group on the basis of results obtained in studies of early symptoms related to lack or deficiency in the ability to initiate/engage in joint attention (Baron-Cohen, Allen & Gillberg 1992; Werner, Dawson, Osterling et al. 2000; Osterling, Dawson & Munson 2002). After piloting of the JA-OBS in 2008, it was decided that screen positivity for autism on the JA-OBS would be defined as failure on any two or more of the five items (Figure 1).

Figure 1. The JA-OBS

Does the child:

1. *react to own name (turns to person addressing the child)?*
2. *try to establish eye-contact with you?*
3. *gaze at something that you point to further away in the room?*
4. *use his/her index-finger to point at something (e.g. in a book)?*
5. *interact with you or parent in pretend play (e.g. during feeding a doll, or putting the doll to bed; does the child use eye contact to monitor that you are watching)?*

3.2.5 The language screen

A speech-language screen (Mattsson, Marild & Pehrsson 2001) consisting of a parent questionnaire and an assessment made by the nurse had been introduced earlier as a routine at the CHCs in Gothenburg, just as in many other parts of Sweden. This screen was used in parallel with the new methods for autism screening. Failure on the language screen was defined as one or more of the following: (1) fewer than 25 single words, (2) lack of 2-word utterances, (3) poor verbal comprehension or (4) parental concern for the child´s language and communicative ability.

3.2.6 The screening procedure

The nurses at the CHCs were the key professionals for the screening procedure. Before the autism screening was introduced they attended seminars about children´s typical developmental milestones, particularly focusing on early symptoms of autism, and on the autism screening per se. The nurses were trained in the use of the screening instruments. Clear instructions were given as to how to act at any child age if suspicion of ASD was raised, including in children under age 2.5 years. The nurses were encouraged to listen to the parents and to any concern they might have about their child´s development.

All parents of children in the age cohort were sent an invitation to their child´s 2.5-year-old visit. The M-CHAT, the parent language questionnaire and information about the study was enclosed with this invitation. The 2.5-year-old visit at the CHC took about 45-60 minutes. About ten of these minutes were needed for the nurse´s JA-OBS and for the language assessment, and 1-5 minutes for the actual scoring of the M-CHAT. Sixty minutes was the recommended nurse time for all 2.5-year-old visits and was estimated to be necessary for children where difficulties were observed, when follow-up M-CHAT-interview was indicated, and also in all cases where an interpreter was needed. If a “preliminary failure” was observed according to the parent report, the nurse completed the M-CHAT-interview during the

CHC visit. If "screen positivity" was confirmed at this interview (any three of the 23 items failed or any two of the 6 critical items failed) that case was regarded as "definitively screen positive". If the child was screen positive for autism, or, if for other reasons, there was a suspicion of autism, there was a plan for a second visit (within a month) to the CHC for an examination made by the paediatrician or general practitioner together with the nurse. If the clinical suspicion of autism remained at this visit, the parents were informed and the child was referred to the CNC for further assessments. Children, who failed the language screening, but not the autism screening, were referred by the nurse to auditory examination and to a speech and language therapist (SLP).

3.3 Diagnostic criteria

Clinical diagnoses in all four studies were assigned at a case conference where all information was reviewed. (For more details about the diagnostics and methods see page 13). The diagnostic criteria according to the DSM-IV and ICD-10 were used for autistic disorder/childhood autism (referred to as "autism" in the following), childhood disintegrative disorder (CDD) and atypical autism/pervasive developmental disorder not otherwise specified (PDD-NOS). For the diagnosis of Asperger syndrome, the diagnostic criteria according to the Gillbergs were used (Gillberg & Gillberg 1989; Gillberg 1991).

3.4 Mental developmental level

Mental development was divided into five broad categories: (1) above average intellectual-developmental level (AA, IQ>115), (2) average intellectual-developmental level (A, IQ 85-115), (3) near average intellectual-developmental level (NA, IQ 71-84), (4) mild mental retardation (MMR, IQ 50-70), and (5) severe mental retardation (SMR, IQ<50).

3.5 Statistical methods used

Study I: Unweighted Cohen´s kappa was used to measure levels of agreement between the interviewers for the majority of items with two or three codes. When kappa could not be calculated (items for which values of the first variable did not match the values of the second variable in a 2-way table) Pearson´s correlation coefficient was calculated. For items with two or more codes (measuring current level of skills) intra-class correlation was used to measure agreement between the two raters.

Study II: Fisher's exact test (Altman 1991) was used for comparing subgroup frequencies of problems observed at in-depth neuropsychiatric evaluation at

age 7 years. For ordered categorical variables (i.e. rating scale 0–3), the Mantel-Haenzel $\chi 2$ test was used (Altman 1991). Bonferroni correction was used to adjust for multiple significancies.

