UiT
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Department of psychology, Faculty of Health Sciences

Autism Spectrum Disorders: Complexities associated with sex differences, screening, and diagnosis

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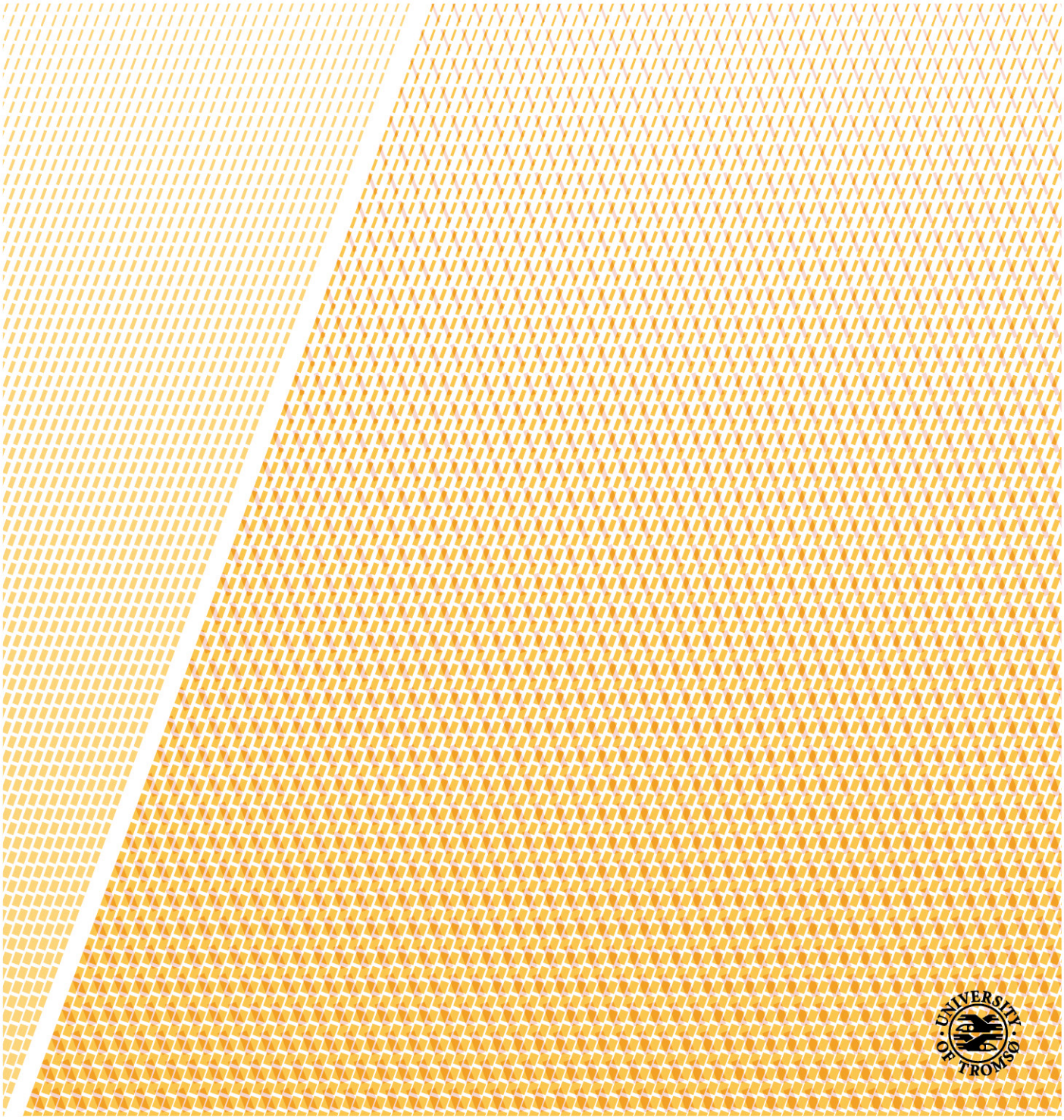
A dissertation for the degree of Philosophiae Doctor – February 2018



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List of abbreviations

ABC	Autism Birth Cohort
ADI-R	Autism Diagnostic Interview – Revised
ADOS	Autism Diagnostic Observations Schedule
AMSE	Autism Mental Status Exam
ASD	Autism Spectrum Disorder
ASQ	Ages and Stages Questionnaire
CHAT	Checklist for Autism in Toddlers
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revisions
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EAS	Emotionality, Activity and Sociability Temperament Survey
ICD-10	International Classification of Diseases, 10th revision
ID	Intellectually disabled
IQ	Intelligence Quotient
M-CHAT	Modified Checklist for Autism in Toddlers
MoBa	Norwegian Mother and Child Cohort
NIPH	Norwegian Institute of Public Health
NPR	Norwegian Patient Register
PPV	Positive Predictive Value
NPV	Negative Predictive Value
SE	Sensitivity
SP	Specificity

Acknowledgements

Firstly, I would like to express my sincere gratitude to my main advisor Prof. Martin Eisemann, PhD for providing me with this opportunity and the continuous support of my PhD project and related research. His guidance and motivation helped me in all the time of research and writing of this thesis. I will always be grateful for this possibility, and I will look back at these years with great appreciation.

Besides my main supervisor, I would like to thank thefollowing thesis advisors:
Prof. Fred R. Volkmar, MD for providing me with countless of possibilities to learn and develop as a researcher. You have exceeded every expectation I could have from an advisor, and I am beyond words grateful for your contribution. It has been an honor for me to have you as my advisor and to get to know you over these years.
Prof. Katarzyna Chawarska, PhD for sharing your knowledge, your insightful comments and encouragement, but also for challenging me and asking me the hard questions. It is sincerely a honor to work with you and to be mentored by you. You have definitely provided me with some understanding of autism and child development which I would not have without our collaboration.
Dr. Frederick Shic, PhD for not only teaching me everything I know by now about statistics and the introduction to R, but also for those breakneck paced deep discussions about autism, sex differences, diagnostic criteria, and the list could go on forever. You are a source of great inspiration and a great role model.
I would also like to thank you all for the opportunity to travel back and forth to work with you at the Yale Child Study Center. And for treating me and my family as family during my research stay. This has provided me with insights, knowledge and friendships which have shaped me as both a person and a researcher.

In addition to my advisors, I would like to thank Synnve Schjølberg at the Norwegian Institute of Public Health. Synnve has been my closest national collaborator, spending hours and hours on the phone and in person discussing research and other topics in the field. You have not only contributed to my research, but through our discussions also taught me an immense amount about child development and autism. Your knowledge is golden, and I thank you for spending both your work days and spare time sharing it with me.

I thank my fellow co-authors and colleagues: Dr. David M. Grodberg, Dr. Domenic V. Cicchetti, Dr. Anders Nordahl-Hansen, Dr. Pamela Ventola, Mr. Logan Hart, Ms Sara M. Vambheim, Ms Carla A. Wall, Dr. Elizabeth S. Kim, Dr. Mady Hornig, Dr. Alexandra Havdahl, Dr. Nina Stenberg, Dr. Anne-Siri Øyen, Dr. Ezra Susser, and Dr. Michael Powers for stimulating discussions, excellent feedback, and for collaborations during these years.

I would also like to thank UiT – The Arctic University of Norway, Department of Psychology, and Head of department Dr. Ingunn Skre, PhD, for continuous support during my PhD. I would also like to extend my thanks and sincere gratitude to the Norwegian Institute of Public Health for providing me with the opportunity to work with the MoBa data.

I would also like to thank my spouse, Camilla, for taking care of our children during my frequent travels, for understanding my working hours during these years. Furthermore, I have to thank my parents for helping out with whatever necessary during the already mentioned frequent travels. Last but not least, I have to thank my children Madelen, Mia, Fredrik and Kristian for not only being the greatest motivation, but also for teaching me quite a bit about child development. I love you to the moon and back.

Madelen, you have provided me with understanding, insights, and motivation that led me to this point, I will always be thankful that you came our way, as fantastic as you are.

Love, Dad

Abstract

Background

Attitudes towards general population screening for Autism Spectrum Disorders (ASD) range from not recommending to supporting it as a necessary step for early identification. The primary goal of screening instruments is to enhance the effectiveness of early identification, thus providing access to treatment and benefits as early as possible. However, as most of the larger studies have been conducted in clinical populations, it is unclear if the existing screening instruments have sufficiently high specificity and sensitivity in unselected general population-based samples. The increased awareness of the heterogeneity of onset and patterns of symptoms in ASD highlights the need to understand the complexities associated with screening. In terms of heterogeneity, it is also uncertain how differences in phenotypic expressions between males and females affect identification and ultimately the male-to-female ratio in ASD. Previous research indicates that females need a greater load of symptoms to be identified by concurrent diagnostic criteria. Sex differences in requirement of genetic load might be related to specific patterns of behaviors, such as strengths and weaknesses, that manifest in females under similar amounts of genetic load. While the understanding of sex differences in autism is emerging, few studies have addressed sex-specific phenotypic expressions of males and females in unselected general population samples.

Objectives

The overall aims of the present thesis are to 1) examine the complexities of behavioral, developmental and temperament expressions in unselected general population screening, and 2) to identify sex specific symptom patterns that might affect screening and ultimately diagnosis through utilization of unselected and selected population samples.

Methods

The three papers presented in the present doctoral thesis utilized data from two different sources: (1) the Norwegian Mother and Child Study (MoBa) and (2) A clinical study utilizing the Autism Mental Status Exam (AMSE).

Paper I

The first paper is based on data from the MoBa's 18-month questionnaire, utilizing the full 23-item M-CHAT to examine sex differences in parent-endorsed behaviors. A two-way

ANOVA (sex by diagnosis) with the total number of failed M-CHAT items as the outcome was conducted to ascertain between-group differences in the total failure rate. Furthermore, logistic regression analyses were conducted on all 23-items. Total N = 53,728, ASD N = 185 (ASD Female N = 32).

Paper II

The second paper presented is also based on data from the MoBa's 18-month questionnaire, including children who passed on the six-critical item criterion of the M-CHAT. Total N = 68,197, True negatives N = 67,969, False negative N = 228(Female N = 36). Univariate ANOVA analyses, with post-hoc testing on domain scores of the Ages and Stages Questionnaire (ASQ) and Emotionality, Activity and Sociability Temperament Survey (EAS) were conducted to describe clinical features of false negative children later diagnosed.

Paper III

The third paper utilized data from a high-risk sample of children referred for ASD specific assessment. In addition to children assessed for ASD at Seaver Autism Center – Mount Sinai. It also included children from Kelly O'Leary Center for ASD at Cincinnati Children's Hospital. Total N = 123, ASD N = 85 (ASD female N = 23). Test performance of the AMSE for males and females separately was conducted by ROC curve analyses, and item level analyses were made using ordinal regression analyses.

Results

Results from Paper I revealed that female toddlers with a later diagnosis of ASD expressed a higher load of symptom severity than male toddlers with a later diagnosis of ASD on the M-CHAT. Item-level analyses of the M-CHAT items showed that female toddlers with a later diagnosis of ASD had a relative strength in joint attention, but weakness in imitation compared to male toddlers with a later diagnosis of ASD.

Paper II revealed that the M-CHAT six-critical item criterion failed to identify 76.8% of children later receiving an ASD diagnosis. Eighteen-month-old false negative children had less developed social, communication, fine- and gross motor skills compared to 18 months old true negative children. Further, similarities in patterns of strengths and weaknesses between males and females in the false negative group were found when compared to sex-matched true negative peers. However, false negative females' weaknesses were more pronounced than those of false negative males' as reflected by the effect sizes. In terms of differences between false negative males and females, the latter were significantly less shy than their false negative male counterparts.

In contrast to the first two studies, which utilized an unselected general population, Paper III aimed to examine sex differences in a selected population at risk for ASD utilizing the Autism Mental Status Exam. The results showed that ASD females expressed more significant language impairment, but fewer oversensitivity issues than males referred for ASD specific assessment. ROC Curve analyses found that the AMSE performed equally well in the female sample as in the male sample at discriminating ASD from non-ASD.

Discussion

Utilizing the M-CHAT in an unselected population revealed difficulties in detecting all children with a later diagnosis of ASD in an unselected general population. Furthermore, it emerged that the true negative children were significantly developmentally delayed compared to true negative children. This reflects that children later diagnosed with ASD, but passing the six-critical item criterion on the M-CHAT already at 18 months show distinct atypicalities compared to those without a later ASD diagnosis. It has to be noted that the true negatives, i.e. children correctly identified by the M-CHAT at risk of ASD, were significantly delayed compared to the false negatives. There are several factors that could contribute to these identification difficulties, such as heterogeneity in time of onset, symptom patterns, parental concern and design of instruments. It might be that recognizable symptom patterns are not yet evident until the social demands exceed the capabilities of the child, or that the symptom expressions are more subtle and harder to recognize for both parents and clinicians. Furthermore, results from all three papers indicate that females diagnosed with ASD were more impaired than males, as reflected by the higher total score on the M-CHAT in Paper I, more pronounced effect sizes of impairment in Paper II, and increased language issues in Paper III. The manifestation of sex differences found in all three studies could influence early identification, as females might demand a greater impairment to manifest the traditional ASD like symptoms, as diagnosed females show better joint attention skills, less shyness and oversensitivity. These strengths could potentially obscure the fundamental nature of autism in females, making it difficult to identify autism early as joint attention, a withdrawn nature, and the presence of significant repetitive/sensory issues are key flags for ASD diagnosis. In practice, this could affect how well screening and diagnostic instruments are at detecting females with similar levels of genetic load. More research is needed to understand the female phenotype of ASD, as the symptoms might be different, and not necessarily fewer.

List of Papers

I

Øien R.A., Hart, L., Schjølberg, S., Wall, C. A., Nordahl-Hansen, A., Kim, E.S., Eisemann, M. R., Chawarska, K., Volkmar, F. R., & Shic, F. (2016) Parent-Endorsed Sex Differences in Toddlers with and Without ASD: Utilizing the M-CHAT. Journal of Autism and Developmental Disorders, 47(1), 126-134.

II

Øien, R.A., Schjølberg, S., Volkmar, F.R., Shic, F., Cicchetti, D.V., Nordahl-Hansen, A., Stenberg, N., Hornig, M., Susser, E., Havdahl, A., Øyen, A-S., Ventola, P., Eisemann, M., & Chawarska, K. (2018) Children with autism who pass 18-month screening: clinical features. In review.

III

Øien, R.A., Vambheim, S.M., Hart, L., Nordahl-Hansen, A., Erickson, C., Wink, L., Eisemann, M., Shic, F., Volkmar, F.R. & Grodberg, D. (2018) Sex-Differences in Children Referred for Assessment: An Exploratory Analysis of the Autism Mental Status Exam (AMSE). Journal of Autism and Developmental Disorders.

1 Background

1.1 Diagnostic Classification

The characteristics of autism were first described in the seminal studies by Kanner[1] and Asperger.[2] The 1943 article by Kanner entitled “Autistic Disturbances of Affective Contact” described the clinical features of eleven children. Kanner termed the condition “infantile autism” and hence coined the term that has been used for decades. In 1979, Lorna Wing and Judith Gould[3] paved the way for the use of term autism spectrum disorders.[4] Wing and Gould described a "triad of impairments in autism", i.e., deficits in social relations, communication, and imagination. The notion that these deficits are expressed as a continuum of impairments promoted the idea that the disorder may affect individuals with different levels of cognitive abilities.[3] Happe and Ronald[5] later proposed the inclusion of repetitive behaviors instead of imagination in this triad. Although autism was first described in the 1940s, it was not until 1980 that it was included as a disorder in the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III).[6] Its inclusion in the DSM-III followed studies by Kolvin (1971)[7] and Rutter (1972),[8] who suggested that autism was not a form of psychosis, but a distinctive condition in its own right. The DSM-III introduced a significant shift in the use of diagnostic criteria, as it focused on observable features and not theoretical features of the diagnosis.[9] Although autism was first included in the DSM-III, the introduction of Asperger Syndrome, Atypical Autism and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) did not occur until the release of the International Classification of Disease, 10th revision, in 1990[10] and the DSM-IV[11] in 1994. In 2013, the American Psychiatric Association introduced the DSM-5[12] which was subject to some criticism and debate.[9,13,14] The DSM-5[12] merged the diagnoses of Autistic Disorder, Asperger Syndrome, and PDD-NOS into a single diagnosis of Autism Spectrum Disorders (ASD). The DSM-5 diagnosis of ASD incorporated specifications of symptom severity, intellectual

impairment, language impairment, medical and genetic conditions, and comorbid neurodevelopmental or behavioral disorders.[12]

The diagnoses in the present thesis are based on the ICD-10 (diagnoses retrieved from the National Patient Registry (NPR)), the DSM-IV-TR (diagnoses extracted from the Autism Birth Cohort (ABC)) and the DSM-5 (diagnoses from the Autism Mental Status Exam study) (Table 1).

