Early detection of autism

Sigríður Lóa Jónsdóttir

Thesis for the degree of Philosophiae Doctor

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Að bera kennsl á einhverfu snemma

Sigríður Lóa Jónsdóttir

Ritgerð til doktorsgráðu

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Ágrip

Markmið

Markmið þessa doktorsverkefnis var að rannsaka hvernig hægt er að finna einhverfu snemma. Sértæk markmið voru: (1) að lýsa auðkennum barna sem greinast einhverf fyrir og eftir 6 ára aldur og að finna þá þætti sem gætu haft áhrif á hvenær þau greinast; (2) að rannsaka innleiðingu skimunar fyrir einhverfu í ung- og smábarnavernd í heilsugæslunni; (3) að meta gildi skimunartækisins Gátlisti fyrir einhverfu hjá smábörnum, breyttur og endurskoðaður með eftirfylgdarviðtali (e. Modified Checklist for Autism in Toddlers, Revised with Follow-Up; M-CHAT-R/F) í lýðgrunduðu úrtaki 30 mánaða barna; (4) að rannsaka tíðni einhverfu í hópi sem boðin var þátttaka í skimun í samanburði við tíðni einhverfu í tveimur hópum sem ekki var boðin skimun.

Efni og aðferðir

Í grein I er fjallað um ferlirannsókn. Öll börn á Íslandi fædd á árunum 1992-1995, sem höfðu fengið einhverfugreiningu (N = 99) og voru á skrá hjá Greiningar- og ráðgjafarstöð ríkisins (GRR), voru þar til rannsóknar. Börn sem greindust fyrir og eftir 6 ára aldur voru borin saman og foreldrar svöruðu spurningum tengdum því hvenær þeir fóru fyrst að hafa áhyggjur af þroska barna sinna.

Greinar II, III og IV eru um framsýnar rannsóknir á snemmgreiningu einhverfu. Skimunin fyrir einhverfu var tveggja þrepa og heilbrigðisstarfsfólk í ung- og smábarnavernd var frætt um einhverfu. Það kom til greina að skima öll börn á Íslandi, sem voru skráð í 30 mánaða skoðun á heilsugæslustöðvum landsins frá 1. mars 2016 til 31. október 2017, en höfuðborgarsvæðið var valið sérstaklega. Slembun var gerð þar sem heilsugæslustöðvarnar voru einingar slembunarinnar. Níu heilsugæslustöðvar voru slembivaldar til þátttöku í skimuninni og átta heilsugæslustöðvum var skipað í samanburðarhóp 1. Heilsugæslustöðvar utan höfuðborgarsvæðisins voru ekki með í slembuninni og var skipað í samanburðarhóp 2.

Heilbrigðisstarfsfólk í ung- og smábarnavernd svaraði spurningalista um þekkingu sína á einhverfu fyrir og eftir námskeiðið sem haldið var fyrir það og tengiliðir á heilsugæslustöðvunum svöruðu könnun um reynslu sína og viðhorf til skimunar. Samkvæmt upplýstu samþykki svöruðu foreldrar M-CHAT-R/F skimunarlistanum þegar þeir komu með barnið í skoðun og tóku þátt í eftirfylgdartviðtali ef vísbendingar komu fram um einhverfu hjá barninu. Börnum sem skimuðust jákvæð var vísað í greiningu hjá GRR og til þjálfunar/sérkennslu á vegum skólaþjónustu síns sveitarfélags. Hefðbundnar aðferðir voru notaðar til þess að meta M-CHAT-R/F.

Öllum börnum, sem skráð voru í 30 mánaða skoðun var fylgt eftir í skrá GRR frá 1. mars 2016 til 31. október 2019, en þá voru þau á aldrinum 54 til 79 mánaða. Nýgengi einhverfutilfella var reiknað fyrir hvern fyrrnefndan hóp. Nýgengi einhverfu í hópnum, sem boðin var skimun, var borin saman við nýgengi í samanburðarhópunum og reiknað áhættuhlutfall með 95% öryggismörkum.

Niðurstöður

Fimmtíu og átta börn (58,6%) greindust einhverf fyrir 6 ára aldur og 41 barn (41,4%) eftir 6 ára aldur. Flestir foreldrar (76,2%) voru farnir að hafa áhyggjur af þroska barnsins fyrir 3 ára aldur þess. Einnig töldu flestir foreldrar (83,3%), eftir á að hyggja, að einkenni einhverfu hefðu verið komin fram fyrir 2 ára aldur og næstum allir foreldrar (97,6%) töldu að svo hefði verið fyrir 3 ára aldur. Síðbúin greining einhverfu tengdist meðal annars góðum vitsmuna- og málþroska og vægum einkennum einhverfu.

Meirihluti heilbrigðisstarfsfólks (79%) sem tók þátt í námskeiðinu (*N* = 56) hafði ekki fengið fræðslu um einhverfu áður. Þátttaka í námskeiðinu stuðlaði að þeirra mati að aukinni þekkingu og meira öryggi til að bera kennsl á einkenni sem gætu bent til einhverfu. Samtals tóku 1586 börn í þátt í skimuninni í heilsugæslunni, eða 72% þeirra barna sem komu í 30 mánaða skoðun. Tuttugu og sex börn skimuðust jákvæð og af þeim 25 börnum sem fóru í greiningu reyndust 18 vera einhverf. Ellefu börn til viðbótar greindust einhverf í hópnum sem skimaðist neikvæður. Næmi M-CHAT-R/F var 0,62 og sértæki var 0,99. Börn sem fundust við skimunina voru að meðaltali 10 mánuðum yngri við greiningu en börn sem skimunin missti af. Alvarleiki einkenna einhverfu og greindartala/þroskatala <70 var svipað í hópum einhverfu barnanna. Meðaltími sem leið frá skimun og þar til þjálfun/sérkennsla hófst var 3,56 mánuðir (*SF* = 4,00) og 18,28 mánuðir (*SF* = 2,72) þar til greining fór fram.

Alls greindust 119 börn í þýðinu einhverf á eftirfylgdartímanum. Nýgengi í öllu þýðinu var 1,66 (95% öryggismörk, 1,37, 1,99) og hlutfall drengja og stúlkna var 4,7:1. Í hópnum sem boðið var til skimunar, samanburðarhópi 1 og samanburðarhópi 2, voru nýgengi tölurnar 2,13 (95% öryggismörk, 1,60, 2,78), 1,83 (95% öryggismörk, 1,31, 2,50) og 1,02 (95% öryggismörk, 0,66, 1,50). Miðað við samanburðarhóp 1 var áhættuhlutfallið 1,16 (95% öryggismörk, 0,77, 1,75) og miðað við samanburðarhóp 2 var áhættuhlutfallið 2,10 (95% öryggismörk, 1,31, 3,37).

Ályktanir

Þrátt fyrir áhyggjur foreldra af þroska barna sinna og að einkenni einhverfu væru komin fram snemma, var síðbúin einhverfugreining algeng, sem benti til að þörf sé á átaki til þess að finna einhverfu snemma. Innleiðing skimunar með M-CHAT-R/F í ung- og smábarnavernd var auðveld í framkvæmd og skimunin stuðlaði að því að einhverfa fannst fyrr. Sértæki M-CHAT-R/F var hátt, en næmið var miðlungs gott, þannig að M-CHAT-R/F missti af ríflega þriðjungi þeirra barna sem voru einhverf. Takmörkuð þekking heilbrigðisstarfsfólks í ung- og smábarnavernd á einhverfu bendir til þess að

þörf sé á meiri fræðslu. Þó að tíðni einhverfu væri hærri í hópnum sem boðinn var til skimunar en í samanburðarhópunum er erfitt að túlka niðurstöðurnar vegna víðra öryggismarka. Því er ekki er hægt að ályktа með vissu, út frá þessari rannsókn, að skimunin stuðlaði að því að einhverfa greinist fyrr en ella. Lægri tíðni einhverfu í dreifbýlinu en á höfuðborgarsvæðinu bendir til þess að efla þurfi þjónustu á þessu sviði í dreifbýli.

Lykilorð:

Einhverfa, snemmgreining, skimun, M-CHAT-R/F, ung- og smábarnavernd

Abstract

Aims

The objective of this thesis was to test surveillance procedures for early detection of autistic children. The specific aims were: (1) to describe the characteristics of children diagnosed with autism before and after the age of 6 years, and to identify factors that influence the age of diagnosis; (2) to study the implementation of a screening program for autism within the well-child care in primary health care centers (PHCs); (3) to validate the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F) on a population sample of 30-month-old children; and (4) to evaluate the rate of autism in a group invited to a screening program in comparison with the rates in two groups who received usual care.

Materials and methods

Study I was a cohort study. We studied all children in Iceland born 1992 to 1995 who had been diagnosed as autistic (N = 99) according to a nationwide database kept at the State Diagnostic and Counseling Center (SDCC). Children diagnosed before and after the age of 6 years were compared, and parents answered a questionnaire about their first developmental concerns.

Studies II, III, and IV dealt with a prospective program on the early detection of autism. The program included a two-stage screening for autism and a course on autism for the well-child care clinicians. The population eligible for screening included all children in Iceland registered for their 30-month well-child visit at a PHC from March 1, 2016, to October 31, 2017. The capital area of Reykjavik was chosen for implementation of the screening, and cluster randomization was used with the PHCs as the units of randomization. Nine PHCs were randomly selected for the screening, while eight PHCs were assigned to control group 1. PHCs outside the capital area were not randomized and were assigned to control group 2.

The well-child care clinicians completed a questionnaire on their pre- and post-course knowledge of autism, and contact persons at the PHCs answered a survey about their experience and attitudes towards the screening. Parents answered the screener during the well-child visit and participated in a follow-up interview if the child showed indications of autism. Children who screened positive were referred to the SDCC for diagnostic assessment and for early intervention provided by their local communities.

The children in the entire population of the corresponding definition were followed up in the database at the SDCC, from March 1, 2016, to October 31, 2019, when they

were between 54 and 79 months of age. The performance of the M-CHAT-R/F was evaluated with classical measures. The occurrence of autistic children during the follow-up was measured by cumulative incidence in the respective aforementioned groups. The comparison between the rate of autism in the invited group (asked to participate in screening) and the rates in the control groups (receiving usual care) were done with rate ratios and 95% confidence intervals (CIs).

Results

Fifty-eight children (58.6%) in Study I received an autism diagnosis before age 6 and 41 children (41.4%) after age 6. Most parents (76.2%) had concerns about the development of their child prior to the third birthday. Further, in hindsight, most parents (83.3%) reported that symptoms of autism were present before age 2 years, and almost all parents (97.6%) that they were present before age 3 years. A delayed diagnosis of autism was associated, among other things, with good cognitive and verbal status, and mild symptoms.

The majority (79%) of the clinicians who participated in the course (N = 56) had not received prior education on autism. Participation in the course contributed to increased self-perceived knowledge and confidence in identifying behaviors indicating autism. A total of 1586 children in the invited group participated in the screening, or 72% of those who attended the 30-month-old well-child visit. Twenty-six children screened positive and 25 of them received diagnostic assessment, eighteen of whom were diagnosed as autistic (true-positive). An additional 11 children received an autism diagnosis in the screened group (false-negative). The sensitivity and specificity of the M-CHAT-R/F were 0.62 and 0.99 respectively. True-positive children were diagnosed 10 months earlier than false-negative children. Autism symptom severity and the proportion of children with verbal and performance IQs/DQs <70 were similar in the true-positive and false-negative groups. The mean time from screening in the PHC to intervention of screen-positive children was 3.56 months (SD = 4.00), and 18.28 months (SD = 2.72) to diagnostic assessment.

A total of 119 children in the study population were diagnosed as autistic during the follow-up period. The overall cumulative incidence was 1.66 (95% CI, 1.37, 1.99), and the male to female ratio was 4.7:1. In the invited group, control group 1, and control group 2, the cumulative incidence rate was 2.13 (95% CI, 1.60, 2.78), 1.83 (95% CI, 1.31, 2.50), and 1.02 (95% CI, 0.66, 1.50), respectively. The rate ratio of invited group versus control group 1 was 1.16 (95% CI, 0.77, 1.75), and the rate ratio of invited group versus control group 2 was 2.10 (95% CI, 1.31, 3.37).

Conclusions

Despite parental concerns about their child's development and the early presence of autism symptoms, children still encountered delays in being diagnosed as autistic, which indicated that better efforts to detect autism early were needed. Implementation

of the screening with the M-CHAT-R/F in well-child care was feasible. The screening contributed to an earlier detection of autistic children. The specificity of the M-CHAT-R/F was high, but the sensitivity was moderate, such that the M-CHAT-R/F missed more than a third of the autistic children. Limited knowledge of autism among some of the well-child care clinicians indicates a need for continuous education. While the rate of autism was higher in the invited group than in the control groups, interpreting the results is difficult because of the wide confidence intervals. So, one cannot firmly conclude from this study that the screening program detected autism more readily than did the usual care. Moreover, the lower rate of autism in the rural areas than in the urban areas may indicate a shortage of developmental services in rural areas.

Keywords:

Autism, early detection, screening, M-CHAT-R/F, primary health care

Acknowledgements

Returning to study at the University of Iceland almost 40 years since graduating with my first degree in psychology was both exciting and challenging. This thesis would not have been possible without the direct and indirect contribution of many people.

First and foremost, I am extremely grateful to my two supervisors, Evald Sæmundsen and Vilhjálmur Rafnsson, for their enormous support, guidance, and encouragement throughout the Ph.D. process. Evald was not only my main supervisor, but also my boss and close co-worker at the State Diagnostic and Counseling Center (SDCC) for nearly 30 years. He significantly influenced my professional development and always paved the path for my research interests. I greatly appreciate the epidemiological expertise Vilhjálmur brought to the research project. His contribution expanded my methodological knowledge and understanding and helped me to critically evaluate existing research on the subject.

Special thanks to the other members of my committee, Gyða S. Haraldsdóttir, Unnur Anna Valdemarsdóttir, and Tony Charman, who offered their expertise and guidance. Tony's participation in a conference on autism screening in Iceland in 2005 sowed the first seeds in my mind about developing a research project on the subject.

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When planning the screening study and during its first phases, I was fortunate to participate in European projects on autism, i.e., Enhancing the Scientific Study of Early Autism, European Cooperation in Science and Technology (ESSEA-COST) in 2010-2014, and Autism Spectrum Disorders in the European Union (ASDEU) in 2015-2018. This participation brought me into contact with a broad range of scientists in the field of autism and gave me an opportunity to develop my research capacities through joint projects, to gain inspiration for the screening endeavor in Iceland, and not least, to forge friendships. Of particular significance was an opportunity for a Short-Term Scientific Mission during the ESSEA-COST Action, where I had the privilege of visiting professor Ricardo Canal-Bedia, PhD candidate María Magán-Maganto and their colleagues at the University of Salamanca in Spain, to collaborate on research projects and learn about their long-standing experience of autism screening.

I thank Margrét Ann Thors for proofreading the English text in this thesis and in studies III-IV. Her thoughtful corrections and comments greatly improved the final text.

I owe thanks to many of my friends whose company and joint adventures helped me to renew my mental and physical energy, which enabled me to sit for long hours and concentrate on tasks related to the study. Special thanks to Bragi Hannibalsson, who

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Contents

List of Abbreviations

AAP	American Academy of Pediatrics
ABA	Applied Behavior Analysis
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention-deficit/hyperactivity disorder
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ADOS-2	Autism Diagnostic Observation Schedule, Second Edition
ANOVA	Analysis of variance
ASD	Autism spectrum disorder
ASDEU	Autism Spectrum Disorders in the European Union
BSID-II	Bayley Scales of Infant Development, Second Edition
BSID-III	Bayley Scales of Infant Development, Third Edition
CARS	Childhood Autism Rating Scale
CCDB	Center for Child Development and Behavior
CHAT	Checklist for Autism in Toddlers
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DQ	Developmental quotient
e.g.	exempli gratia [for example]
ESDM	Early Start Denver Model
FN	False-negative
FP	False-positive
FYI	First Year Inventory
GRR	Greiningar- og ráðgjafarstöð

ICD	International Statistical Classification of Diseases and Related Health Problems
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, 10th revision
ICD-11	International Classification of Diseases, 11th revision
ID	Intellectual disability
i.e.,	id est [that is]
ITC	Infant Toddler Checklist
IQ	Intelligence quotient
LL	Lower limit
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
M	Mean
M-CHAT	Modified Checklist for Autism in Toddlers
M-CHAT-F	Modified Checklist for Autism in Toddlers, with Follow-Up
M-CHAT-R/F	Modified Checklist for Autism in Toddlers, Revised with Follow-Up
MFR	Male to female ratio
MFOR	Male to female odds ratio
N/n	Number of subjects
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
OECD	Organization for Economic Cooperation and Development
OR	Odds ratio
P	P-value
PACT	Preschool Autism Communication Therapy
PEDS	Parents' Evaluation of Developmental Status
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder, not otherwise specified
PHC	Primary healthcare center
PPV	Positive predictive value
Q-CHAT	Quantitative Checklist for Autism in Toddlers
Q-CHAT-10	Quantitative-Checklist for Autism in Toddlers,10-item version
Q-CHAT-10-O	Quantitative-Checklist for Autism in Toddlers,10-item version, ordinal scoring

R	R Statistical Package
RCT	Randomized controlled trial
SD	Standard deviation
SDCC	State Diagnostic and Counseling Center
SE	Standard error
SF	Staðalfrávik [standard deviation]
SLI	Specific language impairment
SPSS	Statistical Package for the Social Sciences
TEACCH	Treatment and Education of Autism and related Communication Handicapped Children
TN	True-negative
TP	True-positive
UK	United Kingdom
UL	Upper limit
US	United States
USPSTF	United States Preventive Services Task Force
vs	versus
VSN	Vísindasiðanefnd [National Bioethics Committee]
WHO	World Health Organization
WISC-III	Wechsler Intelligence Scale for Children, Third Edition
WPPSI-R	Wechsler Preschool and Primary Scale of Intelligence-Revised
WPPSI-RIS	Wechsler Preschool and Primary Scale of Intelligence-Revised, Icelandic Standardization

List of Figures

List of Tables

List of Original Papers

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

I. Jónsdóttir, S.L., Saemundsen, E., Antonsdóttir, I.S. Sigurdardóttir, S., & Ólason, D. (2011). Children diagnosed with autism spectrum disorder before or after the age of six years. *Research in Autism Spectrum Disorders, 5,* 175-184. https://doi.org/10.1016/j.rasd.2010.03.007

II. Jonsdóttir, S.L., Saemundsen, E., Gudmundsdottir, S., Haraldsdottir, G.S., Palsdottir, A.H. & Rafnsson, V. (2020). Implementing an early detection program for autism in primary healthcare: Screening, education of healthcare professionals, referrals for diagnostic evaluation, and early intervention. *Research in Autism Spectrum Disorders, 77*, 101616. https://doi.org/10.1016/j.rasd.2020.101616

III. Jonsdottir, S.L., Saemundsen, E., Jonsson, B.G. & Rafnsson, V. (2022). Validation of the Modified Checklist for Autism in Toddlers, Revised with Follow-Up in a population sample of 30-month-old children in Iceland: A prospective approach. *Journal of Autism and Developmental Disorders, 52*(4), 1507-1522. https://doi.org/10.1007/s10803-021-05053-1

IV. Jonsdottir, S.L., Saemundsen, E., Rafnsson, V., Thorarinsdottir, E.A. Evaluating screening for autism spectrum disorder: Outcome in an invited group compared with outcomes in two control groups using cluster randomization. Submitted for publication.

Declaration of Contribution

The doctoral student, Sigrídur Lóa Jónsdóttir, planned the research work for studies I- IV of which she is the first author, wrote all applications for the appropriate ethical and research approvals, collected the data, and ran the statistical analyses in cooperation with some of her co-authors. The student drafted all manuscripts and wrote this thesis under the sound guidance of her supervisors, the doctoral committee, and in collaboration with the co-authors of each study.

1 Introduction

Autism is a heterogenous neurobiological condition influenced by both genetic and environmental factors that affect the developing brain (Hodges et al., 2020). Autism is behaviorally defined and is characterized by challenges in social communication and the presence of restricted, repetitive behaviors, and/or unusual sensory responses and interests (American Psychiatric Association, 2013; World Health Organization, 2021). There is evidence that behavioral signs indicating autism can be detected during infancy (Zwaigenbaum et al., 2013) and that experienced clinicians can make a reliable diagnosis in the second or third year of life in most children (Charman & Baird, 2002; Chawarska et al., 2007; Zwaigenbaum et al., 2016). Yet, the reported global average age at autism diagnosis is around 5 years (van 't Hof et al., 2021). Researchers agree that a delay in autism diagnosis translates to missed opportunities for early intervention services that can improve developmental outcomes and quality of life among autistic children (Hyman et al., 2020). Delayed diagnosis for many autistic children is a public health concern that needs to be addressed in research that can inform policy and clinical practice. In this thesis, factors associated with early and late autism diagnosis were examined, and a population screening program aimed at earlier detection of autism was tested.

1.1 Brief historical background, definition, and diagnostic criteria

1.1.1 First clinical accounts of autism

Almost eight decades have elapsed since child psychiatrist Leo Kanner, in his article *Autistic disturbances of affective contact,* provided case histories and observations of 11 children who showed similar patterns of behaviors that differed markedly and uniquely from conditions in children reported previously. The children's behaviors included social remoteness, language deficiencies, insistence on sameness, monotonous repetitions of actions and verbal utterances, and oversensitivity to sensory stimuli (Kanner, 1943). Kanner's use of the term *autism* created some confusion with schizophrenia, since the term autism had been used by Eugen Bleuler in the early 1900s to describe withdrawal from reality in adults with schizophrenia (Crespi, 2010). However, Kanner (1943) clearly stated that the

extreme autistic aloneness in his children was inborn, and thus different from the withdrawal observed in schizophrenia.

A year later, pediatrician Hans Asperger published the article *Die "Autistischen Psychopathen" im Kindesalter,* in which he presented detailed case descriptions of four boys who had severe difficulties with social integration, poor motor skills and coordination, unusual special interests, and seemingly good verbal skills; some also had unusual sensory responses (Asperger, 1944, 1991). Although there are similarities between the observations of Kanner and Asperger, there are also differences. For instance, Asperger described a milder condition that was mainly differentiated by functional language, where he noted that his boys spoke like little adults. Kanner, on the other hand, reported that three of his 11 children did not speak at all, and the remainder rarely used language. Also, Kanner emphasized that autism was a developmental condition, while Asperger considered it a personality disorder and speculated that it was an extreme variant of male intelligence. Both men observed a male predominance as well as autistic traits in parents and close relatives, suggesting a genetic predisposition (Asperger 1944, 1991; Kanner, 1943).

It was long thought that Kanner and Asperger had been unaware of each other's work, one living in the US and the other in Austria. However, it was later discovered that one of Kanner's assistants had previously worked for Asperger, which suggests that Kanner had become aware of Asperger's work through the assistant prior to publishing his 1943 paper (Chown & Hughes, 2016). Kanner's paper became widely known, while Asperger's paper received limited attention in the subsequent decades (van Krevelen, 1971), probably because it was written in German during the Second World War. However, Asperger's paper finally began to be recognized for its contribution to a broader understanding of autism when Lorna Wing published a paper on Asperger's syndrome which included a series of case studies on individuals with similar behavioral features. Wing suggested that Asperger's syndrome, together with early childhood autism, be included in a wider group of conditions that have common impairments (Wing, 1981). Wing was also a catalyst in getting Asperger's article translated into English (Asperger, 1991).

1.1.2 Etiological considerations – from psychogenetics to neurobiology

The early behavioral descriptions of autism by Kanner and Asperger include many of the behavioral features that form a part of the current definitions of autism spectrum disorder (ASD). Their work provided leads for further understanding of the condition, both through research and clinical practice. Some of the leads

created confusion in the field, as for example regarding theories on the etiology of autism. Kanner initially thought that autism was due to an innate inability to establish social relationships. His observation that very few of the parents of the 11 children were warm-hearted led him to question "whether or to what extent this fact has contributed to the condition of the children" (Kanner, 1943, p. 250). This sparked the notion by psychoanalysts that autism resulted from maternal rejection, and in the 1950s and 1960s, psychotherapeutic treatment was thought to benefit both parents and children (Bettelheim, 1967; Harris, 2018). This led to some detrimental consequences (Briggs, 2020).

In his later work, Kanner emphasized his assumption that autism was an "innate disability to form the usual, biologically provided contact with people" had become a certainty. However, others ignored that and erroneously attributed autism to psychogenic theories (Kanner, 1971, p. 141). Kanner's opinion set the stage for a biological approach to studying the causes of autism. For instance, a frequent association between autism and epilepsy provided support for its biological origin (Deykin & MacMahon, 1979; Schain & Yannet, 1960). The first twin study found evidence of hereditary influence in the etiology of autism (Folstein & Rutter, 1977). Further studies have confirmed that autism is a highly hereditary condition. Today, multiple genetic, epigenetic, and environmental risk factors, mostly prenatal (e.g., viral infection, parental age, zinc deficiency), but also perinatal (e.g., low birth weight, birth trauma, premature birth), have been identified as underlying the etiology, but their exact mechanisms remain largely unknown. The etiology of autism is heterogeneous as are its behavioral phenotypes. Since a complex interaction between the etiological factors affects the developing brain in various ways to produce the phenotype, autism has been defined as a neurobiological or neurodevelopmental condition (Bölte et al., 2019; Hodges et al., 2020; Scott et al., 2014; Yoon et al., 2020).

1.1.3 Conceptualization of autism in diagnostic systems

1.1.3.1 From childhood psychosis to autism as a distinct diagnostic condition in DSM-III and ICD-10

Another early confusion pertained to the use of the word autism and the long-held belief by some that autism was the earliest manifestation of schizophrenia or childhood psychosis. This was reflected in the diagnostic systems prior to 1980 due to a phenomenological similarity between the conditions (Gyawali & Patra, 2019). The two diagnostic systems that are used around the world for the diagnosis and classification of health conditions are the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) published by the American Psychiatric Association, and the

International Statistical Classification of Diseases and Related Health Problems (ICD) published by the World Health Organization (WHO). These systems have been updated over the years to reflect advances in the numerous health conditions they cover.

In the 1960s and 1970s there was emerging evidence that autism was a distinct condition. Several attempts were made to update Kanner's definition of autism and to develop more formal diagnostic guidelines. One approach by Rutter in the late 1970s included onset early in life and impaired social and language abilities, as well as restricted interests and repetitive behaviors (Rutter, 1978). Rutter's conceptualization has been recognized as influential in including autism as a diagnostic concept separate from childhood psychosis in DSM, third edition (DSM-III) in 1980 (Rosen et al., 2021; Volkmar & McPartland, 2014). DSM-III included infantile autism, a term initially used by Kanner, for the first time as a distinct diagnostic category and specified six characteristics, each one of which had to be met and with onset before 30 months. To emphasize its uniqueness, autism and two other related categories were assigned under a new term, pervasive developmental disorder (PDD).

DSM-III was criticized for lack of flexibility and for not giving attention to developmental change. A major revision, based on a field trial, appeared in 1987 (DSM-III-R) (American Psychiatric Association, 1987), where onset was defined during infancy or childhood and the term infantile autism was replaced with autistic disorder. This emphasized a developmental approach not limited to the youngest children (Volkmar & McPartland, 2014). The category PDD not otherwise specified (PDD-NOS) was included for children who shared some clinical features with autism but did not meet the full criteria. Another revision included an expansion of the behavioral characteristics to 16 total, which were organized into three behavioral domains that had become standard for defining autism, i.e., (1) qualitative impairments in in reciprocal social interaction, (2) impairments in communication, and (3) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. The diagnosis of autism now became more flexible, where at least eight characteristics had to be present, with a minimum number of two from the social domain and one from each of the other domains (American Psychiatric Association, 1987). Despite some improvements in the diagnostic criteria for autism, the DSM-III-R criteria proved to be over-inclusive with an increase in false positive rates, especially if significant intellectual disability (ID) was present (Volkmar & McPartland, 2014).

The conceptualization of autism followed a similar development in the ICD system as in the DSM. Thus, in ICD, ninth edition (ICD-9), autism was classified as a

childhood psychosis (World Health Organization, 1978). During the 10th revision of the ICD, its divergence from DSM-III-R caused concerns and threatened to complicate research comparisons where agreement on diagnostic criteria is essential. A consensus was reached that a comparability of the diagnostic systems, as far as possible, was desired. This resulted in the adoption of a similar set of diagnostic criteria for autism by both the ICD-10 (World Health Organization, 1992, 1993) and the fourth edition of DSM (DSM-IV) (American Psychiatric Association, 1994), reflecting the current literature and the results of a joint field trial (Rosen et al., 2021; Volkmar & & McPartland, 2014).

1.1.3.2 Categorization in ICD-10 and DSM-IV

Both diagnostic systems contained autism and related conditions within the PDD class. ICD-10 included eight diagnostic subcategories, including childhood autism, and DSM-IV included five subcategories, including autistic disorder. For the first time, Asperger's syndrome was added as a separate diagnostic category under the PDD umbrella (American Psychiatric Association, 1994; World Health Organization, 1992). This multi-categorical approach was not without complications. The diagnostic subcategories (except for Rett's syndrome, which was included in both systems) were criticized for lack of specificity, which impacted both classification and diagnosis of neurodevelopmental conditions and treatment research. Moreover, some of the subcategories were unreliable means of assigning a diagnosis. This especially applied to the unspecific PDD-NOS category and to Asperger's syndrome, which was often difficult to differentiate from autism without ID or the so-called "high-functioning" autism (Doernberg & Hollander, 2016; King et al., 2014; Rosen et al., 2021). A review of studies published over a 20-year period showed that there were inconsistencies in the diagnosis of Asperger's syndrome and the claim that it should be a different diagnostic category from autism was not validated (Sharma et al., 2012).

Findings from numerous studies that did not support distinct diagnostic subtypes within PDD, and corresponding treatments, laid the foundation for changes introduced in the latest editions of the diagnostic systems, i.e., the fifth edition of DSM (DSM-5) (American Psychiatric Association, 2013) and the eleventh edition of ICD (ICD-11). The latter was released in 2018 and will officially come into effect on January 1, 2022, but its implementation is expected to take up to a few years in different countries (World Health Organization, 2021). Of particular importance in the revisions of these diagnostic systems was evidence from genetic studies showing that identification of genes and copy number variants associated with autism failed to identify etiological differences between the behaviorally defined subtypes (King et al., 2014). The exception was Rett's syndrome, where a specific genetic etiology had been demonstrated (Armstrong, 2001), and so it was removed from the ASD umbrella term.

1.1.3.3 A dimensional approach in DSM-5 and ICD-11

Changes in the DSM-5 and later the ICD-11 marked a major shift in the conceptualization of autism. The multi-categorical diagnostic system under the PDD umbrella was changed to a single diagnosis of ASD based on multiple dimensions. Also, ASD falls under a class of disorders entitled neurodevelopmental disorders, but despite its long history this term had not been included in the previous versions of the diagnostic systems. Neurodevelopmental disorders include a group of disorders with onset during the developmental period, affecting both cognitive and social communicative development, in most cases throughout the lifespan, and are presumed to be primarily caused by genetic and other factors that are present from birth (Doernberg & Hollander, 2016; Stein et al., 2020). An onset before 3 years of age is no longer required, but as mentioned above, the symptoms must be present during early development; however, it is acknowledged that the symptoms may not fully manifest until later when social demands exceed limited capacities, or that the symptoms may be masked by learned strategies and thus not always apparent to others (American Psychiatric Association, 2013; World Health Organization, 2021) Furthermore, supported by findings from several factor-analytic studies, the three symptom domains were restructured into two symptom domains: the social and communication deficits were combined into one domain. Restricted and repetitive behaviors, interests, or activities were maintained as the second required domain, and excessive and persistent sensory hyper- or hyposensitivity was added to the group of symptoms (Doernberg & Hollander, 2016; Rosen et al., 2021).

Although the latest editions of both diagnostic systems are similar in many ways, such as their use of the term ASD for the unitary classification of the core symptoms and the two symptom domains, they differ in their approaches to describing individual variations within the spectrum. DSM-5 provides severity-level specifiers for each core symptom domain based on support required for individual functioning. Other specifiers describe whether intellectual impairment with or without accompanying language impairment is present. Some specifiers also describe whether a known etiological factor, other neurodevelopmental, mental, or behavioral disorders, and/or catatonia are present (American Psychiatric Association, 2013). To capture the full range of presentations of ASD, ICD-11 provides qualifiers that enable the identification of varying levels of intellectual and functional language impairments as well as developmental history (i.e., with or without loss of previously acquired skills). Qualifiers for co-occurring medical and psychiatric conditions, like in DSM-5, are also provided. Separate codes are assigned based on the qualifiers (World Health Organization, 2021). Indeed, the diagnostic systems are not purely dimensional since they still use categories to

characterize individual differences and/or support needs within the autism spectrum. However, the categories in the revised systems are different from the previous PDD categories in that their severity is dimensional. It has been suggested that it may be helpful to emphasize dimensionality for some purposes, such as research, and categorization for other purposes such as service planning and delivery (Rosen et al., 2021).

The decision to remove the PDD subtypes and conceptualize autism as a single disorder sparked considerably controversy during the development of DSM-5. This was mainly due to concerns that the new diagnostic criteria were too narrow, resulting in fewer individuals getting an ASD diagnosis and the support they needed, particularly the more cognitively able individuals including those with Asperger's syndrome (Rosen et al., 2021; Volkmar & McPartland, 2014). The removal of the category for Asperger's syndrome also generated a heated debate among self-advocates. Some held the view that these changes would threaten the identity of people with the condition and expressed concern that an ASD diagnosis carries a greater stigma than an Asperger's diagnosis. They also worried that some with a previous Asperger's diagnosis would be dismissed by the new criteria, and thus excluded from the support they need (Galligan et al., 2013; Smith & Jones, 2020).

Studies examining the shift from DSM-IV to DSM-5 have shown that 81% to 89% of those who met DSM-IV criteria for ASD continued to meet the DSM-5 criteria. The decrease in diagnostic rates was mainly due to cases with the imprecise PDD-NOS diagnosis who no longer met the ASD criteria in DSM-5 (Kim et al., 2014; Maenner et al., 2014; Mazurek et al., 2017). As for Asperger's syndrome, anywhere from 80% (Mazurek et al., 2017) to 92% (Kim et al., 2014) of those who met the DSM-IV criteria for that subtype also met the final DSM-5 criteria for ASD, providing some support for the aforementioned concerns. Future studies will determine whether the same trend will be found regarding the shift from ICD-10 to ICD-11. It is likely that most individuals who previously met diagnostic criteria for Asperger's syndrome will be captured by ICD-11, where the qualifiers allow for identification of those who are without ID and with mild or no impairment in functional language.

Overall, the change from multiple diagnostic subtypes to a single dimension, has improved diagnostic specificity, making it less likely that individuals without ASD are inappropriately diagnosed with the condition. Also, diagnostic sensitivity is generally considered good, with a high proportion of PDD cases meeting DSM-5 criteria for ASD. Those who do not are likely to meet the new diagnostic criteria for social communication disorder (Rosen et al., 2021), which is included in both diagnostic systems (American Psychiatric Association, 2013; World Health Organization, 2021).

1.1.4 Definition of autism in a nutshell

To sum up, ASD is defined as a neurodevelopmental condition with onset in the early developmental period, characterized by persistent deficits in social communication and interaction across multiple contexts, and the presence of restricted, repetitive behaviors, and/or unusual sensory responses and interests (American Psychiatric Association, 2013; World Health Organization, 2021). Autism is highly heritable with multiple genetic, epigenetic, and environmental risk factors that underlie its etiology (Yoon et al., 2020). Although autistic individuals share the core behavioral features, there is wide heterogeneity between them in symptom severity and intellectual and language functioning, and, accordingly, in support needs (American Psychiatric Association, 2013; World Health Organization, 2021). There is also individual heterogeneity in the development of the core symptoms over time (Pender et al., 2020).

1.1.5 Terminology

The ICD system is used in Iceland, and all children who participated in the present study were diagnosed according to ICD-10. Although the children were diagnosed with one of the PDD subtypes, the terms ASD or autism will be used when referring to them. The same procedure will be followed when referring to participants in other studies that used the PDD term. The terms ASD and autism will be used interchangeably. While the former will be chosen when referring directly to the diagnostic systems as was done above, the latter will generally be used as it is preferred by the autism community including autistic adults (Bury et al., 2020) and professionals, parents, other family members, and friends (Kenny et al., 2016).

There has been increased discussion around the use of person-first language (i.e., person with autism) or identity-first language (i.e., autistic person) when referring to individuals diagnosed with autism (e.g., Botha et al., 2023; Vivanti, 2020). There is a trend in the autism community towards identity-first language (Bury et al., 2020; Kenny et al., 2016). This is related to the growth of the neurodiversity movement that sees autism as a natural form of human diversity that cannot be separated from the individual's identity (Bottema-Beutel et al., 2021). However, a complete shift appears premature, and person-first language is still the preferred phrasing to many with an autism diagnosis (Vivanti, 2020). Thus, both approaches will be used in this thesis.