Study III: ASD prevalence and 95% confidence intervals were calculated on the basis of number of diagnosed cases divided by the number of individuals reached by the screening procedure 2010 (n=5007) and also for diagnosed cases of ASD divided by the number of the total estimated population (n=6220). For the comparison populations (2000 and 2005) the prevalence and 95% confidence intervals (CIs) were calculated in the same way (number of diagnosed cases of ASD divided by number of the total estimated population). In order to test if the prevalence of ASD in 2010 differed from the prevalence in 2000 and 2005, Fisher's exact test was used.

Study IV: Sensitivity was defined as per cent diagnosed children who also had screen positivity on a measure. PPV was defined as per cent of children who had screen positivity on a measure and were diagnosed with ASD. The CIs were calculated assuming binominal distribution and presented with 95% Confidence limits. As a measure of inter-rater reliability per cent agreement was calculated. In several cases kappa statistic was not applicable due to missing values either in an entire column or an entire row.

3.6 Ethics

The studies were approved by the Regional Ethics Committee in Gothenburg. Parents/patients signed written informed participation consent forms.

4 RESULTS

4.1 Psychometric properties of the Swedish DISCO-10

4.1.1 Interrater reliability

For all items included in the DISCO-10 algorithms for ASD (childhood autism ICD-10, Gillberg AS, and Wing & Gould ASD) the inter-rater reliability was at least moderate, and for more than 90% of rated items, the inter-rater reliability was good or excellent. Kappa values ranged from 0.35 (one repetitive behaviour item) to 0.91 (several social impairment items). For certain items, kappa could not be calculated and Pearson correlation coefficient or intra-class correlations were used instead. For these items also, inter-rater reliability was good or excellent.

4.1.2 Validation against ADI-R

The overall agreement across ADI-R and DISCO-10 algorithms for childhood autism was excellent. The ADI-R tended somewhat more to "overdiagnose" autism in relation to clinical gold standard diagnoses. When the ADI-R was clear that a diagnosis of childhood autism applied, the DISCO-10, in addition to the diagnosis of childhood autism, diagnosed or suggested a number of other diagnoses. Five individuals with clinical ASD diagnoses, which were not identified by the ADI-R algorithm for autism, were all picked up with DISCO-10 algorithms for various ASDs. The DISCO-10 identified them as various ASDs, giving specific algorithm diagnoses. There were no differences as regards correspondence between DISCO-10 and ADI-R relating to method of substudy (1), (2) or (3). Gender did not influence the findings.

4.1.3 Validation against clinical diagnosis

The agreement across clinical diagnosis and DISCO-10 diagnosis was moderate-excellent. Thirty-one of the 33 individuals with a clinical diagnosis of autism also met the DISCO-10-algorithm for childhood autism according to ICD-10. The remaining two individuals with a clinical diagnosis of autism had the DISCO-10-diagnosis atypical autism. Twelve individuals with DISCO-10 diagnoses of childhood autism did not meet clinical criteria for this diagnosis. These individuals had AS (5) and atypical autism (6) and no diagnosis (1) according to clinical criteria. Eight subjects had *clinical* diagnoses of AS. Seven out of these met the DISCO-10-algorithm criteria of Gillberg´s AS whereas only two fulfilled ICD-10-algorthim criteria for AS. Some individuals fulfilled both the DISCO-10 criteria for Gillberg´s AS and

for childhood autism. However the DISCO-10 diagnosis of childhood autism (in accordance with the ICD-10 criteria) takes over from the diagnosis of AS.

4.2 Predictive validity of language problems at age 2.5 years as regards ASDs and related conditions at early school age

Thirteen of the 21 children (62%), who screened positive for language disorder at 2.5 years, had a functionally disabling neuropsychiatric disorder (usually ADHD or ASD or combinations of these) according to the in-depth assessment at the age of 7-8 years. Two further children had a learning disorder, borderline IQ (IQ 71-84), without any other major problems. Of the whole examined group 71% had either a neuropsychiatric disorder or a learning disorder or both in addition to any problem they might still have with language.

Five children had ASD. Two of these had autism, two had atypical autism and one had the diagnosis of AS. Their IQ was generally rather low (range 56–73), except in the case of the male with AS (IQ 99). Three of the five males in the ASD subgroup also had ADHD.

Eight children had ADHD as main diagnosis (plus three who had ADHD with ASD as main diagnosis, see above).

Eight males but none of the females had NA IQ or MMR. Two children had severe learning disability without any other major neuropsychiatric disorder.