Table 1 Diagnostic Classification Systems

ICD-10		DSM-IV-TR		DSM-5
F84.0	Childhood autism	**299.00**	Autistic disorder	**Autism Spectrum Disorders (ASD)** No diagnostic subcategories. Individuals with a well-established DSM-IV diagnosis of Autistic Disorder, Asperger's Disorder, or PDD-NOS should be given the diagnosis of ASD. Requirements for diagnosis: Must meet all three behavioral criteria in category A and at least 2 criteria in category B (Appendix 1)
F84.2	Rett syndrome	**299.80**	Rett's disorder	
F84.3	Other childhood disintegrative disorder	**299.10**	Childhood disintegrative disorder	
F84.4	Overactive disorder associated with mental retardation and stereotyped movements			
F84.5	Asperger syndrome	**299.80**	Asperger's disorder	
F84.1	Atypical autism	**299.80**	Pervasive developmental disorder not otherwise specified (PDD-NOS)	
F84.8	Other specified pervasive developmental disorder			
F84.9	Pervasive developmental disorder, unspecified			

1.2 Prevalence

In recent decades, the prevalence of ASD has increased rapidly.[15-18] Based on current, the prevalence of ASD is approximately 1%,[15,19] but rates as high as 2.6% have also been reported.[20] Current estimates from the U.S. Centers for Disease Control and Prevention (CDC) show that approximately one in 68 children receive an ASD diagnosis in the United States, compared to one in 5,000 receiving an autism diagnosis in 1975.[18] This indicates that autism was regarded as a rare condition when compared to the current ASD estimates of 50 to 70 in 10,000.[15,21] Prevalence estimates consistently report a clear male predominance.[22] The etiological and non-etiological factors responsible for this somewhat dramatic increase in prevalence are widely debated. Non-etiological factors, such as increased parental and professional knowledge, public awareness, clinical practices, and the quality of diagnostic instruments,[23] have likely had a profound effect on the increasing prevalence. However, the introduction of Asperger Syndrome and PDD-NOS also represent potential causal factors contributing to the increase in ASD prevalence. In some way, non-etiological factors, such as improvements in clinical knowledge in recent decades, have also impacted our ability to identify children with normal IQ and less severe symptom expression. Non-etiological factors, such as changes in diagnosis, diagnostic substitution and increased public awareness, are the most likely reason for the observed increase in the prevalence of ASD,[24,25] an increase that makes ASD one of the most common developmental disorders.[26,27]

Table 2 CDC ADDM Prevalence History[18]

Year	Prevalence
1975	1 in 5,000
1985	1 in 2,500
1995	1 in 500

2000	1 in 150
2002	1 in 150
2004	1 in 125
2006	1 in 110
2008	1 in 88
2010	1 in 68
2012	1 in 68

1.3 Etiology

Because the concept of autism has evolved significantly since the original studies[1,2], as evidenced by the changes in diagnostic classifications and prevalence, multiple factors have been proposed as causal factors for ASD. In the 1950s, the early psychoanalytical views of autism promoted the hypothesis that autism was a direct result of post-natal influences, particularly distant and cold parenting by mothers, coining the term "refrigerator mother."[28,29] The psychoanalytical explanation for the causal factors for autism dominated the field until the rise of a cognitive-based paradigm during the 1970s and was ultimately replaced by revelations regarding cognitive and genetic etiological factors.[30]

As the term ASD evolved[4] and provided a broader understanding of the heterogeneity of ASD, research suggested that ASD was a multifactorial disorder without a clear universal etiology. For example, studies have demonstrated that a large number of susceptibility genes are involved[31], and environmental and epigenetic aspects are also associated with ASD.[32] Thus, research shows a distinct interplay between behavioral symptoms of ASD and genetic contributions.[33,34] The contribution of genetics is supported by twin, sibling, and family studies of ASD, which often suggest a genetic contribution to the disorder. [33-35] Heritability estimates based on twin concordance rates from the American Psychiatric Association (APA) range from 37% to approximately 90%.[12] Based on the findings from these studies, we know that multiple genes involved, strongly suggesting that multiple causal mechanisms are in play.

In some families, called "multiplex" families, multiple individuals are diagnosed with ASD. Causal factors related to ASD in these families are presumed to be associated with genetically heritable variants of ASD. These families are different from "simplex" families, in which only one individual in the immediate family is diagnosed with ASD, suggesting the presence of "de novo" mutations and other epigenetic, environmental, and emergent etiologies of ASD. Importantly, the multifactorial pathways contributing to autism might include different genetic mutations or none at all.

According to Baron-Cohen and colleagues,[36] elevated fetal steroidogenic activity might be linked to a later autism diagnosis.[36] However, other factors that potentially contribute to the development of ASD have been identified, such as an older parental age[37] and obesity.[38] Moreover, the presence of these factors alone does not necessarily cause a child to develop ASD. Consumption of folic acid supplements during the prenatal period might lower the risk of childhood autism.[39] One of the upcoming challenges in the field of autism is the heterogeneity of the disorder, which might preclude the detection of a universal causal factor.

1.4 Early Identification

Early diagnosis is important for multiple reasons, and thus the number of studies on this topic has increased. Early identification is considered a critical factor for improving adult outcomes, as it facilitates access to services, such as early intensive interventions.[40,41] For parents and caregivers in many developed countries, the timing of the diagnosis is important for obtaining financial aid. For example, in Norway, a range of financial benefits are available from the date a diagnosis is made. These benefits are intended to cover extra expenses related to the disorder and to provide parents with financial benefits to compensate for increased care.[42,43] For the community, an improved outcome in adulthood is known to have long-term benefits, providing more individuals with the opportunity to support themselves to a greater

extent. This system also has cost benefits for society.[44-46] In other words, early identification is also associated with lifelong benefits. Thus, a strong focus on universal screening (i.e., in the general population) has emerged over the past decade[47] to improve and increase early identification. There is evidence for diagnosing younger children with a greater stability of diagnosis.[48,49] Nevertheless, the age of diagnosis in epidemiological samples is still 3 to 5 years of age.[18,50,51]

Research has revealed that the parental educational level is a significant predictor of receiving an early diagnosis, presumably reflecting greater awareness of developmental expectations in more educated parents and greater ability to identify and obtain access to specialized diagnostic services.[52] As the onset of parental concern has been shown to be 15 months of age, with substantial variability (30% before one year of age, and 80% before two years of age),[53] improvements in early identification and the implementation of early interventions are of great importance for maximizing outcomes and improving quality of life and socioeconomic outcomes. The disparity between the age of diagnosis, parental concern, and knowledge of the stability of diagnosis has multiple causal factors. This disparity has been posited to primarily be a consequence of the heterogeneity in the phenotypic expression of ASD,[32] whereas other researchers have proposed that a lack of knowledge about the presentation and heterogeneity of ASD among sub-specialized professionals (i.e., pediatricians and nurses at health care centers) might cause a delay in referral for ASD-specific assessment.[41] A recent study by Macari and colleagues showed an agreement between parents and clinicians on the rating of autism symptoms,[54] supporting parental concern as a vital factor contributing to early identification.

For early identification, an understanding of both early behavioral predictors and the heterogeneity of symptom patterns and onset is critically important to maximize the effect of future screening instruments. Relying on early concerns about the child by parents, healthcare

staff (i.e., pediatric nurses or physicians at well-visits) or kindergarten teachers could be valuable for early referral for ASD-specific screening or assessment and ultimately early identification.[32]

1.4.1 Heterogeneity of symptom patterns and onset. The extreme heterogeneity of autism elicits immense difficulties in clinical detection and treatment planning. Heterogeneity in etiology, behaviors, core symptoms, cognitive skills, adaptive skills, language and communication, the onset of diagnosis and core symptom patterns has been reported.[32] This heterogeneity of symptoms often leads to large variations in the phenotypic expression of the disorder, particularly patterns of symptoms, such as behaviors. However, there is increasing awareness of the heterogeneity of both the time of symptom onset[55] and how the patterns of ASD-related symptoms are expressed.[49] The strict age-of-onset criterion included in previous diagnostic manuals was removed from the DSM-5[12] because ASD symptoms may become evident when social demands begin to exceed the limited capabilities of the child, regardless of age.[48] Additionally, symptoms of ASD may manifest differently depending on the child's verbal and nonverbal levels of functioning.[56]

1.4.2 Early predictors of autism spectrum disorders. The vast majority of research on early predictors of ASD has been conducted based on parent experiences, retrospective studies of children who subsequently received an ASD diagnosis, high-risk sibling studies, and prospective general population studies, such as the Norwegian Mother and Child Cohort (MoBa).[57] Although the presentation and onset of symptoms in children receiving an ASD diagnosis vary in early childhood (e.g., as a result of variance in cognitive and language skills),[32] research shows that some clinical features serve as good predictors of a later ASD diagnosis. Accumulating evidence describes experiences with atypicalities in behaviors (i.e., repetitive and restricted behaviors), speech and language development, motor development,

and social communication/attention. In particular, social communication and interaction are clear predictors of a later diagnosis at 12-24 months of age.[58-63]

1.4.3 Social communication and attention. Although few prospective studies have examined early autistic behaviors, other studies of traditional behaviors associated with ASD have not revealed differences between 6-month-old infants with and without a later diagnosis of ASD.[55] Although the isolation of specific markers for diagnosis at 6 months was difficult,[61,62] infants with ASD exhibited significant impairments in social communication at 12 months of age in terms of atypical gaze and a lack of social smiling and interest in peers, and at 18 months of age, children with ASD presented atypicalities in all measured domains.[55] Atypicalities in eye contact,[56] responding to his/her name,[60,62,64,65] paying attention towards a social stimulus,[66] responding to joint attention (i.e., following a pointing gesture)[56,59,67-69] and initiating joint attention (i.e., using gestures such as pointing to or share objects with others)[56,68,70] have been found to be predictive of a later ASD diagnosis. Of course, early differences in development are quite possibly so subtle that current methods do not detect them. This is a distinct possibility given that studies utilizing more fine-tuned measurement methods show emerging deficits in social attention by 6 months of age.[71-73]

1.4.4 Restricted and repetitive behaviors and interests. Restricted, repetitive behaviors and interests (RRBs) are a core domain in the diagnostic criteria[3-5,11,12] and are probably among the most frequently portrayed autistic traits in popular culture.[74] The presentation of RRBs is diverse and fluctuates in manifestation between individuals. The quantity and strength of RRBs also vary. These behaviors may be very repetitive in some individuals, but in others, these behaviors may present as milder fixations on objects or interests. RRBs are often present as early as 12 months of age,[55] and specific examples of

RRBs include atypical use of objects, such as spinning wheels on toys, lining up toys or objects,[64,75,76] and unusual visual exploration of objects.[65] Lining up objects or toys may reflect a desire for monotony, which could be expressed through a need or desire for conformity. Conformity is also manifested as a need for strict routines, specific apparel, and consequently how children react to unconformity. These behaviors can be systemized into RRB subdomains, where different trajectories of development are associated with different subdomains.[77] RRBs are regarded as more heterogeneous and context-dependent than behaviors related to social communication and attention.[78] Furthermore, children with more severe RRBs have recently been shown to exhibit more issues in early motor development.[79] However, RRBs are also present to some extent for certain periods of time during typical development and are not specific to ASD, even if their frequency is increased in children who are later diagnosed with ASD.[80]

1.4.5 Motor development. In addition to atypicalities in motor development, some motor atypicalities also fall within the RRB domain, such as mannerisms and flapping of hands, which are often regarded as typical autistic traits.[64,65,81] Atypicalities in motor development are possible predictors for ASD, although these atypicalities remain understudied. Atypicalities in motor development might present earlier than some behaviors in the other domains, such as social and communication.[32] In addition, delays and/or atypicalities in gross and fine motor development have been reported in studies of siblings of children with ASD. [63,82,83]Furthermore, Øien and colleagues[67] performed a prospective study of a general population sample (N= 53,728 non-ASD, N=185 ASD) and found that an inability to walk unaided at 18 months was a strong predictor of a later ASD diagnosis. Research has also shown that children with a motor developmental delay at six months also seemed to manifest social communication delays in a high-risk sample.[84] As stated above, a link between RRBs and motor development has also been observed.[79] Although some of these

features may be predictors of ASD, sufficient research is not currently available to make definitive statements. Further studies are needed to determine whether atypicalities in gross and fine motor development are strictly associated with IQ/ID.

1.4.6 Temperament features. According to infant sibling studies, temperamental profiles by 24 months of age differ significantly between children who receive and those who do not receive an ASD diagnosis in terms of a lower positive affect, higher negative affect, difficulty regulating attention and behavior, reduced surgency (i.e., less active and positive emotions), and increased perceptual sensitivity. [62,85,86] As reported in the 2017 study by Macari and colleagues, changes in perceptual sensitivity, inhibitory control, and low-intensity pleasure from ages 2 to 3 ½ were strong predictors of ASD severity and adaptive social skills later in life.[87]

1.4.7 Screening for autism spectrum disorders. The primary goal of screening instruments is to enhance the effectiveness of early identification of children with ASD and to subsequently enable the rapid implementation of effective intervention strategies.[88,89] The screening procedure should be designed to be completed as a brief assessment to identify children at risk for ASD. A screening instrument aims to provide sufficient sensitivity to detect all children with ASD while providing sufficient specificity to primarily detect the intended disorder.[47] Furthermore, we must distinguish between screening measures that are intended for Level 1 screening (i.e., screening in unselected general populations) and Level 2 screening (i.e., screening children already exhibiting developmental concern to differentiate ASD from other developmental disorders).[90] Level 1 screening instruments are often designed to be completed by parents at pediatric well-visits. Level 2 screening instruments are often used when a child already shows developmental concerns, and are used to determine if a child

should be referred for an ASD-specific assessment. These instruments often combine clinical observation and parental reporting. In terms of Level 1 screening instruments, the Modified Checklist for Autism in Toddlers (M-CHAT)(R/F)[90-92] is the most widely used instrument for ASD-specific screening. The M-CHAT is designed to be completed in a primary care provider setting.[92] Among Level 2 screening instruments, the most frequently used examinations are the Childhood Autism Rating Scale (CARS/CARS2)[93,94], the Social Communicative Questionnaire (SCQ)[95], the Screening Tool for Autism in Toddlers (STAT),[96] and the more recent Autism Mental Status Exam (AMSE).[97,98] Most Level 1 screening instruments aim to identify ASD in toddlers and young children under the age of 30 months, whereas Level 2 screening instruments are mostly designed to screen for ASD in a wider age range of children when a concern regarding ASD is noted.[90]

The attitude concerning Level 1 screening (i.e., universal or general population screening) for ASD has ranged from critical[89] to welcoming, [88,99] although this approach remains a subject of broad, ongoing debate. Researchers have not clearly determined whether existing universal screening instruments exhibit sufficient performance to detect ASD in general populations due to a lack of evidence within the existing literature.[89,91,92,100-102] The lack of prospective studies examining sensitivity (SE), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) is a large gap in the current literature.[100,101]

The American Academy of Pediatrics has recommended universal screening for all children at 18- and 24-month well-visits[99,103] utilizing ASD-specific screening measures, such as the M-CHAT. [92] However, the M-CHAT, together with other screening measures, has faced criticism due to its low specificity, which can often result in higher rates of false positives (e.g., the identification of children without ASD but with developmental delays or severe intellectual impairment). Seceral studies have examined the SE and SP of the M-CHAT, in both selected and unselected samples.[92,100-102,104] Robins and colleagues performed

an initial M-CHAT validation study[92] that included both a selected population (children for whom concerns were noted (i.e., high-risk)) and an unselected population (children for whom concerns were not noted (i.e., low-risk)). Most children who received an ASD diagnosis were already children for whom concerns were noted and who had been referred for early interventions. The validation study of the M-CHAT[92] showed an SE of .97, an SP of .95 and a PPV of .36 (NPV .99). Conducting the follow-up increased the SP to .99 and the PPV to .68. Only three children from the unselected population received an ASD diagnosis, indicating that most children who were diagnosed and screened positive showed developmental concerns. Kleinman and colleagues[102] performed a follow-up study of the M-CHAT in 2008, which revealed a PPV of .36. Similar to the results of the validation study, the performance in low-risk (unselected) children was low (PPV .11). Although the M-CHAT and other Level 1 screening instruments have several limitations in correctly identifying all children with ASD, they identify children without ASD who may require treatment. Larger prospective population studies are needed to assess the true performance of current screening instruments and to identify developmental patterns for children who screen negative for ASD but ultimately receive an ASD diagnosis.

Utilizing the Norwegian Mother and Child Cohort (MoBa),[57] a prospective unselected population study that is linked to the Norwegian Patient Registry (NPR), Stenberg and colleagues revealed a PPV of .015 (1.5%) for the 23-item criterion and a PPV of .033 (3.3%) for the six-critical item criterion[101] conducted without follow-up. Stenberg and colleagues showed that 65.3% of later diagnosed children were false-negative cases[101](i.e., children who would not meet the cut-off for receiving follow-up). A recent study performed by Øien and colleagues[105] found that 76.8% of children who were later diagnosed with ASD screened negative on the six-critical item criterion (false negatives). Few studies of screening instruments have been conducted in prospective general populations with linkage to national

patient registries. Most studies with somewhat larger samples report only the SE, SP, and PPV for children who screened positive and received an ASD-specific assessment as a part of the study. More studies in prospective cohorts are needed to understand the true performance of Level 1 screening instruments.

1.5 Sex Differences in Autism Spectrum Disorders

Over the past twenty years, findings related to sex differences in ASD have ranged from revealing sex-specific patterns in behavior and development to reports of minimal differences between sexes or sex differences that mirror the sex differences observed in typically developing children. The most consistent finding related to sex differences is the higher male prevalence, leaving us without a clear explanation.[106] Sex differences in ASD symptoms among children diagnosed with ASD are a focus of increasing research attention. As mentioned above, the most frequently reported sex difference in ASD is the disproportional male-to-female prevalence ratio, which has been reported consistently since the first studies of autism by Kanner[1] and Asperger,[2] with a clear male predominance. Fombonne[16,107] reported a prevalence ratio of 4.3:1 to 5.5:1 across studies, whereas a recent study showed a corrected male-to-female ratio ranging between 3.1:1 and 4.3:1. [22] However, the prevalence estimates vary when controlling for IQ and have been reported to be 5.75:1 in the normal IQ range and 1.9:1 in children with intellectual disability (IQ <70).[20,108,109] Thus, when a child has an intellectual disability, the male-to-female ratio is less pronounced. Although the causal mechanisms of this predominantly high male-female ratio in ASD and sex differences in behavior and development are widely debated and researched in the current literature, several theories have been proposed to explain their existence. One of the more controversial of these theories is the Emphasizing – Systemizing (E-S) theory proposed by Baron-Cohen and colleagues,[110] suggesting that sex differences in ASD symptoms might arise because some of the disorder's characteristics closely resemble an extreme version of the

"systemizing cognitive profile," which is more typically found in males[110,111] The theory hypothesizes a shift in a tendency towards more "extreme systemizing" characteristics in males with ASD than in females, who are more likely to present an "empathizing" cognitive profile than males within the general population. In other words, males with ASD are usually strong "systemizers" and tend to be drawn to predictable, rule-based systems. However, a trade-off of this hyper-development of "systemizing" behaviors is that it may be related to hypo-development of "empathizing" behaviors. Conversely, according to this theory, females in the general population, who more closely resemble an "empathizing" profile on average, are less likely to make this shift to hyper-developed "systemizing" and hypo-developed "empathizing" behaviors.[110]

Several hypotheses have suggested that sex differences in ASD behavior might cause the greater male-to-female ratio in the prevalence of ASD. For example, other theories utilize several components of Baron-Cohen and colleagues' E-S theory, suggesting that the phenomenon may imitate general differences between typically developing males and females[112-114] and similarly perceive ASD as an extreme expression of male phenotypic patterns that are found in the general population.[110,115] For example, in several studies, females with ASD have been reported to exhibit lower levels of RRBs than males with ASD,[116,117] which could be regarded as externalizing disruptive behaviors. Males tend to score higher on indices measuring the externalization of behavior problems, whereas females score higher on indices measuring internalizing symptoms.[118-122] It could be hypothesized that these externalizing symptoms are easier to detect than internalizing symptoms, and ultimately affect how parents and clinicians are rating the more traditional ASD symptoms through observation.