Moreover, an effort will be taken to avoid the use of other terms that have been identified as potentially ableist and to use suggestive alternatives. Examples of alternatives are "impact" or "effect" instead of "burden" of autism, "co-occurring" instead of "co-morbid" conditions, and "increased likelihood of" instead of "at risk

for" autism (Bottema-Beutel et al., 2021). However, the author recognizes that completely avoiding the use of some potential ableist terms that have prevailed in the field for decades and still appear in English journal articles (such as "risk"), is challenging for a non-native user of the English language and is a learning process that will take some time.

1.2 First signs of autism and onset patterns

The first signs of autism usually manifest in infancy or early childhood, with variable onset patterns (Landa et al., 2013; Pearson et al., 2018). Development in observable social behaviors appears to be generally intact for the first 6 months of life in children later diagnosed with autism (Landa et al., 2013; Ozonoff et al., 2010). However, prospective studies have found evidence of prodromal symptoms of autism by 6 months of age, such as reduced spontaneous attention to social stimuli (Chawarska et al., 2013; Yirmiya & Charman, 2010). Several non-social behaviors that are visible in early development before social-communication deficits are clearly manifested have also been identified. These prodromes include impairments in attention disengagement, motor deficits, the presence of repetitive/stereotyped interests and behaviors, atypical sensory experiences, and temperamental characteristics (Canu et al., 2020; Yirmiya & Charman, 2010).

Signs in the core social-communication domains of autism are observable by 12 months in some children, but they usually become pronounced between 14 and 24 months and continue diverging from normal development throughout the third year (Landa et al., 2013; Yirmiya & Charman, 2010). Other children seem to attain developmental milestones but then display a developmental plateau or a regression involving gradual loss of previously acquired skills during the second year of life (Landa et al., 2013; Pearson et al., 2018). However, seemingly normal development prior to observed regression has been questioned (Zhang et al., 2019).

Other onset patterns have also been documented, where the signs of autism emerge later. Some children show little evidence of autism until after the preschool years. In other children with late onset, signs of autism are present during early development, but are subtle and may thus not become clinically detectable until later (Bacon et al., 2018; Ozonoff et al., 2018), or when age-appropriate social demands exceed the child's capacity to meet them (American Psychiatric Association, 2013, World Health Organization, 2021).

1.3 Initial parental concerns

Parents generally feel confident in their knowledge of when their children should attain developmental milestones (C.S. Mott Children´s Hospital, 2021). Studies have confirmed maternal accuracy in estimating their child's developmental age (Pulsifer et al., 1994), and the validity of concerns raised by parents of infants at increased likelihood of autism (Rogers et al., 1992). Accordingly, parents of autistic children are in most cases the first to suspect delays in their child's development (Crane et al., 2016; Locke et al., 2020; Wong et al., 2017), and only a small proportion (4%) of parents of children eventually diagnosed with autism had no concerns (Becerra-Culqui et al., 2018).

Parents of children later diagnosed on the autism spectrum have reported developmental concerns as early as between 6 and 12 months of age (De Giacomo & Fombonne, 1998; Ozonoff et al., 2009), and the majority have recognized deviations in development by their child's second birthday (Baghdadli et al., 2003; Chakrabarti, 2009; Chawarska et al., 2007; De Giacomo & Fombonne, 1998; Young et al., 2003). The mean age of onset of parental concerns was as low as 15 months in a young study population with a mean chronological age under 30 months (Chawarska et al., 2007), but has often been found to be between 17-19 months (Baghdadli et al., 2003; Bejarano-Martín et al., 2020b; De Giacomo & Fombonne, 1998; Locke et al., 2020) or even later. Thus, a comparison between groups of autistic children diagnosed early (≤3 years) and later (≥3 years) showed that the mean age at first developmental concerns by parents was 18 and 35 months respectively (Becerra-Culqui et al., 2018). The most reported first concern is delay in speech and language development, followed by social development (Chawarska et al., 2007; De Giacomo & Fombonne, 1998; Herlihy et al., 2015; Wong et al., 2017). In relation to this, it has been suggested that social milestones may be less well understood by parents than language milestones, and that the former may become more apparent later in development (Herlihy et al., 2015).

Understanding when different behavioral characteristics raise concerns by parents may help to improve earlier recognition of autism. The predictive ability of autism-related concerns was demonstrated in a recent study, where poor eye contact, limited pointing/gesturing, delayed/absent response to name, and delayed/abnormal babbling were associated with an early diagnosis. Concerns about lack of capacity to initiate social interaction was an indicator of a later diagnosis. The authors point out that lack of this behavior may not be of concern until the children get older and expectations to interact with others increase (Becerra-Culqui et al., 2018). This is an example of a retrospective study where parents of children who have already been diagnosed with autism are asked to

recall when or if they became concerned about the child's development and what behaviors raised their concern. Among potential limitations of these studies is that parents' recollection of early signs may be influenced by their knowledge of what behaviors are associated with autism.

Prospective studies of high-risk infants (younger siblings of children diagnosed with autism) have, on the other hand, provided a unique opportunity to learn about the emergence of autism and to track parents' concerns. Already at 6 months, concerns regarding sensory behavior and motor skills have been found to predict an autism diagnosis at 3 years of age, and the same prediction applied to concerns about communication and repetitive behaviors during the second year (Sacrey et al., 2015). Not only the nature of concerns, but also the total number of concerns at 12 months have been found to predict diagnostic outcome. Thus, parents of high-risk children who were later diagnosed with autism reported more concerns than parents of children (both high- and low-risk) who did not receive an autism diagnosis (Ozonoff et al., 2009; Sacrey et al., 2015).

Parents may be reluctant to raise their concerns (Locke et al., 2020), and studies have shown that several months may pass before they share them with a professional (Chakrabarti, 2009; Crane et al., 2016; De Giacomo & Fombonne, 1998). This process may be facilitated during well-child visits, where elicitation of parental concerns about their child's development is a fundamental component of developmental surveillance. This is sometimes accomplished with the help of questionnaires like the Parent Evaluation of Developmental Status (PEDS; Glascoe, 2005). In addition, educating parents about developmental milestones and red flags for autism may help them to accurately identify and report to professionals their child's behaviors (or lack of behaviors) that give rise to their concerns. Likewise, parents have expressed the wish that professionals receive more training on the early signs of autism to be more responsive to their concerns and to be more willing to make appropriate referrals (Locke et al., 2020).

1.4 Age at diagnosis

1.4.1 Mean/median age at diagnosis

Although the diagnostic process is most often prompted by parental concerns (Johnson, 2008) and experienced clinicians can reliably diagnose autism in many children as young as 24 months of age (Charman & Baird, 2002; Chawarska et al., 2007; Zwaigenbaum et al., 2016), there is usually a considerable delay before a diagnosis is made (Bejarano-Martín et al., 2020b; Crane et al., 2016; De Giacomo & Fombonne, 1998; Young et al., 2003). A review of studies published between

1990 and 2012 reported an average age at diagnosis as ranging from 38 to 120 months (median 36 to 82 months) across studies (Daniels & Mandell, 2014). Different methodologies, such as the chronological age of the study populations, might explain some of the variability reported for age at diagnosis. This was demonstrated in a recent meta-analysis of studies from 35 countries published between 2012 and 2019. The average age at diagnosis was 60 months (range 31-235 months) for all study populations of variable ages, but considerably lower, or 43 months (range 31-75), in studies that only included children who were 10 years or younger (van 't Hof et al., 2021).

1.4.2 Stability and change in age at diagnosis over time

Studies reporting on change in the age at diagnosis over time have shown conflicting results. A review of studies published from 1990 to 2012 (Daniels & Mandell, 2014) and a parental survey (Adelman & Kubiszyn, 2017) suggest that the average age at diagnosis has decreased over time. However, a UK study based on parent report did not find evidence of reduction in the median age (55 months) of autism diagnosis from 2004 to 2014 (Brett et al., 2016). Nor did a systematic review of studies from more than 20 countries, using data collected over a 30-year period (1987-2017), find a clear decrease in the age at diagnosis, although there was a trend towards a decline in diagnostic age over the last two decades (Loubersac et al., 2021). Similarly, data from the Autism and Developmental Disabilities Monitoring (ADDM) Network, including 11 sites in the US, indicate little change over the past two decades, with the median age at diagnosis remaining around 50 months for children aged 8 years. The authors point out that this metric might not fully capture progress towards earlier identification. Changes in awareness of autism may thus have resulted in older children being diagnosed, who in previous years would not have received an autism diagnosis by 8 years (Maenner et al., 2020).

A cumulative incidence of autism diagnosis might be more appropriate to reveal progress in early identification (Maenner et al. 2020). Hence, data from the ADDM Network showed that the cumulative incidence of autism diagnoses by 48 months was higher for 4-year-old children than for 8-year-old children (Shaw et al., 2020). Similarly, a Danish study of individuals born 1980-2012 showed a steeper increase in the cumulative incidence of autism diagnosis for younger age groups compared to those who were older (Schendel & Thorsteinsson, 2018).

1.4.3 Factors associated with age at diagnosis

More knowledge about children who are identified both early in the developmental period and later is of great importance for early detection. Numerous clinical, social, and environmental factors that may be associated with the age at autism diagnosis have been investigated, often with conflicting results between studies. Having more autism-specific symptoms was associated with earlier diagnosis in many studies (Daniels & Mandell, 2014). However, studies using standardized tools to assess the clinical severity of autism have reported mixed results in relation to age at diagnosis (Loubersac et al., 2021).

Type of diagnosis on the autism spectrum, based on ICD-10 and DSM-IV, has been found to be associated with age at diagnosis, such that children with autistic disorder/childhood autism have been diagnosed significantly earlier than those with Asperger's syndrome (Loubersac et al., 2021; van ´t Hof et al., 2021; Avlund et al., 2021). This may be linked to the influence of delays in cognitive and language development, which has been associated with an earlier diagnosis in most studies that have reported on these factors (Daniels & Mandell, 2014; Loubersac et al., 2021; Salomone et al., 2016; van 't Hof et al., 2021). However, contradictory results have also been reported, suggesting challenges in differential diagnosis in young children of low mental age (Avlund et al., 2021).

A non-autism diagnosis prior to an autism diagnosis has been associated with a later diagnosis (Adelman & Kubiszyn, 2017; Avlund et al., 2021; Daniels & Mandell, 2014; Davidovitch et al., 2015), but results on other diverse co-occurring conditions and motor skills are inconsistent (Daniels & Mandell, 2014; Loubersac et al., 2021). Most studies have not found an association between sex and age at autism diagnosis (Avlund et al., 2021; Daniels & Mandell, 2014; Loubersac et al., 2021), although a study of young children (<7 years) found that girls with good verbal ability were diagnosed later than boys with the same level of verbal ability (Salomone et al., 2016).

Among the variables in the child's socio-familial environment that have been found to predict an earlier diagnosis are having an older sibling with autism (Adelman & Kubiszyn, 2017; Daniels & Mandell, 2014; Loubersac et al., 2021), higher level of parental education (Avlund et al., 2021; Daniels & Mandell, 2014; Rosenberg et al., 2011), living in higher income areas, and living in urbanized areas, although the level of urbanization had an effect in some studies (Lourbersac et al., 2021). There is little evidence and/or inconsistencies regarding the association of other social and environmental factors with age at diagnosis, such as socioeconomic status, bilingualism within the home, immigrant status, and racial or ethnic background (Daniels & Mandell, 2014; Loubersac et al., 2021).

It is evident that multiple factors contribute to the age at autism diagnoses, and many of them have not been studied thoroughly. Because of variations in age at diagnosis across geographic regions (Adelman & Kubiszyn, 2017; Daniels & Mandell, 2014; Maenner et al., 2020; Rosenberg et al., 2011), attention should also be given to how cultural and health system factors may contribute to earlier or later age at diagnosis. Among the latter is screening for autism which, in conjunction with regular developmental surveillance, has the potential to reduce the age at diagnosis (see section 1.8 below).

1.5 Epidemiology

Epidemiology is the discipline that studies the occurrence and distribution of disease or health conditions in human populations and the factors that determine them. Epidemiology is often referred to as the basic science of public health and as such provides a foundation for directing appropriate public health action and resources. This may include strategies for prevention and intervention of health conditions to improve the health of the population (Rothman, 2012; Schneider, 2017). As for autism, epidemiological surveys can be a starting point in some locations for developing clinical and research expertise on the condition. Also, they provide prevalence estimates that are essential for policy making and in planning service needs throughout the lifespan. Moreover, these surveys can generate etiological hypotheses and thus help to identify potential factors associated with increased likelihood of autism (Fombonne et al., 2021; Honda, 2013).

1.5.1 Frequency measures

Incidence rates and prevalence rates are two types of frequency measures that are commonly used in epidemiology. Incidence refers to the rate of new cases in a specific population over a defined period, divided by the total person-time observation or total person-time at risk during the period (Honda, 2013). Difficulties in defining and determining onset time in neurodevelopmental conditions such as autism has posed challenges for studies estimating its incidence. To overcome these challenges, cumulative incidence has been calculated to measure the number of new cases that are diagnosed and accumulated during a specified time divided by the number of persons in the population at risk (Honda, 2013; Saito et al., 2020). A common method used to calculate cumulative incidence of autism is to follow one or more birth cohorts up to at least 5 years of age, when diagnosis is possible for most cases (McDonald & Paul, 2010; Saito et al., 2020). The cumulative incidence is valuable for measuring the probability of developing the health-related condition under study during the specified period and is thus more

sensitive to changes in possible etiological factors implicated in new cases of autism than are prevalence rates (Honda 2013; Saito et al., 2020).

Prevalence differs from incidence proportion as it includes all cases, both pre-existing and new cases, in the population at a specific time (point prevalence) or during a specific time-period (period prevalence). Prevalence of a condition is a useful measure of its impact (burden of disease) and can help to understand demands on educational- and health services to meet the needs of the respective group of individuals throughout their lifespan (Honda, 2013; Noordzij et al., 2010). Most epidemiological surveys of autism have examined its prevalence. These studies differ in their methodology and may be grouped into three types: studies using administrative databases and registries that routinely collect health information, cross-sectional surveys that collect data at one point in time in a given area or a population, and surveillance programs that monitor autism in the population, often relying on reviews of electronic medical or educational records (Fombonne et al., 2021).

1.5.2 Prevalence and cumulative incidence of autism

Autism was considered a rare condition for decades after Kanner's publication in 1943. The first epidemiological surveys of autism were conducted in England in the mid-1960s and have now expanded worldwide. A review of 23 epidemiological surveys that were carried out in 12 countries between 1966 and 1998 showed that the median prevalence estimate was 5.2 per 10,000 children (0.052%). There was a significant increase in prevalence rates for the later publication years (Fombonne, 1999) such that by the late 1980s and the 1990s, autism was no longer considered to be rare (Wing & Potter, 2002). Reviews published since then have continued to report an increase in the rates of autism (e.g., Chiarotti & Venerosi, 2020; Elsabbagh et al., 2012; Fombonne, 2003; E. Fombonne, 2005; Tsai & Ghaziuddin, 2014).

An examination of studies for which cumulative incidence was available, showed an increase beginning in 1988-1989 (McDonald & Paul, 2010). Recent findings on cumulative incidence of autism diagnosis show that it was 1.31% for children up to 5 years of age in a Japanese total population study (Saito et al., 2020), and 1.32% for children up to 8 years of age in the ADDM Network (Maenner et al., 2020). A Danish study of cumulative incidence of autism for individuals born 1980-2012 and followed-up through 2016, showed the highest value of 2.80% at 16 years of age for those who were born in 2000-2001 (Schendel & Thorsteinsson, 2018). By 2012, a median global prevalence of 0.62% was reported (Elsabbagh et al., 2012). Today, prevalence estimates of autism in child populations with a median age of 8

years are available for 37 countries. Prevalence results ranged from 0.043% to 2.68% between studies, with the highest estimate in Iceland, followed by South Korea. When analysis was limited to 26 of the high-income countries, a median prevalence of 0.97% was found (Fombonne et al., 2021).

1.5.2.1 Possible reasons for changes in frequency rates reported for autism

The increase in prevalence estimates over time and the increase in the cumulative incidence reported depend mostly on changes that have taken place in recent decades. Among them is broadening of the diagnostic criteria and diagnostic shift from other neurodevelopmental disabilities, in particular developmental language disorder and mental retardation, to autism (Bishop et al., 2008; Elsabbagh et al., 2012; King & Bearman, 2009). Changes in clinical practice have also contributed to an increase in frequency rates. Supporting that is evidence of a change in the symptom level of diagnosed cases, where fewer symptoms of autism seem to be required for a diagnosis in recent years than during the previous decades (Arvidsson et al., 2018). Other possible reasons may be availability of services and increased awareness of autism among both the public and clinicians (Elsabbagh et al., 2012). The uptake of revised diagnostic systems will continue to affect prevalence estimates of autism and challenge comparison between studies performed at different points in time. This was reflected in the shift from DSM-IV to DSM-5, where a decrease in the diagnosis of ASD has been documented (Kim et al., 2014; Maenner et al., 2014; Mazurek et al., 2017).

Methodological differences account for much of the variation in prevalence observed between studies, some of which are closely linked to the above-mentioned time related changes in diagnostic criteria. A meta-analytic study that examined reasons for variations in prevalence estimates found that the diagnostic criteria used explained most of the among-study variance. Thus, studies using the ICD-10 or DSM-IV diagnostic criteria reported prevalence estimates that were more than double those in studies that used other (older) criteria.

Other covariates that were significantly associated with the prevalence estimates, when adjusting for diagnostic criteria, were study location and age of the participants. Studies in urban areas found a greater prevalence compared to rural or mixed urban and rural areas, indicating differences in access to services, and an older age was associated with a decline in prevalence (Williams et al., 2006). An examination of autism prevalence by age groups (range 0-79 years) showed that it increased in young children, reached a peak for the 6-11-year-old age group, and subsequently declined (Bachmann et al., 2018). This was not surprising, since many

autistic infants and toddlers do not yet have well established symptoms and have not yet been diagnosed, and the condition remains unrecognized in many adults. For this reason, the inclusion of school-aged children in autism prevalence studies gives the most valid and accurate population estimate and is recommended (Fombonne et al., 2021).

Additional methodological issues that pose challenges when comparing epidemiological studies on autism relate to differences in case definition and case status determination. Surveys that rely solely on parental reports for case determination, where parents are for example asked if a professional has ever told them that their child is autistic, are problematic and have been shown to overestimate prevalence (Fombonne et al., 2021). Another method that is quite common and has for example been used in epidemiological studies of autism in Iceland (Delobel-Ayoub et al., 2020; Magnússon & Saemundsen, 2001; Saemundsen et al., 2013), is to count already diagnosed cases in national registries or administrative databases. This approach is likely to underestimate the population prevalence for the respective age since it does not allow for identification of new cases. An alternative approach to case finding is a two-stage methodology that includes a school-survey, or screening of the target population, in addition to a registry-based approach. Although this method has improved case finding by identifying up to a third of cases that would otherwise be missed by the traditional registry-based approach, the methods used to screen and confirm cases vary and present many challenges that need to be addressed. Important considerations include increasing the validity of the case determination in the study populations, where scoring above autism diagnostic criteria on gold standard tools is not sufficient on its own, and expert clinical judgement is required to reach a conclusion on the diagnosis (Fombonne et al., 2021).

1.5.2.2 Is there an increase in autism?

A crucial question is whether the rise in autism prevalence and cumulative incidence is solely attributable to methodological factors and the above-mentioned time related factors, or if there is an increase in the incidence of autism due to genetic factors, biological vulnerabilities, environmental factors, or a combination of those factors. Generally, epidemiological data does not support the hypothesis that autism rates have increased. After accounting for methodological differences between studies, no clear evidence was found of change in prevalence over a 20-year period from 1990 to 2010 (Baxter et al., 2015). More recently, a study including a total population sample of 5-year-old children in Japan, found no evidence of an increase in prevalence, nor in cumulative incidence over the study years 2013-2016 (Saito et al., 2020).

Nonetheless, an important contribution of epidemiological studies in this field is to identify any potential factors that may increase the likelihood of autism. A study using twin methods assessed whether the relative importance of genetic and environmental factors in association with autism had changed over time. The results showed that there was a small increase in both the genetic and environmental variance underlying autism and autistic traits over time, and that the genetic factors continuously played a greater role in autism than the environmental factors. The authors concluded that environmental factors associated with autism have not increased in importance over time and are unlikely to explain the increase in the prevalence (Taylor et al., 2020).

Whether or not there has been a true increase in autism, the fact is that diagnostic practices and awareness have changed, and the number of individuals diagnosed with the condition has increased with subsequent public health challenges associated with diverse service needs.

1.5.3 Male predominance

A male predominance has consistently been reported in epidemiological surveys of autism over the decades, such that autism is diagnosed on average four times more frequently in males than in females. More precisely, a review of 117 surveys conducted in 37 countries reported a median male to female ratio (MFR) of 4.1:1 and a weighted average of 4.13:1 (range 1.5:1-6.7:1). An analysis of the correlation between MFR and year of publication showed that this ratio has remained remarkably stable over the last 50 years (Fombonne et al., 2021). Data from epidemiological samples in Iceland, (all registry based) show similar MFR, i.e., 4.2:1 (Magnússon & Saemundsen, 2001), and 4.4:1 (Delobel-Ayoub et al., 2020), although a lower MFR of 2.8:1 was also found (Saemundsen et al., 2013).

Several factors may influence the variability in MFR observed across studies. Among them is the age of the participants: a higher MFR for autism was found in toddlers (5.45:1) than in preschoolers (3.5:1) (Ros-Demarize et al., 2020). The same age-related difference in prevalence was also reported in a large-scale total population study from Norway, where the highest MFR for autism was found in the youngest age group of 4-10 years old children (4.46:1), decreasing to the lowest MFR (2.57:1) in adults (Posserud et al., 2021). A similar trend was reported in a prospective longitudinal follow-up study in the Faroe Islands where more females were found in the same cohort at a later assessment (Kočovská et al., 2012) consistent with evidence from other studies that females are more likely than males to have their autism symptoms missed, misdiagnosed, or detected late (Bargiela et al., 2016; Gesi et al., 2021; Loomes et al., 2017). This may be due to a different

clinical presentation in females than in males. Comparisons of measures of autism symptoms between the sexes have generally showed lower levels of restricted repetitive behaviors in females compared to males, although these differences have been small, whereas there have been inconsistent results regarding social and communicative behaviors (Charman, et al., 2017a; Evans et al., 2019; Kaat et al., 2021; Lai & Szatmari, 2020; Ros-Demarize et al., 2020; Tillmann et al., 2018; Van Wijngaarden-Cremers et al., 2014).

There is also evidence that the diagnostic criteria and diagnostic instruments are not sensitive enough to capture the female phenotype (Lai et al., 2015), especially in females with higher cognitive abilities (Ratto et al., 2018). Differences in the core symptomatology that present diagnostic challenges leading to missed or late autism diagnosis, may be that compared to males, females show qualitatively different repetitive behaviors or circumscribed interests that appear to be more socially acceptable (Halladay et al., 2015). Also, there are indications that more females than males use camouflaging, a coping strategy to mask their social communication difficulties, to satisfy social expectations (Tubío-Fungueiriño et al., 2021). However, studies on camouflaging in autistic people have been criticized, mainly for lack of operationalization and construct validity (Fombonne, 2020).

Sex differences in autism prevalence are confounded by other characteristics besides age, such as IQ and level of co-occurring psychiatric conditions (Charman et al., 2017a; Kaat et al., 2021). Regarding IQ, there is evidence that a lower score is associated with a lower MFR (Loomes et al., 2017). Indeed, in a childhood population sample in Iceland, the MFR was 2.1:1 for children with ID (IQ <70) and significantly higher or 3.7:1 for those without ID (Saemundsen et al., 2013). However, such differences in co-occurring ID by sex were not reported for 8-year-old children in recent epidemiological samples in Denmark, Finland, and Iceland (Delobel-Ayoub et al., 2020), which possibly reflects improvements in identification of autistic girls. Overall, the co-occurrence of ID has been reported to decrease the MFR not only in children, but also in adults (Brugha et al., 2016; Posserud et al., 2021).

Methods used for calculation, study quality, and case ascertaining methods have also affected MFR, as demonstrated in a meta-analysis of prevalence studies. The authors argued that using male to female odds ratio (MFOR), which considers gender population in the overall sample (dividing the autism prevalence in males by that in females), is a more accurate measurement of the autism gender ratio than using the conventional method based only on diagnosed cases (dividing the number of autistic males by that of autistic females). Based on OR, the overall pooled MFOR was 4.2:1, similar to outcomes when using the traditional method.

However, when limiting the analysis to studies that were of high quality and used active case ascertaining methods as opposed to passive methods, the MFOR was lower than 3.5:1. The authors concluded that the true MFR is closer to 3:1 rather than the often-reported ratio of 4:1 (Loomes et al., 2017).

An understanding of how sex affects the expression and diagnosis of autism is important to improve early detection and intervention of females with the condition, especially those without ID. Clinicians need to be adequately trained to recognize possible sex variations in autistic individuals and how diagnosis may be affected by different levels of ability and symptom severity. Furthermore, it has been suggested that development of sex-specific norms should be aimed at advancing the psychometrics of instruments measuring autism symptoms (Charman et al., 2017a).

1.5.4 Prevalence of co-occurring conditions in childhood

The prevalence of co-occurring conditions in autistic individuals is high, and it is significantly higher than in the general population (Lai et al., 2019). Co-occurring conditions influence both the presentation of the behavioral symptoms of autism and their severity and thus contribute to the heterogeneity in autism. These conditions may influence the social and functional challenges of autistic individuals in different ways at each age, as well as their quality life and well-being (Hyman et al., 2020; Soke et al., 2018).

A study of 10- to 14-year-old autistic children, derived from an epidemiological sample in the UK, reported that 71% had at least one DSM-IV co-occurring psychiatric condition and 41% had at least two. The most common diagnoses (around 30% each) were social anxiety disorder, oppositional/conduct disorder, and attention-deficit/hyperactivity disorder (ADHD) (Simonoff et al., 2008). Studies based on clinical populations have reported even higher rates in autistic children under the age of 6 for anxiety (50%), ADHD (40%), and specific phobias (40%), but a lower rate (20%) for oppositional/conduct disorder (Lord et al., 2020). Other frequently reported co-occurring psychiatric or mental health conditions confirmed with DSM or ICD criteria and reported as pooled prevalence estimates in a meta-analysis, are sleep-wake disorders (13%), disruptive, impulse control (12%), as well as depressive disorders (11%), bipolar disorders (5%), and schizophrenia spectrum disorders (4%) which become more prevalent with increasing age (Lai et al., 2019).

A study of younger children (4- and 8-year-olds) from five sites participating in the ADDM Network in the US, included more conditions/symptoms than those based on psychiatric or mental health diagnosis, i.e., also developmental-, congenital-, and genetic conditions. The results showed that over 95% of the children in both age groups had at least one co-occurring condition/symptom. A clustering of co-

occurring conditions in the same child was common, and the mean number per child was higher among the 8-year-olds (4.9) than among the 4-year-olds (3.8). The prevalence of most co-occurring conditions was also higher in children in the older age group. The adjusted prevalence ratios between the age groups were highest for ADHD (4.78), oppositional defiant disorder (4.13), and anxiety (2.28) (Soke et al., 2018).

Of the co-occurring developmental conditions, language disorder was the most common, and was significantly higher in 8-year-olds (35%) than in 4-year-olds (26%) (Soke et al., 2018). These proportions are considerably lower than language disorders reported for 8-year-old children (63%) surveyed by the ADDM Network 8 years earlier (Levy et al., 2010). Possible reasons for the discrepancy between the studies could be inconsistency in recording co-occurring conditions in the files that were reviewed, the inclusion of fewer sites in the more recent study (five vs 11), and, as noted by the researchers, the fact that two of the five sites had incomplete case ascertainment, using only health records with no access to educational records (Soke et al., 2018). This could also simply reflect improved identification of autistic children with more proficient language.

Co-occurrent ID (i.e., IQ <70) is frequently reported in epidemiological studies of autism. Among 10- 14-year-olds in the UK, 55% had ID (Charman et al., 2011). In a similar age group (11-15-year-olds) in Iceland, the proportion was 45%, but somewhat higher (52%) for a younger age group (7-11-year-olds) (Saemundsen et al., 2013). Comparison with other studies shows an even greater difference in proportions of co-occurrent ID between age groups, indicating that children with more severe cognitive impairment are evaluated at a younger age. Thus, the most recent data from the ADDM Network shows that 53% of 4-year-olds had ID (Shaw et al., 2020), while the proportion for 8-year-olds was considerably lower, or 33% (Maenner et al., 2020). A meta-analysis of 24 studies including younger children (mean age 7.45 years) found that 48% had ID (Loomes et al., 2017). The proportions of 7-9-year-old children with co-occurring ID ranged widely in recent epidemiological samples in some European countries, i.e., from 12% in Denmark to 39% in SW-France (20% in Finland and 24% in Iceland and SE-France). The authors suggest that this variation could partly be explained by differences in how ID is assessed in autistic children and in how the results are reported in records or registries (Delobel-Ayoub et al., 2020). These results, except for those from Denmark, are similar to the above results (33%) from the ADDM Network for 8-year-old children with co-occurrent ID, ranging from 25 to 42% between the 11 sites (Maenner et al., 2020). Overall, the proportion of school-aged autistic children with co-occurrent ID seems to have decreased over the years, suggesting improvements in the identification of more cognitively able autistic children.

Besides psychiatric and developmental conditions, various medical conditions co-occur in autism. It has been suggested that in some cases these conditions may be a consequence of autism or may represent an associated feature arising from shared etiology. Medical conditions in population samples from seven studies published between 1996 to 2007 ranged from 8% to 25%. This wide range may indicate that the concept is often not well defined in some studies (Bolton, 2009). Similarly, the prevalence of all medical conditions reported in an epidemiological study in Iceland was 17% (Saemundsen et al., 2013). Evidence shows that medical conditions are more common in individuals with ID. Findings from the Icelandic study are in line with this: the majority (63%) of children with associated medical conditions also had ID (Saemundsen et al., 2013). An overview of medical conditions associated with autism, based on 15 epidemiological surveys, shows that the median rate (16.7; range 0-26.4) was highest for epilepsy. The median rates for other medical conditions were low (<1.4), i.e., for both congenital conditions (cerebral palsy, hearing-, and visual deficits) and genetic conditions (Down syndrome, fragile X syndrome, and tuberous sclerosis). It is noteworthy, however, that there was a wide range (0-16.7) in rates of Down syndrome between studies (Fombonne, 2005). A study that reported on a variety of genetic syndromes, collectively called syndromic autism, estimated that ~5% of autistic individuals were affected (Lai, 2014). A more recent study found that even a lower proportion (<1%) of 4- and 8-year-old autistic children had co-occurring genetic conditions, but that a higher proportion (11% and 13% respectively) of children in these age groups had a congenital condition (Sokes et al., 2018) than reported earlier (Fombonne, 2005). Gastrointestinal problems are among other medical conditions that affect 9% to 70% of autistic individuals (Lai et al., 2014), and such gastrointestinal issues are in turn associated with either sleep problems, seizures, or both (Aldinger et al., 2015).

Some of the co-occurring conditions present in young children bring them into frequent contact with the health-care system. This could create an opportunity to screen for autism in children with conditions that have been found to be associated with autism, which may be helpful for early detection and for the sake of providing the most appropriate intervention and support. Likewise, it is important to recognize co-occurring conditions in children who have already been diagnosed with autism and to address them in intervention programs.

1.6 Importance of early detection and intervention

Detection of autistic children at the youngest age possible, followed by intervention services, is a major goal in the field (Hyman et al., 2020; U.S. Department of Health & Human Services, 2017). Evidence supporting this goal comes from a diverse range of studies focusing on the potential benefits that early detection and intervention may have for autistic children, their parents, and society.

1.6.1 The significance of earlier age when starting intervention

Disruptions in brain development in autistic infants (Piven et al., 2017) and distinct patterns of brain activity that are different from those who are not autistic (Dawson et al., 1995; Lord et al., 2020), present special developmental and behavioral challenges for children and their caregivers. Research from neuroscience showing the impact that early learning experiences have on changes in the brain and cognitive development (Johnson & Munakata, 2005), coupled with the possibility of detecting signs indicating autism early (Zwaigenbaum et al., 2013), has increased the demands for specialized early intervention programs. For instance, one study found altered and normalized patterns in brain activity and associated improvements in social behavior in young autistic children who were enrolled in an autism-specific intervention program (Dawson et al., 2012). Early intervention creates enriched experiences tailored to the needs of the children. At the same time, it takes advantage of critical periods of neural plasticity to maximize developmental gains (Landa, 2018), potentially leading to better long-term independence and quality of life outcomes (Fernell et al., 2013; Jónsdóttir et al., 2018).

Further support for initiating intervention at the earliest age possible comes from studies examining age as one of several possible moderators of intervention effects. For example, a meta-analysis of interventions focusing on teaching specific skills that are challenging for autistic children, found that effect sizes were greater for participants who were younger at the start of intervention (Bejarano-Martín et al., 2020a). A study of autistic children who received intervention in the community, found that those diagnosed before 2.5 years exhibited significantly larger reductions in the severity of social symptoms within 1 to 2 years, than did children diagnosed after that age. There was a trend for larger deterioration in restricted and repetitive behaviors in the younger diagnosed children, indicating that intervention may have focused more on the social symptoms (Gabbay-Dizdar et al., 2021). A review of studies that controlled for the covariance between ability level and the age at the beginning of intervention provided some evidence that "earlier is better". All but two of the 14 studies reviewed reported at least one finding where earlier age when starting intervention was a statistically significant predictor of a better outcome. The authors noted that a complex relationship between predictor variables when age was included needs to be examined further to understand the potential benefits of earlier treatment for later outcomes (Towle et al., 2020).

1.6.2 Focused and comprehensive interventions – child outcomes

Many studies have documented clear benefits of specialized intervention methods and programs in enhancing the development of young autistic children. Several randomized controlled trials (RCTs) that were identified in a review included both focused interventions and comprehensive intervention programs. The latter were based on the Early Start Denver Model (ESDM) and Applied Behavior Analysis (ABA). The focused interventions target specific skills that have been identified as being challenging for autistic children, such as social communication and imitation. On the other hand, the comprehensive approaches teach several skills simultaneously and often measure progress in general functioning, using tests for cognitive ability and adaptive behavior. In all studies, outcomes improved significantly for the treatment groups relative to the comparison groups, with large to moderate effect sizes for specific skills (Zwaigenbaum et al., 2015a). More recent reviews have reported similar benefits. Thus, a meta-analysis of social and communication interventions for autistic children (mean age $\leq$43 months) showed a medium effect size for imitation, joint-attention, and play (Bejarano-Martín et al., 2020a). Also, a meta-analysis of comprehensive interventions found that children receiving early intensive ABA intervention showed larger improvement in cognitive ability and adaptive behavior after 2 years compared to children receiving eclectic interventions, often referred to as treatment as usual (Rodgers et al., 2021). Furthermore, a meta-analysis examining the effects of the ESDM reported that children receiving that intervention showed moderate and significantly greater improvements in cognition and language compared to children in a control group who received treatment as usual. However, there were nonsignificant differences between the groups for autism symptomatology and adaptive behavior (Fuller et al., 2020).

1.6.3 Parent-mediated interventions – parent and child outcomes

Based on evidence from numerous studies, the participation of parents or caregivers has been recommended as one of the key components to be included in interventions for young autistic children (Hyman et al., 2020; Landa, 2018; Zwaigenbaum et al., 2015a). Most parent-mediated interventions aim to improve parents' observations of and sensitivity to their child's communication attempts, and to be more responsive when interacting with their child to enhance communication skills and reduce autism symptoms (Oono et al., 2013; Pickles et al., 2016). These interventions are of low intensity, are non-intrusive for families, can easily be adapted to the child's natural environment, can create opportunities for generalization of skills across different contexts, and are cost-effective (Conrad et al., 2021; Lord et al., 2018).

A review and meta-analysis on RCT data of parent-mediated interventions found the strongest effect for improved patterns of parent-child interactions, including shared attention and parent synchrony to the child's communication initiations (Oono et al., 2013). Improvements in child outcomes have been indicated for language comprehension, reduction in the severity of autism characteristics (Oono et al., 2013), disruptive behavior, and hyperactivity (Tarver et al., 2019). Another meta-analysis of RCTs reported small improvements in autism symptom severity, socialization, and cognition, and trivial improvements in language communication. The authors point out that these results are likely influenced by variabilities across studies in the quality and quantity of parent training and by other methodological factors (Nevill et al., 2018). Although adaptive functioning is not a direct target of parent-mediated interventions, a recent review and meta-analysis of RCTs found a small but clinically relevant effect of parent-reporting on this outcome. Moderate and clinically relevant effect of parent-mediated intervention was also found for disruptive behavior which may be a result of improved social communication skills. A small improvement in core autism symptoms was found based on clinician ratings, but not on parent-ratings (Conrad et al., 2021).