4.3 Prevalence of ASD in 2-years-olds

4.3.1 Prevalence rate of ASD in 2-year-old children in 2010

Forty-nine children, all born in 2007 or 2008, were referred at the age of 2 years to the CNC with a suspicion of ASD. Two of these had diagnosed mental retardation and were referred by child neurologists from the local habilitation service for further evaluations under the suspicion of ASD. The other 47 children were all referred from the CHCs. Four of these 47 families refused to come for the in-depth assessment with their child, leaving a total of 45 children who were actually examined.

Forty (8 girls and 32 boys) of the 45 assessed "ASD suspected" children were given an ASD diagnosis after full in-depth clinical assessment. Twenty-six individuals received the diagnosis of autistic disorder, and 14 were diagnosed as having atypical autism. Fourteen of the children had ASD plus developmental delay or diagnosed mental retardation/learning disability (intellectual developmental disorder), and 24 were diagnosed as being in the normal range of intellectual functioning. In two cases the neuropsychological tests had not been completed. The findings correspond to a total ASD prevalence for 2-year-olds of 0.80% in the study population of actually screened children. The estimated prevalence for *all* 2-year-old children in Gothenburg was 0.64% (Table 2).

In 20/40 cases both parents were of Swedish descent and in the other 20 cases one (n=4) or both (n=16) of the parents had been born in another country. Thus, the ratio of Swedish to foreign born parents for the children with ASD was 1:1, which is significantly different (p=0.005) from 2.6:1 for this age group in the general population in Gothenburg (Statistics Sweden 2010).

Table 2. ASD prevalence in 2-year-olds in study population 2010

Diagnosis	Prevalence total		Boys		Girls	
	%	(n)	%	(n)	%	(n)
Autism	0.52	(26)	0.86	(22)	0.16	(4)
Atypical autism	0.28	(14)	0.39	(10)	0.16	(4)
All ASD	0.80	(40)	1.25	(32)	0.33	(8)

N=5007 screened children; 2569 boys, 2438 girls

4.3.2 Prevalence of ASD in 2-year-old children in 2000 and 2005 in comparison with the rate in 2010

Young children with suspected ASD in Gothenburg are all referred to the CNC. This has been the routine since the early 1980s.

Nine 2-year-olds had been diagnosed with ASD at the CNC in 2000 (6 with autistic disorder and 3 with atypical autism, 6/9 had mental retardation). This corresponds to a minimum 2000 population rate of ASD in 2-year-olds of 0.18%. In 2005 only two 2-year-old children had been diagnosed with ASD at the CNC (both with autistic disorder and mental retardation). This corresponds to a minimum population rate of ASD in 2-year-olds of 0.04% in 2005 (Table 3).

Table 3. ASD prevalence and developmental levels of children with ASD in the three study populations 2000, 2005 and 2010

Study population	Autism n (♂/♀)	Atypical autism n (♂/♀)	ASD total n	Indivi-duals with normal DQ n	ASD prevalence %	95% CI
2000						
n=4871	6 (6/0)	3 (1/2)	9	3	0.18	0.08-0.35
2005						
n=5220	2 (2/0)	0	2	0	0.04	0.01-0.14
2010						
n=6220					0.64[a]	0.46-0.87
n=5007 screened	26 (22/4)	14 (10/4)	40	26	0.80	0.57-1.09

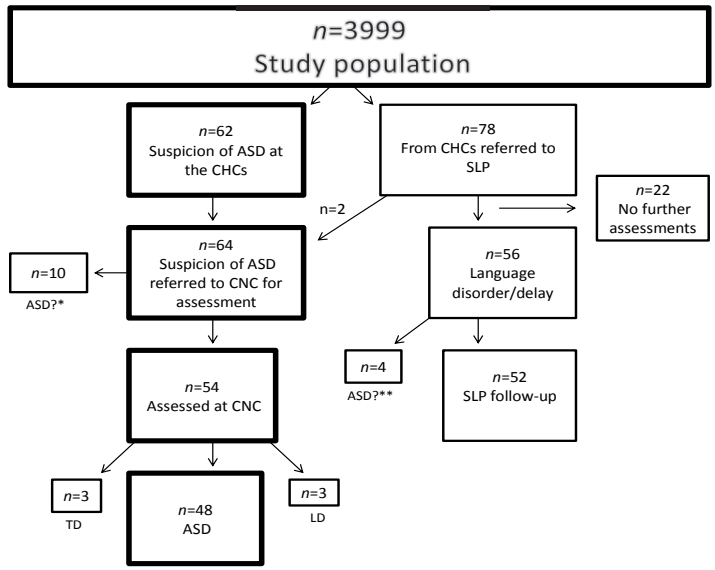
[a] For this calculation, the total population of individuals was used as denominator rather than the total populations screened, so as to allow head-to-head comparison with rates reported for 2000 and 2005