The skewed male-to-female prevalence could in addition indicate a protective effect in females, who may require an increased genetic load to manifest ASD-like behavior of a

certain magnitude or impairment.[123-125] For example, Robinson and colleagues[126] studied siblings of female and males with ASD who scored above the 90th percentile in ASD behavior. The results revealed an increased load of ASD behavior in siblings of females with ASD in comparison to siblings of males with the disorder,[126] supporting the theory of a female protective effect (FPE) against autistic behavior. Support for the female protective effect was also provided by a study that showed a greater mutational burden in affected females than in affected males.[127] In contrast, Messinger and colleagues[114] suggested that sex differences in cognitive performance and repetitive behaviors do not appear to be ASD-specific. Rather, such differences mirror sex differences in cognitive performance and repetitive behaviors that are seen in typically developing children, which poses an alternative hypothesis to the female protective effect.

Chawarska and colleagues[128] examined sex differences in early social orienting, and found that high-risk females showed better attention to social stimuli, such as faces. This finding was observed in comparison between both high-risk males and low-risk males and females. Furthermore, enhanced attention towards social stimuli in high-risk infants was associated with less severe social impairments at 2 years of age. Both findings could indicate that high-risk females are less socially impaired than high-risk males, masking or camouflaging social impairment and complicating diagnostic processes.

Although this discrepancy in the male-female ratio of ASD has been postulated to be due to a greater risk of ASD in males than females, other researchers have posited that subtle cases of ASD in females might go unrecognized, particularly in females with an average IQ, because they display fewer disruptive behavioral outbursts than their male peers[129] or due to camouflaging of symptoms.[130-133] Thus, females might need to exhibit greater impairment to receive an ASD diagnosis. This hypothesis could also suggest that the current diagnostic

criteria and diagnostic instruments are better at detecting typical male phenotypic expressions of the disorder.[134]

As concerns individuals ultimately diagnosed with ASD, research remains somewhat inconsistent regarding the types and severity of ASD traits between sexes. [135-139] However, subtle differences in the mean scores of autistic traits have been observed.[140,141]

2 Measures

The measures used and discussed in the present thesis, represents standards-of-practice in autism screening, early developmental profiling, and more recent screening system development.

2.1 Modified Checklist for Autism in Toddlers (M-CHAT)

The M-CHAT was designed to screen for autism early in development, at approximately 18 months of age.[92] It is based on the Checklist for Autism in Toddlers (CHAT), and has in recent years been revised to reduce false positives (M-CHAT R/F).[91] The M-CHAT includes 23 yes-no questions for parental completion, as well as a follow-up interview with the parents of children screening positive. Each item in the M-CHAT is scored as pass or fail, and six of the 23 items are considered to be critical in predicting an ASD diagnosis (Table 3).[92] The M-CHAT was designed to be completed quickly in the waiting room of primary care providers, such as pediatric well-visits, and has become one of the most frequently used screening instruments for ASD. [90] Its use has been recommended in the United States for toddlers at 18 months of age, with a follow-up at 24 months of age. [99,142]

The psychometric properties of the M-CHAT have been reported in studies from several countries and, as mentioned above, have been debated. The PPV has ranged from .015 to .793, depending on whether a sample was comprised of children from the general population or children who were at high risk or already exhibiting signs of developmental delays. [92,101,102,104] Among unselected pediatric populations, the PPV has been reported as .015 (N = 52,026), [101] and .11 (N=3,309), respectively. [102] In a large population study (MoBa) of 52,026 children conducted in Norway by the Norwegian Institute of Public Health, [101] the SE and SP were .21 and .98, respectively (i.e., a negative screening result was reassuring, whereas a positive screening result was not a strong predictor of ASD).

Table 3 Modified Checklist for Autism in Toddlers[92] - Items

1. Does your child enjoy being swung, bounced on your knee, etc.?
2. Does your child take an interest in other children?
3. Does your child like climbing on things, such as upstairs?
4. Does your child enjoy playing peek-a-boo/hide-and-seek?
5. Does your child ever pretend, for example, to talk on the phone or take care of a doll or pretend other things?
6. Does your child ever use his/her index finger to point, to ask for something?
7. Does your child ever use his/her index finger to point, to indicate interest in something?
8. Can your child play properly with small toys (e.g., cars or blocks) without just mouthing, fiddling, or dropping them?
9. Does your child ever bring objects over to you (parent) to show you something?
10. Does your child look you in the eye for more than a second or two?
11. Does your child ever seem oversensitive to noise? (e.g., plugging ears)
12. Does your child smile in response to your face or your smile?
13. Does your child imitate you? (e.g., you make a face-will your child imitate it?)
14. Does your child respond to his/her name when you call?
15. If you point at a toy across the room, does your child look at it?
16. Does your child walk?
17. Does your child look at things you are looking at?
18. Does your child make unusual finger movements near his/her face?
19. Does your child try to attract your attention to his/her own activity?
20. Have you ever wondered if your child is deaf?
21. Does your child understand what people say?
22. Does your child sometimes stare at nothing or wander with no purpose?
23. Does your child look at your face to check your reaction when faced with something unfamiliar?

Bold items are critical items

2.2 Ages and Stages Questionnaire (ASQ)

The Ages and Stages Questionnaire is a parent-reported questionnaire that measures the developmental status of children.[143] The questionnaire is designed not only to measure developmental skills at a certain time but also to ask parents to recall previous abilities and instruct parents to observe given tasks at the present time. The ASQ consists of 19 questionnaires that assess children aged four to 60 months of age. The ASQ is constructed as a developmental surveillance tool, with six questions in each of five domains

(communication, gross motor skills, fine motor skills, problem-solving and personal-social skills). Each item is scored "yes" (10 points), "sometimes" (5 points) or "not yet" (0 points). In the present thesis and in the Norwegian Mother and Child Study (MoBa), a subset of items from the ASQ was included, belonging to the domains of communication, gross motor skills, fine motor skills, and personal-social skills.

Table 4 Ages and Stages Questionnaire[143] - Included Items

1. When you ask him/her, does your child go into another room to find a familiar toy or object? (when you ask for instance: "Where's your ball?", "Go and get your coat" or "Go and get your blanket")
2. Does your child say eight or more words, in addition to "mamma" and "dada"?
3. Without showing him/her first, does your child point to the correct picture when you say, "Show me the cat" or "Where is the dog?"
4. Does your child move around by walking, rather than by crawling on his/her hands and knees?
5. Can your child walk and seldom fall?
6. Does your child walk down stairs if you hold onto one of his/her hands?
7. Does your child throw a small ball or toy with a forward arm motion?
8. Does your child stack a small block or toy on top of another? (For example, small boxes or toys approximately 3 cm in size)
9. Does your child turn the pages in a book by himself/herself? (He/she may turn over more than one page at a time.)
10. Does your child hug dolls or cuddly toys when playing when them?
11. Does your child try to get your attention/show you something by pulling your hand or clothes?
12. Does your child come to you when he/she needs help, such as with opening a box?
13. Does your child copy the activities you do, such as wiping up a spill, sweeping, shaving or combing hair?

2.3 Emotionality, Activity, Sociability Temperament Survey (EAS)

The EAS Temperament Survey for Children: Parental Ratings[144] is an instrument designed for children aged 1 to 9 years. The EAS was created to measure emotionality, activity, sociability, and shyness. For each item, the parent is asked to rate her/his child on a 5-point Likert rating scale (from 1: very characteristic or typical of your child to 5: not characteristic or typical of your child). In the present study and in the Norwegian Mother and

Child Study (MoBa), 11 items from the EAS were included and comprised four different domains: Sociability, Shyness, Emotionality, and Activity. A short form of the EAS has been validated previously.[145]

Table 5 Emotionality, Activity and Sociability Temperament Survey[144] - Included Items

1. Your child cries easily
2. Your child is always on the go
3. Your child prefers playing with others rather than alone
4. Your child is off running as soon as he/she wakes up in the morning
5. Your child is very sociable
6. Your child takes a very long time to warm to strangers
7. Your child gets upset or sad easily
8. Your child prefers quiet, inactive games to more active ones
9. Your child likes to be with people
10. Your child reacts intensely when upset
11. Your child is friendly towards and trusting of strangers

2.4 Autism Mental Status Exam (AMSE)

The Autism Mental Status Exam (AMSE)[97,98,146,147] is an eight-item observational tool that prompts the examiner to observe and document patients' social, communicative and behavioral functioning in community-based developmental assessments and is intended to guide clinical judgment and decision making. Each item is scored on a 0–2 scale, with possible total scores from 0 to 14. Higher scores reflect greater symptom severity and have been found to correlate with the ADOS-2 comparison score.[98] Social items must be observed during the clinical examination, but communication and behavioral items can be observed or reported by parents. The items that can rely on parental reports are the pragmatics of language, encompassing preoccupations and unusual sensitivities. In these three items, the score is weighted (2) if the item is observed and (1) if the item is reported present by parents. The test performance of the AMSE in a high-risk clinical sample revealed that a score of five or greater produced excellent sensitivity and good specificity.[148]

Table 6 Autism Mental Status Exam[147] - Items

1. Eye contact (observed)
2. Interest in others (observed)
3. Pointing skills (observed)
4. Language (reported and/or observed)
5. Pragmatics of language (reported or observed)
6. Repetitive behaviors/Stereotypy (reported and/or observed)
7. Unusual or encompassing preoccupations (reported and/or observed)
8. Unusual sensitivities (reported and/or observed)

3 Objectives

The overall aims of the present thesis are to 1) examine the complexities of behavioral, developmental and temperament expressions in unselected general population screening, and 2) to identify sex specific symptom patterns that might affect screening and ultimately diagnosis through utilization of unselected and selected population samples.

Paper I

This paper aimed to examine parent-endorsed sex differences in children at 18 months of age who did or did not receive a later diagnosis of ASD. Furthermore, the study aimed to examine whether there was proof for the extreme male brain theory in the behaviors reported by parents on the M-CHAT.

Paper II

This paper aimed to examine parent-reported development and temperament in male and female toddlers who passed the six-critical item criterion of the M-CHAT at 18 months of age, utilizing the Ages and Stages Questionnaire (ASQ) and the Emotionality, Activity, Sociability (EAS) Temperament Survey.

Paper III

This paper aimed to examine the psychometric properties of the AMSE in males and females who were referred for ASD-specific assessment separately. Furthermore, this paper aimed to examine sex differences at the item level in clinician-endorsed symptoms of the AMSE.

4 Data Sources

4.1 The Norwegian Mother and Child Cohort Study (MoBa)

MoBa is a prospective pregnancy cohort study, that was facilitated by the Norwegian Institute of Public Health (NIPH). The NIPH started enrolling participants as pregnant women in 1999 and was completed in 2008. The main objectives of the MoBa were to examine the causes of disease in mothers, fathers and children. [57] The MoBa is a nationwide study, that includes the participation of 50 out of 52 state hospitals in Norway. Among invited mothers, 40.6% consented to participate, which included 114,500 children. The MoBa also obtained biological material, which is stored at the Biobank in Oslo, Norway, providing great opportunities for genetic analyses, biomarker studies, and other studies focusing on biological markers.[38]

The participating mothers received questionnaires during pregnancy and at given time points after birth. The fathers completed questionnaires only during pregnancy. The topics for the MoBa questionnaires are broad and include topics such as health, diet, well-being, socio-economic status (SES), development, and behaviors.

Data from the MoBa are regularly linked to the National Patient Registry (NPR). The Autism Birth Cohort, [149] which is a nested sub-study within the MoBa, collected additional data, such as diagnostic information.

The mothers provided informed consent on behalf of both themselves and their children. MoBa has a broad consent (i.e., the participants consented to provide biological and questionnaire data for a wide range of future projects). In prospective studies such as the MoBa, broad consent is regarded as more appropriate because specific projects are unknown at the time of recruitment.[150] The participants can withdraw at any time and can ask to be removed from the study. The first option would exclude the participants from future questionnaires, while the latter option would delete all data collected.[57] However, the

participants provided informed consent based on the general aims of the study, and that data could be utilized in future research projects. Detailed information related to ethics, such as recruitment and consent, are published at www.fhi.no, from the Norwegian Institute of Public Health.

The MoBa is funded primarily by the Norwegian Ministry of Health and Care Services, the Norwegian Research Council (NRC), the National Institute of Environmental Health Sciences, US, and the National Institute of Neurological Disorders and Stroke, US. In the present doctoral thesis, the MoBa was utilized as the data source for Paper I and Paper II.

4.2 Autism Mental Status Exam Data Source

This study was conducted using data from autism-focused diagnostic assessments that were carried out at two academic centers in the U.S.A., including the Cincinnati Children's Hospital and the Mount Sinai Seaver Autism Center. Each center administered its routine standardized assessment protocols, which included a clinical examination, an Autism Mental Status Exam, an Autism Diagnostic Observation Schedule, an Autism Diagnostic Interview-Revised, and cognitive assessments. Each instrument yielded standardized scores, which were entered into the MSSM online database by the study coordinators at the respective sites. The information from each of these instruments was considered to be highly valid, as the AMSE was administered by clinicians only after establishing high inter-rater reliability. The ADOS and ADI-R evaluations were administered by clinicians who had established site reliability. Cognitive assessments (IQ) were administered by licensed psychologists. Demographic information was also collected, including age, sex, race, and ethnicity.

The patient population included all children, adolescents, and adults who were suspected of having ASD and referred to each center for comprehensive ASD-focused assessment and potential participation in research. There were no exclusion criteria.

4.3 Legal Permits

MoBa and its sub-study ABC are approved by the Regional Committee for Medical and Health Research Ethics South East and have permits from the Norwegian Data Inspectorate.

The AMSE study had all necessary approvals and IRB approvals from Mount Sinai and the Cincinnati Children's Hospital.

5 Study Methods

5.1 Paper I

Participants

The sample included 53,738 children from the Norwegian Mother and Child Cohort Study (MoBa), of whom 185 later received an ASD diagnosis. Among those 185 children who received an ASD diagnosis, 32 females were included. The mothers of the included children had provided complete responses to the 23 items of the M-CHAT.

Measures

The M-CHAT is a yes-no parent-endorsed ASD-specific screening instrument. It was designed to screen for ASD early in development (i.e., approximately 16–30 months of age).[92] The M-CHAT includes 23 yes-or-no questions that are to be completed by parents and followed-up by an interview with parents of children who receive a positive M-CHAT screen score. The M-CHAT was designed to be completed quickly in the waiting room of a primary care provider and has become one of the most frequently used screening instruments for ASD.[90] In the present article, the M-CHAT checklist is used as an ASD-specific behavior measure to examine early sex differences in children with or without ASD.

Statistical analyses

A two-way ANOVA (sex by diagnosis) with the total number of failed M-CHAT items as the outcome was conducted to ascertain between-group differences in the total failure rate. Next, we conducted a logistic regression to explore the specificity of difficulties in the ASD and non-ASD groups through an individual M-CHAT item analysis. We first performed this analysis without controlling for the number of failed items to show the effect of diagnosis

on each item. Next, to explore the difference in the pattern of endorsed items between ASD and non-ASD children, we performed the same analysis with diagnosis as the predictor, controlling for levels of failure. To determine if non-ASD children differ by sex in terms of symptoms endorsed at the M-CHAT item level, we conducted a logistic regression for each M-CHAT item, including sex as the predictor and controlling for levels of failure. Finally, to determine if ASD children differ by sex in terms of symptoms endorsed at the M-CHAT item level, we performed logistic regression analyses of each M-CHAT item, including sex as a predictor and controlling for the overall total failure rate. The statistical analyses were conducted using IBM SPSS 23.

5.2 Paper II

Participants

The sample of participants included 68,197 screen-negative children from the Norwegian Mother and Child Cohort Study (MoBa), and 228 (36 females) screen-negative children later received an ASD diagnosis. All participants had completed at least the six-critical item criterion of the M-CHAT.

Measures

The present study utilized the M-CHAT[92] six-critical item criterion to select for subsequent analyses. The authors listed six specific items that constitute the most important items in predicting an ASD diagnosis.[92] The ASQ is a parent-reported questionnaire, that measures the developmental status of children.[143] A subset of 13 items from the ASQ were included in the MoBa's 18-month questionnaire.

The EAS [144] was designed for children aged 1 to 9 years of age and measures emotionality,

activity, sociability and shyness. A subset of 11 items from the EAS was included in the MoBa 18-month questionnaire.