Encouraging results were reported for the first lengthy follow-up from a large RCT of the Preschool Autism Communication Therapy (PACT), a parent-mediated communication intervention. The 12-month low intensity intervention resulted in long-term improvements in autism symptoms as measured almost 6 years later. The intervention effect was seen for both the social-communication and the restricted repetitive autism symptom domains on the Autism Diagnostic Observation Schedule (ADOS) and in parent-reported symptom measures. This positive long-term outcome strongly supports the addition of PACT to treatment as usual (Pickles et al., 2016), where both parent- and clinician/therapist-implemented intervention components are included.

Parents of autistic toddlers experience more parent-related stress than parents of developmentally delayed and typically developing toddlers (Estes et al., 2013; Hayes & Watson, 2013). Taking on the additional role of implementing evidence-based intervention strategies with their child has the potential to further increase their stress level and needs to be taken into consideration when working with parents. No significant reduction in parent stress was demonstrated in a meta-analysis of RCT parent-mediated interventions (Oono et al., 2013). However, another more recent meta-analysis found a small effect of behavioral parent interventions on parental stress, even though parental well-being was not a direct target of the interventions (Tarver et al., 2019).

The participation of parents in their child's early intervention also has the potential to increase their sense of competence and confidence in the upbringing of their child. Indications about what factors may optimize this come from a study showing an interaction between parental stress at baseline, intervention intensity, and parent sense of efficacy. Parents with higher stress at the beginning of a 1-year low intensity home-based comprehensive intervention program later reported a higher sense of parenting efficacy than parents with lower stress initially who had children in a high intensity program (Estes et al., 2021). Increased sense of efficacy may make parents better equipped to manage the long-term demands of bringing up an autistic child, which again may influence their child's outcome. This was demonstrated in a study where parents received training by community-based therapists in learning to use evidence-based methods with their child. Therapist effectiveness in teaching the parents mediated improvements in parent-reported competence or self-efficacy at the end of a 6-month intervention period, which again was associated with improvements in short- and long-term child behavior outcomes, i.e., 12 and 18 months later (Brookman-Frazee et al., 2021).

1.6.4 Additional benefits for parents

Early detection of autism is not only advantageous for the children and for parents in learning effective strategies in interacting with their child; it also gives parents the opportunity to consult with experts about their child and to learn about autism and intervention methods, which has proved to be effective in reducing parenting stress associated with their child's characteristics (Kasari et al., 2015). Genetic counseling may also be valuable for parents of young autistic children, given the high recurrence rate for autism (Ozonoff et al., 2011) and increased rates for developmental delay in younger siblings (Charman et al., 2017b). An additional benefit of earlier detection is that it may lessen the distress experienced by many parents, leading them to be more satisfied with services compared to parents of children who are diagnosed later (Bejarano-Martín et al., 2020b; Crane et al., 2016).

1.6.5 Economic impact

It is well documented that there is a large economic impact associated with caring for autistic children, most of which is related to the provision of special education in public schools (Lavelle et al., 2014). The lifetime social cost is substantial (Cakir et al., 2020), with expenditures increasing with age (Cidav et al., 2013). However, the use of evidence-based interventions (ABA and ESDM) provided at a young age may reduce long-term costs for families and communities caring for autistic individuals (Cidav et al., 2017; Peters-Scheffer et al., 2012), although not all early

intervention programs appear to be cost-effective (Rodgers et al., 2020). Most important of all, timely evidence-based intervention can affect the long-term outcome of the child (Hyman et al., 2020) and mitigate the lifelong challenges faced by autistic individuals and their families.

1.6.6 Measures of long-term outcome and intervention goals

Historically, the optimal outcome of early behavioral intervention was that the children would become normal functioning and indistinguishable from their peers (Lovaas, 1987), to the point that they would be considered cured (Philanthropy News Digest, 2003) or to have recovered from autism (Helt et al., 2008). Studies on long-term outcomes from childhood through adolescence and adulthood have most often reported on cognitive ability, language skills, adaptive functioning, co-occurring conditions, and severity of autism symptoms. Overall outcome, derived from objective ratings of independent living, work placement, and friendships, is defined as ranging from poor or very poor to good or very good (Magiati et al., 2014). This focus has gradually shifted through the years with the addition of outcome measures such as quality of life that includes subjective well-being (van Heijst & Geurts, 2015). Moreover, subjective experiences relative to objective criteria, on which overall outcome is based, have also been included in studies that have considered the person-environment fit (Henninger & Taylor, 2013).

This shift is also an indication of a movement away from the medical model, which focuses on the individual's disability that requires intervention, and toward a social model that considers adapting the environment to meet the support needs of the individual. In the social model, disability is appraised "as a valued form of human diversity" (Hogan, 2019, p. 17). This opinion is the cornerstone of the neurodiversity movement that was initially endorsed by self-advocates whose voices have become louder over the past few years (Bottema-Beutel et al., 2021). Although the medical model and the neurodiversity paradigm reflect opposing views when it comes to intervention and support, it has been argued that both perspectives must be integrated in order to provide adequate care for autistic individuals (Bölte et al., 2021; Lai et al., 2020). In such an integrated approach, both the individual and the environmental context are targeted in collaboration among all involved parties. Three pillars of evidence-based care and support have been proposed which aim to (i) maximize the individual's potential by enhancing development and teaching skills, (ii) minimize barriers that obstruct the individual's development and adaptation, and (iii) optimize the person-environment fit by making necessary environmental adjustments. The overall long-term goal of this integrated approach is to improve adaptation and well-being and to reduce distress and disability (Lai et al., 2020). Most importantly, outcome measures should be defined in collaboration with autistic individuals to the extent possible and with their caregivers.

1.7 Developmental surveillance and broadband screening

Developmental surveillance is the strategy used by most primary care providers to monitor children's health and development and to detect possible neurodevelopmental disabilities (Rydz et al., 2005). Developmental surveillance refers to a flexible continuous longitudinal process aimed at detecting and addressing behavioral and developmental concerns, whereby primary care providers directly observe the children, elicit concerns from parents, obtain a developmental history, and identify potential developmental risk or protective factors (Delahunty, 2015; Dworkin, 1993). Conducting developmental surveillance efficiently within primary healthcare can be challenging for several reasons. Among them is time-constraint during well-child visits, infrequent attendance by some children who may be seen by different clinicians at different times, and inadequate knowledge, experience, and training of clinicians, which may compromise their skills in early detection of developmental delays (Rydz et al., 2005). Indeed, there are indications that developmental surveillance alone is not very effective in detecting suspicion of developmental delays that need further assessment (Guevara et al., 2013; Rydz et al., 2005; Sheldrick et al., 2011). Studies have shown that healthcare professionals using their clinical judgement during brief observations have missed high rates of children subsequently diagnosed as autistic (Gabrielsen et al., 2015; Miller et al., 2011; Robins, 2008; Robins et al., 2014).

The use of a standardized developmental screening instrument, as a supplement to the developmental surveillance, has greatly improved the detection of developmental delays (Guevara et al., 2013; Rydz et al., 2005). These developmental screening instruments are usually broadband, and many have a high sensitivity, meaning that they can correctly detect most young children with developmental delays (Macy, 2012; Zwaigenbaum et al., 2019). However, a positive screen does not distinguish autistic children from children with other developmental delays. An additional consideration is that many of the broadband screeners miss delays in social and communicative development that are important for the early detection of autism (Glascoe et al., 2007; Kerub et al., 2020; Mozolic-Staunton et al., 2020; Pinto-Martin et al., 2008; Wiggins et al., 2014). However, one broadband screener, the Infant Toddler Checklist (ITC), which focuses on communication delays, detected most young children in a general population sample who later received an autism diagnosis. As is the case with other broadband screeners, a positive screening result on the ITC did not distinguish between autistic children and children with other communication delays (Wetherby et al., 2008). Therefore, adding an autism-specific screening instrument has been suggested to improve the accuracy of the developmental surveillance and broadband developmental screening process in detecting autistic children (Glascoe et al., 2007; Hardy et al., 2015; Wetherby et al., 2008).

1.8 Screening for autism in primary healthcare

1.8.1 Two screening models

Screening for autism in primary healthcare usually includes the administration of a brief parent-rated questionnaire at predetermined ages to identify children who need further assessment (Lord et al., 2022), but observational or interactive components are sometimes included as well (Baron-Cohen et al., 1992; Nygren et al., 2012b). There are two main screening models for early detection of autism that have been used in conjunction with developmental surveillance. The first model involves a two-level screening approach using a broadband developmental screener followed up with an autism-specific screener for children who raise concerns or who have known risk factors such as a positive family history. The second model is population-based, where the intention is to screen all children at specific ages with both a broadband screener and an autism-specific screener (usually simultaneously) regardless of concerns or risk status (Johnson et al., 2007; Mozolic-Staunton et al., 2020). Both approaches have been implemented and studied for feasibility and efficacy. In this section, the focus will be on the second model, i.e., population screening for autism, since it was the subject of Studies II-IV that comprise this thesis.

1.8.2 Screening instruments

Many autism-specific screening instruments have been developed for population screening in primary care. These are termed level 1 screeners as opposed to level 2 screeners, the latter of which are intended for children with suspicion of developmental delays or other risk factors and take more time to administer and interpret than the former (Barton et al., 2012). Some general requirements when choosing a level 1 screener are that the administration and scoring is brief and they are low cost, accepted by the users, and easily integrated into the daily practice (Salgado-Cacho et al., 2021). Moreover, the instruments must meet acceptable psychometric standards. Several metrics are used for that purpose. Sensitivity indicates the proportion of individuals with the condition who screen positive, and specificity indicates the proportion of individuals without the condition who screen negative. An acceptable sensitivity of developmental screening instruments has been estimated to be 0.70 or higher, while an acceptable specificity has been estimated to be closer to 0.80 (Glascoe, 2005). Other important metrics are predictive values. Positive predictive value (PPV) represents the proportion of individuals with a positive screen result who have the condition, and negative predictive value (NPV) represents the proportion of individuals with a negative screen result who do not have the condition (Eusebi, 2013).

The first screening instrument to prospectively detect autism at 18 months, the Checklist for Autism in Toddlers (CHAT), was developed 30 years ago. The CHAT contains both a parent-completed yes/no questionnaire on the child's communication, joint attention, and play, and items for clinician observation (Baron-Cohen et al., 1992). In a 6-year follow-up study of children from the general population who were screened at 18 months, the specificity of the CHAT was high (0.98), but the sensitivity was low (0.38), indicating that the instrument was not effective in detecting autistic children from the general population at this young age (Baird et al., 2000).

The Modified-CHAT (M-CHAT) was developed in 2001 to screen for autism in 16- to 30-month-old children. In this version, the clinician observation was eliminated, and the questions were increased from nine to 23 (Robins et al., 2001). Later, a brief telephone follow-up interview (M-CHAT/F) for positive screens was developed to reduce the number of false-positive cases (Kleinman et al., 2008). The accuracy of the M-CHAT in detecting autism in the general population varies, with sensitivity measures ranging from low to high depending on methodological issues, such as the study population and the extent of the follow-up of screen negative children (Levy et al., 2020; McPheeters et al., 2016; Petrocchi et al., 2020; Sánchez-García et al., 2019). A meta-regression, based on studies using the M-CHAT, showed no meaningful differences in the sensitivity and specificity between low and high proportions of males, indicating that the instrument can detect autism with similar accuracy in both males and females (Yuen et al., 2018).

The most recent revision of the instrument, the M-CHAT Revised with Follow-Up (M-CHAT-R/F) consists of 20 questions, now often referred to as the first screening stage. The second screening stage, the follow-up interview to verify question responses indicating autism, became an integral part of the revised version. It is strongly recommended for children who score in the medium risk range (a total score of 3-7) but can be bypassed for those with a higher score. Compared with the earlier version of the instrument, the M-CHAT-R/F has demonstrated improvements in detecting autistic children in low-risk samples, also referred to as unselected samples. These improvements were achieved by a significant reduction in the screen-positive rate in the first screening stage as well as an increase in the rate of detection of autism (Robins et al., 2014). The M-CHAT, with its subsequent revisions, is the most widely used and studied screening instrument for autism. It has been translated to over 50 languages, including Icelandic (https://mchatscreen.com), along with some cultural adaptations (Soto et al., 2015), and studied in many countries (Levy et al., 2020).

The initial large-scale validation study of the M-CHAT-R/F in the US reported good sensitivity (0.85) and specificity (0.99). PPV for autism was 0.48 and 0.95 for any developmental disability (Robins et al., 2014). Some subsequent validation studies of the M-CHAT-R/F in unselected samples in other countries have reported acceptable sensitivity and specificity (Guo et al., 2019; Magán-Maganto et al., 2020; Windiani et al., 2016), although there are also examples of specificity (Oner & Munir, 2020) and sensitivity below the acceptable level (Sangare et al., 2019). PPVs ranged from 0.26 to 1.00 (Guo et al., 2019; Magán-Maganto et al., 2020; Oner & Munir, 2020; Sangare et al., 2019; Windiani et al., 2016). PPV is largely dependent on the prevalence of the condition, which may provide some explanation for the differences in this value when the same instrument is used across settings and contexts (Levy et al., 2020; Yuen et al., 2018).

Among limitations of most screening studies is insufficient follow-up and assessment of screen-negative children to identify those with autism (false-negatives) (Levy et al., 2020; McPheeters et al., 2016), leading to an overestimation of the sensitivity. Two of the above studies of the M-CHAT-R/F did not provide information about assessment or follow-up of screen-negative children (Sangare et al., 2019; Windiani et al., 2016). The other studies used different methods to detect possible false-negative cases from among a subset of their samples while acknowledging limitations with their approaches (Guo et al., 2019; Magán-Maganto et al., 2020; Oner & Munir, 2020; Robins et al., 2014).

Validation studies of the M-CHAT and the M-CHAT/F in the general population with a systematic follow-up of their participants for many years have reported low sensitives as with the CHAT, or in the range of 0.33-0.39 (Carbone et al., 2020; Guthrie et al., 2019; Stenberg et al., 2014). This evidence suggests that population screening with the M-CHAT misses most young autistic children and is thus not as effective as initially thought for early detection of the condition. It should be noted, however, that the M-CHAT generally performs better for children with pre-existing concerns or risk factors (Yuen et al., 2018). It remains to establish the true sensitivity of the M-CHAT-R/F by long-term follow-up of a screen population, but it is not clear if the accuracy is comparable between versions of the instrument.

There are indications that accuracy measures for the M-CHAT change in relation to the child's age at screening. A meta-analysis of the M-CHAT (with and without the follow-up interview), including studies with both high- and low-risk populations, found that the sensitivity was higher when screening was performed at 30 months compared to 24 months (Yuen et al., 2018). Similarly, a total population study using the M-CHAT/F observed that screenings at older ages (21-26 months) were more sensitive (0.49) than at younger ages (16-20 months; 0.35) (Guthrie et al., 2019). A

different trend was observed in a Spanish study where the sensitivity was higher in a group of 14-22-month-old children (0.82), compared to 23-36-month-olds (0.75). The difference between the age groups was not significant, but the authors point out that it may be larger because of insufficient methods to detect false-negative cases in the older group. The M-CHAT-R/F was used in the study, and the authors speculate whether the improved accuracy in detecting autism in young children, compared to previous versions of the instrument, might be due to improvements in the revised questionnaire and the scoring method (Magán-Maganto et al., 2020).

Recent reviews have identified almost 30 autism screening instruments for children under 3 years (Petrocchi et al., 2020; Salgado-Cacho et al., 2021; Sobieski et al., 2022). Since the M-CHAT-R/F was used in the present project, it is given most attention here. Among the many other level 1 autism screening instruments, some have been identified as promising in reviews (Petrocchi et al., 2020; Salgado-Cacho et al., 2021). Screening instruments for children under 24 months that met the *Consensus-based standards for the selection of health measurement instruments* were the M-CHAT, First Year Inventory (FYI) designed to identify 12-month-old children with an increased likelihood of developing autism, and Quantitative Checklist for Autism in Toddler (Q-CHAT) designed for 18-24-month-olds. Although these instruments were considered promising, psychometric properties for the FYI have not been studied in unselected populations, and measurement properties need to be improved for the other instruments (Petrocchi et al., 2020). New versions of the Q-CHAT have been developed and tested, i.e., Q-CHAT-10, and more recently the Q-CHAT-10-O, where an ordinal scoring of items is used instead of the frequently used dichotomous yes/no responses. The ordinal scoring method may better capture the emergence of autism symptoms when screening children around 18 months of age as demonstrated in a study showing a higher sensitivity for the Q-CHAT-10-O (0.63) than the M-CHAT-R/F (0.36). The specificity was lower for the former (0.79) than the latter (0.89), but PPV was similar, i.e., 0.35 and 0.36 respectively. An additional benefit of the Q-CHAT-10 is that it has only half of the items included in the M-CHAT-R/F and does not require a follow-up interview, which has important practical implications for use in primary healthcare. However, the authors note that future studies might identify follow-up questions to improve the low PPV for this young population (Sturner et al., 2022).

While the results of screening instruments provide important information and can assist in the early detection of autism, it has been emphasized that they should not be used in isolation before deciding to refer a child to specialized diagnostic assessment, but rather in combination with other information including not only clinical judgement but also other tests and parental concerns (Charman et al., 2016).

1.8.3 Population screening – feasibility and barriers

Studies have demonstrated the feasibility of screening in unselected populations, with high participation rates, in both public and private primary care practices (Garcia-Primo et al., 2014; Gura et al., 2011; Guthrie et al., 2019). However, its implementation and practice face many challenges, as indicated by studies showing that where guidelines or policies for autism screening exist, they are not fully complied with (Arunyanart et al., 2012; Snijder et al., 2021). There can be many reasons for noncompliance that are related to professional, practical, and organizational factors, and their interactions.

Among barriers to autism screening in the healthcare system that have often been identified in surveys are the following: unfamiliarity with screening instruments, lack of knowledge about early signs of autism, lack of time, disruption of workflow, and lack of access to specialized services for children identified through the screening process (Zwaigenbaum et al., 2015b). In-depth interviews with primary care providers in the Netherlands confirmed the above challenges and identified additional professional barriers to screening for autism, including doubts about the importance of early detection, hesitation in discussing initial concerns with parents, and cultural and language differences (Snijder et al., 2021). In line with this last point, a US-based study found that cultural and economic differences impacted adherence to autism screening, where minority children from poor families were less likely to be screened for autism than other children (Arunyanart et al., 2012). Additionally, parental literacy level and compliance with attending well-child visits (Siller et al., 2013) and following through with the screening and assessment stages (Levy et al., 2020) have been identified as barriers that need to be addressed in relation to screening.

Implementation of screening with an autism-specific screening instrument has addressed some of the above barriers by securing organizational support, including training clinicians in the use of the instrument selected, providing education on the early signs of autism, clarifying referral protocols, and securing access to diagnostic assessment (Barbaro & Dissanayake, 2010; Canal-Bedia et al., 2011; Pierce et al., 2021). Moreover, a web-based screener with automated scoring has improved adherence to screening guidelines (Steinman et al., 2021).

1.8.4 Different recommendations on population screening

Guidelines and policies on screening for autism issued by organizations and institutions reflect different opinions. In 2007, the American Academy of Pediatrics (AAP) recommended that all children be screened for autism with a standardized autism-specific screening instrument at the 18- and 24- months well-child visits

(Johnson et al., 2007). This guidance has since been reaffirmed (Hyman et al., 2020). On the other hand, the US Preventive Services Task Force (USPSTF) concluded in its report on autism screening, "that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in children aged 18 to 30 months for whom no concerns of ASD have been raised" (Siu, et al., 2016, p. 692). Similarly, the Canadian Task Force on Preventive Healthcare recommends against population-based screening for developmental delays (including autism) in 1-4-year-old children who have no developmental concerns, because of low-quality evidence for a clinically meaningful benefit (Tonelli et al., 2016).

Different recommendations and practices on screening can also be found in Europe, while most countries, including Iceland, do not have a policy on autism screening (ASDEU Consortium, 2018). Following a screening study in Gothenburg in Sweden, screening for autism in children at 30 months of age became routine practice at all child health centers (Nygren et al., 2012b). In Spain, population screening for autism at 18 and 24 months is a part of routine practice in two provinces, also because of a successful screening study (García-Primo, et al., 2014). However, PrevInfad, a working group of pediatricians in Spain, did not find sufficient evidence to recommend population screening for autism (Jullien, 2021). Similarly, in the United Kingdom, a population screening program for autism for children under 5 years of age is not recommended (Exeter Test Group, 2023), and national guidelines in the Netherlands recommend a two-level screening approach (Snijder et al., 2021).

Contrasting views on screening for autism have given rise to debates in the clinical community (see 1.8.5), sharpened research priorities related to screening, and encouraged research to help to close the knowledge gaps on the various aspects of this subject (Hickey et al., 2020; McPheeters et al., 2016; Zwaigenbaum et al., 2015b). However, there is a lack of consensus on the evidence required to recommend screening for autism as a part of regular practice (Zwaigenbaum & Penner, 2018).

1.8.5 What is the evidence for and against population screening?

1.8.5.1 Screening may lower the age of diagnosis

A review on evidence for the AAP recommendation supported the usefulness of autism-specific screening at 18 and 24 months (Zwaigenbaum et al., 2015b). Although screening rates following the recommendation vary among primary care physicians in the US, compliance with the guidelines has increased over the years.

Thus, a screening rate of 28% was reported in a 2009 study (Gillis, 2009), whereas a later study found that a total of 60% of physicians screened for autism at the 18-month visit and 50% at the 24-month visit (Arunyanart et al., 2012). It has been suggested that this increased screening activity has contributed to a decrease in the age of diagnosis in the US (Sobieski et al., 2022; Zuckerman et al., 2021). Supporting that view is data from epidemiological samples showing an increase in the percentage of autistic children diagnosed by age 4 years, or from 58% in 2014 to 71% in 2016, also reflected in a higher cumulative incidence of autism diagnoses in the younger group (Shaw et al., 2020). Most likely, other early detection activities besides screening have contributed to this change in age at diagnosis, such as increased awareness and knowledge of autism among both parents and clinicians (Daniels et al., 2014; Siller et al., 2013).

More direct evidence on the efficacy of screening for the early detection of autism comes from various studies where screening was integrated into routine well-child visits and the outcome was compared with that of the usual procedure. A large-scale study in the US including toddlers that were screened with the M-CHAT-R/F during their 18- and 24-month well-child visits, found that the participants were diagnosed 2 years younger compared with the most recent surveillance findings at that time (Robins et al., 2014). A Swedish study, where screening at age 30 months was implemented in all primary care centers in Gothenburg using the M-CHAT and a five-item interactive observation, reported a large increase in the proportion of children diagnosed by that age compared to the practices used previously. Thus, the prevalence for autism in this young population in the study area ranged from 0.04% to 0.18% in the years before screening and increased to 0.80% after the screening was introduced (Nygren et al., 2012a), although a time-trend effect cannot be excluded. The largest screening study to date in China, where children were screened with the Chinese version of the CHAT/M-CHAT during the 18- and 24-months well-child visits, found that the age at autism diagnosis was 14 months lower in the study district compared with other districts during the same period (Li et al., 2018). Additionally, screening may not only lower the age of diagnosis; it also has the potential to reduce social inequalities in age at diagnosis and access to services (Coury, 2015; Dawson, 2016; Fein, 2016; Mandell & Mandy, 2015; Robins et al., 2016).

While the above studies suggest that screening contributes to lowering the age at autism diagnosis, none of them used a RCT, which is the scientific basis to find out whether autism is in fact detected earlier in a group offered screening than in a control group receiving usual care (Raffle & Gray, 2007).

1.8.5.2 Limited accuracy of screening instruments

The success of a screening program depends largely on the accuracy of the selected screening instrument in identifying children at increased likelihood for autism in the targeted age group. One of the arguments of those who do not recommend population screening for autism is on the limited accuracy of current screening instruments (Al-Qabandi et al., 2011; Allaby & Sharma, 2011; Siu et al., 2016). However, the M-CHAT is mentioned as a promising tool in earlier reports (Al-Qabandi et al., 2011; Allaby & Sharma, 2011), and more recently, the USPSTF found the strongest evidence for the M-CHAT-F and the M-CHAT-R/F for detecting autism in children aged 18 to 30 months (Siu et al., 2016).

While an acceptable sensitivity has been found in some studies using this instrument in unselected populations, high rates of missed cases have been reported in other studies (see 1.8.2). Hence, screening with the M-CHAT or its revisions may not always be effective in detecting most young children who are later diagnosed on the autism spectrum. This highlights the need for repeated screenings for children who screen negative and the importance of using screening in conjunction with other early detection strategies. Despite limitations in screening accuracy, population screening may nevertheless benefit those children who screen positive and have earlier access to diagnostic and intervention services. Indeed, comparisons between children based on screening status showed that screen-positives were diagnosed 7-12 months earlier than false-negatives (Carbone et al., 2020; Guthrie et al., 2019), and 10 months earlier than children who were not screened (Carbone et al., 2020).

1.8.5.3 Lack of evidence on long-term outcome

Several authors have emphasized that the application of a screening instrument is not justified unless it is linked to the availability of services, i.e., diagnostic assessment and intervention for those children who screen positive, and counseling and education for their parents (Fein, 2016; Mandell & Mandy, 2015; Pierce et al., 2016). One of the main arguments against screening for autism in unselected populations is lack of studies on the outcomes of children who have been detected through screening (Allaby & Sharma, 2011; Siu et al., 2016). The USPSTF identified RCT intervention studies that reported improvements in some cognitive and language measures but questioned the applicability of the results to screened children. They assumed that children detected through the usual developmental surveillance had been included in intervention studies, but not screened children who are likely to be younger and to have milder symptoms than other autistic children (Siu et al., 2016). However, the USPSTF assumption that intervention

studies have not included screened children has been questioned (Fein, 2016; Mandell & Mandy, 2015). Arguments have also been presented that refute the assumption that children for whom no concerns have been raised and are thus likely to be detected through population screening, are less symptomatic than other autistic children (Coury, 2015; Pierce et al., 2016).

Research needs and research designs for future studies, particularly designs using RTCs, are outlined in the USPSTF report to better understand both the intermediate and long-term health outcomes of screening for autism (Siu et al., 2016). Indeed, a study using a cluster randomized clinical trial has recently been planned to include both screening for autism and high-quality treatment with long term follow-up of outcomes (McClure et al., 2021). Meanwhile, several authors have argued that when considering the balance between risks and benefits, population screening should not be withheld while research on the outcomes of screening continues to fill existing gaps (e.g., Coury et al., 2015; Pierce et al., 2016; Mandell & Mandy 2015).

1.8.5.4 Potential harms

The USPSTF described potential harms of autism screening as misclassification, labeling, and family distress associated with diagnostic assessment after a positive screening result. The USPSTF did not find any studies that directly addressed harms of screening for autism in primary care settings. Nonetheless, evidence from other studies showing a high dropout rate between the different stages in the screening process, as well as delays for diagnostic assessment, indicates that it may be hard for some families to complete the process (McPheeters et al., 2016; Siu et al., 2016).

Misclassification includes children who screen false-positive and false-negative. No screening instrument is totally accurate all the time (with 100% sensitivity and specificity), and so there will always be both false-positive and false-negative cases, and sometimes a trade-off between the two must be considered. The USPSTF points out that screening children younger than 16 months may result in more classification errors, specifically false-positives, than screening at older ages (McPheeters et al., 2016). The same applies to screening at 18 months compared to screening at 24 months and older (Zwaigenbaum et al., 2015b). However, adding a second stage to the screening by verifying parent responses to a questionnaire, like in the M-CHAT-R/F, has reduced the false-positive rate (Robins et al., 2014). Referring all screen-positive children to autism-specific services may put an unnecessary burden on some children and their parents, i.e., when the result of the screening is false-positive. This involves time-consuming assessment procedures

with autism diagnostic instruments; most parents find the diagnostic process stressful (Crane et al., 2016), and it is likely to be distressful for many children as well. A false-positive result may also cause anxiety in parents that the child is autistic, which ultimately turns out not to be the case. In these cases, a general developmental assessment would be more appropriate, and would at the same time shorten waiting lists for autism-specific assessments. A consideration for a false-negative screening outcome is that parents and clinicians alike may be given a false reassurance that the child is developing normally, understandably making them hesitant about referring the child for further evaluation, which in turn leads to delays in referrals for diagnostic assessment and intervention. However, a false-negative result does not rule out the possibility that the signs of autism were not yet clinically detectable in some of those children (Ozonoff et al., 2018). Efforts to reduce the number of false-negative cases in autism screening studies have included a combination of different tools and strategies in the screening process, such as a focused autism observation and repeated screenings (Magán-Maganto et al., 2017; Robins, 2020).

A recent qualitative study addressed the USPSTF observation about lack of evidence regarding the harms of autism screening and confirmed the potential harms described in their report. Interviews with parents and professionals engaged in screening for autism generated a taxonomy of several domains of harms they experienced personally or observed in others, i.e., psychological-, social-, financial- and physical harms. The authors point out that the results may give providers an opportunity to mitigate harms and the sources of potential harms. While their study outlined types and sources of harms as experienced by the participants, added dimensions remain to be studied. That includes researching the extent to which the reported harms can be causally attributed to the screening process, the extent of the impact that the harms may have on those involved, and whether the harms are transient or persistent (Petruccelli et al., 2022). Others have outlined direct research questions and suggested methods to address them. The key questions address not only children and their families, but also the impact that screening may have on the service system (Hickey et al., 2020). Even though the USPSTF concluded that the potential harms of screening and intervention "are no greater than small" (Siu et al., 2016, p. 695), a better understanding of this issue is nonetheless needed for preventive purposes and to help stakeholders weigh the benefits and drawbacks of screening.

1.9 Diagnostic assessment

While many promising biomarkers have been identified to measure biological processes associated with autism, even before the emergence of observable

behavioral signs, they are preliminary and need to be validated for their use in the detection of the condition (Frye et al., 2019). In the absence of diagnostic biomarkers for autism, the diagnosis is made based on the presence of behavioral features (American Psychiatric Association, 2013; World Health Organization, 2021) and requires a comprehensive collection and integration of information from various sources and across multiple contexts. Diagnostic assessment helps to arrive at a common understanding of the child's condition and needs, with the aim of providing information for intervention and service planning (Lord et al., 2022).

Many diagnostic guidelines for autism have been published to help clinicians to make high-quality diagnostic assessments. A systematic review of autism diagnostic guidelines published in English showed that the quality of the guidelines and the content of their recommendations varied. The highest-rated guidelines were from the National Institute for Health and Care Excellence (NICE) in the UK (Penner et al., 2018). Clinical guidelines for the diagnostic assessment of autism in children and adolescents were not available in Iceland during the present study but have now been published. Their content reflects some recommendations from the NICE guidelines and other high standard guidelines, as well as pathways unique in the Icelandic service system (State Diagnostic and Counseling Center, 2021).

Recently, a Lancet Commission on autism proposed a novel stepped care and personalized health model for delivering services including identification, assessment, and intervention (Lord et al., 2022). In stepped care approaches, the most effective yet least resource-intensive service is delivered first, and treatment only steps up to more intensive services if needed (Bower & Gilbody, 2005). The Commission recommends a transdiagnostic approach, where the stepped and personalized approach to assessment allows for inclusion of children with suspicion of other developmental disorders besides autism. Instead of referring children with developmental concerns to different assessment pathways, this approach allows for consideration of common overlaps between the different conditions from the beginning. The Commission provides examples of how the assessment process may be streamlined by personalizing a threshold to step up an assessment (Lord et al., 2022).

All diagnostic guidelines included in the above review recommend the use of a multidisciplinary team for diagnostic assessment. This is based on the need to assess multiple domains of functioning, including co-occurring conditions, to develop a neurodevelopmental profile of strengths and challenges that ideally requires the involvement of clinicians from several disciplines. The clinicians most often recommended in the guidelines are physicians for a medical assessment, speech language pathologists for a language assessment, and psychologists for a

cognitive assessment. A wide range of other professionals may be involved; for optional input, occupational therapists are most often mentioned for the assessment of sensory processing (Penner et al., 2018). Despite recommendations for a multidisciplinary assessment, there is little empirical evidence to support favoring such an assessment over a single experienced clinician. Indeed, some of the guidelines mention that flexibility is needed in the diagnostic approach and that in cases where an autism diagnosis is obvious, a multidisciplinary assessment may not be necessary (Penner et al., 2018). This aligns with the stepped personalized approach, where for example in obvious cases or low-resource settings, a single clinician may collect all relevant information to establish an autism diagnosis and then refer the child for additional testing or examinations as needed, resources permitting (Lord et al., 2022).

Diagnostic guidelines generally recommend the use of autism diagnostic instruments. However, their recommendations vary as to the endorsement of specific instruments or not, and the number of instruments required. The instruments most often recommended are the ADOS and the Autism Diagnostic Interview-Revised (ADI-R). Their combined use is sometimes referred to as a gold standard for the diagnosis of autism (Zwaigenbaum & Penner, 2018). The ADOS obtains information by observing and interacting with the child (Lord et al., 2002; Lord et al., 2012), and the ADI-R by interviewing caregivers about both the history and the current behavior of the child (Rutter et al., 2003). The use of both instruments requires extensive training.

A Cochrane review aiming to identify which commonly used instruments are most accurate for diagnosing autism in preschool children, assessed six instruments recommended in national guidelines. However, relevant data reported in studies were only available for the ADOS, the ADI-R, and the Childhood Autism rating Scale (CARS; Schopler et al., 1988) which combines observation of the child with information obtained from caregivers. There was substantial variation in sensitivity and specificity of all three instruments. Summary statistics showed that the ADOS was most sensitive (0.94), followed by the CARS (0.80), and the ADI-R was least sensitive (0.52). Specificity was similar (0.80-0.88) for all instruments. The findings support practices that recommend the use of diagnostic instruments as a part of a multidisciplinary practice (Randall et al., 2018). The diagnostic instruments provide standardized information that is more reliable and valid over time than informal clinician observation. Combining clinical observation of the child and information from caregivers increases both the reliability and the validity of the diagnosis. The use of at least one standardized diagnostic instrument over time also allows for assessment of changes in the behavioral presentation (Lord et al., 2022).

The diagnostic systems provide clinical specifiers or qualifiers that require assessment and considerations beyond that of the core features of autism. This helps to capture the full range of the presentation of the condition and is important for prognosis, individualization of support, and intervention planning. In ICD-11 for example, additional assessment of intellectual development and language functioning is necessary to assign qualifiers to indicate impairment in these domains relevant for the diagnostic coding. An example of a diagnostic code is the following: ASD without disorder of intellectual development and with impaired functional language. An autism diagnosis based on DSM-5 should state the presence of cognitive or language impairment or both. The diagnostic systems differ regarding other specifiers or considerations of associated conditions for the assessment and diagnosis of autism (American Psychiatric Association, 2013; World Health Organization, 2021).

The Lancet Commission recommends "that assessments focus on information that is relevant for treatment planning in collaboration with families …" (Lord et al., 2022, p. 30). Their report includes a suggestion of an assessment flow, starting with developmental surveillance, followed by a brief needs assessment in a conversation with the family, and an in-dept diagnostic assessment covering several components. For each component, a stepped and personalized assessment can be used, and examples of standardized assessment instruments are provided. The components include assessment of signs of autism, both by directly observing and interacting with the child and by gathering information from caregivers on the history and the current manifestation of the signs. Other components include the assessment or estimation of the level of verbal and non-verbal development, language functioning, and adaptive functioning in different settings. Additional components are screening for emotional and behavioral problems, and medical evaluation including physical examination and assessment of medical history. Medical evaluation may help to identify potential etiological factors and co-occurring medical conditions that call for further assessment. The diagnostic assessment concludes in a diagnostic formulation in which all available information is integrated and applied to the diagnostic criteria for ASD and their specifiers. Diagnostic criteria for co-occurring conditions are considered if relevant, and differential diagnosis is excluded (Lord et al., 2022).

The way in which the assessment results are communicated to caregivers affects their perception of the diagnostic process and subsequent collaboration with service providers (Zwaigenbaum & Penner, 2018). Numerous studies are available on parents' perceptions of the delivery of the results which also provides suggestions to professionals on how to conduct the delivery session in a respectful, sensitive, and supportive manner (Makino et al., 2021). Some guidelines also

provide detailed recommendations on communicating diagnostic assessment findings (Brian et al., 2019). Considering the rapid developmental changes in young children, the Lancet Commission strongly recommends focused follow-up assessments, with the first visit taking place within a year of the first diagnosis. The follow-up assessments create an opportunity to monitor progress and changes in service needs. They also help to identify and respond to emerging co-occurring conditions and anticipated challenges in the child's environment (Lord et al., 2022).