4.4 A new autism screening programme

4.4.1 Suspicion of ASD within the developmental program at the CHCs in relation to further evaluations and diagnostic work at the specialist CNC

The suspicion of ASD was raised in 64 individuals who were referred to the CNC (62 from the CHCs directly and two from SLPs after referral to them for suspected language delay) (Figure 2). The majority of the children were about 2.5 years old (30-36 months). In 16 of the 64 cases (25%) the suspicion was raised before or after the routine 2.5-year-visit (five children were younger than 24 months, seven were 24-29 months and four were three years old, 37-46 months).

Figure 2. Procedure for ASD screening and diagnostic assessment



*Attrition **Referred to CNC, not yet assessed

4.4.2 Attrition

Ten of the 64 children have not yet been further evaluated at the specialist CNC. The reasons for this are as follows: parents refused to come for in-depth assessment (n=4), parents wanted to wait a further year before diagnostic assessment (n=2), family had moved abroad (n=1), and unknown reason (n=3).

4.4.3 Diagnosis of the children who were comprehensively psychiatrically assessed

Fifty-four children received the comprehensive neuropsychiatric autism diagnostic assessment. Forty-eight (40 boys and 8 girls) of these were confirmed to have a diagnosis of ASD after the assessment at the specialist CNC. The mean age of these children was 2.5 years (SD 0.5). In 27 individuals the criteria for autistic disorder/childhood autism according to DSM-IV/ICD-10 were met, and in 21 individuals the criteria for PPD-NOS/atypical autism were met. Three of the 54 children were diagnosed with

language disorder, of whom one also had autistic features, and three (6%) were considered to have development within the "typical" range.

4.4.4 Parental concerns before referral to CNC

In 35 (of 48) cases the parents had expressed concern for their child´s development already before the screening procedure at the CHC. In twelve of these cases there was a known family history of ASD already noted by the medical staff at the CHC in the referral letter to the CNC.

4.4.5 Migrant status of parents

In 24 (50%) cases with ASD both parents were of non-Swedish descent, in 8 cases one parent had not been born in Sweden, and in 16 cases both parents were of Swedish descent.

4.4.6 Language screen positivity followed by autism suspicion within one year

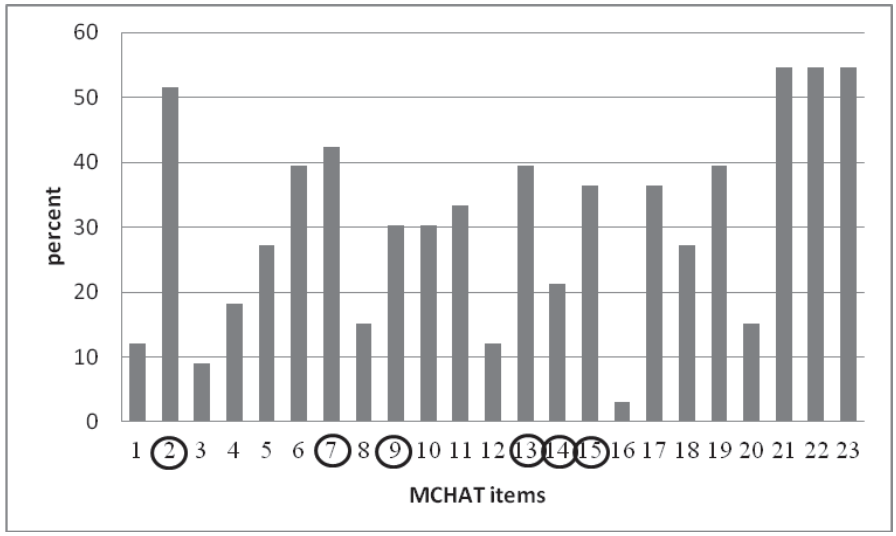
Four children, with no initial failure on the autism screen, but on the language screen, have later been referred from speech and language pathologists (SLP) for neuropsychiatric evaluations at the CNC. The neuropsychiatric assessments have not yet been completed.