Statistical analyses

Children in the false-negative group were compared with children in the true-negative group. We conducted a set of univariate ANOVAs with diagnosis and sex as between-group factors on the ASQ and EAS domain scores. Post-hoc analyses were conducted for between- and within-group differences, utilizing independent samples. The analyses were conducted using IBM SPSS 24 for Mac.

5.3 Paper III

Participants

In total, 123 (28.5% females) children, with a mean age of 5.74 years (S.D.= 2.88), were included from two sites: (1) The Seaver Autism Center for Research and Treatment at Mount Sinai and (2) The Cincinnati Children's Hospital Medical Center. At Mount Sinai, the sample included children who received comprehensive autism-focused diagnostic evaluations as part of their Assessment Core protocol from September 2013 through December 2014.

Measures

The AMSE is an 8-item observational tool that prompts the examiner to observe and document patients' social, communicative, and behavioral functioning in the context of a developmentally focused clinical examination. Each item is scored on a 0 to 2 scale, with possible total scores ranging from 0 to 14. The social items must be observed during the clinical exam, but the communication and behavioral items can be parent-reported or observed. Three items prompt the examiner to specify whether the item is reported or

observed: the pragmatics of language, encompassing preoccupations, and unusual sensitivities. For these three items, the score is weighted if the item is observed.

Statistical analyses

To ensure that the groups were comparable, we (a) examined males and females in terms of age, rates of intellectual disability (ID), and total scores. One-way ANOVA was used to analyze continuous variables, and Fisher's exact test was used for categorical variables. Our subsequent analyses controlled for any variables for which there was a significant between-sex difference. Ordinal regression analyses examined differences between ASD males and ASD females at the item level. Next, the diagnostic accuracy of the AMSE was examined separately for males and females using the nonparametric measure of area under an receiver operating characteristic (ROC) curve. Cohen's d was used as a measure of effect size.[151] The IBM SPSS 23 software was used for statistical analyses.

6 Results

6.1 Paper I

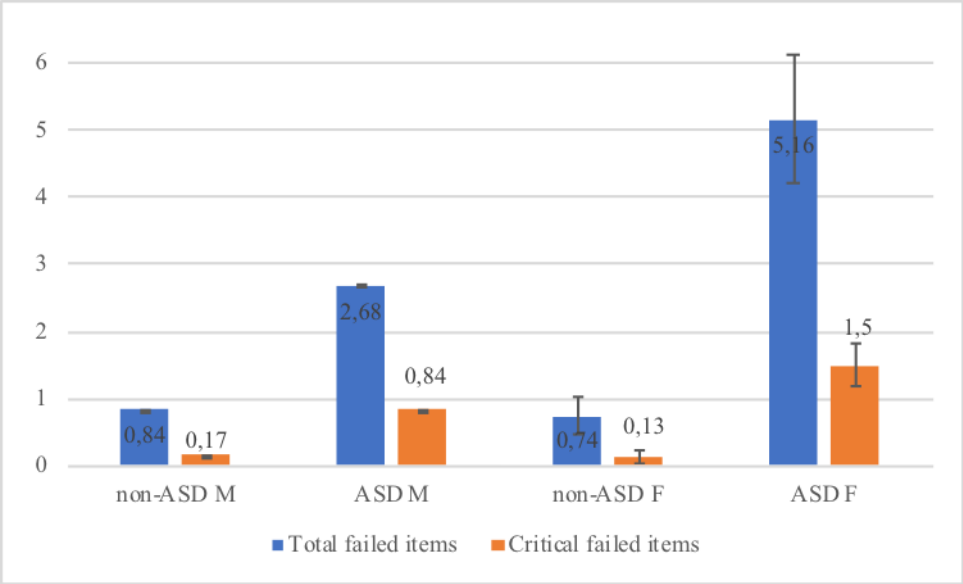

Figure 1 M-CHAT failure by diagnosis and sex

The findings showed that children who were later diagnosed with ASD, as expected, failed significantly more items than children without a later diagnosis of ASD (p <.001, d = .783). Males without ASD failed significantly more items than females without ASD (p <.001, d = .086). However the effect size was small, suggesting a statistical result driven by large sample sizes as opposed to start differences. Females who later received an ASD diagnosis failed significantly more items than males who later received an ASD diagnosis (p <.001 d = .547), indicating greater symptom expression in females than males who were later diagnosed with ASD. This finding stands in contrast to the findings obtained in the group of children without a later diagnosis of ASD, where females failed fewer items than males on both the 23-item criterion and the six-critical item criterion. Controlling for between-group differences revealed a more equivocal male disadvantage, and many of the ASD-associated traits were more common in the non-ASD sample. Analyzing sex differences in the ASD group and controlling for between-group differences showed that males and females screen

fairly similarly. However, two differences emerged between ASD males and ASD females; ASD females showed strength in joint attention (following a pointing gesture) (p = .011) but weakness in imitation (facial expressions) (p = .036). The strengths and weaknesses generally seem non-specific to sex and instead vary based on the presence of an ASD diagnosis.

6.2 Paper II

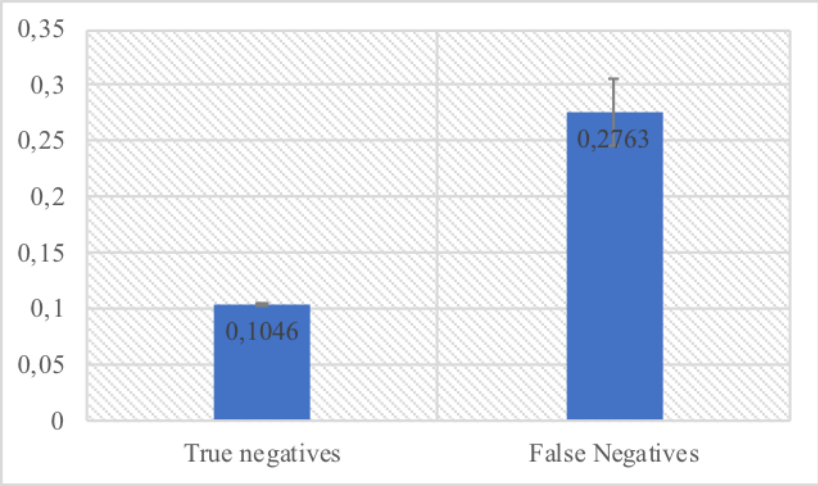

Figure 2 Mean of the six-critical item criterion

In general, children in the false-negative group exhibited delays and atypical features in comparison to children in the true-negative group when using the ASQ and the EAS. Compared to children in the true-negative group, 18-month-old children in the false-negative group were rated by their parents as displaying less social development (p < .001) and fewer communication skills (p < .001) and as showing fine (p < .001) and gross (p < .001) motor delays. Marked differences were not observed between males and females, as in most cases, both males and females in the false-negative group performed worse than their sex-matched counterparts in the true-negative group. However, the differences, as indexed by effect sizes, appeared to be more pronounced in females, particularly in the social, communication, and gross motor domains. Males and females showed a different pattern in only one area: males in

the false-negative group were rated as shyer than males in the true-negative group (p = .003, d = .238), whereas females in the false-negative group were rated as less shy than females (p = .035, d = .369) and males (p = .017, d = .463) in the false-negative group. These findings suggest that at 18 months of age, nuanced differences in temperamental indices are already present between males and females who screen negative and later receive an ASD diagnosis. Females in the false-negative group were rated as less socially inhibited than males. These finding conflicts with those obtained for children in the true-negative group. Supplementary analyses revealed that the true-positive children were rated as less advanced than true-negative children on all ASQ domains and on the sociability, activity and emotionality domains of the EAS.

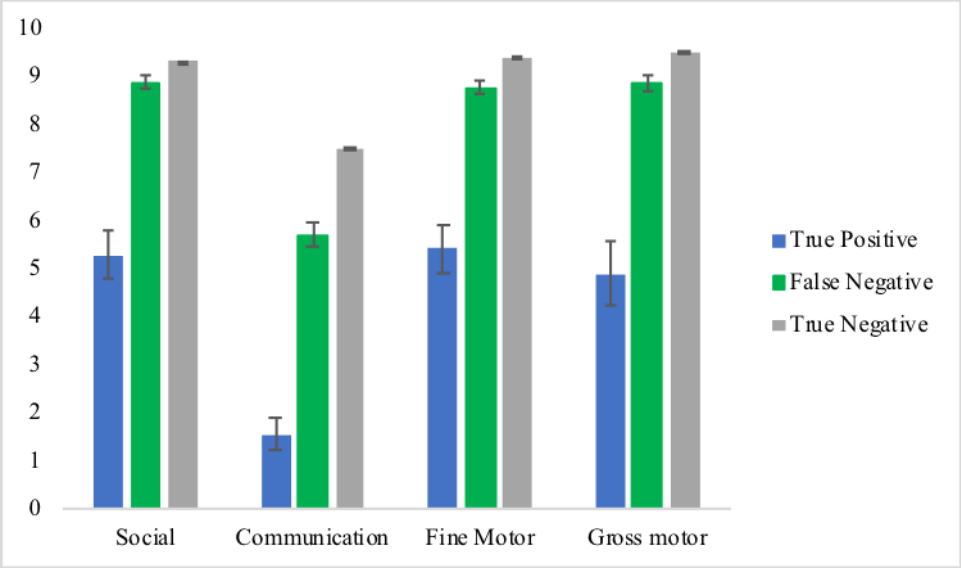

Figure 3 ASQ scores for males

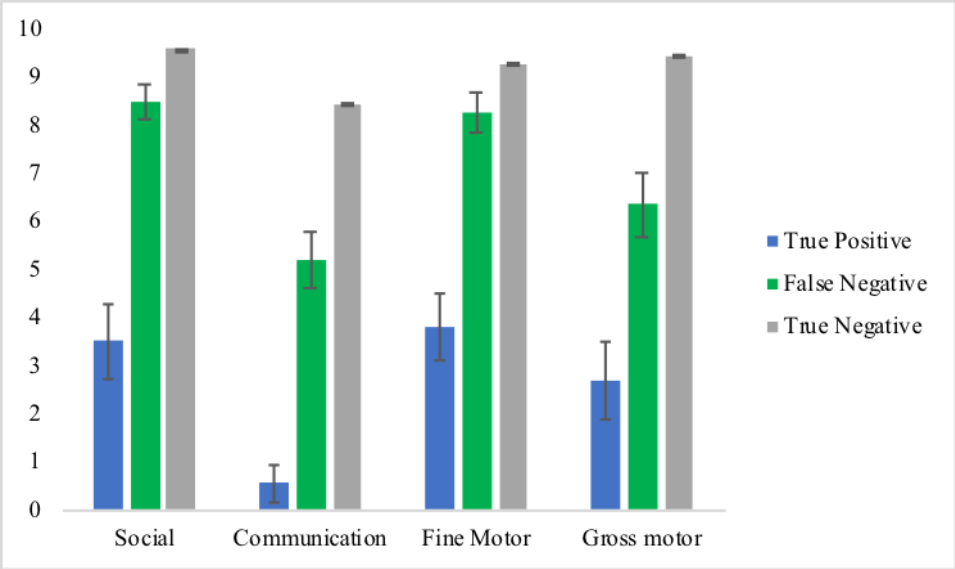

Figure 4 ASQ scores for females

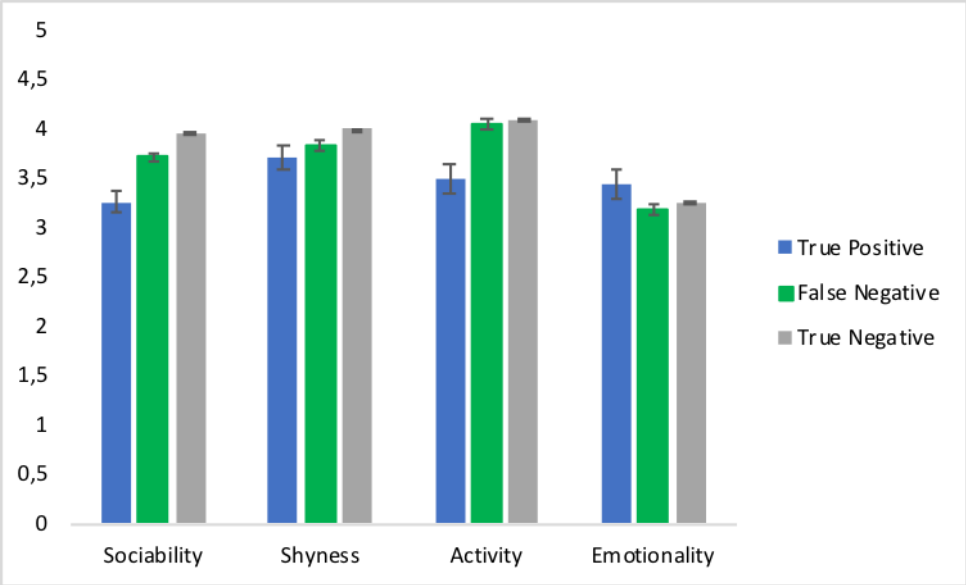

Figure 5 EAS scores for males - Greater scores on shyness and emotionality indicate that the child is less shy and emotional

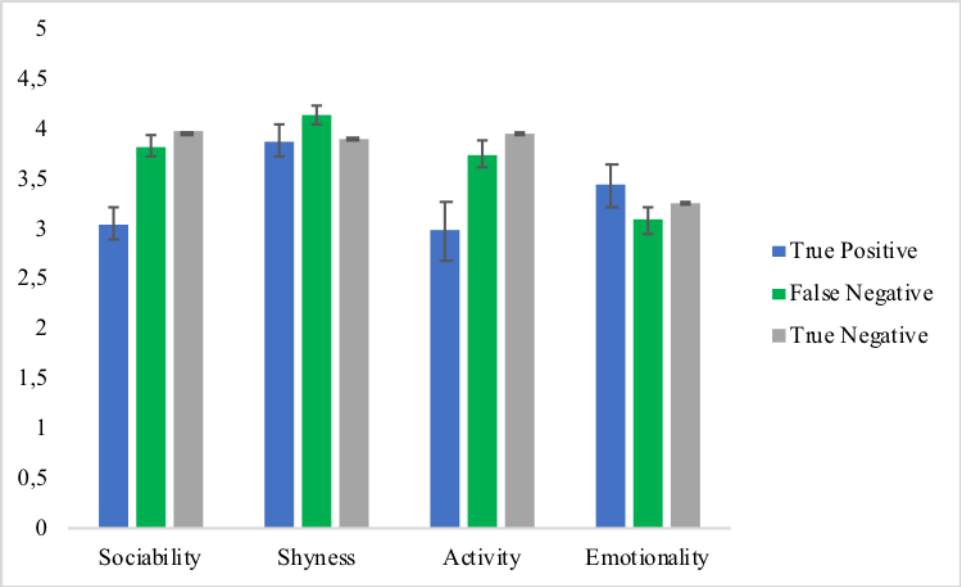

Figure 6 EAS scores for females Greater scores on shyness and emotionality indicate that the child is less shy and emotional

6.3 Paper III

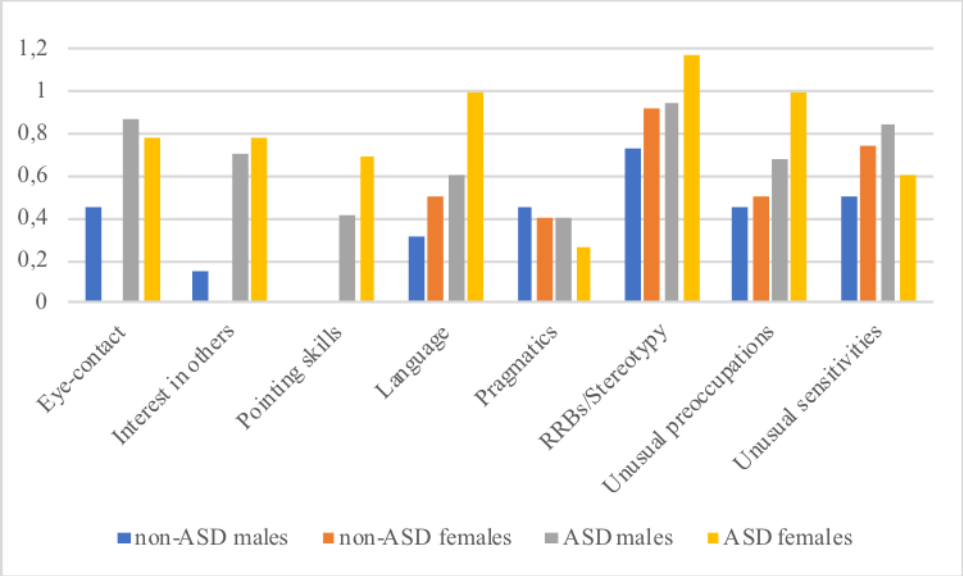

Figure 7AMSE mean score distribution

The findings revealed differences in severity (total AMSE score) ($p < .001$, $d = 2.29$) and rates of intellectual disability (ID) ($p = .046$, $d = .439$) between individuals with ASD and non-ASD individuals who were referred for assessment. Significant differences in severity, ID, and age were not observed between males and females with ASD. The findings showed that children with ASD had a comorbid ID diagnosis and higher levels of symptom severity

more often than non-ASD children. The item-level analyses showed that males and females with ASD differed in their responses to the AMSE, whereas the comparison of children with and without ASD revealed that individuals with ASD exhibit significantly more symptoms in general. Further inspection showed that females with ASD were more likely to have a selective impairment in language than males with ASD (p = .005) but tended to exhibit fewer issues related to over-sensitivities, such as heightened sensitivity to noise, touch, smell or taste, and a high pain threshold (p = .017). The item measuring language deficits were restricted to nonverbal, undeveloped sentences, single word use, and the use of fewer than three words. The ROC curve analysis revealed that the AMSE discriminated between females with ASD and non-ASD females (AUC = 0.95, 95% CI = [0.913, 0.992], as well as between males with ASD and non-ASD males (AUC = 0.95, 95% CI = [0.893, 1.000]).