1.10 A public health perspective

Autism has emerged as a public health priority. This was acknowledged by WHO in a resolution adopted at the 67th World Health Assembly entitled *Comprehensive and coordinated efforts for the management of autism spectrum disorders,* which was supported by more than 60 countries. The following factors are among those that contribute to the public health impact of autism: the global increase in its prevalence; the notion that many autistic individuals remain unidentified or incorrectly identified; that the condition persists throughout the lifespan in most cases; that autistic individuals and their families face major challenges participating in society, including social stigmatization, isolation, and discrimination; that autism has a considerable emotional and economic impact on families; and that there is often poor access to appropriate support and services (World Health Organization, 2014). Key challenges and priorities for national actions have been defined (World Health Organization, 2013), and WHO has worked to strengthen national capacities to promote the optimal health and well-being of all autistic people (World Health Organization, 2022). The recognition by an international organization and governments of the urgency to improve the lives of autistic people may be addressed from a public health perspective that focuses on preventive actions. One common approach is to think of interventions to prevent undesirable health conditions on three levels, i.e., primary, secondary, and tertiary prevention (Schneider, 2017).

Intervention at a primary level aims at preventing a condition from occurring by preventing exposure to risk factors (Schneider, 2017). Although various risk factors have been identified that may contribute to increasing one's susceptibility to autism (Bölte et al., 2019; Yoon et al, 2020), current knowledge does not allow for the prevention of the condition. Even the notion of preventing autism is highly controversial. Prevention implies that the condition is undesirable and should be eliminated, which contrasts with the neurodiversity perspective that values all forms of human diversity and recognizes its potential to enrich and strengthen societies. In this view, autism is regarded as a natural variation of human existence that should

be respected and, like other minorities, be granted dignity and acceptance (den Houting, 2019; Lord et al., 2022). There are certainly controversies in the autism community regarding prevention and cure of the condition. Many parents, for example, experience grief and other difficult emotions when they learn about their child's autism, though in most cases, they eventually land at a place of acceptance (Andreica-Săndică et al., 2011). The views of the neurodiversity movement may undoubtedly help parents to embrace their child's autism and recognize its strengths and potential to live a fulfilling life, provided that the child receives appropriate support. Embracing neurodiversity may also help to teach their other family members to appreciate differences and to treat everyone with dignity and respect.

Public health interventions for autism are mainly focused on secondary and tertiary prevention. Secondary prevention seeks to identify a health condition in the earliest stages with the purpose of minimizing its severity, using screening as the method of choice (Schneider, 2017). In the field of autism, screening is often assisted by other early detection efforts, such as increasing awareness and knowledge of the condition among both clinicians and the public (Siller et al., 2013). As mentioned above, screening has helped to identify autism earlier in many children, although it has limitations (see 1.8). Screening for co-occurring conditions in autistic individuals, both as a part of diagnostic assessment and during focused-follow ups, is recommended (Lord et al., 2022). Among important prerequisites for screening is that a positive result on a screening test leads to diagnostic assessment and intervention.

Tertiary prevention seeks to minimize disability by providing appropriate care (Schneider, 2017). Impairment leads to disability, and when considering a public health action that seeks to minimize the latter for autistic individuals, an integration of a medical and a social model is desirable (se 1.6.6), with the focus on teaching functional skills that may be limited or absent, minimizing barriers, and optimizing the person-environment fit (Lai et al., 2020). The heterogeneity of autism and the diverse needs and strengths of autistic individuals call for personalized evidence-based intervention, as emphasized by the Lancet Commission. Their stepped care personalized model also considers the heterogeneity of families, cultures, and resources when planning intervention. A personalized approach emphasizes that there is no single intervention or method that works for all autistic individuals. This approach also underscores that interventions, support needs, and priorities can change over time due to their effect and to maturation (Lord et al., 2022).

Public health relies on both science and politics. The basic science of public health is epidemiology (see 1.5). This scientific discipline is crucial for policy making and

for planning service needs, but other biomedical sciences, as well as behavioral, social, and environmental sciences also provide knowledge that contributes to policy and public health (Schneider, 2017). Research on autism makes use of various scientific disciplines that help to understand the many aspects related to the condition. Considering the urgent need to improve the lives of autistic individuals and their families, the Lancet Commission suggests that priority be given to research that can have immediate and long-lasting effects in this regard (Lord et al., 2022), which echoes the research priorities identified by the autism community (Roche et al., 2021).

Public health responses to meet the complex needs of autistic individuals across the lifespan have been initiated not only by an international organization as the WHO (World Health Organization, 2013), but also by governments (Newschaffer & Curran, 2003), owing a great deal to autism organizations. For decades, these organizations, with increasing participation of self-advocates, have successfully lobbied governments in different parts of the world to pass legislations on the rights to services (Lord et al., 2022; Wallace et al., 2012).

The Icelandic government has set an ambitious public health policy with a special focus on children and young people up to 18 years of age, where preventive actions on all levels play an important role (Ministry of Welfare, 2016). In addition, several acts pertain specifically to individuals with disabilities, such as the Act on Services for Disabled People with Long-standing Support Needs, which aims to ensure that they have the best care possible to meet their specific support needs. The ultimate goal is to secure full, equal human rights for people with disabilities and to create conditions that enable them to live independently on their own terms. The services emphasize respect for human dignity, self-determination, and independence of people will disabilities. The services are personalized, i.e., based on individual needs, circumstances, wishes, and other relevant factors, such as gender, age, ethnic origin, religion, etc. The implementation of the Act is based on international agreements the Icelandic authorities have entered. In particular, Iceland has pledged to enforce by law the United Nations Convention on the Rights of Persons with Disabilities, and in the case of children and their families, the United Nations Convention on the Rights of the Child. Moreover, the authorities vow to ensure that people with disabilities and their organized interest groups can influence policy and decisions relating to their affairs (Lög um þjónustu við fatlað fólk með langvarandi stuðningsþarfir nr. 38/2018). A newly passed Act on Integration of Services for the Benefit of Children shows promise for all children, as it ranks care based on their need for services to secure their well-being (Lög um samþættingu þjónustu í þágu farsældar barna nr. 86/2021).

While the legislature provides children with developmental disabilities with the right to early intervention, many autistic children do not benefit fully from such services because there is gap between the age when they *can* be detected and the age when they *are* detected and start in intervention. Prior to the present study, no systematic early detection efforts have been undertaken in Iceland. The results may inform administrators and policy makers of whether education of well-child care clinicians and population-based screening for autism can potentially help to close the gap.

2 Aims

General aim of the study was:

To test surveillance procedures for early detection of autistic children in order to increase the possibility of offering optimal intervention.

Specific aims were addressed in the following papers:

Paper I: To describe the characteristics of children diagnosed on the autism spectrum before and after the age of 6 years, and to identify factors that influence the age of diagnosis.

Paper II: To study the implementation of an early detection program for autism within the well-child care in primary health care centers (PHCs) and to evaluate its initial results.

Paper III: To validate the Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F) on a population sample of 30-month-old children and to examine the association of screening status with age at diagnosis and with clinical measures.

Paper IV: To evaluate the rate of autism in a group invited to a screening program in comparison with the rates in two groups who received usual care.

3 Materials and methods

3.1 Setting

3.1.1 The Icelandic background

Iceland is an island of 103.000 km2 in the north Atlantic Ocean. The original population of Iceland was of Nordic and Gaelic origin. From the late 900s when Iceland was settled and up to the late 1700s, the population increased steadily to almost 50,000, but then decreased to about 40,000 from 1783 to 1786. This was mainly due to a large volcanic eruption which was followed by a famine, and smallpox (variola virus) also took its toll (Karlsson, 2013). Prior to the 1990s, there was little immigration to Iceland, but beginning in the late 20th century, Iceland has seen a rapid increase in immigration. In 2017, 10.6% of the population were first-generation immigrants. More than a third of the total immigrant population were born in Poland (Statistics Iceland, 2017). The population of Iceland at the time of the first study (January 1, 2006) was 299,891 (**Paper I**) and 338,349 around the time of the more recent studies (January 1, 2017) (**Papers II-III**). Almost two-thirds of the population live in the capital region (Statistics Iceland, n.d.b), which includes the national capital Reykjavík and five surrounding smaller municipalities. The area outside the capital region consists of rural areas, smaller towns, and villages, mostly dispersed around the coastline. The health system in Iceland is state centered with universal coverage. It is mostly publicly funded, with a partly integrated purchaser-provider relationship, i.e., a tax-based, state-run system (OECD/European Observatory on Health Systems and Policies, 2021). The country is divided into seven health districts, and healthcare centers within each district provide primary care (see Figure 1). The total number of centers in the country is now 77, of which 19 are currently in the capital area, but they were 17 at the time of the study (**Papers II-IV**) (Directorate of Health, n.d.).

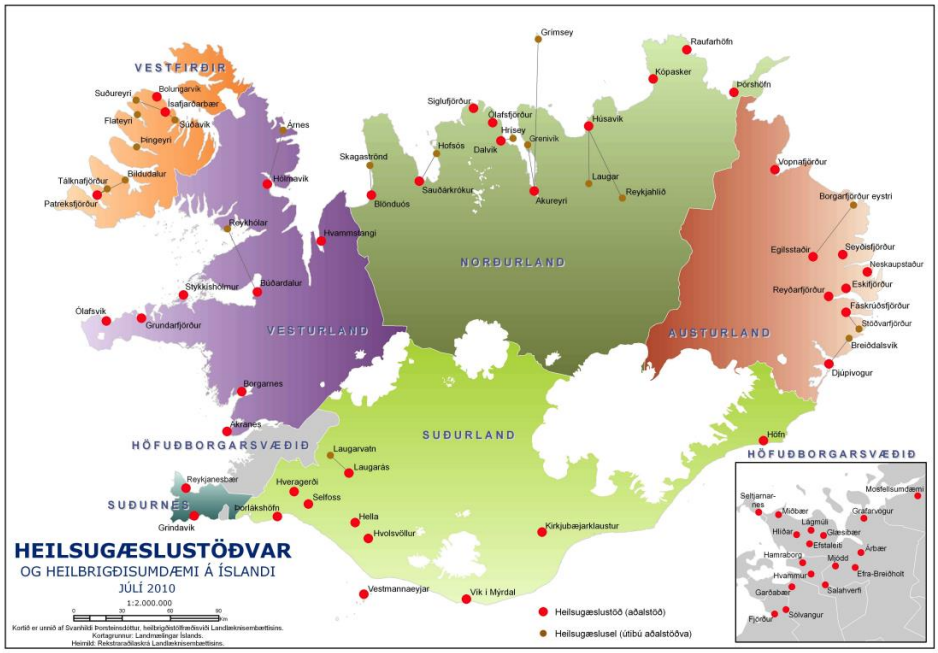

Figure 1. Healthcare centers and health districts in Iceland

Note: The figure shows a map of Iceland where health districts are identified with different colors (capital area in grey). The frame in the lower right corner shows an enlarged image of the capital area. The dots show the location of the healthcare centers (red dots for main centers and brown dots for branches) (Directorate of Health, n.d.).

3.1.2 Early detection of autism and referral to intervention

The health, well-being, and development of young children in Iceland is monitored from birth to school age by nurses and doctors at primary healthcare centers (PHCs) and includes a comprehensive vaccination program. For the first six weeks of the child's life, parents are offered home visits and then subsequently well-child visits at their neighborhood PHC. Broadband developmental screening tests assist with developmental surveillance. The PEDS is administered at child ages 12, 18, 30, and 48 months (Development Center for Primary Healthcare in Iceland, n.d.c), and the Brigance Early Preschool Screen II at child ages 30 and 48 months (Development Center for Primary Healthcare in Iceland, n.d.a). Guidelines on child health care include instructions for the well-child care clinicians to observe if red flags for autism are present at the 12, 18, 30, and 48 months visits (Development Center for Primary Healthcare in Iceland, n.d.b), but formal screening for autism has not been a part of the well-child care program in Iceland.

If developmental concerns are raised by parents or professionals at the primary level of services, which includes the well-child care as well as the preschools, the child is referred for preliminary assessment at the secondary level of services, i.e., the municipal school and service center in the child's neighborhood. Children who have not started preschool when developmental concerns are raised may be referred for preliminary assessment at the Center for Child Development and Behavior (CCDB), a secondary diagnostic institution which is a part of the primary healthcare system (**Papers II-IV**). If preliminary assessment at the secondary level indicates a neurodevelopmental condition such as autism, the child is referred for early intervention. It includes special education in a preschool setting and in most cases also services from private practitioners. These are usually speech- and language pathologists, sometimes occupational- and physiotherapists (Jónsdóttir et al., 2007), and more recently also behavior analysts. The child is also referred for diagnostic assessment at the State Diagnostic and Counseling Center (SDCC), a tertiary institution that receives referrals for suspected serious neurodevelopmental disorders in children from the whole country. Diagnostic assessment of children referred to the SDCC is provided by an interdisciplinary team. The team includes various professionals, including, at minimum, a pediatrician, a clinical child psychologist, and a social worker. An autism diagnosis is based on the results of diagnostic instruments and developmental tests combined with a physical and neurological examination, a review of developmental and medical history obtained from the child's parents by a pediatrician, an interview with parents by a social worker that includes an assessment of family circumstances and support needs, as well as a review of written reports and video clips from the child's preschool. An autism diagnosis for all cases (**Papers I-IV**) was based on the ICD-10 classification system including childhood autism (F84.0), atypical autism (F84.1), Asperger's syndrome (F.84.5), other pervasive developmental disorders (F84.8), and unspecified pervasive developmental disorder (F84.9) (World Health Oraganization,1993).

3.2 Children diagnosed before or after the age of 6 years (I)

3.2.1 Participants

The study reported in **Paper I** included all children in Iceland who were born in 1992-1995 and diagnosed on the autism spectrum before January 1, 2006 (*N* = 99). The participants were 11-14 years old by that date.

3.2.2 Procedure

Children in Iceland with suspicion of serious neurodevelopmental conditions, including autism, were referred to the SDCC during the period when the participants were diagnosed. The study was mainly registry-based, and data on the participants was retrieved retrospectively from the records of the SDCC. In addition, information was collected via a telephone interview with parents based on a questionnaire designed for the study that assessed parental evaluation of their first concerns about their child's development, and some familial and social characteristics (Mat á fyrstu áhyggjum foreldra á þroska barna sinna/ Parental evaluation of first concerns about their child's development (Appendix A)). The participants were divided into two groups, depending on whether they received their initial autism diagnosis before or after the age of 6 years. The age of 6 was chosen because at that age children in Iceland start elementary school, and the period of early intervention then fades out or terminates (**Paper I**).

3.3 The early detection program (II-IV)

The studies reported in **Papers II, III, and IV** were a part of a program on the early detection of autism. The program included education of well-child care professionals and a two-stage screening for autism using the M-CHAT-R/F during regular well-child visits at 30 months of age.

3.3.1 The population and cluster randomization

The population eligible for screening was all children in Iceland registered for their 30-month well-child visits at PHCs during the period from March 1, 2016, to October 31, 2017, a total of 7173 children. The capital area of Reykjavik was chosen for implementation of the early detection program, and cluster randomization was used with the PHC as the unit of randomization. Of the 17 PHCs in the capital area, nine were randomly selected for participation in the program, while eight provided usual care and constituted control group 1. A total of 4714 children in the target population were living in the capital area and were registered at the 17 PHCs that were randomized. Of them, 2531 children were assigned to be invited to screening, called the invited group, and 2183 children were assigned to control group 1. PHCs outside the capital area, with 2459 children registered, were without randomization and were assigned to control group 2. No child in the target population was excluded from the study, as no child had been diagnosed with autism before the start of the screening trial on March 1, 2016, according to the files of the SDCC. Thus, all children living in Iceland and registered for their 30-

month well-child visits at a PHC during the above-mentioned study period were included in the study (**Papers II-IV**).

3.3.2 Planning and implementation of the early detection program

The planning and the implementation phases for the early detection program in the PHCs were inspired by a conceptual *Model of diffusion, dissemination, and implementation of innovations in health service delivery and organization* (Greenhalgh et al., 2004). Strategies that were based on this model are shown in Figure 2. The first step was to guarantee organizational support at all administrative levels involved and to include key people in the planning and implementation of the autism screening. Thus, a steering committee, consisting of five persons who represented the PHC and the SDCC, was formed to develop and oversee the implementation of work processes for the screening. One committee member functioned as a project manager, and another one was the study's contact person with the PHC's directorate, as well as a contact person with all the participating centers. After introductory meetings at each one of the randomly selected PHCs, all agreed to participate in the study. Each center then nominated their own contact person, a nurse who would ensure that the autism screening would run smoothly and that the work processes would be adhered to. During the screening period in the PHCs, the steering committee provided ongoing support to the contact nurses and provided regular feed-back on the screening. This was accomplished both through meetings with the whole committee and through site visits and phone conversations by the committee's contact person. Dissemination of knowledge on autism was carried out at initial meetings with administrators and staff at each one of the participating PHCs, and by providing a half-day educational course for the clinicians who were in direct contact with the children and their parents. The course was offered four times during the study period and focused mainly on early signs of autism and screening. At the end of each course, the participants completed a questionnaire on pre- and post-course knowledge (Að bera kennsl á einhverfu í ung- og smábarnavernd/Detection of autism in well-child care). The questions were rated on a four-point Likert scale (1 = limited, 4 = very good) (Appendix C) **(Paper II**).

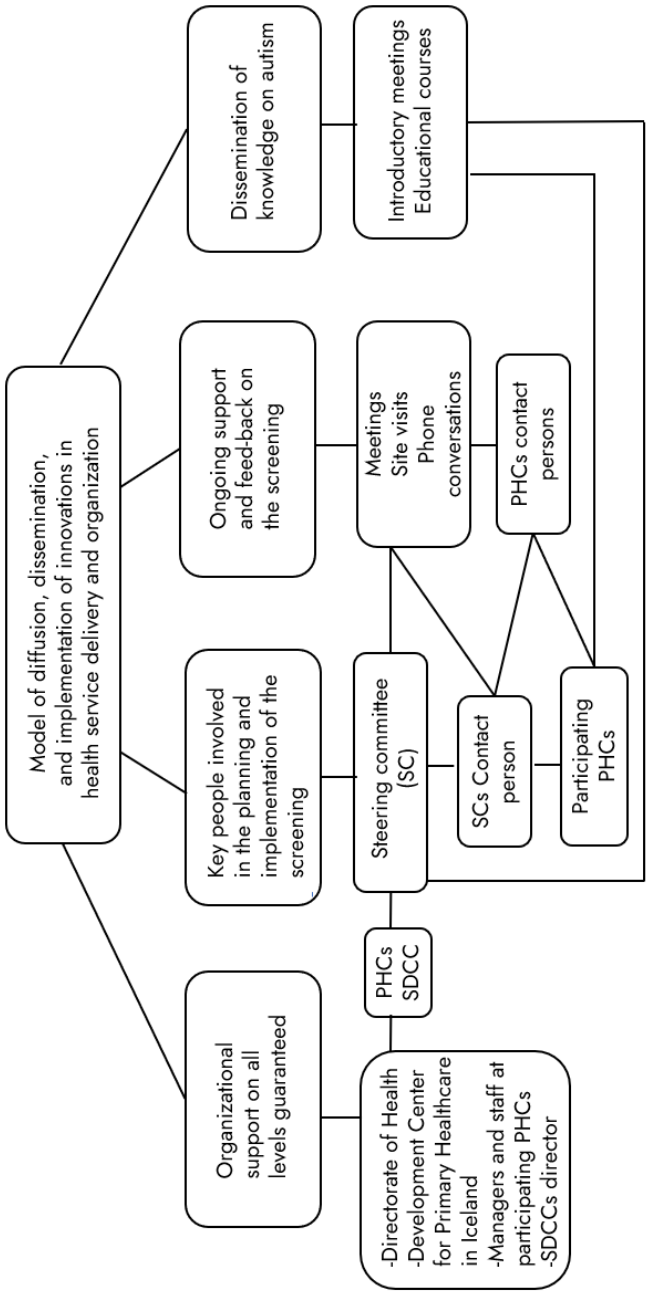

Figure 2. Planning and implementation of the early detection program in the primary healthcare centers

Note: The figure shows organizations, people, and activities included in the planning and implementation of the early detection program in the PHCs. The program was inspired by a conceptual *Model of diffusion, dissemination, and implementation of innovations in health service delivery and organization* (Greenhalgh et al., 2004).
SDCC = State Diagnostic and Counseling Center; PHC = Primary healthcare center; SC = Steering committee.

Screening in the invited group was performed with the M-CHAT-R/F. The first screening stage was integrated into routine well-child visits at 30 months of age during a 20-month period from March 2016 through October 2017. Parents were sent an introductory letter about the study prior to the visit. Those who gave their informed consent to participate in the study answered the 20-item M-CHAT-R questionnaire during the visit (the first screening stage). Completed forms were sent to the researcher (SLJ) for scoring, who also conducted follow-up interviews on the telephone (the second screening stage) with all parents of children who screened positive during the first stage (with a total score of 3 and higher). Children who continued to screen positive after the second stage (with a score of 2 and higher) were referred to the SDCC for diagnostic assessment and for early intervention provided by their local communities in a preschool environment. The PHCs clinicians were blind to the results of the M-CHAT-R/F and were asked to make their own decisions about referrals based on their own observations as usual.

At the end of the screening period, all contact persons at the PHCs answered a survey about their experience of the screening and their attitudes towards screening for autism (Könnun á reynslu og viðhorfi til skimunar fyrir einhverfu/A survey on experiences and attitudes towards screening for autism (Appendix D). Data was collected from the SDCC's database on referral sources and early intervention services received by screen-positive children before diagnosis was confirmed (**Paper II**).

3.3.3 Follow-up of children after their assumed well-child visit at age 30 months

The study used a nationwide database of children diagnosed with autism that was kept at the SDCC, to follow up with children in the Icelandic population from March 1, 2016, the beginning of the screening, to identify cases. The closing date for the follow-up was October 31, 2019, when the children were between 54 and 79 months of age. Data was also collected from this database on clinical characteristics of the children who received diagnostic assessment (**Papers III-IV**).

3.4 Instruments

The M-CHAT-R/F that was used for autism screening (**Papers II-III**) is a two-stage parent-report instrument designed to identify children who show signs of autism and need further assessment. It was originally validated in children between 16 and 30 months of age in the US (Robins et al. 2014). In the first stage, parents complete the M-CHAT-R, which includes 20 yes/no questions. The total score defines a child's risk level for autism. If a child's total score is in the low-risk range (0-2), the

child screens negative in the first stage, and no action needs to be taken. If the child's total score is in the moderate-risk range (3-7), it is recommended that the second stage, the M-CHAT-R/F, which consists of a follow-up interview, be administered. If a total score is initially in the high-risk range 8 or higher), the follow-up interview can be bypassed, and the appropriate referrals can be made immediately. The follow-up interview focuses on items that were failed, and the parent is asked to provide more detailed information and examples of behaviors related to these items. A score of 2 or higher after the follow-up interview has been completed is considered positive, and a referral for diagnostic assessment and early intervention is recommended (Robins et al., 2009). In this study, the follow-up interview was given to parents of all children with a total score of 8 or higher.

For this study, and for future use, the M-CHAT-R/F was translated into Icelandic and back-translated. Any discrepancies with the original text were resolved in discussion among the translators who also had expert knowledge of autism and neurodevelopmental disabilities. The M-CHAT-R/F was piloted on a group of 10 parents, and minor cultural adaptations pertaining to toys were made. Besides using the Icelandic version of the M-CHAT-R/F in this study, non-Icelandic speaking parents were given the questionnaire in their own language accessed from the official website for the instrument (https://mchatscreen.com/) (**Paper II**).

There were some changes in the use of diagnostic instruments over time. Parents of all the participants in **Paper I** were interviewed using the ADI-R (Rutter et al., 2003). Direct observation of behavior was based on the CARS (Schopler et al., 1988) for the oldest participants, and was then replaced with the ADOS (Lord et al., 2002). In the more recent studies (**Papers II-IV**), the ADI-R was only administered in selected cases due to limited resources. For direct observation of behavior, a revised edition of the ADOS (ADOS-2; Lord et al., 2012) was administered.

Various developmental tests were used based on availability at the time of the studies and the age and developmental level of the participants. In the first study (**Paper I**), one of the following tests was administered to the participants: the Bayley Scales of Infant Development, Second Edition (BSID-II; Bayley, 1993), the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989), or the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1992). Since Icelandic norms were not available for these tests at the time of the study, US norms were used for BSID-II and WPPSI-R and UK norms for WISC-III. In the later studies (**Papers II-IV**), the participants were either given an Icelandic translation and standardization of the WPPSI-R (WPPSI-RIS; Gudmundsson & Ólafsdóttir, 2003) or the BSID, Third Edition (BSID-III; Bayley, 2006) using US norms for that test.

3.5 Statistical analyses

Descriptive statistics summarized demographic and clinical characteristics of the participants (**Papers I-IV**), data on early intervention services, responses from the survey (**Paper II**), and the questionnaires (**Papers I-II**). Calculation of prevalence and cumulative incidence rates were based on the number of children diagnosed with autism in each of the studies (numerator) among children in the population and/or their respective target groups (denominator) with corresponding 95% confidence intervals (CIs) (**Papers I-IV**). Pearson's correlation coefficient was used to measure the bivariate correlation between work experience in well-child care and pre-course autism knowledge. A dependent *t*-test was used for comparisons between pre- and post-course ratings, and the effect size *r* was calculated (**Paper II**).

Several tests were used to compare groups. When assumptions for normality and homogeneity of variance were met for continuous variables, an independent *t*-test was used to analyze the difference between the means of two groups (**Paper I**). When assumptions for normality were not met, non-parametric tests were used to determine whether there were differences between groups. Hence, the Mann-Whitney *U* test was conducted to test differences in early intervention services between children diagnosed with autism and children not diagnosed with autism (**Paper II**). The non-parametric equivalent of the ANOVA test, the Kruskal-Wallis *H* test, was used to examine the association of screening status with clinical measures, and findings of interest were followed-up with pairwise comparisons of the true-positive and false-negative groups using the Mann-Whitney *U* test **(Paper III**). A Pearson's chi-square test was used for categorical variables if assumptions for expected cell frequencies were met (**Paper I**). The Fisher's exact test was chosen when there were few observations for individual cells, i.e., when comparing the item responses on the M-CHAT-R between children with autism and all other participants in the screening, as well as between children with autism and children with other neurodevelopmental disorders. Fisher's exact test was also used when comparing the proportions of true-positive and false-negative children with verbal and performance IQs/DQs that indicated ID (**Paper III**). For comparison of the rate of autism in the invited group with the rates in the control groups, rate ratios and rate differences with corresponding 95% CIs were calculated **(Paper IV**).

Cronbach's alpha was used to examine the internal consistency of both the M-CHAT-R and the M-CHAT-R/F, where a level greater than 0.70 was considered adequate (Cortina, 1993). Univariate logistic regression was run to estimate the effect of failing an item on the M-CHAT-R on the odds of an autism diagnosis. The clinical validity of the screening instrument in terms of sensitivity, specificity,

predictive values, and likelihood ratios was calculated with the appropriate formulas for the results from the first screening stage, the results from the second screening stage, and the results from both screening stages (**Paper III**). Kaplan-Meier survival analysis was performed to compare the cumulative probability of an autism diagnosis by age for true-positive and false-negative children, and survival curves were compared with a log-rank test (**Paper III**). A significance threshold was set at 0.05 (**Papers I-III**). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 17.0 (**Paper I),** SPSS 23.0 (**Paper II**), SPSS 26.0 and R Statistical Package 4.00 (**Paper III**), and Epi Info (**Paper IV**).

3.6 Ethics and study approvals

Study I received ethical approval by the National Bioethics Committee in Iceland (VSNb2006010028/03-7). It was also reported to and approved by the Icelandic Data Protection Authority. The part of the study that involved interviewing parents about their first concerns required their informed consent. The other part of the study was registry-based and was therefore exempt from obtaining informed consent.

Ethical approval for **Studies II-IV** was granted by the National Bioethics Committee in Iceland (VSNb2015110029/03.01), the Scientific Committee of the Healthcare of the Capital Area and the University of Iceland, and the Scientific Committee at the SDCC. The study was approved by the Icelandic Data Protection Authority. Parents of children who were screened in the PHCs provided their written informed consent. Informed consent was not required from parents of the participants who did not undergo screening in the PHCs, since the study of these children was solely registry-based.

4 Results

4.1 Children diagnosed with autism before or after age 6 (I)

4.1.1 Total group

A total of 99 children in the four birth cohorts (1992-1995) were diagnosed with autism by January 1, 2006, giving an estimated prevalence of 0.54 (95% CI, 0.44, 0.65). The male-female sex ratio was 4.8:1. The mean age at autism diagnosis was 71.7 months (median 66.0; *SD* = 35.4). At the time of initial autism diagnosis, 55.6% of the children had ID (IQ/DQ <70). When most of the children in Group 1 had been reassessed after starting elementary school around age 6 to 7 years, 47.5% of the total group had ID.

4.1.2 Factors associated with age at diagnosis

Fifty-eight children (58.6%) received an autism diagnosis before age 6 (Group 1) and 41 children (41.4%) after age 6 (Group 2). Their mean age at diagnosis was 45.7 months (*SD* = 12.9), and 108.3 months *SD* = 22.1) respectively. The male-to-female ratio was nearly identical in both groups (4.8:1 vs 4.9:1). Table 1 shows that an earlier diagnosis was associated with meeting diagnostic criteria on the more severe end on the autism spectrum (childhood autism as opposed to other ASDs), a history of autistic regression, and a lower IQ/DQ and verbal status compared with a later diagnosis. Children diagnosed late were more likely to have received other developmental diagnoses prior to an autism diagnosis than children diagnosed earlier. There was no difference between the groups regarding associated medical conditions. Further comparisons between the groups included familial and social characteristics based on responses from 42 parents (Group 1: *n* = 25; Group 2: *n* = 17) on the parent questionnaire (Appendix A). Results showed that an earlier autism diagnosis was associated with having an older sibling (X^2 (1, *N* = 42) = 3.692, *p* = .055), but there were no differences between the groups on parent education (fathers: X^2 (1, *N* = 41) = 0.312, *p* = .557; mothers: X^2 (1, *N* = 41) = 0.117, *p* = .733), or family area of residence, i.e., urban or rural (X^2 (1, *N* = 99) = 0.618, *p* = .432).

Table 1. Comparison of clinical characteristics by groups diagnosed on the autism spectrum before age 6 (Group 1) and after age 6 (Group 2)

	Group 1 (*n* = 58)	**Group 2 (*n* = 41)**
	***n* (%)**	***n* (%)**
ASD diagnosis		
Childhood autism	40 (69.0)	6 (14.6) ***
Other ASDs	18 (31.0)	35 (85.4) ***
History of autistic regression	15 (26.3) [a]	1 (2.4) **
IQ/DQ <70	43 (74.1)	12 (29.3) ***
Verbal status/at least 3-word phrases at diagnosis	31 (53.4)	39 (95.0) ***
Developmental diagnosis prior to ASD diagnosis	8 (13.8)	21 (51.2) ***
Associated medical conditions	9 (15.5)	5 (12.2)

Note. ASD = autism spectrum disorder, IQ/DQ = intelligence quotient/developmental quotient.
[a] n = 57.
$^{**}p < .01$, $^{***}p \leq .001$.

4.1.3 Initial developmental concerns

An interview with 42 parents about their first concerns regarding their child's development showed that the majority (76.2%) reported having had such concerns prior to their child's third birthday. Most parents (45.2%) reported that delayed language development aroused their initial concern. Parents were usually (78.6%) the first ones to mention concerns about their child's development. However, in a majority of the cases (71.4%), professionals were the first to mention suspicion of autism. One or more of the following behaviors first evoked that suspicion: restricted and repetitive behavior (45.2%); the child's lack of interest in communicating with other children (28.6%); delayed language development (21.4%). In hindsight, 83.3% of the parents thought that their children had shown autistic behaviors at or before 2 years of age and 97.6% before 3 years of age. A comparison between the groups showed that there was not a statistical difference regarding age when parents first became concerned about their child's development (X^2 (2, N = 42) = 2.825, p = .244) or recollected first autistic symptoms in hindsight (X^2 (2, N = 42) = 1.232, p = .540).

4.2 Implementation of the early detection program (II)

4.2.1 Participation rate in the screening and attitudes towards the program

Of the 2531 children in the invited group who were registered at the nine PHCs for their 30-month well-child visits, 2201 (87%) attended, and the parents of 1588 children gave informed consent to participate in the study. Two children were excluded from analysis of the accuracy of the screening instrument since they had already been detected with suspicion of autism. Thus, 1586 children were eligible for that analysis, i.e., 63% of the target population and 72% of those who attended the well-child visits. Their mean age at screening during the well-child visit was 31.66 months (*SD* = 1.72), males were 50.5%, and 92.6% had both parents who were of Icelandic origin.

Of the 613 parents from whom informed consent was not available, 60 (2.7%) declined to participate, and the rest failed to receive an invitation to the study. The reason most often mentioned when parents refused to participate, was that they did not see the need to screen their child for autism or other developmental disabilities. All parents of children who initially screened positive on the M-CHAT-R (*n* = 63) agreed to participate in the follow-up interview, and all parents of children who continued to screen positive (*n* = 26) agreed to have their child referred to early intervention and diagnostic assessment. No parent made use of the offer to consult a psychologist because of emotional stress related to participation in the study.

A positive attitude towards the early detection program among healthcare administrators at all organizational levels within the PHC as well as administrators at the diagnostic institutions (CCDB and SDCC), was reflected in their support during the planning and implementation phases. Accordingly, administrators at all nine PHCs that had been randomly selected for participation in the program, confirmed their participation after an introductory meeting with them and their staff.

The participation rate in the screening ranged from 52% to 95% between the nine PHCs. The main reasons for missed screening opportunities expressed at meetings with the contact nurses were a failure to send out invitations and consent forms to parents to participate in the study or to follow-up on the screening during the visit. This negligence was related to insufficient communication within some of the centers.

Ten nurses, who were contact persons at their respective PHCs (two came from the same center), answered the survey about their experience with the screening program and attitudes toward screening for autism. The nurses all expressed

positive experiences with the program, as reflected both in their survey responses and in a discussion session at a final evaluation meeting. Their responses, which were rated on a five-point Likert scale, showed that it was easy to integrate autism screening into the scheduled visit (4.50, *SD* = 0.53), that parents were generally willing to answer the screener (4.90, *SD* = 0.32), and that parents did so without assistance (4.70, *SD* = 0.48). The nurses expressed a positive attitude towards the adoption of population-based screening for autism (4.80, *SD* = 0.42), and there was an interest in doing so at both the 18- and 30-month visits.

4.2.2 Educational course for well-child care clinicians

Fifty-six well-child care clinicians from the participating PHCs attended the educational course, or over 90% of the target group. Their work experience in primary care ranged from within one month to 38 years (*M* = 11.05, *SD* = 9.40). The majority (*n* = 44), or 78.6%, reported that they had not received any previous education on autism. Of those who had (*n* = 12), more than half (*n* = 7) had attended a single lecture. The others (*n* = 5) had attended courses on autism, and two of those reported having done so mainly because there was an autistic child in the family. There was a non-significant relationship between length of work experience in primary care and retrospective pre-course autism knowledge (*r* = .12, *p* = .401, two tailed). Table 2 shows the results of pre- and post-self-assessments which indicated that participation in the course contributed to increased self-perceived knowledge and confidence in identifying behaviors indicating autism.

Table 2. Pre- and post-course self assessment scores of well-child care workers (N = 56).

	Pre-course	Post-course		
Questions and statements [a]	**Mean (*SD*)**	**Mean (*SD*)**	***t***	***r***
Knowledge of autism [b]	2.13 (0.47)	3.11 (0.33)	-20.87***	0.94
Confidence and skill in identifying indications of autism	2.12 (0.51)	3.16 (0.69)	-11.53***	0.85
Usefulness of the course for daily work		3.63 (0.52)		
Overall satisfaction with the course		3.65 (0.52)		

Note. [a] 1 = limited, 4 = very good.

[b] A summary of responses to eight questions.

***$p \leq 0.001$.

4.2.3 Screen positive children

4.2.3.1 Screening outcome

As shown in Figure 3, 63 (4%) of the 1586 participants screened positive after the first screening stage, and 26 (1.6%) after the follow-up interview, the second screening stage. Twenty-five of the children who screened positive completed diagnostic assessment, but one child moved abroad with his family before assessment. Eighteen of the screen-positive children were diagnosed with autism (true-positives), 12 boys and four girls. Seven of the screen-positive children did not receive an autism diagnosis (false-positives), of whom six children were diagnosed with other neurodevelopmental disorders and one child did not meet criteria for a clinical diagnosis. The PPV of the M-CHAT-R/F was 0.72 for autism and 0.96 for any developmental disorder. The mean time from screening in the PHC to diagnosis for the screen-positive children was 18.28 months (*SD* = 2.72).