4.4.7 Psychometric properties of the used instruments

4.4.8 M-CHAT

The *PPV,* calculated from the proportion of children with definitive failure on the M-CHAT (+ interview) and diagnosed with ASD, was 91.7% (95% CI 77.5 -98.2) and the *sensitivity* was 76.7% (95% CI 61.4 - 88.2) (Table 4).
Thirty-three of 36 children with definitive failure on the M-CHAT were confirmed to have a diagnosis of ASD. Only three (2, 7, 13) of the 6 most discriminating items (endorsed by more than 50% of the sample) in the present study "overlapped" with the 6 *critical items* identified by Robins et al (2001) (Figure 3). Most notable was the low endorsement rate for item 14 ("Does your child respond to his/her name when you call?") and the relatively high rate for items 21, 22 and 23.

Figure 3. M-CHAT definitive failure (%) on the different items (1-23) in children with confirmed ASD (n=33)



The circle ○ denotes "critical" item in Robins et al (2001)

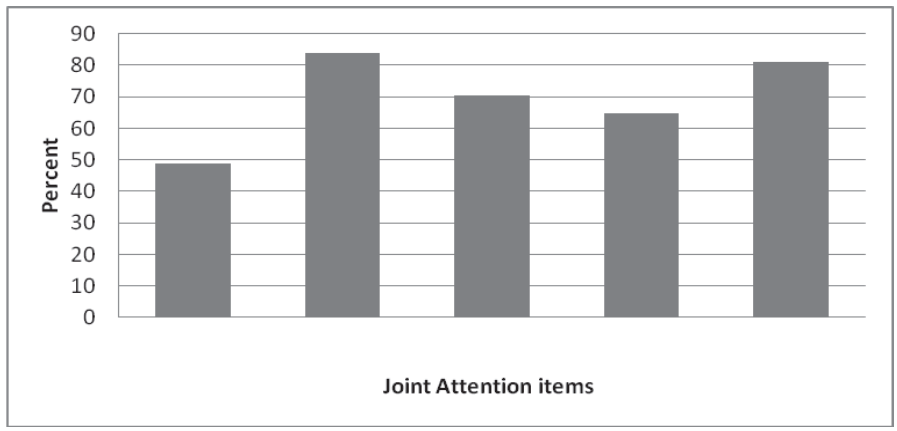
4.4.9 JA-OBS

The *PPV* of the JA-OBS was 92.5% (95% CI 79.6-98.4) and the *sensitivity* was 86.0% (95% CI 72.1-94.7) for the used screen positivity algorithm of failure on ≥2 items (Table 4). Thirty-seven of 40 JA-OBS positive cases were confirmed to have an ASD diagnosis after the comprehensive neuro-psychiatric assessment. Consistent with the results from item 14 on the M-CHAT, item 1 on the JA-OBS ("Reacts to own name") was not highly sensitive (Figure 4.).

A preliminary *inter-rater reliability test* of the instrument was performed as follows: Per cent agreement was studied in 14 cases observed by two nurses independently at the same 2.5-year check-up at the CHC. In one of the 14 cases ASD suspicion was raised at the CHC visit, the remaining 13 were regarded as typically developing. Complete agreement for total scores applied in 93% of the cases (individual item agreement 86-100%). In another sample per cent agreement was studied between JA-OBS performed by the nurse at the CHC and the observation made 2-3 months later by a clinician at the CNC later when the ADOS was performed. Agreement was obtained in 92% of 12 cases (individual item agreement 58-100%) with later confirmed

ASD. (Use of kappa statistic was not possible due to values missing in one column or row.)

Figure 4. JA-OBS (%) endorsed in items 1-5 (n=37)



4.4.10 Combination of M-CHAT and JA-OBS

The combination of instruments had been used in 51 of the 54 further evaluated children and in 45 of the 48 children with a confirmed diagnosis of ASD. Forty-three of these had screened positive in one or both of the instruments. The *PPV* for the combination of M-CHAT and JA-OBS (the proportion of children with a definitive failure on M-CHAT (+interview) *or* on JA-OBS or on both and diagnosed with an ASD) was 89.6% (95% CI 77.3-96.5) and the *sensitivity* was 95.6% (95% CI 84.9-99.5) (Table 4).

Table 4. PPV and Sensitivity of M-CHAT and JA-OBS

Psychometric property	M-CHAT (n=49)	JA-OBS (n=48)	M-CHAT and/or JA-OBS (n=51)
PPV (95% CI)	91.7% (77.5-98.2)	92.5% (79.6-98.4)	89.6% (77.3-96.5)
Sensitivity (95% CI)	76.7% (61.4-88.2)	86.0% (72.1-94.7)	95.6% (84.9-99.5)

5 DISCUSSION

5.1 General findings

In the diagnostic study it was shown that there are instruments that can be of benefit in the diagnostic assessments of ASD. The DISCO is one of these. The psychometric properties for the instrument showed good to excellent values.