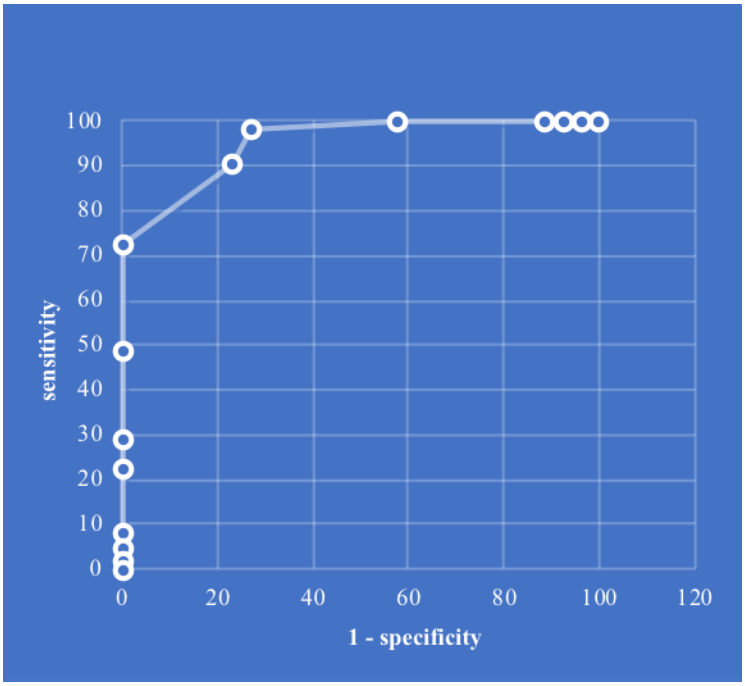

Figure 8 ROC Curve Analysis Males – AMSE total score X diagnosis

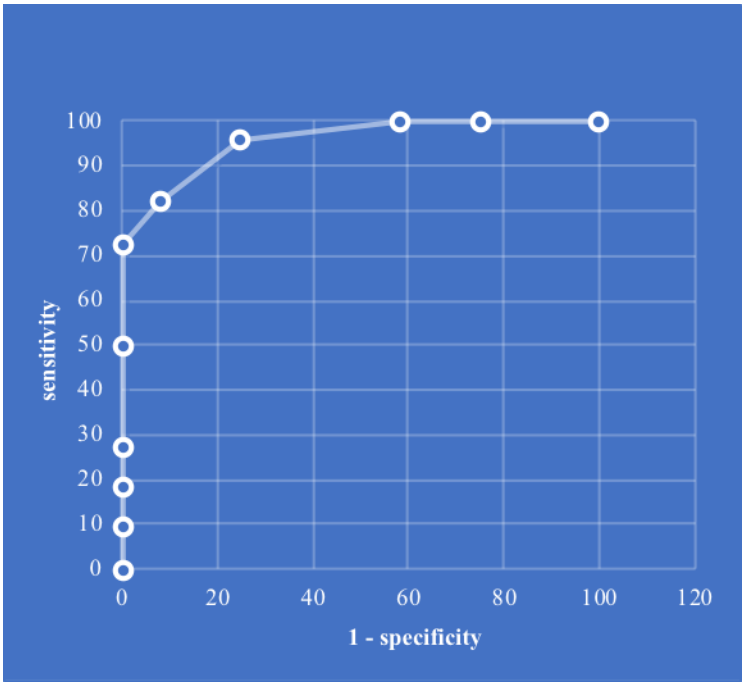

Figure 9 ROC Curve Analysis Females – AMSE total score X diagnosis

7 Discussion

7.1 Summary

The results from the first study demonstrated that male and female toddlers with a later diagnosis of ASD exhibited greater symptom severity on the M-CHAT than toddlers without a later diagnosis of ASD. Females without a later ASD diagnosis had lower total scores than males without a later diagnosis. Furthermore, female toddlers with a later ASD diagnosis expressed greater symptom severity than male toddlers with a later ASD diagnosis. Item-level analyses of the M-CHAT items revealed that compared to male toddlers with a later diagnosis of ASD, female toddlers with a later diagnosis of ASD exhibited a strength in joint attention but a weakness in imitation.

The second study revealed that the M-CHAT six-critical item criterion failed to identify 76.8% of children who were later diagnosed with ASD. Males and females who screened negative on the M-CHAT at 18 months of age but still received an ASD diagnosis

later (false-negatives) displayed less developed social, communication, fine and gross motor skills than children who screened negative on the M-CHAT who did not receive a later ASD diagnosis (true-negatives). The patterns of strengths and weaknesses between males and females in the false-negative group were similar to those observed for sex-matched true-negative peers. However, the effect sizes indicated that the impairment observed in false-negative females in comparison to true-negative females was greater than that observed between false- and true-negative males. Notably, a difference in shyness emerged between false-negative males and false-negative females. False-negative females were significantly less shy than false-negative males but also less shy than true-negative children.

In contrast to the first two studies which utilized an unselected general population, the third study aimed to examine sex differences in a selected population that was at risk for ASD utilizing the AMSE, a Level 2 screening instrument. The results revealed that females with ASD exhibited greater language impairments but fewer oversensitivity issues than males who were referred for ASD-specific assessments. ROC curve analyses indicated that the AMSE discriminated within the male sample (ASD/non-ASD) as well as within the female sample (ASD/non-ASD), according to the DSM-5[12] criteria.

7.2 General Discussion

7.2.1 Screening. The primary goal of screening is to identify children who are at risk for ASD at an early stage to facilitate access to early intervention. In the U.S., universal screening (i.e., unselected general population screening) has been recommended for all toddlers,[88,99,152] while other countries, such as Norway and the United Kingdom, do not support such recommendations. In the United Kingdom, the UK Screening Committee does not recommend universal screening because the evidence concerning screening instrument specificity and sensitivity raises concerns about the efficiency of the current instruments.[89] As

many of the studies conducted using the M-CHAT, which is the most widely used and recommended screening instrument for ASD, show good performance, it is important to note that most studies only assess children who screen positive. Prospective follow-up studies are lacking, such as repeated assessments of all screened children or linkage to a patient registry, as utilized in the MoBa. Without prospective follow-up of children who screen negative, researchers are not able to estimate the true SE and SP. In fact, calculations of SP and SE on positive screening samples are typically the method used to validate Level 2 screening instruments and provide little information on how the instrument performs in a Level 1 screen (i.e., universal screen). Current issues are related to both the over-identification of children who never receive an ASD diagnosis (false-positives, Type I error) and the under-identification of children who receive an ASD diagnosis (false-negatives, Type II error).

In Paper II, the six-critical item criterion of the M-CHAT failed to identify a substantial portion of the children who later received an ASD diagnosis (76.8%). To date, the authors who developed the M-CHAT[92] have yet to address the Type II error issue associated with the M-CHAT and have instead focused primarily on reducing the number of false positives by suggesting new cut-offs and follow-up routines. Both Paper I and Paper II utilized the MoBa questionnaire, which included the M-CHAT without a follow-up interview. However, as Paper II revealed, most children who received an ASD diagnosis did not fail the recommended cut-off test and would not be identified as eligible for the follow-up interview. There is still a pressing need to address and understand why most children in an unselected general population who develop ASD are missed by the M-CHAT. The findings from Paper II revealed that true-positive children have significantly fewer advanced skills in all domains, as rated by the ASQ, in comparison to false-negative children. This finding indicates that the M-CHAT identifies primarily children with an early symptom onset that causes early parental concern. This outcome could also be affected by greater symptom severity or ID.[150] There

might be other factors that cause the M-CHAT and similar screening instruments to perform better in identifying children with an early established concern[92,102] or ID.[150] Those factors might be related to the design of the instruments, parental perception and interpretation of items, and the heterogeneity of symptom patterns and time of onset.

In contrast to Papers I and II, which relied on the use of the M-CHAT in an unselected general population, Paper III examined the performance of the Autism Mental Status Exam (AMSE)[97,98,146,147] in a selected population of children with an established developmental concern. Screenings in unselected general populations are often referred to as Level 1 screenings, whereas screenings in selected clinical populations are referred to as Level 2 screenings. These two dimensions of screening must be distinguished since they have different aims. Level 1 screening instruments are mainly used to identify children who do not otherwise raise concern, whereas the aim of Level 2 screening instruments is typically to provide clinical guidance and to specify the presence of developmental concerns.[90]

Consistent with previous studies of the AMSE,[97,98,146,147] Paper III found that the AMSE discriminates well between children receiving a DSM-5-guided diagnosis of ASD and those who do not. Importantly, the PPV strongly relies on the prevalence of the disorder. Naturally, the baseline rates of ASD and the PPV are higher in clinical samples of children for whom developmental concerns exist than in unselected general population samples. The use of the AMSE for clinical guidance in community settings may represent an effective strategy for more precise and informative referrals, which might potentially reduce the number of false-positive referrals from sub-specialized clinical personnel.

7.2.2 Heterogeneity of symptoms and time of onset. Studies of the heterogeneity of symptom patterns and time of onset have shown that the symptoms of ASD emerge and evolve over time;[55] thus, symptoms might not be evident at 18 months of age for all children

who are eventually diagnosed with ASD. This observation lends support for the recommendation of repeated assessment across early ages, through well-visits at 24 months of age, in addition to 18 months of age. Furthermore, the heterogeneity in the expression of symptoms[56] that exists in terms of the levels of symptom severity and ID indicate that using only one screening instrument to capture all children with ASD might have little success. For some, actionable concern might only be identified as the child's difficulties become evident due to increasing social demands, which is also supported by the DSM-5 removal of the age-of-onset criterion.[12]

7.2.3 Parental interpretation. Both Paper I and Paper II of the present thesis are based on parent reports, through the MoBa 18-month questionnaire, which includes the M-CHAT. As mentioned previously, parental concern is vital for the early detection of ASD.[53,153] The construction of the M-CHAT and similar screening instruments might affect the instrument's performance in identifying ASD in children. First, the performance of screening instruments requires that parents are able to identify ASD-specific behaviors to some degree.[53] As a result, it is likely that the wording of items, the examples used and the response options used, contribute to how parents report behaviors. In Paper I, it was revealed that ASD males had better imitation than ASD females and ASD females had better joint attention than males. However, the imitation item of the M-CHAT provides an example of imitation that could be regarded as a very early emerging imitative behavior in toddlers: "*Does your child imitate you? (*e.g.*, you make a face, will your child imitate it*)." This form of imitation could be classified as a less complex social ability than the strength in joint attention that was observed for females, which might be more complex in terms of the demands to understand the dyadic bid from the adult.[141]

Furthermore, in Paper II of this doctoral thesis, it emerged that although most children with a later ASD diagnosis passed the six-critical item criterion and most of those false-negative children failed none of the six-critical items (72.3%), they were rated on the ASQ as significantly delayed compared to true-negative children. Since these children are endorsed as showing significant social and communicative delays on the ASQ but not on the M-CHAT, this finding might indicate that there are issues with how the questions and response categories are framed. One hypothesis is that the categorical "Yes/No" response options of the M-CHAT do not provide parents with a more nuanced judgement, such as "Sometimes," which could indicate less than expected, but not totally absent. Research utilizing the First Year Inventory (FYI) has shown good agreement between parent-clinician ratings of specific autistic behaviors,[54] suggesting that response options other than "yes/no" could improve the screening performance or at least provide a more nuanced rating of the presence/absence of autistic behaviors.

7.2.4 Sex differences. In the present doctoral thesis, sex differences were observed in all three studies. In Paper I, females with ASD showed greater symptom severity than males. Furthermore, females with ASD displayed stronger joint attention skills than males, while also presenting a weakness in imitation. In Paper II, the patterns of atypicalities were fairly similar between false-negative males and females. However, the atypicalities were more pronounced in the female comparison than in the male comparison. False-negative females were rated as less shy than false-negative males. Sex differences were also reported in Paper III, where females with ASD exhibited more language difficulties and fewer sensory issues than males, but no differences in the rate of ID or severity were observed between females and males with ASD.

The findings from the parental ratings of children at 18 months of age in Papers I and II suggested that females aged 18 months showed more autism-related symptoms on the M-CHAT and similar but more pronounced ratings of atypicalities on the ASQ and EAS domains. This finding might indicate that females who are later diagnosed with autism present with greater symptom severity or developmental delays/impairments at 18 months of age than males who are later diagnosed with ASD. This finding is consistent with previous studies suggesting that females who receive an ASD diagnosis require a greater load of symptom severity, developmental issues or intellectual disability to meet the threshold for ASD.[126]

As reported in Papers I, II and III, marked sex differences were observed in both unselected and selected populations. We hypothesized that stronger joint attention skills in females with ASD, together with presenting as less shy, may cause females with ASD to be interpreted as less socially inhibited/avoidant than males with ASD.[154,155] For example, behaviors such as being more friendly towards strangers and needing less warm-up time towards strangers might also be interpreted as being more socially capable, but they may in fact indicate an inhibitory control issue.[156] According to recent research, females with a normal range IQ have fewer social issues and concerns,[157,158] potentially contributing to camouflaged symptoms. Nonetheless, this observation might also be related to the insistence on sameness and rigidity, potentially indicating that females who are later diagnosed with ASD are less rigid or demand less sameness than males who are later diagnosed with the disorder. As noted by Chawarska and colleagues,[53] some of the earliest parental concerns are related to social and motor skill delays, accompanied by sensory issues and stereotypical behaviors.[53] The findings from Paper III showed that females with ASD were rated as having lower levels of sensory issues than males with ASD, while expressing more language difficulties. With respect to language, previous studies have suggested that females who

receive an early ASD diagnosis more often show increased language difficulties.[135,159,160]

.[116,119,161]

A theoretical interpretation of the findings in the present doctoral thesis suggest that the behavioral, developmental, and temperamental patterns found in all of these three papers could influence age and the level of parental concern, identification, and diagnosis. Lower levels of sensory issues, better joint attention and less social avoidance could be consistent with findings of better social skills,[128,154,155,157] less RRBs,[116,119,161] and less disruptive behaviors,[129] contributing to camouflaged ASD symptoms in females. This could then result in a later age of diagnosis or a failure to meet the cut-off criteria for diagnosis at all. Furthermore, this finding could indicate that the presence of impairments in language, motor development or greater ASD symptom severity are necessary for females to meet the cut-off on screening and diagnostic instruments. This is consistent with previous studies reporting that females with more complex language abilities are diagnosed significantly later than males,[137,162] suggesting that differences in symptom expression exist between females and males who ultimately receive an ASD diagnosis.

How these sex differences affect the performance of screening instruments, such as the M-CHAT, and the performance of diagnostic instruments remains unclear. To date, no systematic reviews on the performance of screening instruments for males and females separately have been conducted. It is also possible that the differences in symptom expression could affect parental concern (i.e., parents of female toddlers might be less concerned if the child is less socially avoidant and there is an absence of RRBs and decreased sensory issues). Several questions surrounding the topic of sex differences and how they affect early identification emerge: criteria and goodness of fit (e.g., females have the same intensity of symptoms but look different than males), perceptive/cultural/societal (e.g., a female acting in a certain way might be considered appropriate, while for a male, the behavior is not

appropriate), or behavioral characteristics (e.g., females have less externalizing behaviors and less disruptive behaviors than males).

As diagnostic criteria, screening check lists and diagnostic instruments have been developed and validated on samples of ASD subjects who are male-predominant.[134] Thus, it could be hypothesized that these instruments are better at detecting a male phenotypic expression of ASD. If females necessitate a greater load of symptoms or impairment to meet diagnostic criteria, that might favor a male phenotypic expression, it could provide a theoretical, but nuanced support for both the extreme male brain theory and the female protective effect theory. Accordingly, females might need a greater load of symptoms[126] to meet the threshold for diagnosis. This observation indicates that there are females who do not meet the criteria for ASD who might have different atypicalities than males. Thus, greater symptom severity could cause females to look more similar to a male phenotype and might fit better within the criteria of ASD. On the other hand, it might be that strengths found in females with ASD obscure the fundamental nature of autism, precluding early identification of the disorder. As joint attention, a withdrawn nature, and the presence of significant repetitive/sensory issues are key flags for ASD diagnosis. In practice, this could affect how well screening and diagnostic instruments are at detecting females with similar levels of genetic load. While this is a strictly hypothetical viewpoint, females who do not meet the threshold for ASD might benefit from a separate phenotypic classification that captures the impairment faced by girls more accurately.

7.3 Implications for future research

The findings obtained from the papers included in this doctoral thesis have a number of implications. In terms of screening instruments and early identification, the findings imply a need to focus on improving screening instruments, including separate assessments of

parental concern and differences in parental concern and the heterogeneity of symptom patterns and development for males and females. Furthermore, future studies should explore whether improvements in the current screening instruments or adaptations of new items or instruments would increase the performance for detecting both males and females at risk for ASD.

As presented in this doctoral thesis, the M-CHAT or other Level 1 screening instruments are unlikely to be able to detect the vast majority of children who will receive a later diagnosis of ASD due to the heterogeneity of symptoms and the time at which they become evident to parents. Moreover, the use of a combination of ASD-specific screening instruments with an instrument such as the ASQ may help improve the detection of at-risk children. Since many ASD-specific behaviors might not be evident until the child's limitations are revealed due to increasing demands, other developmental markers might provide more general signs that are not ASD-specific.

Future studies should also focus on conducting prospective screening at both 18 and 24 months to determine if this approach will increase performance in unselected populations. Future studies of current screening instruments should also evaluate all children included in their studies prospectively, rather than settling for screening only positive children, as this approach would not provide the true SE and SP of the instrument. An understanding of how the M-CHAT and other screening instruments perform in males and females and in different languages and cultures is also a pressing need. Future meta-analyses are required.