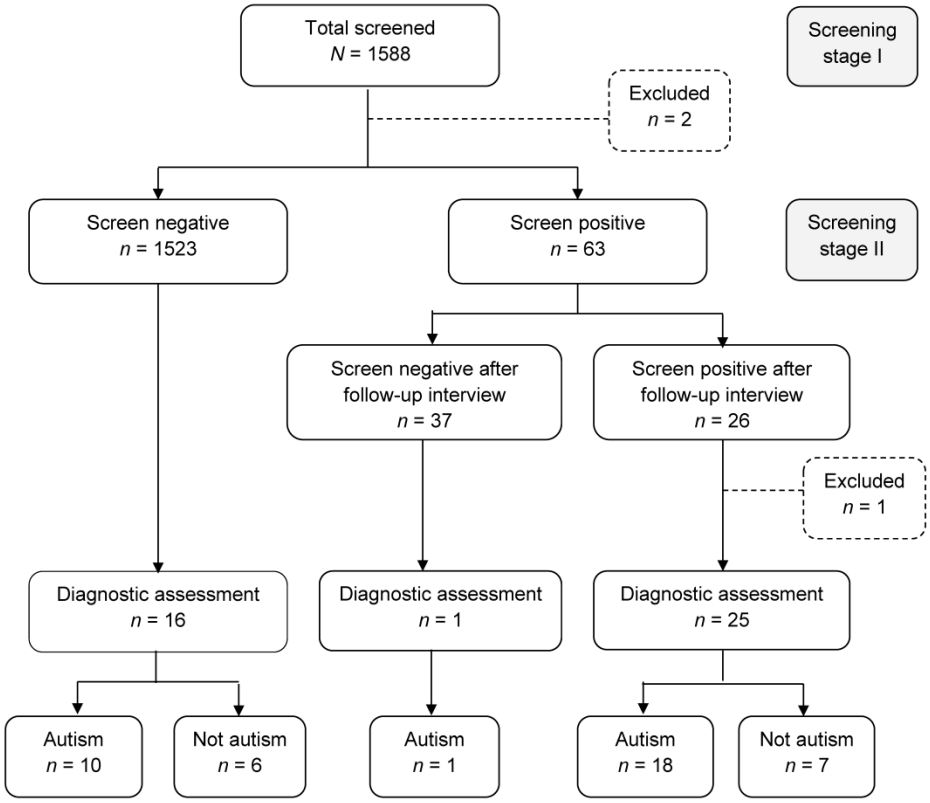

Figure 3. Flowchart of the screening and diagnostic assessment results

Note: The flowchart shows the outcome of the two-stage screening with the Modified Checklist for Autism in Toddlers, Revised with Follow-Up, and diagnostic results for screen positive and screen negative children who were referred for assessment.

4.2.3.2 Sources of referrals

Table 3 shows sources of referrals based on diagnostic outcome for the 25 children who screened positive on the M-CHAT-R/F and received assessment. All of these children were referred by the study, and a total of 14 children were also detected with suspicion of autism by the well-child care clinicians or the preschool services and referred for assessment, independent of the screening. Of the 11 children who were only referred by the study, eight were diagnosed with autism, two with non-autistic neurodevelopmental disorders, and one child did not receive a clinical diagnosis.

Table 3. Referral sources for screen-positive children who received diagnostic assessment and their diagnostic outcome (n = 25)

	Diagnostic outcome (n)			
Referrers	**Autism**	**Other diagnosis**	**No clinical diagnosis**	**Total**
Study	8	2	1	11
Study and PHC	3	3		6
Study and preschools	7	1		8

Note. PHC = primary healthcare center.

4.2.3.3 Early intervention before diagnostic assessment

At the time of screening in the PHC, all screen-positive children attended preschool for eight to nine hours per day. The mean time that passed from screening in the PHC and until early intervention started was 3.56 months (SD = 4.00). The intervention consisted of special education in the preschool, where two thirds of the children were in an autism-specific comprehensive program based on ABA (n = 8) or the Structured teaching/TEACCH® program (n = 8). The average number of hours in special education per week was 21.67 (SD = 8.36). Twelve children received additional services from private practitioners, most often consisting of speech and language therapy (n = 9). Parents of 11 children attended courses on autism and teaching methods. A comparison between intervention services for children diagnosed with autism and children not diagnosed with autism can be seen in Table 4.

Table 4. Early intervention of screen-positive children before diagnostic assessment by diagnostic groups

	Autism diagnosis (*n* = 18)	**Not an autism diagnosis (*n* = 7)**	***U***
Wait time in months for early intervention, median (*SD*)	3.50 (3.60)	4.00 (5.58)	59.50 [a]
Hours of intervention per week in preschool, median (*SD*)	20.00 (7.48)	20.00 (10.58)	55.50 [a]
Comprehensive intervention			
ABA, *n* (%)	7 (38.9)	1 (14.3) [b]	
TEACCH, *n* (%)	8 (44.4)	0 [b]	
Additional intervention, *n* (%)	9 (50.0)	4 (57.1) [b]	
Parents attended courses, *n* (%)	9 (50.0)	2 (28.6) [b]	

Note. ABA = Applied Behavior Analysis; TEACCH = Treatment and Education of Autism and Related Communication Handicapped Children.
[a] $p > 0.05$.
[b] Too few participants in the group for statistical comparison.

4.3 Validation of the M-CHAT-R/F (III)

4.3.1 Follow-up of screen-negative children

During the follow-up period, 17 of the screen-negative children were identified who had been referred to diagnostic assessment,16 from the first screening stage and one from the second screening stage. Of them, 11 were diagnosed with autism (false-negatives) and six were not diagnosed with autism (true-negatives). Of the six true-negative children, five were diagnosed with other developmental disorders and one child did not receive a clinical diagnosis (Figure 3).

4.3.2 Attributes of the screening instrument

The internal consistency of the 20 items on the M-CHAT-R was inadequate (Cronbach's α = .677). In the whole sample, the items with the highest percentage of fails were two of the auditory items, i.e., item 2, wondering if the child might be deaf (9.3% fails), and item 12, child is upset by everyday noises (15.7% fails). Deleting these two items increased the internal consistency to an adequate level (Cronbach's α = .745). The internal consistency of the M-CHAT-R/F, i.e., after the follow-up interview, was good (Cronbach's α = .831).

Clinical Validity of the M-CHAT-R/F in terms of sensitivity, specificity, predictive values, and likelihood ratios for detecting autism is shown in Table 5. Calculations based on screening status for all 1585 participants gave a similar sensitivity and specificity for the first screening stage (0.66 and 0.97, respectively) and for both screening stages combined (0.62 and 0.99, respectively). When calculations were based only on the screening status of the 62 participants who entered the second screening stage and received a diagnostic assessment, the sensitivity was 0.95, and the specificity was 0.84. The PPV was 0.31 after the first screening stage and 0.72 after the second screening stage when the follow-up interview had been administered. The positive likelihood ratio (LR+), based on screening status after both screening stages, showed that a positive test result was 138 times more likely to occur in autistic children than in those who were not autistic. Sensitivity, specificity, and predictive values for any developmental disabilities were 0.60, 0.99, and 0.96 respectively.

Table 5. Sensitivity, specificity, predictive values, and likelihood ratios of the M-CHAT-R and the M-CHAT-R/F

	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	LR+	LR-
M-CHAT-R [a]	19	10	43	1513	0.66 (0.48–0.83)	0.97 (0.96–0.98)	0.31	0.99	23.71	0.35
M-CHAT-R/F [b]	18	1	7	36	0.95 (0.85–1.00)	0.84 (0.73–0.95)	0.72	0.97	5.82	0.06
M-CHAT-R/F [c]	18	11	7	1549	0.62 (0.44–0.80)	0.99 (0.99–1.00)	0.72	0.99	137.97	0.38

Note. TP = true-positive, FN = false-negative, FP = false-positive, TN = true-negative, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value, LR+ = likelihood ratio positive, LR- = likelihood ratio negative, M-CHAT-R = Modified Checklist for Autism in Toddlers, Revised, M-CHAT-R/F = Modified Checklist for Autism in Toddlers, Revised with Follow-Up.

[a] Screening status after the first screening stage.

[b] Screening status after the second screening stage.

[c] Screening status after the first and second screening stages.

The effect of failing an item on the M-CHAT-R on the odds of an autism diagnosis is shown in Table 6. The items were arranged in descending order based on their predictive power, as measured by their standardized coefficients, and based on their standard errors. All but two of the 20 items on the M-CHAT-R significantly contributed to classifying children as either autistic or not autistic. Table 6 also shows that 17 of the 20 items were more frequently failed by autistic children. The three items that were not significantly different between the groups (item 4, likes climbing (p = .131); item 12, upset by everyday noises (p = .245); and item 13, walks (p = 1.000)) were also the items that had the least predictive power for autism. There were no significant differences in any of the items between children diagnosed with autism and children diagnosed with other neurodevelopmental disorders.

Table 6. Effect of failing an item on the M-CHAT-R on the odds of an autism diagnosis arranged in descending order and failure rates of each item on the M-CHAT-R by group

Items		Coeficient	*SE*	95% CI			Autism (*n* = 29)	Not autism (*n* = 1556)	
				LL	UL	*p*	%	%	*p*
17	Gains parent's attention	3.992	.439	3.113	4.870	<.001	41.4	1.3	<.001
9	Shows things	4.398	.503	3.392	5.405	<.001	34.5	0.6	<.001
16	Follows gaze	3.434	.420	2.594	4.274	<.001	41.4	2.5	<.001
19	Social referencing	3.468	.426	2.616	4.320	<.001	37.9	1.9	<.001
14	Makes eye contact	3.784	.497	2.790	4.778	<.001	27.6	0.9	<.001
2	Wondering if child is deaf	2.889	.394	2.102	3.676	<.001	62.1	8.3	<.001
10	Responds to name	4.617	.679	3.260	5.975	<.001	20.7	0.3	<.001
1	Follows a point	3.920	.579	2.761	5.079	<.001	20.7	0.5	<.001
8	Interested in other children	3.646	.551	2.543	4.748	<.001	20.7	0.7	<.001
7	Points to show	2.997	.456	2.086	3.909	<.001	27.6	1.9	<.001
18	Understands commands	4.254	.668	2.919	5.590	<.001	17.2	0.3	<.001
15	Imitates actions	3.433	.735	1.962	4.903	<.001	10.3	0.4	<.001
11	Responds to a smile	3.357	.888	1.582	5.132	<.001	6.9	0.3	.008
20	Likes movement activities	2.950	.839	1.272	4.629	<.001	6.9	0.4	.013
3	Pretend play	2.288	.654	.980	3.597	<.001	10.3	1.2	.006
5	Unusual finger movements	2.437	.799	.840	4.034	.002	6.9	0.6	.026
6	Points to get help	1.491	.556	.379	2.603	.007	13.8	3.5	.034
4	Likes climbing	1.285	.627	.031	2.539	.04	10.3	3.1	.131
12	Upset by everyday noises	.544	.440	-.335	1.424	.215	24.1	15.6	.245
13	Walks	-12.592	665.514	-1343.620	1318.436	.985	0	0.8	1.000

Note. M-CHAT-R = Modified Checklist for Autism in Toddlers, Revised, SE = standard error, CI = confidence interval, LL = lower limit, UL = upper limit.

4.3.3 Clinical data for children who participated in the screening

Clinical data for the children who were screened with the M-CHAT-R/F and received diagnostic assessment (n = 42) is presented in Table 7 based on their screening status. Overall, there was a significant association of screening status with age at referral (p = .000), age at diagnosis (p = .000), M-CHAT-R total score (p = .000), and ADOS-2 comparison score (p = .000), but not between age at screening (p = .061), IQ/DQ verbal score (p = .366), or IQ/DQ performance score (p = .456).

The main findings of interest were comparisons between the children who were diagnosed with autism, i.e., the true-positives (n = 18) and the false-negatives (n = 11). Pairwise comparisons between these groups showed that the true-positive children were 8 months younger at the time of referral (U = 20.00, z = −3.58, p = .000) and 10 months younger at the time of diagnosis (U = 1.00, z = −4.43, p = .000), than the false-negative children. The difference in age at diagnosis between the groups is also reflected in Kaplan-Meier survival curves that show cumulative probability of an autism diagnosis by age (Figure 4).

Table 7. Clinical data by screening status for children who were screened with the M-CHAT-R/F and received diagnostic assessment

	True-positive (*n* = 18)		False-negative (*n* = 11)		False-positive (*n* = 7)		True-negative (*n* = 6)			
	Mean	**(*SD*)**	**Mean**	**(*SD*)**	**Mean**	**(*SD*)**	**Mean**	**(*SD*)**	***H***	***p***
Age at screening (months)	32.50	(2.20)	30.64	(1.12)	31.00	(1.63)	31.50	(1.23)	7.37	.061
Age at referral (months)	33.28	(2.56)	41.00	(5.42)	32.14	(1.46)	42.67	(5.96)	22.47	.000
Age at diagnosis (months)	51.22	(2.39)	61.36	(3.75)	50.43	(1.72)	63.17	(5.35)	29.33	.000
M-CHAT-R total	6.83	(3.66)	0.82	(0.87)	5.86	(2.55)	0.83	(0.41)	29.81	.000
M-CHAT-R/F total [a]	6.00	(3.61)	1.00	-	4.29	(2.87)	-	-	-	-
ADOS-2 comparison	5.33	(2.00)	5.55	(1.70)	1.00	(0.00)	2.20	(0.84)	23.55	.000
IQ/DQ verbal	65.44	(25.34)	79.91	(25.25)	80.86	(13.89)	70.50	(13.32)	3.17	.366
IQ/DQ performance	81.00	(21.22)	92.82	(20.18)	92.57	(12.80)	84.67	(26.93)	2.61	.456

Note. M-CHAT-R = Modified Checklist for Autism in Toddlers, Revised, M-CHAT-R/F = Modified Checklist for Autism in Toddlers, Revised with Follow-up, ADOS-2 = Autism Diagnostic Schedule, Second Edition, IQ/DQ = intelligence quotient/developmental quotient.

[a] The follow-up interview was only administered to parents of one of the false-negative participants, see Fig. 3. The Mann-Whitney test indicated a non-significant difference between the true-positive group and the false-positive group, $U = 42.00$, $z = -1.282$, $p = .200$.

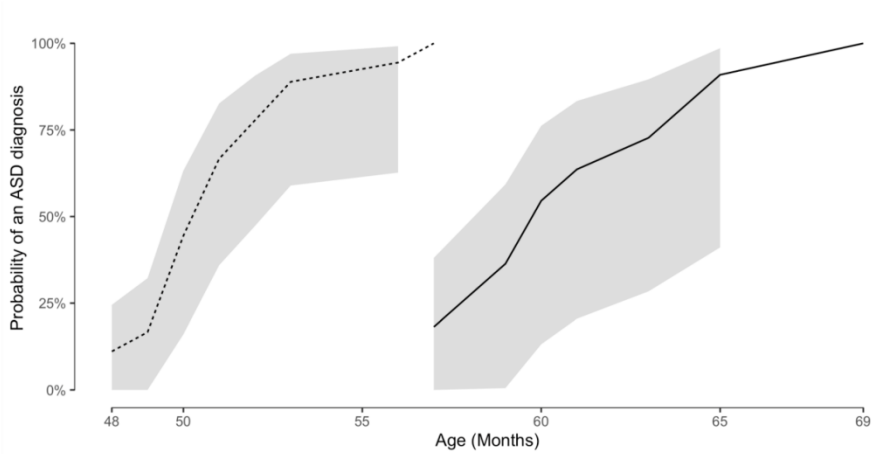

Figure 4. Kaplan-Meier survival curves for the cumulative probability of an autism diagnosis

Note: The survival curves show the cumulative probability of an autism diagnosis by age in months for true-positive (dotted line) and false-negative (continuous line) children.

At the time of diagnosis, the two groups were similar on clinical measures (Table 7). Thus, there was a nonsignificant difference between the groups on measures of autism symptoms and intellectual functioning, i.e., ADOS-2 total score (U = 94.50, z = −0.205, p = .837), verbal IQ/DQ (U = 70.5, z =−1.281, p = .200), and performance (IQ/DQ (U = 69.50, z =−1.327, p = .185). Regarding intellectual disability, similar proportions of true-positive (50%) and false-negative (45.5%) children had a verbal IQ/DQ <70 (p = 1.000). A somewhat higher proportion of true-positive children (27.8%) than false-negative children (18.2%) had a performance IQ/DQ <70, but this difference was not significant (p = .677).

4.4 Outcome in a group invited to screening compared with outcomes in two control groups (IV)

4.4.1 Total group

Of the 7173 children who were targeted to attend their 30-month-old well-child visit from March 2016 through October 2017, 119 were diagnosed with autism by the end of the follow-up period October 31, 2019. The overall cumulative incidence of autism was 1.66 (95% CI, 1.37, 1.99). The mean age of the children at referral to diagnostic assessment was 36.97 months (SD = 8.07), and the mean age at diagnosis was 55.71 months (SD = 8.21). Of the children, 98 (82.4%) were male and 21 were female (17.6%), with a male-female ratio of 4.7:1. Eighty children

(67.2%) had parents who were both of Icelandic origin, 16 children (13.5%) had one parent of Icelandic origin, and 23 children (19.3%) had both parents of non-Icelandic origin.

4.4.2 Comparison between groups

Figure 5 shows how the children in the study population and the 119 autism cases were divided to each of the three groups, i.e., the invited group, control group 1, and control group 2. Of the 54 autistic children in the invited group, about half (*n* = 29, 53%,) participated in the previous studies (**Papers II-III**) where they were screened for autism, but the remaining children in that group either did not meet inclusion criteria for screening since referrals for diagnostic assessment were already in preparation (*n* = 2) or they did not undergo screening (*n* = 23).

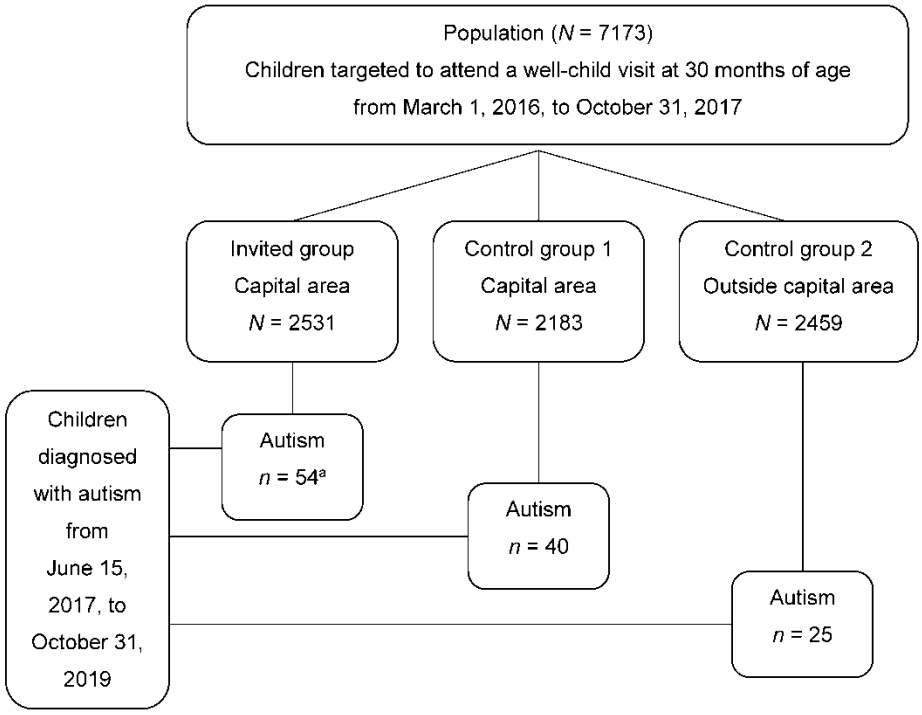

Figure 5. Children diagnosed with autism in a group invited to a screening program and in two control groups

Note: The flowchart shows the study population that included all children in Iceland who were registered at primary healthcare centers and were targeted to attend a routine well-child visit at 30 months of age from March 1, 2016, to October 31, 2017. The chart also shows the number of children in each of the study groups, i.e., the group invited to the screening

program during the above-mentioned period and the control groups who received usual care. Children in the invited group and control group 1 were registered at PHCs in the capital area of Reykjavik that were a part of the cluster randomization. Children in control group 2 were registered at PHCs that were outside the capital area and were not a part of the randomization. Finally, the chart shows the number of children in each group who were diagnosed with autism according to a nationwide autism registry, from June 15, 2017, when the first child was diagnosed and to the end of the follow-up period on October 31, 2019.
PHC = Primary healthcare center
[a] True-positive = 18, false-negative = 11, did not participate in the screening = 23, identified with concerns before screening = 2.

Table 8 shows the number of cases and the cumulative incidence of autism, with 95% CIs, for the population and the study groups. The rate was highest in the invited group and lowest in control group 2. The comparison of the rate of autism in the invited group with the rates in the combined control groups, control group 1, and control group 2, are shown in Table 9 by rate ratio, and rate difference with the corresponding 95% CIs. The rate ratio of the invited group versus the combined control groups was 1.52 (95% CI, 1.06, 2.19); the rate ratio of invited group versus control group 1 was 1.16 (95% CI, 0.77, 1.75); and the rate ratio of invited group versus control group 2 was 2.10 (95% CI, 1.31, 3.37).

Table 8. Number of cases, cumulative incidence per 100 of autism cases and 95% confidence interval (CI) in the population, the invited group, the combined c ontrol groups, control group 1, and control group 2

Population/groups	Denominator	Cases	Rate per 100	95% CI, lower/upper
Population	7173	119	1.66	1.37 to 1.99
Invited group	2531	54	2.13	1.60 to 2.78
Combined control groups	4642	65	1.40	1.08 to 1.79
Control group 1	2183	40	1.83	1.31 to 2.50
Control group 2	2459	25	1.02	0.66 to 1.50

Table 9. Comparison of the invited group with the control groups, rate ratio, 95% confidence interval (CI), rate difference, and 95% CI

Groups and combination	Rate ratio	95% CI, lower/upper	Rate difference	95% CI, lower/upper
Invited group versus combined control groups	1.52	1.06 to 2.19	0.73	0.07 to 1.40
Invited group versus control group 1	1.16	0.77 to 1.75	0.30	-0.50 to 1.11
Invited group versus control group 2	2.10	1.31 to 3.37	1.12	0.42 to 1.81

The clinical characteristics of the autism cases in the groups are shown in Table 10. The proportion of males was highest in the invited group, and lowest in control group 1. Age at referral to the SDCC for diagnostic assessment and age at diagnosis were similar in all groups.

Table 10. Clinical characteristics of autism cases in the group invited for screening and in the two control groups

	Invited group	Control group 1	Control group 2
	n = 54	*n* = 40	*n* = 25
Male, *n* (%)	47 (87.0)	31 (77.5)	20 (80.0)
Both parents of Icelandic origin, *n* (%)	39 (72.2)	21 (52.5)	20 (80.0)
Age at referral (months), *M* (*SD*)	36.15 (8.16)	37.13 (6.93)	38.52 (9.54)
Age at diagnosis (months), *M* (*SD*)	55.44 (8.27)	55.25 (7.81)	57.04 (8.90)
ADOS-2 comparison score, *M* (*SD*)	5.69 (1.56)	5.68 (1.88)	5.30 (1.87)
IQ/DQ verbal, *M* (*SD*)	66.05 (28.02)	59.11 (21.81)	62.15 (17.87)
IQ/DQ performance, *M* (*SD*)	85.29 (19.38)	79.20 (20.22)	80.56 (21.18)

Note. ADOS-2 = Autism Diagnostic Schedule, Second Edition, IQ/DQ = intelligence quotient/developmental quotient.

5 Discussion

5.1 Main findings

A high proportion of autistic children in four birth cohorts were diagnosed late (after age 6) even though most parents had developmental concerns prior to the child's third birthday, and with hindsight thought that autistic behavior had been present at or before 2 years of age. A late diagnosis was associated with meeting criteria on the less severe end of the autism spectrum, better cognitive and language status, and having previously received other neurodevelopmental diagnosis. The mean age at autism diagnosis for all participants was almost 6 years (**Paper I**). The early detection program was generally well accepted by administrators, clinicians, and parents. The majority of well-child care clinicians had not previously received education on autism. They reported increased knowledge and confidence in identifying signs of autism following their participation in the educational course. Screening with the M-CHAT-R/F detected more autistic children than the usual procedures in the invited group (**Paper II**). The screening also missed cases that resulted in a suboptimal sensitivity of the M-CHAT-R/F. Other psychometric properties of the instrument were acceptable. The screening was advantageous for the true-positive children who were diagnosed 10 months earlier than the false-negative children (**Paper III**). The invited group had a higher rate of autism than the control groups who received usual care. However, wide confidence intervals do not allow a firm conclusion that the screening detected autism more readily than the usual care (**Paper IV**).

5.2 Early and late diagnosis of autism (I)

The proportion of children diagnosed early and age at diagnosis are important findings from Study I, that can be used as an indicator of how effective the developmental surveillance and the diagnostic assessment systems are in detecting and diagnosing autism in young children. We found that a relatively high proportion (41.4%) of autistic children born 1992-1995 were not diagnosed with the condition until after age 6. It is important to note that for these children, the wait time from referral to diagnosis was insignificant. The mean/median age at initial autism diagnosis was 72/66 months, which is comparable to the age (median 67 months) found in a study based on data from the ADDM Network in the US for children born in 1994 (Shattuck et al., 2009).

Considering the time that has elapsed since these studies were conducted, one may anticipate that efforts to improve early detection of autism have contributed to reducing the age at diagnosis. Examples of such undertakings in the US are awareness campaigns such as *Learn the Signs. Act Early* (Centers for Disease Control and Prevention, 2022) and a recommendation on screening for autism in all children at 18 and 24 months (Johnson et al., 2007). Recent data from the ADDM Network indicates improvements in the detection of young children compared to the above finding, where the median age at diagnosis is now 50 months (Maenner et al., 2021). But in Iceland, there have not been any systematic early detection efforts prior to the present study (**Papers II-III**). Although increased media coverage on autism has likely resulted in greater awareness of the condition, it may not have influenced earlier detection of autism. Thus, more recent data on 7-9-year-old children shows that the age at diagnosis (mean 62 months, median 60 months) remains relatively high for children in Iceland. Moreover, only a third of the children were referred for diagnostic assessment before age 3, and a minority (10%) were diagnosed before that age (Delobel-Ayoub et al., 2020; E. Saemundsen, personal communication, June 26, 2020). These findings show that there is a critical need for improvement in the early detection of autism In Iceland to help to close the gap between the age when most of the children can be detected and the age when they are detected.

5.2.1 Factors associated with early vs late diagnosis

We compared children diagnosed with autism early (before age 6) and late (after age 6) on several variables that were accessible and that might help to understand factors that may potentially affect the age at diagnosis. Our results confirmed previous findings on certain individual characteristics that were associated with an earlier diagnosis. These included an ICD-10 diagnosis of childhood autism as opposed to other ASD diagnostic categories that usually represent milder variants of the condition (Loubersac et al., 2021; van ´t Hof et al., 2021), and a history of developmental regression (Daniels & Mandell, 2014; Shattuck et al., 2009), typically appearing before age 2 (Tan et al., 2021). Our finding that a lower language level and ID were associated with an earlier autism diagnosis added to the literature that has reported inconsistent results (Avlund et al., 2021; Daniels & Mandell, 2014; Loubersac et al., 2021; Salomone et al., 2016; Shattuck et al., 2009; van ´t Hof et al., 2021).

Our finding that a non-autism diagnosis prior to an autism diagnosis was associated with a later diagnosis is consistent with other research (Adelman & Kubiszyn, 2017; Avlund et al., 2021; Daniels & Mandell, 2014; Davidovitch et al., 2015). More than half of the later diagnosed children in our study had previously received other

neurodevelopmental diagnoses, but that pertained only to a few of the children diagnosed earlier. Previous contact with the diagnostic system and a diagnosis of specific language impairment (SLI) and ID were most common in the late diagnosed group, which shows that the presence of co-occurring conditions can present a challenge in the recognition of autism. When children have ID, differential diagnosis may be complex (Thurm et al., 2019), and there are indications that in severe ID cases, clinicians may be hesitant to give an autism diagnosis until later (Avlund et al., 2021). Autism and SLI share some common features in early social development. Some children with a clear profile of SLI in middle childhood will later develop features that are more characteristic of autism and meet criteria for that condition (Conti-Ramsden et al., 2006). In other cases, with a primary diagnosis of severe language disorders and a delayed autism diagnosis, features of autism were present at initial assessment, but did not meet diagnostic criteria or were thought to be secondary to the language disorder (Michelotti et al., 2002).

To sum up, some possible reasons for a delayed autism diagnosis for children with previous assessments may be that (1) other developmental concerns masked the symptoms of autism, (2) clinical caution was applied because of unclear symptoms or a low mental age, (3) the behavioral features of autism were overlooked by the clinicians, or (4) the symptoms of autism had not yet developed to be clinically detectable with current methods (Avlund et al., 2021; Bacon et al., 2018; Ozonoff et al., 2018). The last-mentioned point may also be relevant for the late diagnosed children who had not previously been in contact with the diagnostic system. The good cognitive and verbal status of many of these children may have overshadowed and possibly to some degree compensated for their social-communication challenges at younger ages.

Among family characteristics, we found that children diagnosed early were more likely to have an older sibling than those diagnosed late. This finding suggests that parents' experience with having an older child may have increased their sensitivity to deviations from typical development, leading to an earlier diagnosis. This is supported by research showing that parents of children later diagnosed with autism who have an older typically developing child, will be concerned at an earlier age than parents who do not have an older child, but not as early as parents who have an older child with autism (Herlihy et al., 2015). We do not know if any of the participants in our study had an older sibling with autism. That would have been informative, since studies have consistently shown that having an older sibling with autism predicts an earlier autism diagnosis for younger siblings who have the condition (Adelman & Kubiszyn, 2017; Daniels & Mandell, 2014; Loubersac et al., 2021).

There was no difference between the early and late diagnostic groups on parental education, whether it pertained to fathers or mothers. This is contrary to what most studies have found, where higher level of parental education was associated with an earlier autism diagnosis (Avlund et al., 2021; Daniels & Mandell, 2014; Rosenberg et al., 2011), although there is also an example of a study showing no effect of parental education on age at diagnosis (Salomone et al., 2016). If parental education is used as a proxy for socioeconomic status, then a review of findings on its effect on age at diagnosis reported mixed results (Daniels & Mandell, 2014), possibly reflecting different local resources.

Family area of residence was not associated with age at autism diagnosis, unlike many other studies reporting on an earlier age of diagnosis in urban areas (Lauritsen et al., 2014; Loubersac et al., 2021). However, reviews have also reported inconsistencies between studies, both regarding the relationship between urban/rural residency and age at diagnosis and between the availability of child health professionals in the area and age at diagnosis (Daniels & Mandell, 2014). This inconsistency may reflect different definitions of urbanicity/rurality, different local policies, and types of services available. The concentration of child health and educational professionals is less in the rural areas in Iceland compared to the urban area, consisting mainly of the greater capital area. In case of suspicion of serious neurodevelopmental conditions, specialists in the child's area of residency are required to make a preliminary assessment before the child is referred to diagnostic assessment which then takes place at the SDCC in the capital area. Since lack of resources in many of the rural areas and practical reasons related to travelling may lengthen the time from suspicion to referral and diagnosis for some children living in in these areas, it was unexpected to find that there was no association between residency and age at autism diagnosis. Different access to services in rural and urban areas may, however, be reflected in different rates of autism as reported in **Paper IV** (see 5.4).

5.2.2 Initial developmental concerns and recollection of early signs of autism

Our finding that most parents were concerned about their child's development at an early age is consistent with other studies (e.g., Baghdadli et al., 2003; Bejarano-Martín et al., 2020b; De Giacomo & Fombonne, 1998; Locke et al., 2020). Their early concerns were most often prompted by delayed language development, similar to other findings (Chavarska et al., 2007; De Giacomo & Fombonne, 1998, Herlihy et al., 2015; Wong et al., 2017).

In our study, professionals were usually the first to mention suspicion of autism. This was not surprising, since parents may not have the knowledge to associate their developmental concerns with autism, except perhaps for multiplex families. However, keeping in mind the time that has elapsed since the participants in Study I were toddlers, the internet has brought revolutionary changes with regards to information that can be easily accessed. Parents of young children today who are concerned about their child's development are probably more active in seeking information, which may be reflected in a more recent study, where parents and pediatricians were equally likely to be the first to mention autism (Becerra-Culqui et al., 2018).

Considering the late autism diagnosis of many children, a finding of interest was that most parents (83.3%) recollected that behavioral features of autism had been present before the child's second birthday and almost all (97.6%) before the third birthday. Even though a recall bias cannot be ruled out, this suggests that signs of autism may have been overlooked in children in the late diagnostic group that had received assessment by an interdisciplinary team prior to a later assessment that confirmed an autism diagnosis. Although it is not realistic to diagnose autism early in all cases (Ozonoff et al., 2018), there is still room for improvement. Public health interventions should aim at eliciting and responding to parental concerns, screening for autism in children who present with developmental and behavioral conditions that are known to co-occur with autism and educating professionals who are in contact with young children on the early signs of autism. Screening for autism at different ages should also be considered and studied for efficacy.

5.3 The early detection program (II-III)

5.3.1 Implementation, acceptance, and challenges

We used cluster randomization to select nine of the 17 PHCs in the capital area for implementation of the early detection program. The population-based program included application of the M-CHAT-R/F in connection with regular developmental surveillance at 30 months of age, education of well-child care clinicians, and referrals for diagnostic assessment and early intervention. One of the elements of the evidence-based model (Greenhalgh et al., 2004) that inspired the planning and implementation of the screening was to guarantee support from health administrators at different organizational levels. This was easily obtained, since data from our previous study (**Paper I**) provided a convincing argument for the importance of studying an intervention that has the potential to detect more autistic children at an earlier age.

There was a wide range of participation rates in the screening across the nine PHCs (52% to 95%). One possible reason is that parents are not obliged to bring their children to the PHC at which they are registered but rather can choose to attend another PHC. We were not able to keep track of such movements. The main reason for missed screening opportunities that was expressed at meetings with the contact nurses, was a failure to send out invitations and consent forms to parents to participate in the study or to follow-up on this issue during the visit. This challenge was related to insufficient communication within some of the PHCs. Additionally, when meeting new tasks, healthcare personnel may be pressed for time in very busy PHCs, which has been identified as one of the challenges for screening in primary child care (Barton et al., 2012; Broder-Fingert et al., 2019). However, once the parents had been given the M-CHAT-R to complete, there was no difficulty in integrating it within the time limits of each visit.

The PHC with the lowest participation rate was in a neighborhood with the highest rate of immigrants. Even though we provided all printed material in different languages and translation services during the well-child visits were available if needed, children who had one or both parents of non-native origin were underrepresented in the study (7.4%) compared with the proportion (22.6%) of 2-3-year-old children who in 2016 met the same criterion for parental background (Statistics Iceland, n.d.a). The exact reasons for this underrepresentation are unclear. Thus, we do not know if some of these parents did not bring their child to the well-child visit. Future studies should examine if there are disparities in access to healthcare services at this level for children in Iceland, similar to what has been demonstrated in studies from Western countries on immigrant families of autistic children (Sritharan & Koola, 2019). It is also possible that the parents did attend, but for some reason did not participate in the autism screening. Since the screening was part of a study project, engaging non-Icelandic speaking parents may have presented extra challenges for the clinicians when communicating information about the study and asking for informed consent, which may have increased the likelihood of dismissing it altogether. These challenges may be reduced if the use of an autism screening instrument becomes part of the regular well-child program.

Despite some challenges related to the screening, the contact nurses at the participating centers expressed satisfaction with the program, both in a survey and at a final evaluation meeting. Their responses indicated that it was feasible to embed the first screening stage into the time frame and the procedure of the regular well-child visit. However, we cannot generalize their responses to other well-child clinicians at the PHCs. Since the doctoral student conducted the second

stage of the screening, the follow-up interview, we do not know if it is feasible to include this portion within the regular visit. Parents are usually contacted later for the interview, which then requires extra time and resources. This may contribute to low rates of the follow-up interview completion among clinicians using the M-CHAT-R (Wallis et al., 2020). Another concern related to the use of a two-stage screening instrument is the risk of a high drop-out of parents between the stages (Brennan et al., 2016; Guo et al., 2019; Magán-Maganto et al., 2020; Robins et al., 2014), often related to socio-economic barriers in contacting them (Khowaja et al., 2015). A promising alternative is to use a table-based digital version of the M-CHAT-R/F, where both screening stages can be completed in one visit. Parents' responses are automatically scored and parents then self-complete relevant follow-up questions. This approach not only leads to fewer scoring errors and fewer children missing the follow-up interview, but also provides the well-child clinicians with immediate access to the results of the screening instrument that can be addressed during the same visit (Brooks et al., 2016; Campbell et al., 2021; Major et al., 2020).