The language cohort study confirmed that children with language delay at 2.5 years need to be followed up comprehensively. Language delay in toddlers must be regarded as an indicator of other possible developmental problems e.g. ASD, ADHD and learning disorders (ESSENCE).

Early detection of ASD is realistic. The prevalence rate of ASD in 2-year-old children in Gothenburg in 2010 was 0.80% of c. 5000 screened children. Corresponding rates for 2-year-olds referred to the same specialist centre in 2000 and 2005 (when no population screening had occurred) were 0.18% and 0.04%.

In the screening study it was shown that trained nurses and the use of a combination of instruments, M-CHAT and JA-OBS, enables early detection of ASD within a developmental child health program. The PPV and the sensitivity for the combination of instruments were excellent.

5.2 Limitations

In study I the sample analysed was relatively small, albeit not much smaller than those included in the validation studies of the ADI-R or the previous validation study of the DISCO-10 (Wing et al. 2002). Second, the study included individuals of various ages, and numbers in different age subgroups were too small for normative purposes. Third, the DISCO sample was not population-based, and it is unclear what degree of generalisability to other samples of ASD can be assumed. About one-third of the individuals included in the reliability study were non-ASD cases. The reliability might have been lower if the number of non-ASD cases had been higher or if there had been a greater mix of clinical diagnoses within the non-ASD group. Part of the validation against the ADI-R included assessments made by the same investigator in one session. The succession of items, as well as the type, succession and wording of the ‘‘probe’’ questions within items differ across the two schedules. This means that the majority of the ADI-R interviews performed during the present study were rated on the basis of information

elicited differently than is described by the ADI-R instructions. Thus, the present report might be taken to constitute a comparison between the ICD-10/DSM-IV algorithms of the two interviews, rather than between the two instruments themselves. However, this limitation was counterbalanced by the adult two-rater part of the validity study in which two independent researchers made ratings on two different occasions.

The sample size in Study II was small, which is a limitation and calls for caution in interpreting the results. The lack of a blindly examined control group in the neuropsychiatric follow-up study is also a potential limitation. It is possible that further follow-up studies and in-depth studies of these language impaired children would reveal possible other psychopathology, such as conduct, affective and anxiety problems The most important finding remains the confirmation of language delay/disorder at 2.5 years as an indicator of probable other neurodevelopmental problems.

The level of attrition in Study III-IV poses a limitation. Only 80% (5000 children) of the 2.5-year-olds were screened. Twenty per cent were neither screened nor assessed. There were several reasons for this attrition, most of which appeared to be related to organisational and random accidental events, including the unforeseeable acute proposed and media-exaggerated risk of outbreak of swine flu, and the sudden administrative change in the delivery of CHC services in the city of Gothenburg coinciding with the ASD screening. Some families were not reached despite several invitations to the CHC. Some other children were not screened or examined at all at the CHCs because they already were followed up by other specialists for developmental and neurological disorders and other chronic diseases. In all these subgroups from the “attrition cohort”, the rate of ASD would, if anything, probably be higher than in the screened/assessed group.

In the screening study (IV) written informed consent for participation in the study was received by the parents of 3999 children (80% of the screened population). Only data from these children could be further analysed. This is not ideal but considering that a large scale study of this kind is influenced by several political an organisational decisions (as described above) we still regard the results as meaningful. The individual decisions from parents must also be respected. There might however have been deficits in the information given to parents at the CHCs, especially as regards parents of foreign descent (in spite of the use of interpreters). The written information about the study was not translated into different languages.

5.3 Discussion of the results obtained in each of the four studies

5.3.1 The DISCO

The inter-rater reliability for more than 90% of the DISCO items included in the algorithm for ASD diagnoses proved to be good to excellent. In addition, the validity for the DISCO as tested against the ADI-R was excellent. The correspondence between clinical gold standard diagnoses and the algorithm diagnoses of the Swedish DISCO-10 was also good.

The DISCO-10 has advantages over the ADI-R. It covers many more areas of developmental skills i.e. motor skills, several aspects of "activities of daily living" (ADL), including a number of symptoms that are not part of the diagnosis or algorithm for the diagnosis of ASD (i.e. sleep disorders). Given the very high rate of co-existing problems in autism, it is important to cover aspects of ASD, which are not specifically included in the diagnosis per se. The DISCO-10 is particularly effective for diagnosing both the narrow variant of autism and disorders in the broader autism spectrum. The DISCO-10, unlike the ADI-R has diagnostic algorithms for all the commonly used clinical (and research diagnostic) categories in the autism spectrum, ICD-10, DSM-IV, Kanner autism, Wing & Gould criteria for ASD and Gillberg´s AS criteria. In all, the present study supports the use of the DISCO-10 for clinical and research purposes in the diagnostic process of ASD.