Furthermore, the present doctoral thesis emphasizes the need to examine early developmental and temperamental features of males and females who ultimately receive an ASD diagnosis. Obviously, studies of these features are needed to create the next generation of screening instruments. It is important to acknowledge that females might have somewhat different

symptom patterns than males, potentially affecting early diagnosis. An understanding of these phenotypic differences and how they ultimately affect treatment is also important.

8 Strengths and Limitations

The strength of the present doctoral thesis is related to the prospective general population design. Linkage to the national patient registry (NPR) provides the possibility of identifying children who will develop an ASD diagnosis but show subtler symptom expressions at 18 months of age. The diagnoses in the present doctoral thesis are drawn from the NPR or the ABC (Autism Birth Cohort),[149] which is a nested sub-study of the MoBa. In contrast, most studies assessing the performance of the M-CHAT and similar screening instruments are conducted in selected populations. This design is a strength of the MoBa, in that the true performance of level one screening can be assessed and recommendations for future research and clinical settings can be made.

However, as discussed in Paper I and Paper II, relying on questionnaire data combined with diagnostic information has some limitations, as the data from assessments (e.g., data from IQ, ADI-R, ADOS, Vineland and other clinical measures) are not included. With regard to linkage to the NPR, there is the limitation that the person-specific identifiable diagnosis registered in the NPR can only be utilized if the individual was diagnosed after 2008. Children who were diagnosed earlier than 2008 and who were not seen by specialized services might have an unknown ASD diagnosis. This setup also generates an issue related to determining the age at diagnosis and the level of functioning, parameters which would not be reliable with the current data.

For Paper III, the strengths lay within the clinical design of the study, which allows the inclusion of more clinical data on each participant. A limitation of the data was the absence of an exact IQ, since only information about intellectual disability was available.

In terms of external validity, it is important to keep in mind that there are potential selection biases in both the unselected and the selected population samples included in the present doctoral thesis. For example, in the MoBa, only 40.6% of mothers consented to participation, which is compromising the generalizability of the results for the entire population. The MoBa also published an article that addresses some of the selection biases in the study population, revealing an under-representation of single mothers, mothers under 25 years of age, mothers who smoked during gestation, and mothers who did not use folic acid during the prenatal period.[163,164]

In Paper III, the use of a selected population of children for whom concerns have already been noted has implications for selection bias. In these samples, the baseline rate of ASD would be much greater than the rate in an unselected population of children. This selection bias is important to note, as it might impact both the observed psychometric properties of the AMSE and the male-to-female ratio. For example, parents of a male child with ASD who displays more disruptive behaviors might be more likely to seek a clinical assessment, whereas parents of a female child with language issues might have a hard time recognizing or understanding the specific phenomenology of ASD-specific traits. This difference might cause a selection bias, in which more males with disruptive behaviors and more females with more significant language issues are represented.

In terms of the measurements, all instruments were used according to the original manuals. However, the ASQ and EAS were used as a sub-set of items in the MoBa questionnaire. Future research should strive to conduct similar studies with the complete instruments. On the other hand, the MoBa is an unselected general population study that aims to measure a wide range of topics, and thus including full scales of all instruments would be impossible. In the MoBa, a follow-up assessment for children who screened positive on the M-CHAT was not conducted, which may reduce the rate of false-positives. However, most children with an

ASD diagnosis screened negative on both the six-critical item and the total 23-item criterion, making them ineligible for follow-up assessments. Thus, if the follow-up interview was conducted, it would not increase the number of children diagnosed with ASD. These follow-up assessments would also be impossible to conduct in a general population study. Finally, future prospective general population studies should also consider a screening at 24 months of age to assess the performance of screening instruments at different times. Notably, the present study did not have access to concurrent direct measures of children in the MoBa (e.g., ADOS-2, ADI-R or IQ).

9 Concluding Remarks

The present doctoral thesis sheds light on important aspects of screening in unselected and selected populations. Based on the results presented in Paper II, the M-CHAT has severe issues in detecting the majority of children who develop ASD. This finding is likely a consequence of the large heterogeneity in ASD, in terms of both symptom patterns and time of onset. Thus, the identification of ASD in 18-month-old children using parent reports might be impossible in the vast majority of children who later receive an ASD diagnosis. True-positive children who were identified by the M-CHAT at 18 months of age had significantly greater delays/impairments than false-negative and true-negative children, suggesting that the M-CHAT identifies children with more severe symptom patterns.

Furthermore, sex differences in ASD are evident at 18 months of age in children who are later diagnosed, pointing to marked sex differences between ASD males and ASD females. A strength in joint attention and social behaviors for females could theoretically affect how well screening and diagnostic instruments are at identifying the disorder in females, as symptoms patterns might be different at the same genetic load.

The findings obtained in the present thesis highlight the necessity to enhance our understanding of methods for designing and improving screening instruments by obtaining knowledge of the behavioral, developmental and temperamental features of males and females who receive an ASD diagnosis later in life. This goal can be achieved only through additional prospective studies with linkage to diagnostic registries. Parental understanding and interpretation of items and atypicalities stratified by sex are important topics for designing sex-sensitive next-generation screening instruments that aim to identify more subtle cases of ASD, in addition to children who present distinct ASD-specific behaviors at 18 months of age.

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den norske **Mor & barn undersøkelsen**

Questionnaire 5 – Your child at 18 months

In this questionnaire we will ask you some questions which you may recognise from previous questionnaires. We do this because we want to continue following your and your child's progress. It will help if you have child's Health card to hand so that you can use the information contained in it.

If you feel that a question is too upsetting or difficult to answer you can skip this question and go on to the next one.

The questionnaire will be processed by a computer. *It is therefore important that you following these instructions when completing it:*

- Use a blue or black ballpoint pen.
- Put a *cross* in the box that is most relevant like this: ☒
- If you put a cross in the wrong box, correct it by filling in
- Write numbers in the large green *boxes.*

It is important that you only write in the white area of each box like this:

Number: 1 2 3 4 5 6 7 8 9 0

Please do not use this questionnaire. Contact us at morbarn@fhi.no or phone + 47 53 20 40 40 if you need a questionnaire.

- Numbered boxes have two or more squares. When you enter a single-digit number, use the square on the right. *Example: 5 is entered as follows* 5
- Specific information concerning, *for example, medication* should be written on the lines provided. *Write clearly in CAPITAL LETTERS.*
- Remember to fill in the date on which you completed the questionnaire

As soon as you have completed this questionnaire, return it to us in the stamped addressed envelope provided.

Specify the day, month and year when the questionnaire was completed

Day ☐☐ Month ☐☐ Year ☐☐☐☐ *(write the year in full, e.g. 2005)*

ABOUT YOUR CHILD

Food and drink

1. What type of milk has your baby been given since he/she was 6 months old?
(You can enter more than one cross.)

Milk type	Child's age in months 6 - 8	9 - 11	12 - 14	15 - 18
1. Breast milk	☐	☐	☐	☐
2. Formula	☐	☐	☐	☐
3. Formula in the case of milk intolerance	☐	☐	☐	☐
4. Whole milk (sweet)	☐	☐	☐	☐
5. Low-fat milk normal (sweet)	☐	☐	☐	☐
6. Extra low-fat milk (sweet)	☐	☐	☐	☐
7. Skimmed milk (sweet)	☐	☐	☐	☐
8. Yogurt with active Lactobacillus, all types	☐	☐	☐	☐
9. Other yogurt	☐	☐	☐	☐
10. Other types of sour milk	☐	☐	☐	☐

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2. How often do you give your child the following to drink now that he/she is 18 months old? Select the frequency which is most applicable on average.
(Enter a cross in a box for each item.)

	Never	Less than once a week	1-3 times a week	4-6 times a week	1-2 times in 24 hrs	3-4 times in 24 hrs	5 or more times in 24 hours
1. Breast milk	☐	☐	☐	☐	☐	☐	☐
2. Formula	☐	☐	☐	☐	☐	☐	☐
3. Whole milk	☐	☐	☐	☐	☐	☐	☐
4. Low-fat milk	☐	☐	☐	☐	☐	☐	☐
5. Extra low-fat milk	☐	☐	☐	☐	☐	☐	☐
6. Skimmed milk	☐	☐	☐	☐	☐	☐	☐
7. Yogurt with active Lactobacillus, all types	☐	☐	☐	☐	☐	☐	☐
8. Yogurt, natural	☐	☐	☐	☐	☐	☐	☐
9. Yogurt with fruit	☐	☐	☐	☐	☐	☐	☐
10. Other types of sour milk	☐	☐	☐	☐	☐	☐	☐
11. Tap water	☐	☐	☐	☐	☐	☐	☐
12. Bottled water	☐	☐	☐	☐	☐	☐	☐
13. Cordial, sweetened	☐	☐	☐	☐	☐	☐	☐
14. Cordial, artificially sweetened	☐	☐	☐	☐	☐	☐	☐
15. Juice	☐	☐	☐	☐	☐	☐	☐
16. Fizzy drinks	☐	☐	☐	☐	☐	☐	☐
17. Diet fizzy drinks	☐	☐	☐	☐	☐	☐	☐
18. Other: _____	☐	☐	☐	☐	☐	☐	☐

3. Do you give your child the following to drink during the night now that he/she is roughly 18 months old?
(Enter a cross in a box for each item.)

	Never/ seldom	Now and then	Yes, most nights
1. Water	☐	☐	☐
2. Milk or cordial from a cup	☐	☐	☐
3. Milk or cordial from a bottle	☐	☐	☐
4. Breast milk	☐	☐	☐

4. How often do you give your child the following to eat now that he/she is 18 months old? Select the frequency which is most applicable on average.
(Enter a cross in a box for each item.)

	Never	Less than once a week	1-3 times a week	4-6 times a week	1-2 times in 24 hrs	3 or more times in 24 hrs
1. Liver paste sandwich	☐	☐	☐	☐	☐	☐
2. Meat sandwich	☐	☐	☐	☐	☐	☐
3. Fish sandwich (e.g. sardines, mackerel)	☐	☐	☐	☐	☐	☐
4. Cheese sandwich	☐	☐	☐	☐	☐	☐
5. Jam/honey sandwich	☐	☐	☐	☐	☐	☐
6. Sandwich with other filling	☐	☐	☐	☐	☐	☐
7. Baby porridge (instant)	☐	☐	☐	☐	☐	☐
8. Home-made porridge	☐	☐	☐	☐	☐	☐
9. Meat, sausages, meat balls, etc.	☐	☐	☐	☐	☐	☐
10. Fish, fish balls, fish pudding, etc.	☐	☐	☐	☐	☐	☐
11. Pancakes	☐	☐	☐	☐	☐	☐
12. Potatoes	☐	☐	☐	☐	☐	☐
13. Pasta	☐	☐	☐	☐	☐	☐
14. Rice	☐	☐	☐	☐	☐	☐
15. Peas, beans	☐	☐	☐	☐	☐	☐
16. Other cooked vegetables	☐	☐	☐	☐	☐	☐
17. Raw vegetables	☐	☐	☐	☐	☐	☐
18. Fruit	☐	☐	☐	☐	☐	☐
19. Cakes/waffles/biscuits	☐	☐	☐	☐	☐	☐
20. Dessert/ice cream	☐	☐	☐	☐	☐	☐
21. Chocolate	☐	☐	☐	☐	☐	☐
22. Other sweets, jelly beans, other confectionery	☐	☐	☐	☐	☐	☐

5. Do you give your child a home-made dinner or readymade (processed) baby food in a jar?

- ☐ Only home-made
- ☐ Mostly home-made
- ☐ About half and half of each
- ☐ Mostly ready-made
- ☐ Only ready-made

6. How often do you give your child organic food/drink?
(Enter a cross in a box for each item.)

	Never	Sometimes	Often	Almost always
Sweet milk	☐	☐	☐	☐
Buttermilk/yogurt . .	☐	☐	☐	☐
Vegetables/fruit . . .	☐	☐	☐	☐
Porridge/flour/bread	☐	☐	☐	☐
Meat	☐	☐	☐	☐

7. Does your child have a reaction to certain foods?

- ☐ No
- ☐ Yes
- ☐ Don't know

8. If yes, what type of food does your child have a reaction to? *(You can enter a cross in more than one box.)*

1. ☐ Whole milk
2. ☐ Skimmed milk/low-fat milk
3. ☐ Cream
4. ☐ Yogurt/buttermilk
5. ☐ Ice cream
6. ☐ Cheese
7. ☐ Raw egg (e.g. egg flip)
8. ☐ Boiled or fried egg
9. ☐ Fish/fish products
10. ☐ Additives
11. ☐ Wheat
12. ☐ Nuts
13. ☐ Soya
14. ☐ Fruit, berries
15. ☐ Vegetables/potatoes
16. ☐ Chocolate
17. ☐ Other sweets
18. ☐ Sugar
19. ☐ Other: _____

9. Are there any foods which you specifically avoid giving your child?

- ☐ No
- ☐ Yes

10. If yes, which foods do you try to avoid and how strict are you with your child's diet?

	Some reduced use compared to normal diet	Not used unmixed but allowed a little bit in different dishes	Use completely avoided (also "hidden" in dishes)
1. Milk	☐	☐	☐
2. Eggs	☐	☐	☐
3. Fish/fish products	☐	☐	☐
4. Meat/meat products	☐	☐	☐
5. Wheat	☐	☐	☐
6. Sugar	☐	☐	☐
7. Other: _____	☐	☐	☐

11. Do you give your child cold liver oil, vitamins, iron or any other dietary supplement?

- ☐ No
- ☐ Yes

12. If yes, specify which product(s) and how often you give them to your child. How old was your child when you first started giving him/her the product?

	How often do you give it to your child?		How old was your child when you first gave him the product?
	Every day	sometimes	Number of months
1. Cod liver oil	☐	☐	☐☐
2. Biovit	☐	☐	☐☐
3. Sanasol	☐	☐	☐☐
4. Nycoplus Multi-Vitamin mixture for children	☐	☐	☐☐
5. Fluoride tablets	☐	☐	☐☐
6. Iron supplement, specify: _____	☐	☐	☐☐
7. Other dietary supplement, specify:_____	☐	☐	☐☐

Growth, health and illness

Consult your child's health card and use the information contained in it to complete the following questions.

13. How many times have you been to the mother and child health centre since his/her birth?

- ☐ 0 - 4
- ☐ 5 -10
- ☐ 11 -15
- ☐ 16 or more

14. Do you want your child to be given the vaccinations that are recommended for children in Norway?

- ☐ Yes, all the recommended vaccinations
- ☐ Yes, some vaccinations
- ☐ No, no vaccinations

15. Indicate whether your child has had any vaccinations. If yes, how many times, and indicate if there have been any sideeffects requiring a doctor or hospital to be contacted. *(Enter a cross in a box for each item.)*

Vaccinations	No	Yes	If yes, how many times? 1	2	3	Side-effect resulting in extra contact with a doctor? No	Yes	Side-effect resulting in examination/admission to hospital? No	Yes
1. DTP (diphtheria, tetanus, whooping cough)	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. Hib (Haemophilus influenzae type b)	☐	☐	☐	☐	☐	☐	☐	☐	☐
3. Polio	☐	☐	☐	☐	☐	☐	☐	☐	☐
4. MMR (measles, mumps, rubella)	☐	☐	☐	☐	☐	☐	☐	☐	☐
5. DT (diphtheria, tetanus - sometimes given instead of DTP)	☐	☐	☐	☐	☐	☐	☐	☐	☐
6. Hepatitis B	☐	☐	☐	☐	☐	☐	☐	☐	☐
7. BCG (tuberculosis)	☐	☐	☐	☐	☐	☐	☐	☐	☐
8. Pneumococcus (Prevenar)	☐	☐	☐	☐	☐	☐	☐	☐	☐
9. Other vaccination:_____	☐	☐	☐	☐	☐	☐	☐	☐	☐

The following questions concern any illnesses or health problems your child has had. We will first ask you about more long-term problems, then about illnesses and problems of a more acute nature.

16. Does your child have or has he/she had any of the following health problems? If yes, has your child been referred for a specialist examination? *(Enter a cross in a box for each item.)*

Health problem	No	Yes, has now	Yes, had previously	If yes, has child been referred? for a specialist examination? No	Yes
1. Dislocated hip (hip problem)	☐	☐	☐	☐	☐
2. Reduced hearing	☐	☐	☐	☐	☐
3. Impaired vision	☐	☐	☐	☐	☐

(cont.)

Health problem	No	Yes, has now	Yes, had previously	If yes, has child been referred for specialist examination? No	Yes
4. Delayed motor development (e.g. sits/walks late)	☐	☐	☐	☐	☐
5. Too little weight gain	☐	☐	☐	☐	☐
6. Too much weight gain	☐	☐	☐	☐	☐
7. Abnormal head circumference	☐	☐	☐	☐	☐
8. Heart defect	☐	☐	☐	☐	☐
9. Testicles not descended into scrotum	☐	☐	☐	☐	☐
10. Asthma	☐	☐	☐	☐	☐
11. Atopic eczema (childhood eczema)	☐	☐	☐	☐	☐
12. Urticaria (hives)	☐	☐	☐	☐	☐
13. Food allergy/intolerance	☐	☐	☐	☐	☐
14. Late or abnormal speech development	☐	☐	☐	☐	☐
15. Sleep problems	☐	☐	☐	☐	☐
16. Behavioural problems	☐	☐	☐	☐	☐
17. Social problems	☐	☐	☐	☐	☐
18. (Other) malformations: _____	☐	☐	☐	☐	☐
19. Other: _____	☐	☐	☐	☐	☐

17. If a specialist referral was made, what did this examination show?

- ☐ Everything was fine
- ☐ Still some doubts/further examinations needed
- ☐ Has not been for any examination yet
- ☐ Diagnosis I: _____
- ☐ Diagnose II: _____
- ☐ Diagnose III: _____

18. Has your child been treated with a "cushion" for a hip problem?

- ☐ No
- ☐ Yes How long? ☐☐ months

19. Has your child had any of the following illnesses/health problems between 6 and 11 months and/or 12 and 18 months? Specify how many times and whether your child has been admitted to hospital for this health problem. *(Enter a cross in a box for each item.)*

Illness/health problem	At 6 –11 months No	At 6 –11 months Yes	Number of times	At 12 -18 months No	At 12 -18 months Yes	Number of times	Was admitted to hospital for this? No	Was admitted to hospital for this? Yes
1.Common cold	☐	☐	☐☐	☐	☐	☐☐	☐	☐
2. Throat infection with confirmed streptococcal infection	☐	☐	☐☐	☐	☐	☐☐	☐	☐
3. Other type of sore throat	☐	☐	☐☐	☐	☐	☐☐	☐	☐
4. Ear infection	☐	☐	☐☐	☐	☐	☐☐	☐	☐
5. Pseudocroup	☐	☐	☐☐	☐	☐	☐☐	☐	☐
6. Bronchitis/RS virus/pneumonia	☐	☐	☐☐	☐	☐	☐☐	☐	☐
7. Gastric flu/diarrhoea	☐	☐	☐☐	☐	☐	☐☐	☐	☐
8. Urinary tract infection	☐	☐	☐☐	☐	☐	☐☐	☐	☐
9. Conjunctivitis	☐	☐	☐☐	☐	☐	☐☐	☐	☐

(cont.)