Some measures suggest that the screening was well received by parents. Not only was refusal to participate in the first screening stage low, but there was also no attrition between the screening stages of the M-CHAT-R/F, and attrition was insignificant between screening in the PHC and diagnostic assessment. This finding is inconsistent with other screening studies using the M-CHAT-R/F (e.g., Brennan et al., 2016; Guo et al., 2019; Magán-Maganto et al., 2020; Robins et al., 2014). These studies all took place in relatively large communities where it is likely to be more challenging to keep track of parents to follow through with the different stages, unlike in our small community. An indirect measure of parental experience of the screening was that none of them made use of the offer to consult a psychologist. This suggests that participation in the screening did not evoke anxiety or other difficult emotions, although it cannot be ruled out that parents sought support elsewhere. However, a finding from another study shows that most parents do not report anxiety after seeing the results of the M-CHAT (Harrington et al., 2013).

5.3.2 Education of well-child care clinicians

A high proportion of the well-child care professionals who participated in the educational course had not received any previous education on autism. Their self-perceived post-course knowledge, as well as confidence and skill in identifying autism, showed significant improvements in mean scores compared to retrospective (prior to the course) scores. Our findings are in line with other surveys showing that knowledge of autism and self-perceived competence in providing primary care to children with autism are inadequate (Carbone et al., 2016; Golnik et al., 2009;

Heidgerken et al., 2005; Will et al., 2013). Similarly, limited knowledge and a need for information and training were among the key themes identified in a review of studies of healthcare providers' experiences with autism (Morris et al., 2019). We measured short-term improvement, but to sustain autism knowledge, continued education is needed (McCormack et al., 2020). A collaborative learning approach that uses a variety of teaching methods has been found to successfully bring about long-term sustained behavior and practice change among primary healthcare professionals, resulting in improved detection of autistic children (Carbone et al., 2016).

5.3.3 Screen-positive children

5.3.3.1 Screening outcome

Of the 1586 children, 63 (4%) screened positive with the M-CHAT-R after the first screening stage. This initial screen-positive rate is lower than that found in most other population-based screening studies using this revised edition of the instrument, where it ranged from 7% to 14% (Brennan et al., 2016; Guo et al., 2019; Khowaja et al., 2015; Robins et al., 2014), although a lower rate has also been found (Magán-Maganto et al., 2020). Contributing to our understanding of this variation in initial screen-positive rates is evidence that higher rates are associated with lower parental education and racial minorities, likely due to reduced knowledge of child development and literacy challenges (Khowaja et al., 2015). If low literacy is suspected, the screening method can be adapted by using an illustrated version of the questionnaire (https://mchatscreen.com/mchat-rf/translations/) or by reading the questions aloud for parents (Khowaja et al., 2015). The latter has been found to reduce the initial false-positive screens in disadvantaged populations (Kara et al., 2014).

In line with the above studies, the follow-up interview proved to be critical in reducing the final screen-positive rate (n = 26) and subsequent referral to diagnostic assessment. Moreover, the M-CHAT-R/F was effective in detecting not only children with autism, but also children with other developmental disabilities who needed early intervention. Of the 25 children receiving diagnostic assessment, 18 were true-positive and seven false-positive. Of the latter, six children were diagnosed with other neurodevelopmental disorders. Only one of the children who screened false-positive did not meet criteria for a clinical diagnosis. This child failed two items on the follow-up interview, which is the minimum for a screen-positive result. One was item 12 (upset by everyday noises) which is among the items where studies have found a non-significant failure rate between children with and without autism (Brennan et al., 2016; Magán-Maganto et al., 2020). The other was item 8

(interest in other children). The mother reported that language acquisition was slightly delayed, and that the child preferred to play alone, rarely initiated contact with other children, and responded listlessly to parents' approaches. Diagnostic assessment, which took place 20 months after screening in the PHC, showed scores on the ADOS below the cutoff for autism spectrum supported by other clinical observations. Language and cognitive test results were in the normal range. The mother no longer had concerns but noted that ADHD might become an issue later, as in an older sibling. The preschool noted good progress in the child's language and social interaction with peers.

Considering the relatively long period of time that passed from screening in the PHC to diagnostic assessment in our study, and variabilities that have been documented in autism symptom trajectories over time in young children suspected of autism (Kim et al., 2018), a change in the severity of symptoms, i.e., worsening in some cases and improving in other cases, was expected for many children. Thus, it is possible that in the above case, as in some of the other false-positive cases, the symptoms identified as indicating autism at the time of screening might have followed an improvement trajectory because of maturation and perhaps also intervention. However, it is also possible that the symptoms were indeed subthreshold at the time of screening and followed that trajectory.

5.3.3.2 Sources of referrals

The well-child care clinicians and the specialists at the preschool/educational services continued to make their own referrals to diagnostic assessment independent of the screening. We found that screening with the M-CHAT-R/F was more effective in detecting autistic children at 30 months of age than the usual procedures that missed eight of the 18 true-positive children. This relates to findings of other studies showing that a brief observation as a part of developmental surveillance fails to detect signs of autism in many children (Miller et al., 2011; Robins, 2008; Robins et al., 2014). The same even applies to clinicians who are experts in child development and autism, since neurotypical behavior in some autistic children can exceed autistic behaviors during a narrow time frame (Gabrielsen et al., 2015). Likewise, the PEDS, a broadband developmental screener that is a part of the surveillance procedure in Iceland, has been found to miss many autistic children (Pinto-Martin et al., 2008, Wiggins et al., 2014).

When referring to the usual procedures, we are including not only primary healthcare, but also the educational services. When developmental concerns arise, the staff at these service systems sometimes inform each other, and a decision to refer a child to assessment can be carried out by either one. All the participants in

the study had started in preschool by 30 months of age, providing a unique opportunity to observe children and see how they interact and communicate with their peers on a daily basis. Even so, the screening surpassed the combined efforts of both systems to detect autism in children in the invited group where no concerns had been raised.

5.3.3.3 Early intervention before diagnostic assessment

Given the long time that elapsed from screening in the PHC to diagnostic assessment, it was encouraging to find that early intervention was initiated for all screen-positive children before the diagnosis was confirmed. Thus, the average time from screening to intervention was 3 months, but 18 months to diagnostic assessment. These waiting times are comparable to those found in a larger sample of preschool children in Iceland referred to the SDCC for assessment (Gunnarsdóttir, 2020). Also consistent with our results, a European survey found that the average waiting time to diagnosis was 18 months. However, contrary to our findings, only a minority (15%) of the children later diagnosed with autism, started in an intervention program before a formal diagnosis, and there was a delay of 6 months on average from diagnosis to intervention (Bejarano-Martín et al., 2020b).

There were no differences in intervention hours for the screen-positive children based on their diagnostic results, unlike that found in another screening study where autistic children received significantly more pre-diagnostic intervention hours than other children (Pierce et al., 2011). However, most (83%) of the true-positive children started in an autism-specific comprehensive intervention program before diagnosis and many of their parents (50%), attended a course on autism, with lower figures found for the false-positive children and their parents. This indicates that the service needs of many of the children and their parents were met to some degree before a formal diagnosis was established. The small number of false-positive children limited comparison between them and the true-positive children. Nonetheless, a larger study later confirmed our results on pre-diagnostic services received by children referred to the SDCC, based on an autism or a non-autism diagnosis (Gunnarsdóttir, 2020).

Our findings on the pre-diagnostic services are of importance since autistic children who experience less delay in starting in an autism-specific intervention have better educational outcomes than those who experience longer delays (Dimian et al., 2021). Nevertheless, the delay from referral to diagnosis is of concern and needs to be addressed. It not only has a negative emotional effect on the parents (Bejarano-Martin et al., 2020b), but can also delay the provision of even more

intensive and focused intervention for the child, based on a better understanding of service needs that are reconsidered during the diagnostic assessment.

5.3.4 Screen-negative children

The screen-negative children were followed-up in the SDCC database for at least 2 years after the 30 months well-child visit to identify cases missed by the screener. A total of 17 screen-negative children had been detected and referred for assessment by the health- and educational services. Among these children, 11 were diagnosed with autism (false-negatives), including one child who passed the second screening-stage. Other screening studies that used versions of the M-CHAT and had sufficient follow-up of screen-negative children have reported that large proportions of autistic children are missed in young populations (Carbone et al., 2020; Guthrie et al., 2019; Øien et al., 2018; Stenberg et al., 2014). Because of variability in how and when the symptoms of autism emerge (Landa et al., 2013; Ozonoff et al., 2018; Pearson et al., 2018; Zwaigenbaum et al., 2013), it is possible that they were not yet clinically detectable in the false-negative children at the time of screening in the PHC, at least not with the instrument used. Supporting that is evidence showing that children who passed the M-CHAT at 18 months and were later diagnosed with autism did indeed display signs consistent with autism at that age based on other information obtained from parents (Øien et al., 2018). Studies have also shown that the M-CHAT is more likely to miss signs of autism in young children who have better functional language and intellectual development than in children who have greater impairment (Stenberg et al., 2020). Other reasons for false-negative cases may be that some parents are unable to report accurately on signs indicating autism in their child because they lack knowledge about typical development that helps to recognize deviations therefrom or that they are unwilling to do so because of fear of stigma and other reasons (Petrocchi et al., 2020; Robins, 2020).

Although autism screening instruments will always miss some children, efforts to minimize false-negative cases should be considered to enhance earlier detection and intervention for these children. This could include the use of a combination of different instruments and strategies in the screening process, beyond the parent-report, and repeated screenings for autism (Magán-Maganto et al., 2017; Robins, 2020). Development of more sensitive screening instruments could also be considered (Øien et al., 2018).

5.3.5 Comparison between true-positive and false-negative children

While there was a significant difference between the 18 true-positive children and the 11 false-negative children on the M-CHAT-R scores, the groups did not differ on

symptoms of autism as assessed with the ADOS-2 at the time of diagnosis, which is consistent with other studies (Kamio et al., 2014; Robins et al., 2014). These results relate to challenges of screening studies targeting behaviors in young children that often change over time, particularly where there is a considerable time delay from the application of the screening instrument and until diagnostic assessment takes place (Marks et al., 2008; Robins, 2020). This delay may affect the false-negative rate as discussed above.

Although a higher proportion of true-positive children had a performance- and verbal IQ/DQ <70 than false-negative children, the difference between the groups was not statistically significant. This finding is comparable to that found in a screening study including participants who were of the same age or older than in our study (Eaves et al., 2006). On the contrary, studies of younger populations (17-18 months) have found that a significantly greater proportion of true-positive children had ID than false-negative children (Dereu et al., 2010; Kamio et al., 2014; Stenberg et al., 2020).

An important finding supporting the value of the screening was that the true-positive children were 10 months younger when diagnosed than the false-negative children. This also meant an earlier age when intervention was initiated. Others have demonstrated similar benefits for screen-positive children, who were diagnosed 7 to 12 months earlier than false-negative children (Carbone et al., 2020; Guthrie et al., 2019). The comparison of measures between the true-positive and false-negative groups in our study should be interpreted with caution because of the small sample size in the latter group. Nonetheless, these results are supported by data from a larger study on children referred to the SDCC in 2018 (N = 132), which included our screen-positives, and showed that they maintained their 10 months earlier age at diagnosis when compared to the other participants in that study (Gunnarsdóttir, 2020).

5.3.6 Clinical validity of the M-CHAT-R/F

The M-CHAT-R/F's sensitivity to detect autism was 0.62. This is below the recommended standards for sensitivity (0.70-0.80) of developmental screening instruments (Glascoe, 2005). However, the specificity was high (0.99) meaning that most children who were not autistic were screen-negatives. Contrary to our results, many population-based screening studies using the M-CHAT-R, with or without the follow-up interview (Guo et al., 2019; Magán-Maganto et al., 2020; Oner & Munir, 2020; Robins et al., 2014; Windiani et al., 2016), have reported acceptable sensitivity. However, it is possible that the estimated sensitivity of the M-CHAT-R/F in these studies was inflated since they either did not report on follow-up

of screen-negative children (Sangare et al., 2019; Windiani et al., 2016) or acknowledged limitations with their approach to detect possible false-negative cases (Guo et al., 2019; Magán-Maganto et al., 2020; Oner & Munir, 2020; Robins et al., 2014). It is likely that if we extend the follow-up period, we will identify more false-negative cases, resulting in further weakening of the sensitivity. Sensitivity and specificity measures indicate how well a test discriminates between those who have and those who do not have the condition that is targeted, and are helpful in health policy decisions (Eusebi, 2013), for example when decisions are taken to use a particular instrument for screening in specific populations. The moderate sensitivity obtained in this study supports recommendations that a single screening for autism with the M-CHAT-R/F in unselected populations is insufficient, and that other early detection strategies should be used in conjunction with screening in developmental surveillance programs (Hyman et al., 2020).

On the other hand, measures that predict the probability of an individual having or not having the targeted condition, based on whether he/she screened positive or negative, are useful in clinical practice (Eusebi, 2013). Thus, the high NPV found in this study (0.99) indicates that there was a high likelihood that a child with a negative screening result was not autistic. The PPV for autism was 0.31 after the first screening stage and 0.72 after both screening stages, supporting the use of the follow-up interview to rule out as many false-positives as possible. We found a somewhat higher PPV for autism after both screening stages than reported (0.48) in the initial validation study of the M-CHAT-R/F (Robins et al., 2014). PPV is largely dependent on the prevalence of the condition, which may provide some explanation for the differences in this value when the same instrument is used across settings and contexts. In addition, the age of the participants may also have an effect (Levy et al., 2020; Yuen et al., 2018), considering that the children in our study were on average almost 11 months older than in the study of Robins et al., (2014). However, consistent with that study, the M-CHAT-R/F was highly effective in predicting any developmental disorder (PPV, 0.96).

5.4 Comparing the rate of autism in a group invited to screening to two control groups receiving usual care (IV)

The study compared the rates of autism detected in a group invited to a screening program with the rates of autism in two groups that received usual care. The invited group had a higher rate of autism than the combined control groups, but that was evident only in the comparison with control group 2. The comparison of the invited group with control group 1 yielded an elevated rate ratio, but with a wide 95% CI which included one. The comparison between the invited group and control group 1 was the most important since it came into being through cluster randomization

with the PHCs as the units of the randomization. These groups were considered comparable in terms of cultural and social status and were determined to have equal access to specialized developmental services. Based on that comparison, the screening did not have a clear impact on the detection of autism.

Control group 2 included PHCs that were mostly located in villages, and smaller towns outside the capital area, indicating that residence could be an influencing factor for the lower rate of autism found in that group compared with the invited group. Accordingly, a systematic review of prevalence studies found that an urban residence was associated with higher prevalence estimates for autism compared to rural or mixed urban and rural areas (Williams et al., 2006). Later studies have confirmed an association between higher level of urbanicity and the likelihood of an autism diagnosis (Hsu et al., 2022; Lauritsen et al., 2014; Luo et al., 2020). Different diagnostic practices and record keeping in urban and rural areas, which have been suggested as possible explanations for the geographical difference reported in prevalence studies (Williams et al., 2006) do not apply to our cases, since they were all referred to the SDCC for diagnosis. A more plausible explanation is different access to developmental and pre-diagnostic services for children living in the capital area compared to those living outside that area (see also the discussion in 5.3 in relation to age at diagnosis). In line with this, other researchers suggest that identification factors that include better knowledge of autism and access to and availability of services and resources in urban areas are related to higher prevalence and incidence of autism. Moreover, research suggests that some families with autistic children move to an area with a higher level of urbanicity seeking better diagnostic services (Lauritsen et al., 2014; Mazumdar et al., 2013).

We did not collect data on parental education in **Paper IV**, but a higher parental educational level has been associated with higher incidence of autism, suggesting that it could act as a proxy of better knowledge of child development and awareness of autism symptoms (Hsu et al., 2022). However, another study in Iceland found that the proportion of those with university education is twice as high in the capital area compared with other parts of the country (Bjarnason, 2018). Thus, it is likely that parental education plays some role in the geographical differences in the rates of autism in our study.

We found that children in the invited group were not referred for diagnostic assessment at a younger age than children in each of the control groups, nor did they receive their autism diagnosis earlier. These results are inconsistent with the results of previous studies reporting that population screening for autism lowered the age at diagnosis (Li et al., 2018; Nygren et al., 2012a; Robins et al., 2014).

However, it must be taken into consideration that these studies used other methods for comparison (see 1.8.5.1). Autism screening studies using RCTs to investigate the impact of screening, where the outcome is not only autism diagnosis, like in our study, but more importantly immediate and long-term clinical outcomes are needed (Siu et al., 2016), but such a study is already in progress (McClure et al., 2021).

There are some plausible explanations for the lack of difference in average age at diagnosis between the invited group and the control groups. Firstly, almost half of the children in the invited group did not participate in the autism screening, a situation that can always be expected in screening programs. Secondly, other children participated in the screening but screened negative despite subsequently receiving an autism diagnosis (i.e., false-negative). Thus, it can be assumed that these children did not benefit from the screening procedure. It is even possible that the screening hampered early referral and diagnosis of the false-negative children, given that they did not present with late emerging symptoms of autism that have been observed in some children (Bacon et al. 2018; Ozonoff et al. 2018). Indeed, the false-negative children were diagnosed 10 months later than the true-positive children. Hence, a later diagnosis of the false-negative children contributed to the lack of difference in age at autism diagnosis between the invited group and the control groups. This finding is consistent with the results of another study that identified a high proportion of false-negative children at follow-up and did not find a difference in age at diagnosis between screened and unscreened groups (Carbone et al., 2020).

The overall cumulative incidence of autism was 1.66% (95% CI, 1.37, 1.99) when the children were between 54 and 79 months of age. This rate is considerably higher than that found in the previous study included in this thesis (**Paper I**) which looked at 11-14-year-old children and found a prevalence of autism of 0.54%. Despite an older age of the participants in that study, where a peak in autism prevalence may be anticipated (Bachmann et al., 2018), the increase in rates observed during the decade that elapsed between the studies is consistent with the time trends reported for autism prevalence due to the combined effects of various factors (Fombonne et al., 2021; Zeidan et al., 2022). The cumulative incidence of 1.66% is indeed higher than reported in a recent systematic review where the overall median global prevalence of autism was estimated at 1% (Zeidan et al., 2022), and it exceeds the upper range (0.37% to 1.56%) of that reported for 4-year-old children in different studies (Rydzewska et al., 2019; Schendel & Thorsteinsson, 2018; Shaw et al., 2020).

5.5 Strengths, limitations, and future studies

The main strength of the study reported in **Paper I** was that it comprised complete birth cohorts of children in Iceland who had received an autism diagnosis before the census date. The other studies (**Papers II-IV**) were also population-based. Diagnostic assessment of all cases was conducted by an interdisciplinary team at one national diagnostic center, allowing for consistency in procedures. The diagnosis was based on standardized autism diagnostic instruments administered by experienced clinicians, clinical observations from other team members, and information from caregivers. A well-organized and accessible nationwide database on autism diagnosis enabled us to retrieve clinical data on individual children (**Papers I-IV**) and to follow-up screen-negative children to establish the validity of the M-CHAT-R/F (**Paper III)**. Using this database, we are confident that we were able to capture all children in the study population who had been diagnosed with autism by the closing date of the follow-up period, when the children were up to 79 months old. Similarly, we were able to follow-up non-screened children in the population to identify cases (**Paper IV**).

The implementation of the screening was consistent with key strategies that have been identified as facilitating success in the implementation of innovations in services for autistic children (Broder-Fingert et al., 2019). There was no attrition between the M-CHAT-R/F screening stages, and all parents of the screen-positive children accepted diagnostic assessment of their children. The doctoral student, who has extensive clinical experience with autistic children, conducted all follow-up interviews to ensure consistency of implementation and to reduce potential bias introduced by different clinicians. Referral pathways for screen-positive children were well defined, and early intervention and diagnostic services were available (**Papers II-III**).

A limitation of the study reported in **Paper I** relates to data that was collected in the parent interview on first concerns about their child's development and behavior. Parents of only 42 of the 99 children gave their consent to be interviewed. The relatively high rate of the responding parents with a university education (mothers 56%, fathers 54%) compared to the national average (30%) at the time of the study (Statistics Iceland, n.d.c) suggests a self-selection bias that may have affected the results. Higher level of parental education has been associated with younger age at autism diagnosis (Avlund et al., 2021; Hsu et al., 2022), possibly due to better awareness and literacy of autism by these parents (Hsu et al., 2022). Hence, the proportions of parents who had developmental concerns before the child's second or third birthday may be overestimated in this study. In the interview, parents were asked to recall information about their first developmental and behavioral concerns.

Thus, a retrospective recall bias may have limited the accuracy of their report, and perhaps more so for parents of children diagnosed late. Parents' knowledge about autism at the time of the interview might furthermore have influenced their memories of their child's early development and first signs of autism.

There were several limitations related to the screening. Of the children in the invited group who were registered at the nine PHCs for their 30-month well-child visit, 63% were screened. Thus, a selection bias may have affected the external validity of the study, such that the screened children may not fully represent the target population or may include children whose parents were more likely to seek screening services (**Papers II-IV**).

Some of the PHCs did not achieve acceptable screening rates. There were indications that the main reason was a failure to act in accordance with the work processes for the screening. One of the challenges with the screening procedure was probably related to the engagement of non-Icelandic speaking parents in the study; the PHC with the lowest participation was in a neighborhood with a high proportion of non-native residents. Hence, we observed that in the screening population, there was a relatively low participation of children who had one or both parents of non-Icelandic origin, likely contributing to the selection bias. This low participation rate was observed even though efforts were made to overcome potential language barriers related to conveying information to parents about the study (**Paper II**). Future screening endeavors, whether they are a part of a study or regular practice, should be aware of and address possible ethnic disparities in autism screening.

The measure of short-term change in autism knowledge and self-confidence among course participants relied on a single methodology. The use of well-established assessments to measure autism knowledge (Harrison 2017) and the use of multiple measurements and methods to assess change (Lam & Bengo, 2003) would have added validity to the results. Educational programs that have the potential to sustain autism knowledge should be made available and evaluated for efficiency in future studies. The survey on attitudes towards autism screening was only distributed to the contact nurses at the PHCs, and the positive results expressed by them cannot be generalized to other well-child care clinicians or administrators. Only informal measures were used to assess parental attitudes to screening (**Paper II**). Both quantitative and qualitative studies are needed to gain more knowledge about parents' attitudes to screening for autism in their children and their experiences with the screening process.

Concurrent case confirmation to evaluate the performance of the M-CHAT-R/F was not possible in this study, neither of screen-positive children nor of a subset of screen-negative children. This was because we used the regular diagnostic services for children with suspicion of neurodevelopmental disabilities, where the waiting time from referral to diagnostic assessment was 18 months on average at the time of the study. Thus, the study (**Papers II-III**) was affected by limitations inherent in prospective validation studies of screening instruments that rely on parent report and target behaviors in young children that emerge gradually and often change over time (Marks et al., 2008; Robins, 2020). Therefore, we do not know if some of the children who screened false-positive or false-negative would have been diagnosed with autism at the time of initial screening. Future screening studies should aim for concurrent confirmation of cases to evaluate the performance of screening instruments.

Blinding between the screening with the M-CHAT-R/F and the diagnostic stage was not possible for the screen-positive children, as their screening results were stated in a letter accompanying the referral for assessment (**Paper II**). Hence, it is possible that knowledge about a positive screening result could have influenced the clinicians to diagnose a child with autism, leading to an overestimation of the accuracy measures of the M-CHAT-R/F. On the other hand, no information was available to the diagnostic teams about the participation of the screen-negative children in the autism screening since they were not referred to assessment by the investigators (**Paper III**).

In the study reported in **Paper IV** it was not possible, partly due to privacy protection, to follow an individual child in each group from the start of the screening to the diagnosis of autism, or to the end of the follow-up. However, the age at referral and the age at diagnosis were similar in the study groups, and the cases had similar clinical features. For the similarity between the groups, it was considered unnecessary to test different lengths of follow-up.

The rationale to use cluster randomization with the PHCs in the capital area as the units of randomization was mainly the accessibility, and that may have diminished the risk of contamination of the control groups. However, we cannot be sure that the reported gains resulting from the educational course on autism, held for clinicians serving children in the invited group, did not contaminate the control groups, particularly in the capital area, for reasons such as temporary rotations of staff between different PHCs.

Almost half of the autistic children in the invited group did not participate in the autism screening**,** likely compromising the comparison with the control groups. However, even though these children did not receive the main intervention being tested (screening), they were impacted by another important variable: the education

of the well-child care clinicians. In future studies, the effects of screening on one hand, and the education of the well-child care clinicians on the other hand, should be better teased apart.

The comparability between the invited group and control group 2 was hampered not only because control group 2 included rural areas, but also because of a difference in educational levels between the rural areas and the capital area (Bjarnason, 2018). Future studies should examine whether population screening for autism in the whole of Iceland, preferably in a younger population than was included in this study, and autism education that has now been provided for all PHCs in the country, contributes to reducing geographical differences in the detection of autism in young children.

The study base was the entire population of children in Iceland and, with the inclusions criteria, framed the size of the study. If we had extended the inclusion period, then we would have obtained larger groups. However, simultaneously that may have introduced time-trend effects in the detection of autism. Similarly designed studies on a larger scale, comparing groups invited to screening to external control groups, are needed to explore whether screening detects autism earlier than the usual developmental surveillance, as the present study is not large enough to be considered a null study.

Finally, no parents or representatives from the autism community were included among the key people involved in the planning and the execution of the studies (**Papers I-IV**). Recently, there has been increased acknowledgement of participatory research that seeks to include the views of autistic individuals, and people who support them, about research priorities and methods (Fletcher-Watson et al., 2019; Roche et al., 2021). Involvement of the autism community in future screening studies will help to define important research questions, improve the quality of research methods, and contribute to meaningful benefits for autistic children and their families.

5.6 Contributions of the study

The study provided information on the age of autism diagnosis of children in Iceland and added to the literature on factors associated with early and late diagnosis. The study also added knowledge on the accuracy of the M-CHAT-R/F in detecting autism in an unselected group of 30-month-old children, and on the effectiveness in detecting autism in a group invited to screening compared to the usual developmental surveillance.

The finding from **Paper I** raised concerns about the late diagnosis of many autistic children in Iceland. The investigators followed this up and planned the first autism early detection project in the country. The project included a translation, minor cultural adaptation, and validation of the M-CHAT-R/F. An Icelandic translation of the previous version of the instrument, the M-CHAT (Robins et al., 2001), was used for many years by some clinicians in conjunction with other information before deciding to refer a child to the SDCC for assessment, although its performance characteristics among toddlers in our geographical location were unknown. Use of the revised version (M-CHAT-R/F) in Iceland has mostly replaced the M-CHAT and it is accessible without cost from the instrument's webpage (https://mchatscreen.com/). One effect of the project was perhaps increased awareness and knowledge of autism among well-child clinicians in the PHCs serving the invited group. Educational material from the course has now been made available on an internal webpage for clinicians at all PHCs in the country for further use.

This study spurred an increased interest in early detection of autism in the primary healthcare with a special focus on 18-month-old children belonging to groups that are known to have increased likelihood of autism, or when parents or clinicians raise concerns. At the urging of administrators from the Development Center for Primary Healthcare in Iceland, a developmental project was initiated in 2020 in cooperation with the SDCC and the investigators. An educational course on autism and screening with the M-CHAT-R/F was held over the internet in 2020 and 2021 with participants from all PHCs in the country. It was based on our previous course but had been reviewed and extended in collaboration with colleagues at the Development Center. Recordings from the course are accessible for PHC clinicians for future use. Additionally, special training courses were offered to child psychologists who had been tasked to conduct the follow-up interview. Screening with the M-CHAT-R/F and a focused observation with items from the Joint Attention Observation Schedule (Nygren et al., 2012b) was then implemented in PHCs throughout the country. A flow-chart was designed to assist with decision making regarding screening for autism, as well as the screening and the observation process. It also includes guidance about what additional information should accompany a referral for diagnostic assessment, and instructions about a follow-up within the PHC and referral to early intervention if in doubt about the need for assessment at a tertiary institution.

After the initiation of this project, a substantial increase in referrals to the SDCC following the 18-month well-child visit has been observed. The project calls for validation of the M-CHAT-R/F in the selected group mentioned above, and for further studies on its contribution to early detection of autism in Iceland.

6 Conclusion and clinical implications

We found that many autistic children were diagnosed late despite early parental concerns. The presence of good cognitive and language status, mild symptoms of autism, and a previous neurodevelopmental diagnosis contributed to a delay in autism diagnosis. Thus, it is important that professionals who monitor children's development elicit and respond to parental concerns. Additionally, diagnosticians need to be aware of factors that may affect the age of autism diagnosis, and of challenges related to differential diagnosis of children referred with suspicion of a neurodevelopmental condition.

With the aim to advance early identification and intervention of children in Iceland, we initiated the first early detection program for autism in the country. The program was well received by administrators, clinicians, and parents, which indicates that there is room for innovations that have the potential to benefit young autistic children and their parents.

A gap that was identified in the autism education of well-child clinicians highlights the need for regular courses on the topic. Even a short course like the one we provided resulted in a self-perceived increase in autism knowledge, and in skill and confidence in identifying children who require further assessment.

Implementation of the first screening stage of the M-CHAT-R/F in well-child care was feasible in terms of time, cost, ease of administration, and receptivity. More resources are needed to incorporate both screening stages into the system. Consideration should be given to the use of a low-resource approach like a table-based digital version of the M-CHAT-R/F, which can be completed during the same visit. Barriers in engaging non-Icelandic speaking parents in screening should also be addressed.

Screening with the M-CHAT-R/F at 30 months of age detected more autistic children than the usual procedures. Moreover, the screening was clinically meaningful for the true-positive children, who were considerably younger at the time of diagnosis than those who screened false-negative. Although intervention was initiated for all screen-positive children before diagnostic assessment, the wait time for the latter needs to be shortened. This may reduce stress in parents related to uncertainty about their child's condition and allow for the diagnostic results,

which include assessment of service needs of the child and the family, to inform the intervention.

The screening also missed some children, which resulted in a suboptimal sensitivity of the M-CHAT-R/F for detecting autism. Hence, using the M-CHAT-R/F for population screening at the 30-month well-child visit should be accompanied with other strategies to detect children who need further assessment. Integrating the M-CHAT-R/F into the usual developmental surveillance procedures, and adding a short, focused autism observation has the potential to reduce the number of false-negative cases and further advance early detection of autism. Continued screening of screen-negative children throughout childhood is also advised to detect children with later emerging symptoms of autism. Additionally, considerations should be given to strategies to streamline referrals to diagnostic assessment and intervention services that best meet the needs of screen-positive children and make the best use of time and resources. These could include the use of an interactive level 2 screener following a positive screen result on the M-CHAT-R/F, especially if it falls into the moderate-risk range.

The rate of autism was higher in the invited group than in the control groups; however, interpreting the results is difficult because of the wide confidence intervals. So, one cannot firmly conclude from this study that the screening program detected autism more readily than did the usual care.

Comparison of the groups in the capital area (invited group and comparison group 1) showed that the routine developmental surveillance was reasonably effective in detecting autistic children, although adding autism-specific screening might have improved this success.

A lower rate of autism in the rural areas (control group 2) than in the urbanized capital area (control group 1) calls for improved access to developmental services in the former. While it is unrealistic to establish specialized developmental services in some of the rural areas, support from such services in the capital area and from regional centers or teams in other parts of the country should be considered.

The public health benefits of a population screening program for autism cannot be fully estimated until data are available from larger studies on the long-term outcomes of children detected through screening compared to children detected through the usual care.

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Children diagnosed with autism spectrum disorder before or after the age of 6 years

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ABSTRACT

This study compared children with early and late diagnosis of autism spectrum disorder (ASD). All children in four consecutive birth cohorts in Iceland diagnosed with ASD were divided into two groups based on their age at initial ASD diagnosis: 58 children were diagnosed before age 6 (group 1) and 41 children after age 6 (group 2). Children in group 1 were more likely to receive a diagnosis of childhood autism ($p \leq 0.001$), their average IQ/DQ was lower ($p < 0.001$), verbal status was lower ($p < 0.001$), and a history of autistic regression was more common ($p < 0.01$) than in group 2. Half of the children in group 2 had received other developmental diagnoses prior to the ASD diagnosis, but this applied to only a few of the children in group 1 ($p < 0.001$). There was no difference between the groups with regard to autistic symptoms as measured by the Autism Diagnostic Interview-Revised ($p = 0.224$), frequency of associated medical conditions ($p = 0.640$), age of first parental concern ($p = 0.244$), and age of first autistic symptoms on hindsight ($p = 0.540$). The majority of parents (76.2%) had developmental concerns before age 3, and with hindsight 83.3% thought that autistic symptoms had been present before age 2.

1. Introduction

The symptoms of autism spectrum disorders (ASD) usually become manifest in infancy or early childhood. Not only is early identification of specific symptoms in the three domains that define autism possible (see Chawarska & Volkmar, 2005; Landa, 2008, for reviews), but autism can also be reliably diagnosed in children as young as 2–3 years of age. Stability of an ASD diagnosis has been observed into and throughout the preschool years (see Charman & Baird, 2002, for a review; Chawarska et al., 2007; Kleinman et al., 2008), and into elementary school age (Charman et al., 2005; Lord et al., 2006; Sigman & Ruskin, 1999).

Studies of parental concerns show that the majority recognized abnormalities in development by their child's second birthday (Baghdadli, Picot, Pascal, Pry, & Aussilloux, 2003; Chakrabarti, 2009; Chavarska, Klin, Paul, & Volkmar, 2007; De

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; AMC, associated medical conditions; ASD, autism spectrum disorder; BSID-II, Bayley Scales of Infant Development, Second Edition; CARS, Childhood Autism Rating Scale; DQ, developmental quotient; ID, intellectual disability; PDD, pervasive developmental disorder; RRB, restricted repetitive behavior; SDCC, State Diagnostic and Counseling Center; SLI, specific language impairment; WISC-III, Wechsler Intelligence Scale for Children, Third Edition; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised.

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Giacomo & Fombonne, 1998; Short & Schopler, 1988; Young, Brewer, & Pattison, 2003). Speech and language delays were the first concerns of most parents of children who were later diagnosed with ASD and abnormal social development was usually the second major concern reported (Chakrabarti, 2009; Chavarska et al., 2007; De Giacomo & Fombonne, 1998; Howlin & Moore, 1997; Young et al., 2003). Many of the first developmental abnormalities to arouse parental concerns are not specific to autism. Besides language impairments, earlier age of recognition of first abnormalities by parents has been associated with intellectual disability (ID) (Baghdadli et al., 2003; De Giacomo & Fombonne, 1998), medical problems (Baghdadli et al., 2003; De Giacomo & Fombonne, 1998), the presence of a neurological condition, an infectious disease, a perinatal condition and auditory deficit (Baghdadli et al., 2003).

Among the variables that have not been found to influence the age of first parental concern is the child's birth-order (Baghdadli et al., 2003; Chavarska et al., 2007; De Giacomo & Fombonne, 1998), family variables such as having an older child with developmental difficulties, including ASD (Chavarska et al., 2007), social class (Baghdadli et al., 2003; De Giacomo & Fombonne, 1998), and area of residence (De Giacomo & Fombonne, 1998).

Studies that have examined the relationship between age of recognition by parents and the child's gender, IQ, and severity of autism symptoms have reported mixed results. A number of studies have not found an association between the child's sex and age of first parental concern (Baghdadli et al., 2003; De Giacomo & Fombonne, 1998; Rogers & DiLalla, 1990; Young et al., 2003), but when girls have aroused parental concern earlier than boys it has been related to lower IQ's of girls than of the boys (Short & Schopler, 1988). While Short and Schopler (1988) reported an association between lower IQ level and earlier age of parental recognition (before or after 30 months of age), others did not find such a relationship (Rogers & DiLalla, 1990; Volkmar, Stier, & Cohen, 1985). Some studies have not found an association between age when parents first became concerned and severity of symptoms as measured by the Autism Diagnostic Interview-Revised (ADI-R) (De Giacomo & Fombonne, 1998), or as measured by the Childhood Autism Rating Scale (CARS) (Rogers & DiLalla, 1990; Tolbert, Brown, Fowler, & Parsons, 2001). However, other studies have found a moderate association between early recognition by parents and the severity score on the CARS (Baghdadli et al., 2003; Short & Schopler, 1988). If diagnostic categories are considered, parents of children with Asperger's syndrome have reported initial concerns at a significantly later age than parents of children with autism or other ASD (Howlin & Asgharian, 1999; Sivberg, 2003). However, the type of ASD diagnosis (childhood autism versus other ICD-10 PDD categories) was not related to age of first parental concerns in De Giacomo and Fombonne's study (1998).

A delay for several months on parents' behalf in seeking professional advice, after they become concerned about their child's development, has been documented (Chakrabarti, 2009; De Giacomo & Fombonne, 1998; Howlin & Moore, 1997; Sivberg, 2003; Young et al., 2003). A further significant delay until an ASD diagnosis is given has also been observed across different countries (Chakrabarti, 2009; Howlin & Moore, 1997; Sivberg, 2003; Wiggins, Baio, & Rice, 2006; Young et al., 2003), such that ASD often remains undiagnosed until late preschool age, and sometimes even at a later age.