5.3.2 The language screen, ESSENCE

The results from the language cohort study confirms that so-called 'specific language impairment' is rarely 'specific'. Children with major language delay at the age of 2-3 years may have a more complex neuropsychiatric clinical presentation already at this age or other symptoms might later on be more obvious. Language delay at age 2.5 years should be regarded as a "signal" of ESSENCE (Gillberg 2010). Other frequently co-existing symptoms causing developmental impairment during the first 4 years are motor abnormality, general developmental delay, social interaction/communication problems, behaviour problems, inattention, hyperactivity/impulsivity, sleep problems and feeding difficulties. The awareness of ESENCE has important consequences for SLP services, the child health and school health organisations and for child psychiatry and paediatrics. This means that when speech and language delay has been confirmed in a child it is usually not appropriate to concentrate only on the language disorder. Instead SLPs,

psychologists, paediatricians, neurologists and child psychiatrists need to work in close collaboration.

5.3.3 The prevalence of autism

The high ASD prevalence rate reported over the last two decades was confirmed in this thesis. The prevalence rate of 0.80% in 2-year-old children must be considered as a minimum rate of ASD in the general population. Only about 80% of the 2-year-olds were screened for ASD; 20% were neither screened nor assessed. There were also ten children identified in the CHC screening with a strong suspicion of ASD, who, for different reasons, were never assessed in depth. The data from screening and the available developmental histories from the CHCs for these ten individuals indicated a probable ASD diagnosis. If these children had been included the prevalence rate for ASD for 2-year-old children would have been 1%. The rates of diagnosed ASD in 2-year-olds for 2000 and 2005 (0.18% and 0.04% respectively) were strikingly different from the approximately one per cent of the 2-year-olds with an ASD diagnosis in 2010. The majority of the children diagnosed with ASD in 2010 had a developmental level within the normal range, and only 35% were diagnosed with mental retardation or developmental delay. This was in contrast to results of the earlier study populations and to the results from our group from the 1980´s in which 75% of children with ASD had mental retardation (Gillberg, Steffenburg & Schaumann 1991). The male: female ratio in 2-year-olds with ASD in 2010 was 4:1 corresponding to the gender ratio found in most prevalence studies from different age groups and different populations.

It would appear that the educational effort directed to the CHC staff in combination with the introduction of general population formal screening, the M-CHAT and the nurse observation of "joint attention", was very successful and must have accounted for much of the dramatic change regarding the increase in referrals of very young children with a suspicion (and documented diagnosis) of ASDs. Even so, "milder cases" (e.g. AS) of ASD will still be missed at the age of 2 years and also, as has been pointed out in many studies, girls might be missed to a greater extent.

Although, the widening of the diagnostic criteria over the years and the general increased awareness of symptoms might explain the increase in prevalence, there are possibly other, as yet unknown, factors contributing to the prevalence surge. Regarding the biologically complex ASDs there may also be regional differences. In the present study there was an over-representation of ASD in children from immigrant families. Similar findings have been reported in many other studies (Gillberg, Steffenburg & Schaumann 1991; Dealberto 2011).

5.3.4 The autism screening

The most important psychometric value for an instrument used in population screening is the PPV. In study IV, the PPV for the combined M-CHAT/JA-OBS was excellent (90%) and actually higher than in previously published studies (Kleinman et al. 2008; Robins 2008). It is not possible to determine how many children with ASD were missed at this time point (the screen negative group has not been evaluated or followed up in registers). Under the assumption that all obvious ASD cases in the population would be known at the CNC, we estimated that the false negative severe ASD cases at autism screening were few. It is, however, also likely that the instruments used, designed to screen children with ASD symptoms detectable around the age of 2-3 years, will miss a number of cases with mild symptoms (and more obvious symptoms later in childhood, including those with typical AS). The *"true specificity"* and the *"true NPV"* for the methods used would not be possible to estimate until long-term follow-up studies have been performed.

Fifty-four children were further evaluated after the suspicion of ASD had been raised at the CHCs in 2010. The diagnosis of ASD was confirmed in 48 of these (three children were diagnosed with language disorder and only three were regarded as "typically developing"). The majority of these children were 2.5 years old, but in 25% the suspicion of ASD was raised before or after the 2.5-year check-up (five children were younger than 24 months). The CHC nurses were the key professionals who made early detection possible. For the 2.5-year-old children included in the study both the instruments for autism screening had been used. In cases where a suspicion of ASD had been raised before or after the 2.5-year-old check-up the screening instruments had not been used consistently, but, in most cases, at least one of them had been applied.