Illness/health problem	At 6 –11 months No	At 6 –11 months Yes	Number of times	At 12 -18 months No	At 12 -18 months Yes	Number of times	Was admitted to hospital for this? No	Was admitted to hospital for this? Yes
10. Febrile convulsions	☐	☐		☐	☐		☐	☐
11. Other convulsions (without any fever)	☐	☐		☐	☐		☐	☐
12. Chickenpox	☐	☐		☐	☐		☐	☐
13. Injury or accident	☐	☐		☐	☐		☐	☐
14. Other: _____	☐	☐		☐	☐		☐	☐

20. Has your child been to see the doctor or to the hospital between 6 and 11 months and/or 12 and 18 months? If yes, specify how many times. *(Enter a cross in a box for each item.)*

	At 6 – 11 months No	At 6 – 11 months Yes	At 6 – 11 months Number of times	At 12-18 months No	At 12-18 months Yes	At 12-18 months Number of times
GP (excluding mother and baby health centre)	☐	☐		☐	☐	
Casualty doctor	☐	☐		☐	☐	
Private specialist	☐	☐		☐	☐	
Hospital outpatient clinic	☐	☐		☐	☐	
Admitted to hospital	☐	☐		☐	☐	

21. Has your child been referred to any of the following services?

	No	Yes
Habilitation service	☐	☐
Educational psychology service	☐	☐
Child psychiatric outpatient clinic/department	☐	☐

22. If your child has been examined at or admitted to hospital, give the name of the hospital:

Hospital name: _____

Hospital name: _____

Hospital name: _____

23. Has your child had any of the following symptoms since the age of 6 months? If yes, at what age? *(Enter a cross in a box for each item.)*

	Had symptoms? No	Had symptoms? Yes	If yes, at what age? 6-8 mth	9-11 mth	12-14 mth	15 mth or more
1. Wheezing/whistling in the chest	☐	☐	☐	☐	☐	☐
2. Tightness in the chest	☐	☐	☐	☐	☐	☐
3. Coughing at night	☐	☐	☐	☐	☐	☐
4. Runny nose without a cold	☐	☐	☐	☐	☐	☐
5. Constipation	☐	☐	☐	☐	☐	☐
6. Diarrhoea	☐	☐	☐	☐	☐	☐
7. Itchy rash that comes and goes	☐	☐	☐	☐	☐	☐

24. Has your child ever been tested for allergies?

☐ No
☐ Yes

25. If yes, what allergens were tested for and what was the result?
(You can enter a cross in more than one box.)

Test:		Was the test positive? No	Yes	Don't know
1. ☐	Milk	☐	☐	☐
2. ☐	Egg	☐	☐	☐
3. ☐	Fish	☐	☐	☐
4. ☐	Mould	☐	☐	☐
5. ☐	Mites	☐	☐	☐
6. ☐	Animals	☐	☐	☐
7. ☐	Pollen	☐	☐	☐
8. ☐	Other: _____	☐	☐	☐

26. Have you ever tried any kind of so-called alternative medicine on your child since he/she was 6 months old?

☐ No
☐ Yes ☐☐ times

27. If yes, what kind of alternative medicine?

_____
_____
_____
_____
_____

28. Has your child received any medication since the age of 6 months? *(This means any type of medication, including natural medicines and herbal remedies)*

☐ No
☐ Yes

29. If yes, give the name of the medication and what age your child was when he took it. *(Include all types of medication, as well as natural medicines)*

Name of medicine *(WRITE IN CAPITALS, e.g. APOCILLIN, PARACET)*	How old was your child when he/she took this medication? 6-8 mth	9-11 mth	12-14 mth	15-18 mth
_____	☐	☐	☐	☐
_____	☐	☐	☐	☐
_____	☐	☐	☐	☐
_____	☐	☐	☐	☐
_____	☐	☐	☐	☐

30. What were your child's length, weight and head circumference when he/she was around 8 months, 1 year and the last time they were measured (15–18 months)?
(Refer to your child's health card)

	Date of measurement Day	Month	Year	Length	Head circumference	Weight
Around 8 mth	☐☐	☐☐	☐☐	☐☐,☐ cm	☐☐,☐ cm	☐☐☐☐☐ g
Around 1 year	☐☐	☐☐	☐☐	☐☐,☐ cm	☐☐,☐ cm	☐☐☐☐☐ g
15 - 18 mth	☐☐	☐☐	☐☐	☐☐,☐ cm		☐☐☐☐☐ g

Development and behaviour

In this section you will find some questions repeated in a different form. However, please answer all the questions as well as you can.

31. Can your child walk unaided? No ☐ Yes ☐

If yes, how old was your child when he/she could first walk unaided? **Number:** ☐☐ months.

32. The questions that follow are about your child's development at around the age of 18 months. *(Enter a cross in a box for each item.)*

	Yes	Sometimes	Not yet
1. When you ask him/her, does your child go into another room to find a familiar toy or object? (When you ask, for instance: "Where's your ball?", "Go and get your coat" or "Go and get your blanket")	☐	☐	☐
2. Does your child say eight or more words, in addition to "mamma" and "dadda"?	☐	☐	☐
3. Without showing him/her first, does your child point to the correct picture when you say "Show me the cat" or "Where is the dog"?	☐	☐	☐
4. Does your child move around by walking, rather than by crawling on his/her hands and knees?	☐	☐	☐
5. Can your child walk well and seldom fall?	☐	☐	☐
6. Does your child walk down stairs if you hold onto one of his/her hands?	☐	☐	☐
7. Does your child throw a small ball or toy with a forward arm motion? (If he/she simply drops the ball, enter a cross under "Not yet")	☐	☐	☐
8. Does your child stack a small block or toy on top of another? (For example, small boxes or toys about 3 cm in size)	☐	☐	☐
9. Does your child turn the pages in a book by himself/herself? (He/she may turn over more than one page at a time.)	☐	☐	☐
10. Does your child hug dolls or cuddly toys when playing with them?	☐	☐	☐
11. Does your child try to get your attention show you something by pulling your hand or clothes?	☐	☐	☐
12. Does your child come to you when he/she needs help, such as with opening a box?	☐	☐	☐
13. Does your child copy the activities you do, such as wiping up a spill, sweeping, shaving or combing hair?	☐	☐	☐

33. More about your child's development *(Enter a cross in a box for each item.)*

	Yes, usually	Very seldom	Not yet
1. Does your child use sounds or words together with gestures (e.g. uses sounds when pointing or reaching towards toys or objects)?	☐	☐	☐
2. When you look at a distant object and, surprised and excited, say: "Waoo...what's that?", – does he/she turn his/her head in the same direction as you?	☐	☐	☐
3. When you enthusiastically say: "Where is the ball (or other toy)?", will your child point towards the toy, even if it is more than 1 metre away?	☐	☐	☐
4. Does your child show you a toy by looking at you and holding the toy up towards your face (from a distance just so you can look at it)?	☐	☐	☐

34. How typical is the following behaviour of your child? *(Enter a cross in a box for each item.)*

	Very typical	Quite typical	Neither/ nor	Not so typical	Not typical
1. Your child cries easily	☐	☐	☐	☐	☐
2. Your child is always on the go.	☐	☐	☐	☐	☐
3. Your child prefers playing with others rather than alone.	☐	☐	☐	☐	☐
4. Your child is off running as soon as he/she wakes up in the morning	☐	☐	☐	☐	☐
5. Your child is very sociable.	☐	☐	☐	☐	☐
6. Your child takes a long time to warm to strangers	☐	☐	☐	☐	☐
7. Your child gets upset or sad easily	☐	☐	☐	☐	☐
8. Your child prefers quiet, inactive games to more active ones.	☐	☐	☐	☐	☐
9. Your child likes to be with people	☐	☐	☐	☐	☐
10. Your child reacts intensely when upset.	☐	☐	☐	☐	☐
11. Your child is friendly towards and trusting of strangers	☐	☐	☐	☐	☐
12. Your child complains that certain garments are too tight	☐	☐	☐	☐	☐
13. Your child becomes distressed by having his/her face or hair washed	☐	☐	☐	☐	☐

35. About your child's behaviour We are asking you about how your child usually is. If something happens seldom (for instance, if you have only seen it one or twice), enter a cross under "No". *(Enter a cross in a box for each item.)*

	Yes	No
1. Is your child interested in different sorts of toys or objects and not for instance mainly in cars or buttons?	☐	☐
2. When your child expresses his/her feelings, for instance by crying or smiling, do you usually understand why your child is laughing or crying?	☐	☐
3. Does your child react in a normal way to sensory stimulation, such as coldness, warmth, light, pain or tickling?	☐	☐
4. Can you easily tell from the face of your child how he/she feels?	☐	☐
5. When your child has been left alone for some time, does he/she try to attract your attention, for instance, by crying or calling?	☐	☐
6. Is your child's behaviour without stereotyped repetitive movements, e.g. banging his/her head against the wall or rocking his/her body back and forth?	☐	☐
7. Does your child like to be cuddled?	☐	☐
8. Does your child ever laugh directly at you or at other people?	☐	☐
9. Does your child react when spoken to, for instance, by looking, listening, smiling, speaking or babbling?	☐	☐
10. Does your child ever try to comfort you if you are sad or hurt?	☐	☐
11. Has your child ever had things that he/she seemed to have to do in a very particular way or order, or rituals that he/she has to have you do?	☐	☐
12. Does your child ever do things to get you to laugh?	☐	☐

36. More about your child's play and behaviour. We are asking you again about how your child usually is. If something seldom happens (for instance, if you have only seen it one or twice), enter a cross under "No". *(Enter a cross in a box for each item.)*

	Yes	No
1. Does your child enjoy being swung, bounced on your knee, etc.?	☐	☐
2. Does your child take an interest in other children?	☐	☐
3. Does your child like climbing on things, such as up stairs?	☐	☐
4. Does your child enjoy playing peek-a-boo/hide-and-seek?	☐	☐
5. Does your child ever pretend, for example, to talk on the phone or take care of dolls, or pretend other things?	☐	☐
6. Does your child ever use his/her index finger to point, to ask for something?	☐	☐
7. Does your child ever use his/her index finger to point, to indicate interest in something?	☐	☐
8. Can your child play properly with small toys (e.g. cars or bricks) without just mouthing, fiddling or dropping them?	☐	☐
9. Does your child ever bring objects over to you to show you something?	☐	☐
10. Does your child look you in the eye for more than a second or two?	☐	☐
11. Does you child ever seem oversensitive to noise (e.g. plugging ears)?	☐	☐
12. Does your child smile in response to your face or your smile?	☐	☐
13. Does your child imitate you (e.g. you make a face - will your child imitate it?)?	☐	☐
14. Does your child respond when you call his/her name?	☐	☐
15. If you point at a toy across the room, does your child look at it?	☐	☐
16. Does your child look at things you are looking at?	☐	☐
17. Does your child make unusual finger movements near his/her face?	☐	☐
18. Does your child try to attract your attention to his/her own activity?	☐	☐
19. Have you every wondered if your child is deaf?	☐	☐
20. Does your child understand what people say?	☐	☐
21. Does your child sometimes stare at nothing or wander with no purpose?	☐	☐
22. Does your child look at your face to check your reaction when faced with something unfamiliar?	☐	☐

37. To what extent are the following statements true of your child's behaviour during the last two months? *(Enter a cross in a box for each item.)*

	Not true	Somewhat or sometimes true	Very true or often true
1. Can't concentrate, can't pay attention for long	☐	☐	☐
2. Quickly shifts from one activity to another	☐	☐	☐
3. Can't sit still, restless or hyperactive	☐	☐	☐
4. Gets into everything	☐	☐	☐

(cont.)

	Not true	Somewhat or sometimes true	Very true or often true
5. Is mostly happy and contented	☐	☐	☐
6. Clings to adults or too dependent	☐	☐	☐
7. Gets too upset when separated from parents	☐	☐	☐
8. Gets into many fights	☐	☐	☐
9. Hits others	☐	☐	☐
10. Is defiant	☐	☐	☐
11. Doesn't seem to feel guilty after misbehaving	☐	☐	☐
12. Punishment doesn't change his/her behaviour	☐	☐	☐
13. Doesn't eat well	☐	☐	☐
14. Likes almost every kind of food	☐	☐	☐
15. Resists going to bed at night	☐	☐	☐
16. Doesn't want to sleep alone	☐	☐	☐
17. Afraid to try new things	☐	☐	☐
18. Disturbed by any change in routine	☐	☐	☐
19. Too fearful or anxious	☐	☐	☐

38. How often does your child usually wake during the night?

- ☐ 3 or more times every night
- ☐ Once or twice every night
- ☐ A few times a week
- ☐ Seldom or never

39. How many hours in total does your child sleep in 24hrs?

- ☐ 10 hours or less
- ☐ 11 - 12 hours
- ☐ 13 -14 hours
- ☐ 15 hours or more

40. About your worries *(Enter a cross in a box for each item.)*

	No	Yes	Don't know
1. Are you worried about your child's physical development?	☐	☐	☐
2. Are you worried about your child's behaviour?	☐	☐	☐
3. Are you worried because your child is demanding and difficult to cope with?	☐	☐	☐
4. Are you worried because your child is so uninterested in other children?	☐	☐	☐
5. Have you any other worries with regard to your child's health	☐	☐	Specify_____

(Use the last page if you need more space to write)

Your child's daily routine

41. Where has your child been cared for during the day? Enter a cross for the various age groups. *(Enter a cross in a box for each item.)*

	At home with his/her mother his/her father	At home with unqualified childminder	At a childminder's	In a day nursery
1. 0–6 months	☐	☐	☐	☐
2. 7-9 months	☐	☐	☐	☐
3. 10-12 months	☐	☐	☐	☐
4. 13-15 months	☐	☐	☐	☐
5. 16-18 months	☐	☐	☐	☐

42. How many hours a week is your child looked after in the current childcare scheme (other than by his/her mother and father)?

☐☐ hours

43. How many children in total are looked after in this childcare scheme (if day-care centre, how many in the department)?

☐☐ children

44. Do you and your child live with your child's father?

- ☐ Yes
- ☐ No

45. If your child does not live with his/her father, how much time does your child spend with him?

- ☐ At least half the time
- ☐ At least once a week
- ☐ At least once a month
- ☐ Less often than once a month
- ☐ Never

46. How many times have you moved house since your child was born?

☐☐ times

47. Roughly how many square metres is the living area where you currently live?

☐☐☐ m²

48. Are the rooms where your child is heated by electrical underfloor heating?

☐ No ☐ Yes

49. If yes, which rooms? *Enter a cross in more than one box, if appropriate)*

- ☐ Living room
- ☐ Kitchen
- ☐ Child's room
- ☐ Bedroom
- ☐ Hall
- ☐ Bathroom
- ☐ Other rooms

50. Has their been any damage caused by damp, any visible fungal/mould growth or mouldy smell in your home during the last year *(You can enter a cross in more than one box.)*

- ☐ No
- ☐ Yes, damage caused by damp
- ☐ Yes, visible fungal/mould growth
- ☐ Yes, mouldy smell

51. What type of drinking water do you have where you live?

- ☐ Water from a public or private water company
- ☐ Water from your own water supply (e.g. own well)
- ☐ Don't know

52. Do you live close to high-voltage lines?

- ☐ No
- ☐ Yes, closer than 50 metres
- ☐ Yes, 50–100 metres away
- ☐ Yes, but more than 100 metres away

53. Are there pets where your child lives or at the childminder's?

- ☐ No
- ☐ Yes, at home
- ☐ Yes, at the childminder's

54. If yes, what kind of pets?
(You can enter a cross in more than one box.)

- ☐ Dog
- ☐ Cat
- ☐ Guinea pig, rabbit, mouse, rat, etc.
- ☐ Budgie, other type of bird
- ☐ Other type of animal:_____

55. Is your child ever present in a room where someone smokes?

- ☐ Yes, every day Number of times per day ☐☐
- ☐ Yes, several times a week
- ☐ Yes, sometimes
- ☐ Don't know
- ☐ No

56. How many months old was your child when he/she got his/her first tooth?

Number of months ☐☐

- ☐ Don't remember

57. How often are your child's teeth brushed?

- ☐ Twice a day or more
- ☐ Once a day
- ☐ sometimes
- ☐ Never

58. Do you use fluoride toothpaste when brushing your child's teeth?

- ☐ No
- ☐ Sometimes
- ☐ Yes, usually

59. How often is your child outside at the moment?

- ☐ Seldom
- ☐ Often, but less than one hour a day on average
- ☐ 1 - 3 hours a day on average
- ☐ More than 3 hours a day