A population-based study from 13 sites in the United States, aimed at identifying 8-year-old children with ASD, revealed that the median age of ASD identification was 5.7 years (Shattuck et al., 2009). A survey among parents in the United Kingdom showed a steady reduction over time regarding mean age at diagnosis, although it was still around 6 years (Howlin & Moore, 1997). A more recent survey among parents in five English speaking countries (Goin-Kochel, Mackintosh, & Myers, 2006) confirmed a still lower average age of ASD diagnosis over time, and furthermore, that within all ASD diagnostic categories, children in the younger study group (age 11 and younger) were diagnosed significantly earlier than children in the older group. Mandell, Novak, and Zubritsky (2005) observed that this general decrease in age of diagnosis over time was happening at a faster rate for the higher functioning children.

Symptoms related to ASD may in some cases go unnoticed for several years, as suggested by studies finding an association between degree of ASD impairment and the age of diagnosis, where children with the most severe symptom presentation are evaluated and diagnosed earlier than those with milder symptoms (Mandell et al., 2005; Wiggins et al., 2006). Since the degree of symptom severity and impairment within the autism spectrum varies considerably, it is informative to consider the different ASD categories when studying age at diagnosis. Studies have shown that the mean age of initial ASD diagnosis is significantly influenced by diagnostic subtypes, where a lower average age of diagnosis has constantly been documented for childhood autism compared to Asperger's syndrome and other ASD categories (Chakrabarti & Fombonne, 2001; Goin-Kochel et al., 2006; Howlin & Asgharian, 1999; Mandell et al., 2005; Wiggins et al., 2006).

While level of ASD impairment independently predicted age at first documented ASD diagnosis in Wiggins et al.'s (2006) study, this was not the case for sex and ID after level of ASD impairment was considered. Neither did sex and ID predict age at diagnosis in Mandell et al.'s (2005) study. Among family and demographic variables that have been associated with an earlier age of diagnosis are higher level of parent education (Goin-Kochel et al., 2006), higher income (Goin-Kochel et al., 2006; Mandell et al., 2005), and urban residence (Mandell et al., 2005).

Various health system characteristics have been identified as barriers to early diagnosis. Thus, later age of diagnosis has been found to be associated with the number of health care professionals that the family has had contact with before the child received an ASD diagnosis (Goin-Kochel et al., 2006; Mandell et al., 2005). In one study, more than two thirds of the children received a diagnosis by their third clinical visit. Many of the parents reported that they were frequently and incorrectly reassured by their general practitioner that they need not worry, or that the child would get better (Howlin & Asgharian, 1999). This may both be attributed to the physician's lack of knowledge about ASD (Shah, 2001) as well as to the heterogeneous symptom presentation in children with ASD which presents specific challenges when it comes to further consideration of possible ASD by primary care professionals and referral to specialists in the field. Even when qualified

professionals are involved, a delay of an average of 13 months has been documented between first evaluation and the time when a formal diagnosis of ASD is given (Wiggins et al., 2006).

Early identification and diagnosis are critical for several reasons, one of which is to make children eligible for suitable intervention services at a young age, which in turn may affect their future outcome. Early intervention for children with ASD and their parents has been recommended as a "best practice" provided that it is based upon scientific evidence available in the field (Myers, Johnson, & The Council on Children with Disabilities, 2007; National Research Council, 2001; New York State Department of Health, 1999). Numerous studies have shown that early, intensive and specialized intervention can produce significant gains in many children with ASD (see Eikeseth, 2009; Howlin, Magiati, & Charman, 2009; Rogers & Vismara, 2008, for reviews) and that "recovery" is indeed possible in some cases (see Helt et al., 2008, for a review). Children diagnosed after they start elementary school have thus missed the opportunity of benefiting from appropriate intervention during their early years. Evidence-based early intervention may not only result in gains in functioning and improved quality of life for the child and the family, but also in long-term cost savings for parents and service systems (Gylfason, Sigurdardóttir, Peersen, & Arnadottir, 2004; Jacobson, Mulick, & Green, 1998; Motiwala, Gupta, & Lilly, 2006). Furthermore, early identification allows etiologic investigation, as well as genetic counseling to parents regarding the risk of recurrence (Johnson, Myers, & The Council on Children with Disabilities, 2007).

When collecting data for a recent follow-up study on children in four birth cohorts in Iceland, we observed that the age at initial ASD diagnosis ranged from under 2 years of age to 12 years of age. While the majority of the participants received their ASD diagnosis during the preschool years, more than 40% of them were not referred for assessment because of suspected ASD until after 6 years of age (Jónsdóttir et al., 2007). Knowledge about the possible differences in these "early" and "late" diagnostic groups may contribute to earlier detection and diagnosis in our service system so that more children and their families could benefit from appropriate early intervention services.

The objectives of the present study were to describe and to compare the characteristics of children diagnosed with ASD before and after the age of 6 years and to identify factors that influence the age of ASD diagnosis. The age of 6 years was chosen because children in Iceland start elementary school at that age, and the period of early intervention then normally fades out or terminates. We hypothesized first, that there would be differences in these "early" and "late" diagnostic groups, such that children diagnosed before 6 years of age would have more severe autistic symptoms, lower cognitive and verbal status, and be more likely to have a history of regression, than children diagnosed after 6 years of age. Second, that diagnosed medical conditions would lead to an earlier ASD diagnosis, perhaps leading parents to seek professional opinion earlier than if no apparent medical condition was present. Third, that the diagnosis of other neurodevelopmental disorders such as mental retardation, unspecified disorders of psychological development or behavioral and emotional disorders, delay the diagnosis of ASD. Fourth, that area of residence and concentration of professional expertise in the area affects whether children are diagnosed early or late, and thus children living in rural areas would be diagnosed later than children living in urban areas. Fifth, that parents of children diagnosed before 6 years of age would have recognized developmental abnormalities at an earlier age than parents of children diagnosed after 6 years of age. And sixth, that family characteristics, such as the presence of older siblings, and higher educational status of parents, would lead to an earlier concern of developmental disturbances, and thus an earlier age of ASD diagnosis.

2. Method

2.1. Participants

Participants were all registered at the State Diagnostic and Counseling Center (SDCC) in Iceland, born during the years 1992–1995, and diagnosed with ASD before January 1, 2006. A total of 99 children met these criteria. During the study period, all children in Iceland with suspected ASD were referred to the SDCC.

2.2. Procedure

Assessment and diagnosis were carried out by an interdisciplinary team. The composition of the team varied, but always included at least a developmental pediatrician, a clinical child psychologist and a social worker. The diagnosis was based on the results of diagnostic instruments and developmental tests combined with medical data and clinical observations from team members.

All children had a physical examination, including a neurological evaluation. Based on clinical findings the children had various medical tests. The classification of medical conditions with a suspected etiologic relationship with autism was based on the categorization used by Barton and Volkmar (1998). The results of standardized assessments, medical data, as well as past and present diagnoses, were collected from individual records at the SDCC, which has been previously described (Jónsdóttir et al., 2007). In addition, a questionnaire was administered to parents through a telephone interview.

2.3. Diagnostic classification

The ICD-10 classification system (WHO, 1992, 1993) was used for diagnosing ASD. The ICD-10 divides pervasive developmental disorders (PDD), referred to as ASD in this article, into eight subcategories, but only five were relevant for our

participants: childhood autism (F84.0), atypical autism (F84.1), Asperger's syndrome (F84.5), and other PDDs (F84.8). No child in the present study had a diagnosis of Rett's syndrome (F84.2), other childhood disintegrative disorders (F84.3), overactive disorder associated with mental retardation and stereotyped movements (F84.4), or PDD unspecified (F84.9).[4]

2.4. Data analysis

The participants were divided into two groups depending on whether they received their initial ASD diagnosis before or after 6 years of age: 58 children were diagnosed before age 6 (group 1) and 41 at 6 years of age or older (group 2). Comparisons between the age groups addressed ASD diagnostic categories, symptoms of autism, cognitive measures, verbal status, regression, associated medical conditions (AMC) at the time of the initial ASD diagnosis, frequency of developmental diagnosis prior to ASD diagnosis, family area of residence, parental concerns, the presence of older siblings, and parent education. When comparing groups we used chi-square and *t*-tests. For the calculation of prevalence we used the traditional method.

2.5. Ethics

The study was reported to and approved by the Icelandic Data Protection Authority and was also approved by the National Bioethics Committee in Iceland (VSNb2006010028/03-7).

2.6. Measures

2.6.1. Diagnostic instruments

The ADI-R (Lord, Rutter, & Le Couteur, 1994) is a standardized, semi-structured investigator-based interview for caregivers of individuals with suspected autism. It provides a diagnostic algorithm for the ICD-10 and the DSM-IV definitions of autism where behavioral symptoms are classified into three domains: qualitative abnormalities in reciprocal social interaction, qualitative abnormalities in communication, and restricted, repetitive and stereotyped patterns of behavior, all with specified cutoffs. The ADI-R was administered to parents by experienced clinicians who previously had established reliability with a consensus group led by the authors of this instrument. Two instruments were used for direct assessment of behavior, the CARS (Schopler, Reichler, & Renner, 1988) and the Autism Diagnostic Observation Scedule (ADOS; Lord, Rutter, DiLavore, & Risi, 2002). The CARS consists of 15 items which are scored on a seven-point scale with all the items contributing equally to one total score. The cutoff for autism is $\geq$30 points. The ADOS is a semistructured, standardized observational assessment. The diagnostic algorithm consists of domains related to the core features of autism and ASD. The instrument consists of four modules, one of which is chosen for administration in each individual case, based upon the individual's expressive language ability and age. Cutoffs are provided for autism and for autism spectrum diagnoses. The number of points required for reaching those cutoffs depends on which module is being used.

Due to changes in diagnostic practices, the behavior of most of the children in group 1 was evaluated with the CARS and in group 2 with the ADOS. However, during a period of transition, some children were given both of these instruments. When reporting the results of these measures, the instrument that was concurrent with the ADI-R was chosen. Thus, 55 children in group 1 and one child in group 2 had CARS scores concurrent with the ADI-R, and the same applied to ADOS scores for 39 children in group 2 and two children in group 1.

2.6.2. Cognitive tests

Various cognitive tests were used based on the child's age and developmental level at the time of administration. These tests included the Bayley Scales of Infant Development, Second Edition (BSID-II; Bayley, 1993), the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989) and the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1992). The tests were used to obtain standard deviation scores, or an intelligence quotient (IQ), except for the BSID-II where a ratio developmental quotient (DQ) was computed. This was done to obtain comparable measures on this test across children, since some of them scored below standardization values and in other cases chronological age exceeded the age specific norms. US norms were used for BSID-II and WPPSI-R and UK norms for WISC-III, since Icelandic norms were not available for these tests at the time of the study.

2.6.3. Classification of language abilities

Language abilities were classified into categories based on the ADI-R definition of overall level of language. According to this definition, being verbal requires: "functional use of spontaneous echoed or stereotyped language that, on a daily basis, involves phrases of three words or more that at least sometimes includes a verb and is comprehensible to other people."

[4] The ICD-10 PDD categories F84.0, F84.2, F84.3, and F84.5 may roughly be considered parallel to the corresponding DSM-IV PDD categories (autistic disorder, Rett's disorder, childhood disintegrative disorder, and Asperger's disorder). Three of the ICD-10 categories, atypical autism, other PDDs, and PDD unspecified (F84.1, F84.8, F84.9), may be considered to be included in the DSM-IV PDD-NOS category. The ICD-10 F84.4 category does not have any correspondence with the DSM-IV. (Adapted from Jónsdóttir et al., 2007).

Table 1
Comparison of ICD-10 ASD[a] diagnostic subgroups by diagnosis before age 6 (group 1) and after age 6 (group 2).

	Group 1 *n* (%)	Group 2 *n* (%)	Total *N* (%)
Childhood autism	40 (69.0)	6 (14.6)***	46 (46.5)
Other ASDs[a]	18 (31.0)	35 (85.4)***	53 (53.5)
Total	58 (100)	41 (100)***	99 (100)

[a] Autism spectrum disorder.
*** $p \leq 0.001$.

Non-verbal status is defined by either: no use of phrases, "but uses speech on a daily basis with at least five different words in the last month"; or by use of "fewer than five words total or speech not used on a daily basis" (Le Couteur, Lord, & Rutter, 2003, p. 8). Based on this definition, two specialists, a speech and language pathologist and a clinical psychologist, classified, independently of each other the language abilities of 70% of the children in group 1, using all available information in their files. Their observed agreement was 97.5%.

2.6.4. Questionnaire

Initially, our intention was to use information collected with the ADI-R on the first developmental concerns reported by parents. However, this was not possible as the ADI-R protocols for many of the participants were not accessible, but only their symptom domain and total scores. A questionnaire was developed to compensate for this lack of information on developmental concerns. It included parents' first concerns about their child's development, such as the age of the child when parents became concerned, what caused their initial concern, who was the first to suspect autism and what symptoms evoked that suspicion, also the number of older siblings, and parent education.

3. Results

According to Statistics Iceland 18,251 children were born during the years 1992–1995, and living in Iceland on January 1, 2006, of whom 99 had been diagnosed with ASD, 82 boys and 17 girls (4.8:1). The estimated prevalence was 54.2/10,000 (95% CI, 43.5–64.9). The median age at diagnosis was 66 months. Almost half of the total group (46.5%) was diagnosed with childhood autism and the rest with other ASDs[5] (53.5%) of whom 10.1% had Asperger's syndrome. At the time of initial diagnosis, 55.6% of the children had IQ/DQ scores below 70. At elementary school age, when most of the youngest children had been reassessed, 47.5% of the total group had IQ/DQ scores below 70.

The mean age at the initial ASD diagnosis in the younger age group (group 1) was 45.7 months ($SD = 12.9$; range 22–70 months) and in the older age group (group 2) it was 108.3 months ($SD = 22.1$; range 72–146). The sex ratio was similar in both groups. A diagnosis of childhood autism was predominant in group 1 and a diagnosis of other ASDs in group 2 ($\chi^2(1, N = 99) = 22.127$, $p \leq 0.001$) as can be seen in Table 1.

There was no difference between the groups on the ADI-R total symptom score ($t(1, N = 99) = 1.224$ $p = 0.224$), or on the three subdomain symptom scores, i.e., social interaction ($t(1, N = 99) = 1.488$, $p = 0.958$); communication ($t(1, N = 99) = 1.456$, $p = 0.755$); and restricted repetitive behavior ($t(1, N = 99) = -0.655$, $p = 0.240$). The observed agreement between behavior reaching cutoff for autism on two or three subdomains on the ADI-R and a cutoff for autism on the CARS in group 1 was 79.2% ($n = 55$). The observed agreement between ADI-R and ADOS in group 2 was 75.0% ($n = 39$), when the same criteria for cutoff on the ADI-R was used and a cutoff for either autism or autism spectrum on the ADOS.

Group 1 had lower mean IQ/DQ scores than group 2, with a mean IQ/DQ of 57.9 ($SD = 19.3$; range 14–95), whereas the mean IQ/DQ for group 2 was 77.0 ($SD = 22.5$; range 25–126) ($t(1, N = 98) = 4.506$ $p \leq 0.001$). The proportion of children with IQ/DQ scores below 70 was thus significantly higher in group 1 ($\chi^2(1, N = 99) = 17.601$, $p \leq 0.001$) as shown in Table 2. The verbal status of the children in group 1 was lower than that of the children in group 2 ($\chi^2(2, N = 97) = 18.885$, $p \leq 0.001$). About half of the children in group 1 (54.4%) had a functional use of phrases of at least three words, 24.6% used words but no phrases, and 21.0% had fewer than five words and/or did not use speech on a daily basis. The respective figures for group 2 are 95.0%, 2.5%, and 2.5%. Children in group 1 were more likely to have a history of autistic regression than the children in group 2, usually involving loss of words ($\chi^2(1, N = 97) = 10.186$, $p < 0.01$).

There was no difference between the groups in the frequency of AMC ($\chi^2(1, N = 99) = 0.218$, $p = 0.640$). In group 1, nine children (15.5%) had medical conditions with a suspected etiologic relationship with autism. One girl had Turner's syndrome, one boy had Soto's syndrome associated with a minor brain malformation (occipital polymicrogyria) and one child had a chromosomal defect (partial duplication of chromosome #8). Furthermore, one child was microcephalic, one had suffered herpes meningitis in infancy, and four children had epilepsy with normal brain imaging. Other significant medical findings in the younger age group included visual defects in three children. Seven children had postnatal macrocephaly (one of them also had an aortic valve defect) and one child was born with a cleft soft palate. In group 2, five (12.2%) children had medical conditions with a suspected etiologic relationship with autism; one child had velo-cardio

[5] ICD-10 atypical autism (F84.1), Asperger's syndrome (F84.5), and other PDDs (F84.8).

Table 2
Comparison of various characteristics of children with ASD[a] by diagnosis before age 6 (group 1) and after age 6 (group 2).

	Group 1 ($n = 58$) (%)	Group 2 ($n = 41$) (%)	Total ($N = 99$) (%)
IQ/DQ < 70[b]	74.1	29.3***	47.5
Verbal status/at least 3-word phrases[b]	54.4	95.0***	71.1
A history of regression	26.3	2.4**	16.3
Associated medical conditions	15.5	12.2	14.1
Developmental diagnosis prior to ASD[a] diagnosis	13.8	51.2***	29.3

[a] Autism spectrum disorder
[b] At the time of initial ASD diagnosis
*** $p \leq 0.001$
** $p < 0.01$

facial syndrome, one had Smith–Magenis syndrome and epilepsy, and two other children had epilepsy with normal brain imaging. One child had suffered perinatal asphyxia. Other significant medical findings in the older age group included three children with postnatal macrocephaly and one child with postnatal macrocephaly and diabetes mellitus. One child was premature and had had low birth weight (gestational age 27 weeks, birth weight 1074 g).

Group 1 was less likely to have received any other developmental diagnosis prior to the ASD diagnosis than group 2 ($\chi^2(1, N = 99) = 16.245$, $p < 0.001$). Of the eight children in group 1 with a previous diagnosis, ID was the most common diagnosis given prior to the ASD diagnosis. Half of the children in group 2 ($n = 21$) had received a developmental diagnosis before their ASD diagnosis, where disorders of language ($n = 10$) and ID ($n = 8$) were the most frequent initial diagnosis. Usually they also ranked first when children received multiple diagnoses at the same time. Children in group 2 with a previous diagnosis had lower mean IQ scores than children in group 2 without a previous diagnosis ($t(1, N = 41) = 4.392$, $p < 0.001$), but the groups did not differ on age at ASD diagnosis ($t(1, N = 41) = 1.832$, $p = 0.075$), on the total symptoms score on the ADI-R ($t(1, N = 41) = 0.718$, $p = 0.478$), or on proportion of children reaching cutoffs for autism or ASD on the ADOS ($\chi^2(2, N = 39) = 0.688$, $p = 0.709$).

Of the 42 parents who answered the questionnaire, 25 had children in group 1 and 17 in group 2. The majority of the parents (76.2%) had had concerns regarding the development of their child prior to their child's third birthday. Most parents (45.2%) reported that delayed language development aroused their initial concern. Parents were the first ones to mention concerns about their child's development in 78.6% of the cases. Suspicion of autism arose with professionals in 71.4% of the cases. One or more of the following symptoms first evoked suspicion of autism: restricted and repetitive behavior (RRB) (45.2%); the child's lack of interest in communicating with other children (28.6%); delayed language development (21.4%). Upon hindsight, 83.3% of the parents thought that their children had shown autistic behaviors at or before 2 years of age and 97.6% before 3 years of age.

Between group comparison showed that there was no difference regarding age when parents first became concerned about their child's development ($\chi^2(2, N = 42) = 2.825$, $p = 0.244$), or of first autistic symptoms on hindsight ($\chi^2(2, N = 42) = 1.232$, $p = 0.540$). Children in group 1 were more likely to have older siblings ($\chi^2(1, N = 42) = 3.692$, $p = 0.055$). The groups did not differ on measures on parent education (fathers: $\chi^2(1, N = 41) = 0.312$, $p = 0.557$; mothers: $\chi^2(1, N = 41) = 0.117$, $p = 0.7329$), and there was no difference between the groups regarding family area of residence ($\chi^2(1, N = 99) = 0.618$, $p = 0.432$).

4. Discussion

This study compared children in four birth cohorts in Iceland, diagnosed with ASD before and after 6 years of age. Our hypotheses addressing the differences in these groups were partly supported. ASD was diagnosed earlier in children with lower IQ/DQ scores, lower verbal status and a history of autistic regression. These children were also more likely to receive a diagnosis of childhood autism than children diagnosed after 6 years of age, whose diagnosis is associated with milder variants of the autism spectrum. This finding is similar to that reported in other studies (Goin-Kochel et al., 2006; Howlin & Asgharian, 1999; Mandell et al., 2005; Shattuck et al., 2009; Wiggins et al., 2006). Surprisingly, however, there was no difference between the groups on autistic symptoms as measured by the ADI-R.

One plausible explanation for this lack of difference between the groups on the ADI-R, could be that for some of the younger children, certain symptoms had not yet appeared unambiguously when the interview took place, as for example some of the RRBs. Sixteen children (27.6%) in group 1 were under 3 years of age at the time of the ADI-R. Although some types of RRBs are clearly manifested in children as young as 2 years of age (Charman et al., 2005; Lord, 1995; Moore & Goodson, 2003), such as sensorimotor behaviors (Richler, Bishop, Kleinke, & Lord, 2007), studies of young children with ASD have found that these behaviors were identified less consistently in children under 2 and 3 years of age than in older children with ASD (Cox et al., 1999; Stone et al., 1999). Studies have also suggested that RRBs increase as the children get older (Charman et al., 2005; MacDonald et al., 2007; Moore & Goodson, 2003). Another explanation might relate to the ADI-R algorithm's treatment of verbal and nonverbal subjects. A verbal status opens up the possibility of obtaining a higher score on the ADI-R verbal subdomain, where items that do not apply to individuals who are nonverbal come into consideration, such as reciprocal conversation, stereotyped utterances and pronominal reversal, to name a few. Almost

all of the children in group 2 were verbal, i.e., had a functional use of phrases, while this pertained to about half of the children in group 2.

Yet another explanation might be that the parents of the younger children were perhaps not yet aware of the deviant aspect of some of the behaviors present. This might thus reflect, as De Giacomo and Fombonne (1998, p. 135) suggest, "a natural parental ignorance of autistic behaviors". Furthermore, the ADI-R focuses to a large extent on symptoms that parents have observed at 4–5 years of age, when the most prototypical autistic symptoms are present, creating a potential for greater inaccuracy in recall and in reporting of symptoms on the ADI-R for the children diagnosed late.

Direct observation of behavior with the CARS and the ADOS was also a part of the diagnostic process. Because of changes in the diagnostic practice at the SDCC most of the children in the younger group were assessed with the CARS and most of the children in the older group with the ADOS, thus making comparison of observed symptom scores difficult. It was interesting to note, however, that the observed agreement between the ADI-R and CARS results, on one hand, and the ADI-R and ADOS on the other hand, was very similar.

However, the fact that there was no difference between groups 1 and 2 on autistic symptomatology, as measured with the ADI-R, arouses the question why ASD was not identified and diagnosed in children in group 2 until after they started elementary school. This question is especially pertinent for children in this group without previous diagnosis, since their behavioral and/or developmental deviances went unnoticed for a considerable time. The relatively good cognitive and verbal status of many of these children might have contributed to a delay in identification and diagnosis.

The rate of AMC was within the range of what has been reported in population-based studies of individuals with ASD (see Bolton, 2009, for a review). There was no difference between the groups with regard to frequency of AMC as hypothesized. At first glance this result of the group comparison was surprising, since we postulated that the presence of AMC would be associated with more severe developmental problems, resulting not only in an earlier medical and developmental diagnosis but also in earlier identification of the nature of the presenting behavioral symptoms. The nature of the AMC brought the children into an early contact with professionals, which is consistent with other studies that have shown that the presence of a medical condition is associated with an earlier recognition of first disturbances by parents (Baghdadli et al., 2003; De Giacomo & Fombonne, 1998), and a lower age when professionals were consulted (De Giacomo & Fombonne, 1998). It seems that, at least in some cases, the symptoms of the specific AMCs might have masked the symptoms of autism and thus contributed to the delay of ASD diagnosis.

The presence of other neurodevelopmental disorders delayed the diagnosis of ASD, as hypothesized. Half of the children diagnosed with ASD after 6 years of age had previously received other neurodevelopmental diagnosis, but this pertained to few of the children diagnosed earlier (14%). Specific language impairment (SLI), or more specifically a receptive subtype, was the most common previous diagnosis given to children with a late ASD diagnosis ($n = 10$). ASD and SLI share some common features, such that differential diagnosis becomes challenging. Thus, children with semantic-pragmatic deficits have been found to exhibit difficulties in early social development similar to those observed in young children with autism (Vostains et al., 1998). Longitudinal studies of children initially diagnosed with severe SLI of a receptive type have provided evidence for their long-term social impairments (see Charman & Baird, 2002, for a review; Howlin, Mawhood, & Rutter, 2000).

Some children with a clear profile of SLI in middle childhood may later develop symptoms more characteristic of autism, and a proportion of them will then meet the criteria for ASD (Conti-Ramdsen, Simkin, & Botting, 2006). This developmental trajectory perhaps does not apply to our cases with a previous diagnosis of SLI since symptoms of autism were observed by parents at 4–5 years of age, as reflected by their ADI-R scores. It is possible that professionals with whom the children in the present study had been in contact with had focused on the language impairment as a primary deficit, even though clear features of autism were present. This is perhaps in line with what Michelotti, Charman, Slonims, and Baird (2002) found in their study of children who had features of autism, but received a primary diagnosis of severe language disorders, and then all met diagnostic criteria for ASD at follow-up in middle childhood. At the initial assessment, features of autism did not meet criteria for ASD, either in number or severity, or they were thought to be secondary to the language disorder. In the present study, we did not have a formal assessment of autistic symptoms at the time the children were diagnosed with SLI, so we can only speculate about how marked these symptoms were at that time and we do not know if they had indeed increased over time, or had just not been given due attention at initial diagnostic work-up. Since there is an overlap between SLI and ASD, professionals should be aware of the increased risk of ASD and include in their diagnostic battery assessments designed to evaluate ASD if a child presents with a language delay/disorder (Conti-Ramdsen et al., 2006).

ID diagnosis was the second most common diagnosis (previous to ASD) given to children in group 2 in the present study ($n = 8$). Since a high proportion of children with autism are also cognitively impaired (Fombonne, 2009), this presents a challenge for differential diagnosis, especially when children are severely impaired (Vig & Jedrysek, 1999). Thus, the reason for the late ASD diagnosis in this subgroup might be that they were relatively more impaired than those with ID and diagnosed with ASD before 6 years of age. However, this was not the case as the proportion of children with <IQ70 and <IQ50 was exactly the same in those with ID in group 1 and those in group 2 who received an ID diagnosis prior to ASD diagnosis. Neither did a closer look at the symptoms of autism as measured by the ADI-R provide an explanation for late ASD diagnoses of children with an initial ID diagnosis in group 2, since their scores on each of the symptom subdomains did not deviate from the mean scores for those with ID in group 1. Other variables, such as AMC were also similar. Thus, the reason for a late ASD diagnosis of children with ID in group 2 remains unclear.

Other investigators that have studied diagnoses assigned prior to an ASD diagnosis found that in a sample of Medicaid-eligible children in Philadelphia, Pennsylvania, attention deficit/hyperactivity disorder was most common in this respect,

followed by conduct-related disorders, adjustment disorders and cognitive disorders (Mandell, Ittenbach, Levy, & Pinto-Martin, 2007).

We hypothesized that children living in rural areas would be diagnosed later than children living in urban areas, where there may be a greater concentration of specialized professional expertise. To test this hypothesis, two different definitions of rural and urban residence were applied. Neither affected the age of diagnosis, which is indeed encouraging and suggests that in Iceland there are equal opportunities in rural and urban areas for early identification and reference to specialized services, unlike what has been found in larger societies (Mandell et al., 2005). There was no difference between the groups in our study with regard to parents' education as hypothesized, which is also inconsistent with other findings, where a higher level of parent education was associated with an earlier diagnosis (Goin-Kochel et al., 2006).

Our sample was 98% Caucasian, and ethnicity was thus not an issue, as in other studies on identification of ASD and age at diagnosis (Mandell et al., 2009; Shattuck et al., 2009). Icelandic society has been quite homogeneous with regard to race, although this is rapidly changing because of immigration. Reflecting this relatively recent immigration, 8% of the children had a parent who was of non-Icelandic origin and, in the case of one child, both parents were of non-Icelandic origin. If growing up in a bilingual environment is used as a proxy for ethnicity, it did not contribute to a delay in diagnosis, since only two of the eight children were diagnosed late. Our hypothesis that children in group 1 were more likely to have older siblings, was partly supported. Parents' experience with normal child development may have facilitated earlier recognition of developmental problems and thus an earlier diagnosis. However, we do not know if some of the older siblings also had developmental problems. De Giacomo and Fombonne (1998) also found a trend for an earlier age of parental concern for children who had older siblings, although this fell short of statistical significance.

The majority of the parents had concerns about their child's development before the age of three, usually involving language development, a finding which is consistent with other studies (Chakrabarti, 2009; Chawarska et al., 2007; De Giacomo & Fombonne, 1998; Howlin & Moore, 1997; Young et al., 2003). It was interesting to find that there was no difference between the groups with regard to age of first parental concerns, as hypothesized. Most parents probably do not associate these early concerns with autism. Our telephone interview about early concerns took place when all parents had gained some knowledge about autism through the diagnostic process and most of them also through subsequent courses on autism. Upon hindsight, when asked specifically about certain behavioral symptoms of autism, over 80% of the parents thought that their child had shown such symptoms before the age of two, and all except one thought their child had symptoms before the age of three. Despite early emergence of symptoms and early parental concerns, considerable time elapsed until the actual identification of ASD took place. The median age of a diagnosis of ASD was 66 months, which is the same as reported for an entire sample in a large scale population-based surveillance study in the United States (Shattuck et al., 2009).

This study has some limitations. Most of the data were collected retrospectively and the hypothesis that we tested were thus largely confined to the information available in the children's files. Another limitation of this study is inherent in retrospective parental reports that create potential for inaccurate recall and reporting, and more so for parents of children diagnosed late. This applies both to the ADI-R, which focuses to a large extent on symptoms that parents have observed at 4–5 years of age, and to our questionnaire. Parents' knowledge about autism at the time they responded to the questionnaire might furthermore have confounded their memories of their child's early development. A further limitation is the use of different diagnostic instruments for direct assessment of behavior related to ASD. The strength of the current study is that data were systemically collected at a national developmental centre over many years by relatively few clinicians allowing for stability in diagnostic methods and procedures. The study included all children in four birth cohorts in Iceland who had received an ASD diagnosis before the census date, thus excluding selection and/or volunteer bias. The study had access to diagnostic histories and assessment data of all the participants. A formal diagnosis of ASD was based on standardized, well-founded autism diagnostic tools, combined with clinical assessment, thus minimizing case misclassification.

5. Conclusion and recommendations

This study showed that ASD is identified late in many children, even though their parents had concerns at an early age. These were children who had either good cognitive and verbal status and were without a previous diagnosis of developmental or behavioral disorders, or children with a previous diagnosis of which neurodevelopmental disorders were the most common. The importance of early identification and intervention becomes especially urgent in light of evidence that intensive behavioral intervention can affect behavior and brain mechanisms in young children such that "recovery" may be possible in some cases (Helt et al., 2008), and furthermore, that prevention of the full development of ASD is plausible if children at risk are identified and treated early (Dawson, 2008). Since it is most likely that parents bring up their concerns in the primary health care visit that is offered to all children in Iceland from 6 weeks of age, we suggest that steps be taken to educate primary health care staff about ASD, especially regarding the different ways it can emerge in young children (Johnson et al., 2007; Ozonoff, Heung, Byrd, Hansen, & Hertz-Piciotto, 2008). It is an important and attainable goal to find many children with autism during the first 2–3 years of life. However, whilst diagnosis is based entirely on appraising past and present behaviors, without biological markers, it may be unrealistic that all children with ASD can be identified during these early years. From the census date of this study in 2006 we have observed an increase in ASD diagnosis in the study cohort. There are indications that the majority of children diagnosed so late are cognitively high functioning and with relatively subtle autistic symptomatology, which is a subject for further study.

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Paper II

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Implementing an early detection program for autism in primary healthcare: Screening, education of healthcare professionals, referrals for diagnostic evaluation, and early intervention

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ABSTRACT

Background: Improving early detection of children with autism spectrum disorder (ASD) is critical because it allows for earlier intervention, which has been shown to improve outcomes in core behavioral and skill deficits related to ASD. We studied the implementation of an early detection program for ASD in primary healthcare and evaluated its results.

Method: Nine primary healthcare centers in the capital area of Reykjavik, Iceland were randomly selected for participation. The program included the following: screening for ASD with the Modified Checklist for Autism in Toddlers, Revised with Follow-up during routine developmental surveillance at 30 months of age; education of well-child care professionals; referrals for diagnostic evaluation; and early intervention.

Results: Among the 1586 children screened, 26 screened positive and 25 were evaluated, of whom 18 were diagnosed with ASD and six with other neurodevelopmental disorders, giving positive predictive values (PPVs) of 0.72 and 0.96, respectively. The screening detected eight children with ASD who were missed by other referrers. The mean time from screening to intervention was 3.56 months (SD = 4.00), and 18.28 months (SD = 2.72) from screening to diagnostic evaluation. Of the well-child care professionals who attended an educational course, 79 % had not received prior education on ASD. Participation in the course contributed to increased self-perceived knowledge and confidence in identifying behaviors indicating ASD.

Conclusion: The screening was well received by stakeholders, and PPV for ASD was relatively high, providing evidence of its feasibility. The long wait-time for diagnostic evaluation and the lack of ASD education among well-child care professionals needs to be addressed.

1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by impairments in social interaction, communication, and restricted and stereotyped interests or behaviors (American Psychiatric Association., 2013; World Health

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Organization., 1992). A report of the global prevalence estimate of ASD indicates an increase over time (Elsabbagh et al., 2012), a trend that started in the late 1980s (McDonald & Paul, 2010). In Iceland, the prevalence was estimated to be 1.2 % in school-aged children born between 1994 and 1998 (Saemundsen, Magnusson, Georgsdottir, Egilsson, & Rafnsson, 2013), and it has more recently been found to be 2.7 % in children born between 2006 and 2008 (Delobel-Ayoub et al., 2020). This new estimate falls within the range of that reported for a similar age group in a recent study in the United States (Baio et al., 2018).

The symptoms of ASD usually manifest in infancy or early childhood. Development appears to be generally intact for the first 6 months of life in children later diagnosed with ASD (Ozonoff et al., 2010; Zwaigenbaum, Bryson, & Garon, 2013). However, prospective studies have found evidence of prodromal symptoms by 6 months of age (Canu et al., 2020; Yirmiya & Charman, 2010). Symptoms in the core social-communication domains of ASD are observable by 12 months in some children, but they usually become pronounced between 14 and 24 months and continue diverging from normal development throughout the third year (Jones, Gliga, Bedford, Charman, & Johnson, 2014; Landa, Gross, Stuart, & Faherty, 2013). Other children attain developmental milestones that are then followed by a developmental plateau or by loss of skills during the second year of life (Landa et al., 2013; Pearson, Charman, Happe, Bolton, & McEwen, 2018).

A reliable diagnosis can be made in children as young as 2–3 years of age (Chawarska, Klin, Paul, & Volkmar, 2007; Landa, 2008). However, considerable time often elapses between the initial concerns and the formal diagnosis of ASD. The median age of ASD diagnosis was 66 months in an Icelandic study, despite early parental concerns (Jónsdóttir, Saemundsen, Antonsdóttir, Sigurdardóttir, & Ólason, 2011). A review of 42 studies found that the median age at diagnosis for ASD ranged from 36 to 82 months. Among the factors associated with age at diagnosis were symptom severity, socioeconomic status, interaction with the service system, and study methods (Daniels & Mandell, 2013). More recent studies report a median age at ASD diagnosis of 52 and 55 months, indicating that there is still need for improvement in terms of earlier detection and diagnosis (Baio et al., 2018; Brett, Warnell, McConachie, & Parr, 2016).

There is evidence that early detection and intervention is advantageous for children with ASD (Estes et al., 2015; MacDonald, Parry-Cruwys, Dupere, & Ahearn, 2014, Zwaigenbaum et al. 2015a). Children diagnosed after they start elementary school have already missed the opportunity to benefit from intervention during their early years, when brain plasticity is at its optimum level (Dawson, 2008; Pierce, Courchesne, & Bacon, 2016). Delayed diagnosis may also result in increased burden and cost for families and communities with respect to long-term care for individuals with ASD (Baxter et al., 2015; Buescher, Cidav, Knapp, & Mandell, 2014). Considering the rising prevalence of ASD, the delay in diagnosis for many children, and the burden of the condition, ASD is a public health concern that calls for preventive actions.