It appears that the two instruments M-CHAT, and JA-OBS, complement each other and optimise early detection of autism. The recommended two-step use of the M-CHAT (questionnaire followed up by interview in screen positive cases) proved to be necessary for several reasons. Many parents had difficulties with the questionnaire; some items were difficult to understand. Specific items could be clarified to the parents at the CHC and false positive could also be ruled out. Trained medical staff at the CHCs, responsible for the screening, was essential for the success of the screening programme as were the routines established à priori for further evaluations whenever developmental problems were noted.

6 CONCLUSIONS AND IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

The concept of autism and its classification have changed over the years. During the last decades there has been a reconceptualisation of autism as a spectrum condition, which will also be found in the upcoming DSM-5 (Wing, Gould & Gillberg 2011). ASDs constitute a heterogeneous group of disorders with different biological backgrounds where the core symptoms are deficits in social communication and the presence of restricted interests and behaviour.

ASDs are not rare conditions and several recent studies (including the present one study of ASD in 2-year-olds) show prevalence rates around 1% (Gillberg & Wing 1999; Baird et al. 2006; Gillberg et al. 2006; Fombonne 2009; Kocovska, Biskupsto, Gillberg et al. 2012). There is still often a huge gap of several years between the first symptoms, the parental first concern, and later diagnostic assessments and possibilities for interventions. Although most children are regularly followed up at the CHCs very early ASD symptoms are still missed in a majority of the cases. The findings in this thesis show that early detection of ASD is possible within the developmental programme at the CHCs, and that there is a need for a specific autism screening programme. The combination of the parent questionnaire, M-CHAT with follow-up interview, and the nurse observation, JA-OBS, showed high PPV and sensitivity for general population screening and appeared to hold promise for future use within the developmental surveillance programmes. Trained medical staff is, however, a basic requirement and enables earlier detection and the use of the screening tools also beyond routine screening time-points. It is essential that effective routines for further diagnostic assessments and interventions are in place, if screening programmes within CHC organisations are to be implemented more widely.

The emergence of symptoms in ASD varies from one child to another. Some symptoms may be part of other developmental problems (Fernell, Hedvall, Norrelgen et al. 2010). The diagnosis of ASD is clinically based and must rely on comprehensive neuropsychiatric assessments. The diagnostic procedure, in which specific strengths, difficulties and comorbidities are clarified, constitutes the foundation for individualised interventions for each child. The DISCO can be of great value in the diagnostic assessment covering the broad autism spectrum and different developmental levels. The ADI-R contributes little more than “confirmation” of, or a criterion base-line for the diagnosis of ASD.

Although there is an ongoing debate, and much future research is needed as to the specifics of different intervention programmes, there is a growing consensus that early interventions are valuable for children with ASD (Fernell et al. 2011). Clinical programs for autism screening, broad diagnostic assessments and interventions should be developed in close connection with each other and in accordance with evidence (Oosterling, Wensing, Swinkels et al. 2010). If this is the common goal, and if it leads to parent involved interventions and individualised interventions for each child, autism screening at the CHCs can have the potential to lead to improved prognosis for many children with ASD. This, in turn, would have consequences on many levels for the children, their families and for society at large, both in terms of quality of life (Billstedt, Gillberg & Gillberg 2011) and costs (Ganz 2007) . There will, of course, be organisational and financial implications; however, in the long run the changes implemented are likely to be cost effective.

In terms of future research needs in the field, the following proposed avenues should be pursued over the next several years: 1) The DISCO, the ADI-R and the ADOS all need to be exposed to more psychometric studies on general population and clinical samples and be tested against clinical diagnoses and briefer screening and diagnostic instruments such as the ASSQ, the ASDI and the CARS; 2) The prevalence of ASD and the need for additional ASD screening, for instance around school age, should be monitored in the cohort studied here with a view to assessing the scope of the problem of false negative ASD cases and the NPV and specificity of the proposed M-CHAT/JA-OBS 2.5-year-old screening device; 3) Further studies are needed as regards psychometric properties of the screening instruments in different age groups (e.g. regarding 12-23 months, 24-35 months and 36-48 months); 4) The findings in this thesis regarding the sensitivity for different M-CHAT items in comparison with the original studies in the US indicate possible cultural differences in terms of "critical items", and this calls for further cross-cultural studies.

A final "combined clinical – research" implication/conclusion is warranted. Autism is but one aspect of a usually complex neurodevelopmental disorder with, often, a variety of important "comorbidities". It is still a clinical diagnosis with smudged boundaries (Wing 2005). In clinical practice and research the full spectrum of ESSENCE needs to be acknowledged and ASD should be neither over- nor underestimated in this context.

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