60. How many hours on average does your child sit in front of a TV/video every day?

- ☐ 4 hours
- ☐ 3 hours
- ☐ 1 -2 hours
- ☐ Less than 1 hour
- ☐ Seldom/never

61. Does your child go to or has been to swimming classes for babies?

- ☐ No
- ☐ Yes

If yes, how long has your child been going? ☐☐ months

62. Does your child use a dummy/pacifier now at 18 months?

- ☐ Seldom or never
- ☐ Only when he/she goes to sleep
- ☐ Quite often
- ☐ Most of the time

ABOUT YOURSELF

Health, illness and use of medication

63. What is your civil status at the moment?

- ☐ Married
- ☐ Cohabiting
- ☐ Single
- ☐ Separated/divorced
- ☐ Widowed
- ☐ Other

64. Are you pregnant at the moment?

- ☐ No
- ☐ Yes

If yes, how many weeks? ☐☐

65. Are you suffering from a long-term illness that has started during the last 12 months?

- ☐ No
- ☐ Yes, specify _____

66. Have you yourself been admitted to hospital during the last 12 months?

- ☐ No
- ☐ Yes, which hospital? _____

67. Are you taking at the moment any cod liver oil, vitamins or other dietary supplements?

- ☐ No
- ☐ Yes, specify

1. _____
2. _____
3. _____
4. _____

68. What is your current weight?

☐☐☐,☐ kg

69. Have you during the last 6 months or at any time previously: *(Enter a cross in a box for each item.)*

	Last 6 months			Previously		
	Yes	Perhaps	No	Yes	Perhaps	No
1. Felt yourself that you were too fat?	☐	☐	☐	☐	☐	☐
2. Been really afraid of putting on weight or becoming too fat?	☐	☐	☐	☐	☐	☐
3. Heard others say you were too thin, while you yourself thought that you were too fat?	☐	☐	☐	☐	☐	☐
4. Felt that it was extremely important for your self-image to maintain a particular weight?	☐	☐	☐	☐	☐	☐

70. Have you at some time during the last 6 months or previously in your life - for a period lasting at least 3 months - experienced any of the following situations, and if so, how frequently was this? (Select the period you were affected the most.) *(Enter a cross in a box for each item.)*

	Last 6 months			Previously		
	At least twice a week	1-4 times a mth	Seldom/ never	At least twice a week	1-4 times a mth	Seldom/ never
1. Felt that you were losing control when eating and couldn't stop before you had eaten too much?	☐	☐	☐	☐	☐	☐
2. Used vomiting to control your weight?	☐	☐	☐	☐	☐	☐
3. Used laxatives to control your weight?	☐	☐	☐	☐	☐	☐
4. Used fasting to control your weight?	☐	☐	☐	☐	☐	☐
5. Used hard physical exercise to control your weight?	☐	☐	☐	☐	☐	☐

71. Have you at some time during the last six months or previously in your life gone at least three months without any periods (without you being pregnant or giving birth/breast-feeding) in connection with a period when you had eating problems?

- ☐ No, never
- ☐ Yes, during the last 6 months
- ☐ Yes, previously

72. Have you experienced pain during the last 12 months in any of the following places? *(Enter a cross in a box for each item.)*

	Seldom/never	Slight pain	Some pain	Major pain
1. Stomach	☐	☐	☐	☐
2. Arms/legs	☐	☐	☐	☐
3. Neck/shoulders	☐	☐	☐	☐
4. Head	☐	☐	☐	☐
5. Back	☐	☐	☐	☐
6. Pelvis (pelvic girdle pains)	☐	☐	☐	☐

73. Have you experienced any pain in your back or pelvis during the last 12 months. Enter a cross to indicate how much pain you have felt in different places:

	Some pain	Major pain
1. In the small of the back	☐	☐
2. One of the pelvic//sacroiliac joints at the back	☐	☐
3. Both pelvic/sacroiliac joints at the back	☐	☐
4. Over the coccygeal bone	☐	☐
5. In the buttocks	☐	☐
6. Over the pubic bone	☐	☐
7. Groin	☐	☐
8. Other back pains	☐	☐
9. Other pains	☐	☐

74. Currently, do you wake during the night because of pelvic pain?

- ☐ No, never
- ☐ Yes, but seldom
- ☐ Yes, often

75. Do you have such problems walking at the moment because of pelvic pains that you have to use a stick or crutches?

- ☐ No, never
- ☐ Yes, but not every day - the pain varies from day to day
- ☐ Yes, must use a stick or crutches every day

76. Did you receive any treatment for pelvic pain after your last birth?

- ☐ No
- ☐ Yes

77. If yes, what type of treatment did you receive?
(You can enter a cross in more than one box.)

- ☐ Physiotherapy
- ☐ Chiropractic
- ☐ Medication
- ☐ Other:_____

78. Do you have any of the following problems at the moment? *(Enter a cross in a box for each problem.)*

	How often do you have problems?					How much at a time?	
Problems:	Never	1–4 times a month	1–6 times a week	Once a day	More than Once a day	Drops	Large amounts
1. Incontinence when coughing, sneezing or laughing	☐	☐	☐	☐	☐	☐	☐
2. Incontinence during physical activity (running/jumping)	☐	☐	☐	☐	☐	☐	☐
3. Incontinence with a strong need to urinate	☐	☐	☐	☐	☐	☐	☐
4. Problems retaining faeces	☐	☐	☐	☐	☐		
5. Problems retaining flatus	☐	☐	☐	☐	☐		

79. Do you regularly take medication? *(This means any type of medication, including natural medicines.)*

- ☐ No
- ☐ Yes

80. If yes, give the name of the medicines and how often you take them. *(Include all types of medication, as well as natural medicines.)*

Name of medicine *(e.g. APOCILLIN, PARACET)*	How often do you take them? Every day	Every day for certain periods	Sometimes
_____	☐	☐	☐
_____	☐	☐	☐
_____	☐	☐	☐
_____	☐	☐	☐

Finances – lifestyle

81. How much leave did you and the child's father take after the birth? *(Specify either the number of months or weeks.)*

	Months		Weeks
Yourself	☐☐	or	☐☐
Child's father	☐☐	or	☐☐

82. Are you in paid employment?

- ☐ No
- ☐ Yes

83. If so, how many hours do your work a week?

☐☐,☐ hours

84. If you are in paid employment, have you taken any time off sick since you went back to work? If yes, specify how many days you were off sick.

	Number of days
☐ No	
☐ Yes, due to own illness.	☐☐☐
☐ Yes, due to your child being ill.	☐☐☐

85. Would your current finances allow you to cope with an unexpected bill of NOK 3,000 for a dental visit or a repair, for instance?

- ☐ No
- ☐ Yes
- ☐ Don't know

86. Have you found it difficult sometimes during the last six months to cope with running expenses for food, transport, rent, etc.?

- ☐ No, never
- ☐ Yes, but infrequently
- ☐ Yes, sometimes
- ☐ Yes, often

87. How often are you so physically active (during your spare time or at work) that you get out of breath and sweat?

	Spare time	At work
1. Never	☐	☐
2. Less than once a week	☐	☐
3. Once a week	☐	☐
4. Twice a week	☐	☐
5. 3-4 times a week	☐	☐
6. 5 times or more a week	☐	☐

88. How often do you exercise at present? *(Enter a cross in a box for each item.)*

Activity	Never	1-3 times a month	Once a week	Twice a week	3 times or more a week
1. Walking	☐	☐	☐	☐	☐
2. Brisk walking	☐	☐	☐	☐	☐
3. Running/jogging/orienteering	☐	☐	☐	☐	☐
4. Cycling	☐	☐	☐	☐	☐
5. Training studio/weight training	☐	☐	☐	☐	☐
6. Aerobics/gymnastics/dance without running and jumping	☐	☐	☐	☐	☐
7. Aerobics/gymnastics/dance with running and jumping	☐	☐	☐	☐	☐
8. Dancing (swing/rock/folk)	☐	☐	☐	☐	☐
9. Skiing	☐	☐	☐	☐	☐
10. Ball sports	☐	☐	☐	☐	☐
11. Swimming	☐	☐	☐	☐	☐
12. Riding	☐	☐	☐	☐	☐
13. other	☐	☐	☐	☐	☐

89. What are your and your partner's smoking habits at home at the moment?

	Yourself	Your partner/ husband
1. Don't smoke	☐	☐
2. Smoke sometimes	☐	☐
3. Smoke every day	☐	☐
4. If every day, number of cigarettes per day	☐☐	☐☐

90. How often do you consume alcohol at the moment?

- ☐ Roughly 6–7 times a week
- ☐ Roughly 4–5 times a week
- ☐ Roughly 2-3 times a week
- ☐ Roughly once a week
- ☐ Roughly 1-3 times a month
- ☐ Less often than once a month
- ☐ Never

91. How many units do you usually drink when you consume alcohol? (Enter a cross for both weekends and weekdays). *(See explanation below.)*

	Weekend	Weekdays
10 or more	☐	☐
7-9	☐	☐
5-6	☐	☐
3-4	☐	☐
1-2	☐	☐
Less than 1	☐	☐

Alcohol units

In order to compare different types of alcohol, we ask for the number of alcohol units (= 1.5 cl of pure alcohol). This means the following in practice:

1 glass (1/3 litre) of beer	= 1 unit
1 wine glass of red or white wine	= 1 unit
1 sherry glass of sherry or other fortified wine	= 1 unit
1 brandy glass of spirits or liqueur	= 1 unit
1 bottle of alcopop/cider	= 1 unit

A little more about yourself and how you are keeping now

92. If you have a husband/boyfriend/partner, to what extent do you agree with the following descriptions? *(Enter a cross in a box for each item.)*

	Totally agree	Agree	Slightly agree	Slightly disagree	Disagree	Totally disagree
1. My husband/partner and I have a close relationship	☐	☐	☐	☐	☐	☐
2. My partner and I have problems in our relationship	☐	☐	☐	☐	☐	☐
3. I am very happy in my relationship	☐	☐	☐	☐	☐	☐
4. My partner is usually understanding	☐	☐	☐	☐	☐	☐
5. I often think about ending our relationship	☐	☐	☐	☐	☐	☐
6. I am satisfied with my relationship with my partner	☐	☐	☐	☐	☐	☐
7. We often disagree about important decisions	☐	☐	☐	☐	☐	☐
8. I have been lucky in my choice of partner	☐	☐	☐	☐	☐	☐
9. We agree on how children should be raised	☐	☐	☐	☐	☐	☐
10. I think my partner is satisfied with our relationship	☐	☐	☐	☐	☐	☐

93. Do you have anyone other than your-spouse/boyfriend/partner whom you can seek advice from in a difficult situation?

- ☐ No
- ☐ Yes, 1 or 2 people
- ☐ Yes, more than 2 people

94. How often do you see or talk on the telephone to your family (apart from your household) or close friends?

- ☐ Once a month or less often
- ☐ 2-8 times a month
- ☐ More than twice a week

95. Do you often feel lonely?

- ☐ Almost never
- ☐ Seldom
- ☐ Sometimes
- ☐ Generally
- ☐ Almost always

96. How accurate are these statements to you? *(Enter a cross in a box for each item.)*

	Not accurate	Slightly accurate	Almost accurate	Totally accurate
1. I always manage to solve difficult problems if I try hard enough	☐	☐	☐	☐
2. If anyone opposes me, I find a way to get what I want	☐	☐	☐	☐
3. I am sure that I can cope with unexpected events	☐	☐	☐	☐
4. I am calm when I encounter difficulties because I trust my ability to cope	☐	☐	☐	☐
5. When I am in a difficult situation, I usually find a solution	☐	☐	☐	☐

97. In your daily life, how often do you *(Enter a cross in a box for each item.)*

	Seldom/ never	Fairly seldom	Sometimes	Often	Very often
1. Feel pleased about something	☐	☐	☐	☐	☐
2. Feel happy	☐	☐	☐	☐	☐
3. Feel joyful, as though everything is going your way	☐	☐	☐	☐	☐
4. Feel that you will scream at someone or hit something.	☐	☐	☐	☐	☐
5. Feel angry, irritated or annoyed	☐	☐	☐	☐	☐
6. Feel mad at somebody	☐	☐	☐	☐	☐

98. How do you feel about yourself? *(Enter a cross in a box for each item.)*

	Totally agree	Agree	Disagree	Totally disagree
1. I have a positive attitude towards myself	☐	☐	☐	☐
2. I feel completely useless at times	☐	☐	☐	☐
3. I feel that I do not have much to be proud of	☐	☐	☐	☐
4. I feel that I'm a valuable person, as good as anyone else	☐	☐	☐	☐

99. Have you been bothered by any of the following feelings during the past 2 weeks? *(Enter a cross in a box for each item.)*

	Not bothered	A little bothered	Quite bothered	Very bothered
1. Feeling fearful	☐	☐	☐	☐
2. Nervousness or shakiness inside	☐	☐	☐	☐
3. feeling hopeless about the future	☐	☐	☐	☐
4. Feeling blue	☐	☐	☐	☐
5. Worrying too much about things	☐	☐	☐	☐
6. Feeling everything is an effort	☐	☐	☐	☐
7. Feeling tense or keyed up	☐	☐	☐	☐
8. Suddenly scared for no reason	☐	☐	☐	☐

100. Have you experienced any of the following situations in the last year (since the previous questionnaire)? If yes, how painful and difficult was this for you? *(Enter a cross in a box for each item.)*

			If yes		
	No	Yes	Not so bad	Painful/ difficult	Very painful/ difficult
1. Have had problems at work or where you study	☐	☐	☐	☐	☐
2. Have had financial problems	☐	☐	☐	☐	☐
3. Have been divorced, separated or ended your relationship with your partner	☐	☐	☐	☐	☐
4. Have had problems or conflicts with your family, friends or neighbours	☐	☐	☐	☐	☐
5. Have been seriously worried that there is something wrong with your child	☐	☐	☐	☐	☐
6. Have been seriously ill or injured (your self)	☐	☐	☐	☐	☐
7. Has anyone close to you been seriously ill or injured	☐	☐	☐	☐	☐
8.Have been involved in a serious accident, fire or robbery	☐	☐	☐	☐	☐
9. Have lost someone close to you	☐	☐	☐	☐	☐
10. Have been pressurized into having sexual intercourse	☐	☐	☐	☐	☐
11. Other	☐	☐	☐	☐	☐

101. How would you rate your quality of life?

- ☐ Very poor
- ☐ Poor
- ☐ Neither poor nor good
- ☐ Good
- ☐ Very good

102. How satisfied are you with your health?

- ☐ Very dissatisfied
- ☐ Dissatisfied
- ☐ Neither satisfied nor dissatisfied
- ☐ Satisfied
- ☐ Very satisfied

103. The following questions ask about how much you have experienced certain things in the last two weeks. *(Enter a cross in a box for each item.)*

	Not at all	A little	A certain amount	A lot/ very	Totally/ extremely
1. To what extent do you feel that (physical) pain prevents you from doing what you need to do?	☐	☐	☐	☐	☐
2. To what extent do you need medical treatment to be able to function in your daily life?	☐	☐	☐	☐	☐
3. How much do you enjoy life?	☐	☐	☐	☐	☐
4. To what extent do you feel your life to be meaningful?	☐	☐	☐	☐	☐
5. How well are you able to concentrate?	☐	☐	☐	☐	☐
6. How safe do you feel in your daily life?	☐	☐	☐	☐	☐
7. How healthy is your physical environment?	☐	☐	☐	☐	☐

104. The following questions ask about how completely you experienced or were able to do certain things in the last two weeks. *(Enter a cross in a box for each item.)*

	Not at all/None	A little	To a certain extent	Mostly Almost	Always
1. Do you have enough energy for everyday life?	☐	☐	☐	☐	☐
2. Are you able to accept your bodily appearance?	☐	☐	☐	☐	☐
3. Have you enough money to meet your needs?	☐	☐	☐	☐	☐
4. How accessible is the information that you need in your day-to-day life?	☐	☐	☐	☐	☐
5. To what extent do you have the opportunity for leisure activities?	☐	☐	☐	☐	☐

105. How well are you able to get around?

- ☐ Very badly
- ☐ Badly
- ☐ Neither well nor badly
- ☐ Well
- ☐ Very well

106. The following questions ask you to say how good or satisfied you have felt about various aspects of your life over the last two weeks. *(Enter a cross in a box for each item.)*

	Very dissatisfied	Dis-satisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
1. How satisfied are you with your sleep?	☐	☐	☐	☐	☐
2. How satisfied are you with your ability to perform your daily living activities?	☐	☐	☐	☐	☐
3. How satisfied are you with your capacity for work?	☐	☐	☐	☐	☐
4. How satisfied are you with yourself?	☐	☐	☐	☐	☐
5. How satisfied are you with your personal relationships?	☐	☐	☐	☐	☐
6. How satisfied are you with your sex life?	☐	☐	☐	☐	☐
7. How satisfied are you with the support you get from your friends?	☐	☐	☐	☐	☐
8. How satisfied are you with the conditions where you live?	☐	☐	☐	☐	☐
9. How satisfied are you with your access to health services?	☐	☐	☐	☐	☐
10. How satisfied are you with your transport?	☐	☐	☐	☐	☐

107. The following question relates to how often you have experienced or had negative feelings during the last two weeks?

	Never	Seldom	Quite often	Very often	Always
How often do you have negative feelings, such as blue mood, despair, anxiety, depression?	☐	☐	☐	☐	☐

COMMENTS:

CHILD'S MEASUREMENTS AND WEIGHT

108. If any of the measurements in Question 30 are missing from the child's health card, can we contact the well baby clinic for them?

☐ No

☐ Yes Name of well baby clinic _____

Post code or district _____

Have you remembered to fill in on page 1 the date on which you completed the questionnaire?

Thank you very much for your help!

Please return the completed questionnaire in the stamped addressed envelope provided to:

Den norske Mor og Barn undersøkelsen
Nasjonalt folkehelseinstitutt
Avd. for medisinsk fødselsregister
Kalfarveien 31
5018 Bergen