There has been an increased effort to screen for ASD in young children with the aim of enhancing early detection and intervention. The American Academy of Pediatrics (AAP) added weight to this initiative with its recommendation that all children be screened with an ASD-specific tool at 18 and 24 months of age, in addition to general developmental surveillance and screening (Johnson, Myers, & the Council on Children with Disabilities, 2007). Although screening studies have demonstrated effectiveness in detecting young children with ASD (Daniels, Halladay, Shih, Elder, & Dawson, 2014; Zwaigenbaum et al., 2013), the adoption of population-based or universal screening has been a subject of debate (Al-Qabandi, Gorter, & Rosenbaum, 2011). This debate escalated when the US Preventive Services Task Force (USPSTF) issued a report in 2016 stating that there is insufficient evidence to recommend for or against universal screening for ASD in children aged 18–30 months. Of particular concern was the lack of studies on the long-term outcomes of children who have been detected through screening. However, the report did find evidence for valid screening instruments for the above age group and evidence that early intervention has positive effects on the prognosis for children with ASD (McPheeters et al., 2016; Siu et al., 2016).

Many investigators in this field have responded to the USPSTF report by expressing concerns and providing empirical evidence against withholding universal screening for ASD while waiting for more research to be carried out. Among their arguments is that early universal screening is more effective in identifying children with ASD than are parental or physician concerns, resulting in a lowered average age of diagnosis and earlier access to intervention (Coury, 2015; Dawson, 2016; Fein, 2016; Mandell & Mandy, 2015; Pierce et al., 2016; Robins et al., 2016). The USPSTF assumption that children for whom no concerns have been raised and are thus targeted for universal screening are less symptomatic than other children with ASD has been refuted (Coury, 2015; Pierce et al., 2016), and their assumption that intervention studies have not included screened children has been questioned (Fein, 2016; Mandell & Mandy, 2015). Moreover, screening has the potential to reduce social inequalities in age at diagnosis and access to services (Coury, 2015; Dawson, 2016; Fein, 2016; Mandell & Mandy, 2015; Robins et al., 2016). Although it can be argued that scientific evidence supports universal screening for ASD, such screening is not warranted if other services are not readily available for children who screen positive and their families (Fein, 2016; Mandell & Mandy, 2015; Pierce et al., 2016). Thus, studies on the efficacy of screening should include several links in a process chain that also includes diagnostic evaluation, intervention, and the clinical outcomes that result from these services (Silverstein & Radesky, 2016).

In Iceland, there exists a standard procedure for developmental surveillance. This procedure consists of regular well-child visits in public primary healthcare centers for the first four years of life. The developmental surveillance is assisted by the use of broadband developmental screening tests. Prior to this study, there had been no attempts at systematic screening for ASD in Iceland. As soon as professionals in the primary services become aware of signs that may indicate impairment, they have a legal obligation to inform the parents and to take measures in collaboration with the family to refer the child to early intervention and assessment at a secondary service level. Thus, in terms of intervention, the child is given the benefit of the doubt before diagnostic results are available. Early intervention on a daily basis is provided in preschools. The number of hours provided in special education before diagnosis is confirmed is tentative and can vary based on the child's needs and community regulations. Some children are referred to private practitioners for additional services such as speech and language therapy and physiotherapy. If the initial assessment indicates a neurodevelopmental disability, the child is then referred to a tertiary institution for diagnostic assessment. During the diagnostic

process, the child's needs for intervention are reassessed, both in terms of intensity and teaching methods in the preschool, and the need for additional services. A diagnosis of ASD always leads to a recommendation to use ASD-specific evidence-based intervention methods, if the use of such methods has not already been initiated to some degree. The diagnosis may also result in increased hours in special education. Since universal screening for ASD has the potential to lower the age at diagnosis, it may benefit children in Iceland by providing them with earlier access to more specific and intensive evidence-based interventions. This is crucial, since age at the start of intervention has been linked to outcomes in core behavioral and skill deficits related to ASD (Fuller & amp, 2019).

The Modified Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001) and the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F; Robins et al., 2014) are the screening instruments that have been most widely studied and adopted in primary healthcare. The M-CHAT is a brief questionnaire for parents, and a follow-up interview has been developed to reduce a relatively high false positive rate (Kleinman et al., 2008; Robins et al., 2001). A large validation study in the United States of the revised version, the M-CHAT-R/F, found that the instrument significantly reduced the initial screen-positive rate, increased the detection rate for ASD, and lowered the age of ASD diagnosis by 2 years compared with recent surveillance findings (Robins et al., 2014). These instruments have demonstrated the strongest evidence according to the USPSTF (McPheeters et al., 2016).

Population-based screening studies that have used the M-CHAT-R/F have reported sensitivity and specificity above 70 %–80 % (Guo et al., 2019; Magan-Maganto et al., 2018; Robins et al., 2014), which has been estimated to be acceptable for developmental screening instruments (Charman & Gotham, 2013). Less encouraging results have also been reported in large-scale population-based studies using the M-CHAT and the M-CHAT/R, where sensitivity was as low as 34.1 % (Stenberg et al., 2014) and 38.9 % (Guthrie et al., 2019). Children with ASD who are missed by a screen may experience delays in receiving services. Indeed, Guthrie et al. (2019) found that the mean time to diagnosis was 7.5 months shorter for children with ASD who screened positive than for those who screened negative. Given the importance of detecting children with ASD and initiating intervention at the earliest possible age, screening efforts require instruments with relatively high sensitivity in order to minimize false negative cases. Reports of low screening accuracy may undermine the feasibility of universal screening for ASD. However, as has been mentioned above, there are strong arguments for continuing universal screening in primary care while research continues to fill in the gaps where evidence or improvement is still needed. In fact, as noted by Zwaigenbaum and Maguire (2019), "the potential added value of ASD screening must be considered relative to what would happen in its absence" (p. 2).

Improving the early detection of ASD also involves other activities, such as increasing awareness among parents and professionals of developmental milestones and early signs of ASD. Some awareness studies have focused on the education and training of primary healthcare professionals (Daniels et al., 2014; Major, Peacock, Ruben, Thomas, & Weitzman, 2013). This is an important undertaking, since surveys have shown that these professionals' knowledge of ASD and self-perceived competence in providing primary care to children with ASD are inadequate (Golnik, Ireland, & Borowsky, 2009; Heidgerken, Geffken, Modi, & Frakey, 2005; Will, Barnfather, & Lesley, 2013). Among the variables that have been found to be associated with primary care physicians' knowledge in this field is continuing medical education on ASD (McCormack, Dillon, Healy, Walsh, & Lydon, 2019). There are limited opportunities available in Iceland for professional development related to ASD for those who work in primary healthcare. For instance, the State Diagnostic and Counseling Center (SDCC) provides regular one- to three-day courses on ASD and teaching methods and holds occasional conferences on the subject, but other opportunities are lacking. A review of the literature indicates that effective educational approaches to improve knowledge for these professionals exist. Such approaches have used a variety of teaching methods, including lectures, case studies, workshop training, and videos (McCormack et al., 2019). When developing a course for primary healthcare professionals, who collaborated with us in this study, we sought inspiration from the Autism Case Training (ACT): A Developmental-Behavioral Pediatrics Curriculum (Centers for Disease Control & Prevention., 2016). Findings from the study of Major et al. (2013) indicate that the ACT curriculum was well received and was associated with increased short-term knowledge and increased self-perceived competence in communicating with families about ASD.

The results of ASD early detection studies in one country may not be generalizable to other countries. Not only does the organization of primary healthcare systems and practices vary, but the variations in awareness and knowledge of ASD and population and cultural characteristics may also play a role. No information is available on the potential benefits of adding screening for ASD to the developmental surveillance program in Iceland or on the knowledge of ASD among well-child care professionals. This is the first part of a prospective study that aims to address this gap in the literature by attempting to increase the knowledge base on early detection of ASD in Iceland. The aim is to study the implementation of an early detection program for ASD within well-child care in primary healthcare centers (PHCs) and to evaluate its initial outcome. The research questions of the present study are as follows: (1) What is the length of time from screening positive to diagnostic confirmation? (2) Will screening for ASD with the M-CHAT-R/F detect and refer more children with the condition than does the usual developmental surveillance? (3) How do well-child care professionals assess their knowledge of ASD and confidence in detecting indications of ASD when using a retrospective pre-test and post-test method? (4) How will screening for ASD be rated by nurses in well-child care who were contact persons between the PHCs and the study? (5) What is the rate of parental participation in the screening and use of psychological services after participation? (6) What is the length of time from screening positive to the start of intervention?

2. Method

2.1. Setting

Iceland's population was 343,000 during the period of study, with just over 4000 live births per year (Statistics Iceland, 2020a). The healthcare system is state-run and covers the whole country. There are public PHCs throughout the country that offer a broad

range of primary care services, including well-child care and immunizations. Parents are free to choose to obtain services at any PHC they want, whether or not they are registered there. Besides the free services of the PHCs, parents can also access medical specialists outside the PHC system. Thus, many parents of children with disabilities have established contact with a pediatrician in addition to the PHC services.

Well-child care is provided by nurses and doctors at the PHCs. The nurses pay home visits to families with newborn babies to observe growth and development. The children then visit the PHC 11 times during the first four years. They are always seen by a nurse, and at 6 weeks, 10 months, and 18 months of age they are also seen by a family doctor or a pediatrician. The main emphasis is on developmental surveillance and carrying out a comprehensive vaccination program. Developmental surveillance is assisted by a formal instrument at 12 and 18 months of age using the Parents' Evaluation of Developmental Status (PEDS). The PEDS is a brief questionnaire which parents have the option to complete on their own or to have someone go through it with them (Glascoe, 2009). In our experience, parents usually choose to fill out the questionnaire themselves. The PEDS is administered again at 30 and 48 months of age, accompanied by the Brigance Screens (Brigance, 2017). Developmental surveillance is rarely combined with autism-specific screening instruments.

The screening for ASD was implemented during well-child visits at 30 months in nine PHCs in the capital area of Reykjavik, Iceland. These nine PHCs were randomly selected from among the 17 centers in that area. In contrast to many other countries, Iceland does not offer well-child visits at 24 months. Thus, when planning the study, we had the option to select either the 18- or 30-month well-child visits (or both) for the ASD screening. We decided to select the 30-month visits, since screening at this age tends to be associated with a lower false positive rate than screening at 18 months (Zwaigenbaum et al., 2015b). We considered screening at 30 months to be advantageous, because part of the early detection project involved studying the implementation of the ASD screening and the feasibility of adding it to the developmental surveillance. At the same time, we minimized the risk of burdening our diagnostic services with too many referrals of cases that would turn out to be false positives.

2.2. Participants

Parents of all children scheduled for their 30-month well-child visit from March 2016 through October 2017 at the nine PHCs were invited to participate in the study. Of the 2201 children who completed the well-child visit, written informed consent was obtained from the parents of 1588 children. Two children who screened positive were excluded from the analysis, as they had already been referred for evaluation due to suspected ASD. Table 1 shows demographic data for the remaining 1586 participants.

2.3. Measures

2.3.1. Screening instrument

The M-CHAT-R/F is a two-stage parent-report screening instrument designed to identify children 16 to **30** months of age who should receive a more thorough assessment for possible ASD or developmental delay. In the first stage, parents complete the M-CHAT-R, which includes 20 yes/no questions. If the total score is 3–7, it is strongly recommended that the follow-up interview (FUI), the second stage of the MCHAT-R/F, is administered. If a child receives a total score of 8 or higher, it is acceptable to bypass the FUI and make appropriate referrals. The FUI is usually a telephone interview. In order to obtain additional information on behaviors indicating ASD, parents are asked structured questions based on the items that the child failed.

If the score is 2 or higher at the completion of the FUI, the child has screened positive, and it is recommended that an immediate referral for diagnostic evaluation and early intervention be made (Robins, Fein, & Barton, 2009). This process was carried out for all screen-positive cases in our study.

With the permission of Dr. Robins, the M-CHAT-R/F was translated into Icelandic by two of the authors (SLJ and ES). It was then back-translated by a third author (GSH), and discrepancies with the original text were resolved in discussions among the translators. The translation was reviewed by a colleague and a linguistic expert. Minor cultural adaptations were made pertaining to examples of

Table 1
Sample demographics (N = 1586).

Characteristics	
Age in months at screening, mean (*SD*)	31.66 (1.72)
Gender, *n* (%)	
Male	801 (50.5)
Female	785 (49.5)
Nationality, *n* (%)	
Both parents Icelandic	1469 (92.6)
One parent Icelandic	28 (1.8)
Both parents Polish	47 (3.0)
Other	42 (2.6)
Person who answered the M-CHAT-R, *n* (%)	
Mother	1325 (83.5)
Father	219 (13.8)
Both parents	42 (2.7)

toys in question 3 of the FUI. Children in Iceland often use Playmobil and Lego figures in their play, so to specify what was meant by "an action figure" ("Does he/she ever put an action figure or doll into a car …? "), we replaced this wording with "a Playmobil or Lego figure." The instrument was piloted on a group of 10 parents. They were asked to report any items or examples that were unclear. One of the translators (SLJ) who administered the screening was at the same time alert to possible misunderstandings. No further cultural adaptation or change of wording was needed after this procedure.

2.3.2. Questionnaire on pre- and post-course knowledge

A questionnaire was designed for well-child care professionals to complete at the end of an educational course. This form included eight questions for which the respondents were asked to rate their knowledge of ASD in relation to the course objectives, which were the following: (1) international diagnostic criteria; (2) risk factors; (3) early signs; (4) parental concerns; (5) etiology; (6) co-occurring conditions; (7) prevalence; and (8) early intervention. One question pertained to respondents' confidence and skill in identifying early indications of ASD. Immediately after the completion of the course, the participants were asked to provide ratings based on a retrospective pre-test and post-test method. There is evidence that this method allows for a more accurate estimate of change than does the traditional pre- and post-test approach, causing less response-shift bias (Lam & Bengo, 2003). In addition, the participants were asked to assess how useful they thought the course would be in their daily work and their overall satisfaction with the course. All questions were rated on a four-point Likert scale (1 = limited, 4 = very good).

2.3.3. A survey on experiences and attitudes

A post-screening survey about the experience of the screening program and attitudes towards screening for ASD was designed for contact persons at each of the participating centers to complete. This survey included five statements (see Table 3) with five response options that were rated on a Likert scale (1 = strongly disagree, 5 = strongly agree). Space was also provided for open-ended feedback.

2.4. Procedure

The implementation was inspired by a conceptual *Model of diffusion, dissemination, and implementation of innovations in health service delivery and organization.* This is an evidence-based model that takes into account the many complex factors and their interactions when considering innovations in health service delivery, and is mainly intended as a memory aide (Greenhalgh, Robert, Macfarlane, Bate, & Kyriakidou, 2004). Based on this model, several strategies were used in the preparation and implementation process. Among these strategies were efforts to guaranty organizational support at all levels by involving key people in the planning and implementation, dissemination of knowledge through courses, and ongoing support and feedback on the screening.

During the preparation phase, the project was introduced to the Director of Health, the administrators of the Primary Healthcare in the Capital Area, and the Development Center for Primary Healthcare in Iceland. After receiving encouragement to follow through with the project, a steering committee was formed to oversee the implementation of work processes for the ASD screening; this committee also provided feedback on the study design. The committee included representatives from the PHC and the SDCC. One committee member was the study's contact person with the PHC's directorate, as well as a contact person with all the participating centers. After introductory meetings at the PHCs, they all agreed to participate in the study. Each center then nominated its own contact person to ensure that the ASD screening ran smoothly. All the contact persons were experienced nurses and project managers at their respective PHCs. The committee held three meetings with the contact persons to exchange experiences and to boost continued adherence to the screening procedures.

2.4.1. An educational course

All professionals in well-child care at the participating PHCs were offered a half-day course on ASD. The main emphasis was on early indications of ASD. Content material was based primarily upon the first module from the ACT Curriculum from the Centers for Disease Control and Prevention (Centers for Disease Control & Prevention., 2016). The course also included presentations on the following: prevalence; diagnostic criteria; screening; communication of developmental concerns to parents; and the importance of early detection, diagnosis, and intervention.

2.4.2. The screening stages

One week before a scheduled visit, parents were sent a letter containing information and an invitation to the study. The letter was available in six languages in addition to Icelandic, as recommended by the PHC staff. During the visit, a nurse mentioned the study and provided a consent form. The parents were then asked to answer the M-CHAT-R after they completed the PEDS. The nurses collected the M-CHAT-R from the parents and sent the forms to the investigators for scoring. The potential risk of parents experiencing emotional distress was addressed in the letter, and an interview with a psychologist unrelated to the study was offered free of charge.

The first author conducted the FUIs by telephone with parents of all children with a total score of 3 or higher on the M-CHAT-R. Although the FUI can be bypassed if the score is 8 or higher, this option was not chosen, in order to maintain consistency. If a child still screened positive at the completion of the FUI (with a score of 2 or higher), the parent was informed about the results during the same telephone call and was asked for permission to refer the child for further assessment and early intervention.

2.4.3. Referrals to evaluation and early intervention

Children who screened positive were referred to the SDCC for evaluation. The SDCC is a tertiary institution that receives referrals from the whole country for children who are suspected to have serious neuro-developmental disorders. This institution provides an interdisciplinary evaluation that includes at least a physical and neurological examination by a pediatrician, an assessment by a psychologist with the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012) in Icelandic, and an interview with parents by a social worker. Diagnosis is based on the ICD-10 classification system (World Health Organization., 1992). The service center in the child's neighborhood was informed of the referral and asked to perform cognitive assessment and to provide appropriate intervention in the preschool. The nurses at the PHCs were blind to the M-CHAT-R results and were asked to make their own decisions about referrals independent of the ASD screening.

In a separate study, the participants will be followed-up after their well-child visit at 48 months of age to identify false negative cases.

2.5. Data analysis

Descriptive statistics summarized demographic data, participation rate, screening results, sources of referrals, data on early intervention, and questionnaire and survey results. Pearson's correlation coefficient was used to measure the bivariate correlation between work experience in well-child care and pre-course ASD knowledge. A dependent *t*-test was used for comparisons between pre- and post-course ratings, and the effect size *r* was calculated. The Mann-Whitney *U* test was used to test differences in early intervention services between children diagnosed with ASD and children not diagnosed with ASD. A significance threshold was set at 0.05. Statistical analysis was performed using SPSS 23.0 for Windows.

2.6. Ethics

Permissions to perform the study were granted from the National Bioethics Committee of Iceland (VSNb2015110029/03.01), the Scientific Committee of the Healthcare of the Capital Area and the University of Iceland, and the Scientific Committee at the SDCC. The study was approved by the Icelandic Data Protection Authority.

3. Results

3.1. Attendance and participation rates

A total of 2531 children born at the target age of the study were registered at the participating PHCs. Of these children, 2201 (87 %) came for their 30-month visit, and of those, 1586 (72.1 %) agreed to participate in the study; these participants constituted 62.7 % of the total target population. The participation rates in the ASD screening among the PHCs ranged from 51.7 %–95.2 %. The difference in number between those attending the 30-month visit (2201) and those participating in the ASD screening (1586) was 615 children. Of these, 60 parents declined to participate, and two children had been identified with an indication of ASD before the screening. The rest failed to receive an invitation to the screening or visited PHCs that were not included in the study.

3.2. Screening

Of the 1586 participants, 63 (4 %) initially screened positive (with a score of 3 or higher) on the M-CHAT-R. The male-female sex ratio was 2.2:1. All parents of these children could be reached by telephone and agreed to take part in the FUI. The length of time from screening to the FUI ranged from six to 45 days ($M = 19.88$, $SD = 10.95$), with the longest period of time occurring over the summer holidays. Twenty-six children (sex ratio 4.2:1) screened positive after the FUI (41.3 % of the children who initially screened positive, and 1.6 % of the total sample). The parents of these 26 children agreed to have their child referred for diagnostic evaluation and early intervention.

3.3. Diagnostic evaluation

Fig. 1 shows that 25 children (male-female sex ratio 4.0:1) screened positive on the M-CHAT-R/F and completed the diagnostic evaluation, but one child had moved abroad and thus was not evaluated. Eighteen children were diagnosed with ASD, six received a diagnosis other than ASD, and one child did not receive a clinical diagnosis. The positive predictive value (PPV) of the M-CHAT-R/F was 0.72 for ASD and 0.96 for any developmental disorder. Their mean age was 32.08 months ($SD = 2.14$) at screening and 51.00 months ($SD = 2.22$) at diagnosis. The average time between screening and diagnosis was 18.28 months ($SD = 2.72$).

The estimated ASD prevalence was 0.80 %, 95 % CI [0.45, 1.15] when accounting for the two children who had been detected and referred prior to the screening; these children were excluded from other analyses.

3.4. Referrers

Of the 25 children who were evaluated, six were also detected by well-child care professionals with indications of ASD; these six children were referred for evaluation, independent of the screening. Three of them were diagnosed with ASD and three with other

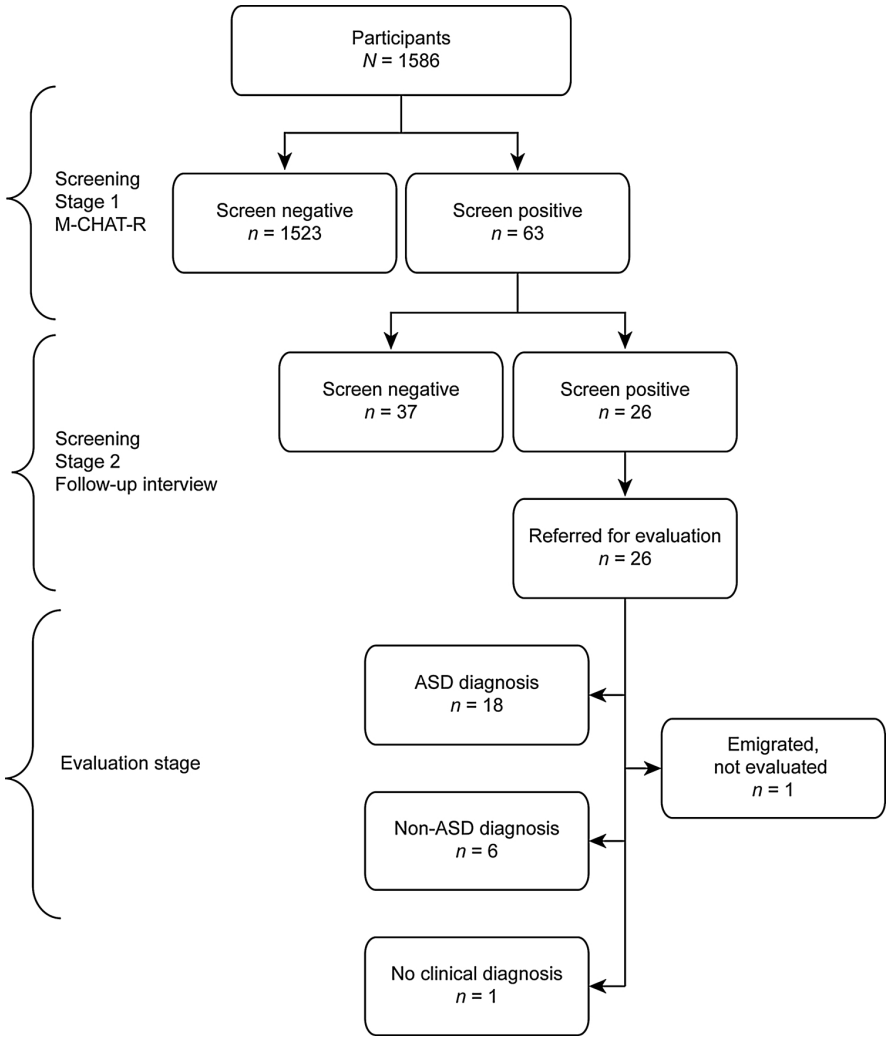

Fig. 1. Flowchart of the screening and evaluation stages.

neurodevelopmental disorders. The preschools flagged another eight children around the time of the screening and were preparing referrals. Seven of these children were diagnosed with ASD and one with another disorder. Of the 11 children who were referred only by the study, eight were diagnosed with ASD, two were diagnosed with other disorders, and one child did not receive a clinical diagnosis.

3.5. Educational course

Fifty-six well-child care professionals from the participating PHCs, or over 90 % of the targeted group, attended the educational course. Fifty-two were nurses, three were pediatricians, and one a GP. All except one were female. Their work experience in well-child care ranged from being recently employed to 38 years (M_{yrs} = 11.05, SD = 9.40). Seventy-nine percent reported that they had not received any previous education on ASD. The association between length of work experience in well-child care and retrospective pre-course ASD knowledge (r = 0.12) was non-significant (p = 0.401, two-tailed). Table 2shows the results of pre- and post-self-assessments.

3.6. Experiences and attitudes towards screening for ASD

Ten nurses, who were contact persons at their respective PHCs, answered the survey about their experience with the screening program and attitudes toward screening for ASD. Two of them came from the same center, where they had taken shifts at different

Table 2
Mean and standard deviation (SD) of pre- and post-course self assessment scores of well-child care workers (N = 56).

Questions and statements[a]	Pre-course Mean (*SD*)	Post-course Mean (*SD*)	*t*	*r*
Knowledge of ASD[b]	2.13 (0.47)	3.11 (0.33)	−20.87***	0.94
Confidence and skill in identifying indications of ASD	2.12 (0.51)	3.16 (0.69)	−11.53***	0.85
Usefulness of the course for daily work		3.63 (0.52)		
Overall satisfaction with the course		3.65 (0.52)		

ASD: Autism spectrum disorder.
[a] 1 = limited, 4 = very good.
[b] A summary of responses to eight questions.
*** $p \leq 0.001$.

Table 3
The PHCs 'contact persons (N = 10) responses to questions about screening for ASD.

Statements[a]	Mean (*SD*)
Parents were generally willing to answer the screener	4.90 (0.32)
Parents answered the screener without assistance	4.70 (0.48)
Screening for ASD was easily integrated into the scheduled visit	4.50 (0.53)
I would like to receive training in using the follow-up interview	4.10 (0.57)
Screening all young children for ASD should be formally adopted	4.80 (0.42)

PHC: Primary healthcare clinic; ASD: Autism spectrum disorder.
[a] 1 = strongly disagree, 5 = strongly agree.

time periods during the study. The nurses all expressed having positive experiences with the program, as reflected both in a discussion session at a final evaluation meeting and in their survey responses (see Table 3). Although the nurses indicated an interest in being trained to use the FUI, they were concerned about how to provide extra time for it when needed. They expressed a positive attitude towards the adoption of universal screening for ASD, and there was an interest in doing so at both the 18- and 30-month well-child visits.

3.7. Parental participation

The majority of parents who brought their child to the 30-month well-child visit (72.0 %) agreed to participate in the first screening stage. All parents of children who initially screened positive agreed to participate in the FUI, the second screening stage. The PHC with the lowest participation rate (51.7 %) also had the highest rate of immigrants. No parent chose to consult a psychologist as a result of emotional stress related to participation in the study.

3.8. Early intervention before diagnostic evaluation

At the time of screening, the 25 children who were referred for diagnostic evaluation attended preschool for eight to nine hours per day. The mean length of time between screening and the beginning of early intervention was 3.56 months (*SD* = 4.00). The intervention consisted of special education in the preschool, where two-thirds of the children were in an autism-specific comprehensive program based on applied behavior analysis (n = 8) or the TEACCH program (n = 8). The average number of hours in special education per week was 21.67 (*SD* = 8.36). Twelve children received one or more additional services from private practitioners, most often consisting of speech and language therapy (n = 9), as well as physiotherapy (n = 3) and occupational therapy (n = 1). Parents of four children received home consultation because of sleep or other challenging behaviors, and one child was on psychotropic medication targeting such behavior. Parents of 11 children attended courses on autism and teaching methods. A comparison between intervention services for children diagnosed with ASD and children not diagnosed with ASD is shown in Table 4.

4. Discussion

This study presents the initial results of an early detection program for ASD in primary healthcare in Iceland. It included screening with the M-CHAT-R/F in connection with regular developmental surveillance of 1586 children at 30 months of age in nine randomly selected PHCs, an educational course on ASD for well-child care professionals, and referrals for diagnostic evaluation and intervention. More children in the study sample were detected and referred with indications of ASD based on the M-CHAT-R/F than were referred independent of the screening. This finding is consistent with those of other studies showing that brief but focused observations by experienced clinicians (Gabrielsen et al., 2015) and the use of broadband developmental instruments, such as the PEDS (Pinto-Martin et al., 2008), fail to identify many children with ASD. The well-child care professionals had referred six of the 25 screen-positive children who were evaluated, and the preschool services had referred eight. Thus, 11 children were referred solely by

Table 4
Early intervention before diagnostic evaluation by diagnostic groups.

	ASD diagnosis (n = 18)	Not an ASD diagnosis (n = 7)	U
Wait time in months for early intervention, median (*SD*)	3.50 (3.60)	4.00 (5.58)	59.50[a]
Hours in intervention per week in preschool, median (*SD*)	20.00 (7.48)	20.00 (10.58)	55.50[a]
Comprehensive intervention			
ABA, *n* (%)	7 (38.9)	1 (14.3)[b]	
TEACCH, *n* (%)	8 (44.4)	0[b]	
Additional intervention, *n* (%)	9 (50.0)	4 (57.1)[b]	
Parents attended courses, *n* (%)	9 (50.0)	2 (28.6)[b]	

ASD: Autism spectrum disorder; ABA: Applied behaviour analysis; TEACCH: Treatment and education of autism and related communication handicapped children.
[a] $p > 0.05$.
[b] Too few participants in the group for statistical comparison.

the study, of whom eight were diagnosed with ASD. These children would perhaps not have been identified until later, lending some support for the use of an ASD-specific screening procedure in well-child care.

Similar to other studies, the M-CHAT-R/F detected children with different developmental disorders in addition to children with ASD. However, this was not considered a drawback, since these children are also in need of early intervention. In the initial validation study of the M-CHAT-R/F, the PPV was 0.47 and 0.95 for ASD and for any developmental delay, respectively (Robins et al., 2014). The present study found a somewhat higher PPV for ASD (0.72) but a similar PPV for all disorders (0.96). The average age of the participants was 10.72 months older than the age of the participants in the study by Robins et al. (2014). Since the behavioral signs of ASD emerge over time (Ozonoff et al., 2010), this age difference may account for some of the above differences in PPV.

In a recent study, variability in autism symptom trajectories, as measured by the ADOS, were observed over time in young children referred for possible ASD. Four clusters with approximately equal proportions were identified: worsening, severe-persisting, moderately-improving, and non-spectrum, which included children who consistently scored below the ADOS cutoff for ASD (Kim et al., 2018). Considering the relatively long period of time that passed from screening to evaluation in our study, a change in the severity of symptoms, i.e., worsening in some cases and improving in other cases, was expected for many children. Thus, it is possible that in some of the false positive cases, the symptoms identified as indicating ASD might have ameliorated as a result of maturation or intervention, and in other cases, the symptoms might have followed a subthreshold trajectory from the beginning.

The estimated prevalence of ASD in this study was 0.80 %, which is similar to that reported in a population screening study in Sweden with children of similar age (Nygren et al., 2012). However, it is much lower than the most recent estimate of 2.7 % among children in Iceland (Delobel-Ayoub et al., 2020). Different methodologies may explain this gap, to which age and time are contributing factors. In the study by Delobel-Ayoub et al. (2020), the prevalence of ASD was estimated in 2015 when the children were 7–9 years of age, while the present study estimated the prevalence in 2018 when the children were 30 months of age. We do not yet have follow-up data of screen-negative children, some of whom might have presented with small or subtle signs of ASD that may not unfold until later (Landa, et al., 2013; Ozonoff et al., 2018).

A high proportion of the well-child care professionals who participated in the course had not received any previous education on ASD. This is similar to what has been found in other studies. Limited knowledge and a need for information and training were among the key themes identified in a review of studies of healthcare providers' experiences with ASD (Morris, Greenblatt, & Saini, 2019). Self-perceived post-course knowledge, as well as confidence and skill in identifying ASD, showed significant improvements in mean scores compared to retrospective (prior to the course) scores. Comparable short-term improvement was observed in a study including all seven modules in the ACT curriculum (Major et al., 2013). Continued education and experience in the field of ASD is needed to sustain knowledge (McCormack et al., 2019). However, other interventions are also essential to bring about long-term sustained behavior and practice change among primary healthcare professionals, such as improved detection of children with ASD. Among such interventions, collaborative team-based approaches have been found to be effective (Carbone, Norlin, & Young, 2016; Chauhan et al., 2017).

When planning this project, we introduced it to administrators at all levels at the PHC. They all expressed interest and willingness to support the implementation as planned. At the completion of the screening period, the contact persons at the participating centers expressed satisfaction with the program. However, the response rate among the PHCs varied from 52 % to 95 %. One possible reason for this is that parents are not obliged to bring their children to the PHC at which they are registered but rather can choose to attend another PHC. We were not able to keep track of such movements. Another reason that was expressed at meetings with the contact persons was a failure to send out invitations and consent forms to parents to participate in the study or to follow-up on this issue during the visit. This challenge was related to insufficient communication within some of the centers. Additionally, when meeting new tasks, healthcare personnel may be pressed for time in very busy PHCs, which has been identified as one of the challenges with screening in primary child care (Barton, Dumont-Mathieu, & Fein, 2012; Dosreis, Weiner, Johnson, & Newschaffer, 2006). However, once the parents had been given the M-CHAT-R to complete, there was no difficulty in integrating it within the time limits of each visit.

Our data suggest that the project was generally well received by parents. Parental refusal to participate was relatively rare. The

main reason given was that the parents did not see the need for the child to be screened for ASD or other developmental disabilities. This finding is consistent with the literature showing that parents of children with more apparent atypical development are more likely to participate in screening (Garcia-Primo et al., 2014). No parent made use of the offer to consult a psychologist, suggesting that participation in the screening did not evoke undue anxiety. A similar result was obtained in a study in which most parents did not report anxiety after seeing the results of the M-CHAT (Harrington, Bai, & Perkins, 2013). Another indication of parental acceptance was the 100 % compliance between the screening stages, as well as the acceptance of the diagnostic evaluation. The contrary was found in recent population-based ASD screening studies using the M-CHAT-R/F (Brennan, Fein, Como, Rathwell, & Chen, 2016; Guo et al., 2019; Magan-Maganto et al., 2018; Robins et al., 2014). The high compliance rate in Iceland is perhaps due to the rather small community and a generally high economic and educational level, according to OECD data (2019b, OECD, 2019a). Thus, the socioeconomic and educational barriers found in other studies (Kara et al., 2014; Khowaja, Hazzard, & Robins, 2015) may have had a minimal effect in the present study. This may also be reflected in the relatively low initial screen-positive rate (4 %) in our study, given that inflated initial screen-positive rates have been associated with lower parental education and racial minorities (Khowaja et al., 2015).

In light of the long waiting time for evaluation, it was encouraging to find that early intervention was initiated for all screen-positive children before diagnosis was confirmed. Although the average time from screening to intervention was around three months, there were great variations in time. Of particular concern is that seven of the 25 children did not receive such services until seven to 11 months after screening. Early access to diagnosis and intervention is important not only for the child, but also for the family, as it has been associated with greater satisfaction with the services provided (Bejarano-Martin et al., 2019). The initiation of early intervention before a formal diagnosis for children suspected of ASD has also been documented in other studies. However, contrary to our results, children later diagnosed with ASD were more likely to receive services (Monteiro et al., 2016) and received significantly more intervention hours (Pierce et al., 2011) than children who were not diagnosed with that condition. Although our study showed no differences in early intervention hours based on the diagnostic results, a higher proportion of children diagnosed with ASD were in a comprehensive intervention program and had parents who attended courses compared to children who were not diagnosed with ASD. Once diagnosis was confirmed, the service needs of the child and the family were reconsidered, but the extent to which this approach may change the quantity and focus of the intervention needs to be examined in greater detail in a future study.

This study has several limitations. The demographic data were limited; thus, we do not know if the characteristics of the parents of the participating children were comparable to those of parents in the general population. However, the 2531 children registered at the participating PHCs constitute approximately one-third of the total number of children of the target age in the Icelandic population. The data on nationality indicates that children of non-native parents were underrepresented in the study (7.4 %), even though we made an effort to provide all printed material in different languages and had translation services available. Immigration is increasing in Iceland; in 2017, 14.2 % of inhabitants in the capital area were first- or second-generation immigrants (Statistics Iceland, 2020b). Barriers to equal access to healthcare services, which have been identified in studies from Western countries on immigrant families of children with ASD (Sritharan & Koola, 2019), need to be addressed beyond mere translations of printed materials. Further, the survey on attitudes towards ASD screening was only distributed to the contact nurses at the PHCs, and the positive results expressed by them cannot be generalized. The measure of change in ASD knowledge and self-confidence among course participants relied on a single methodology. The use of multiple measurements and methods to assess change is recommended (Lam & Bengo, 2003) and would have added validity to the results. Although the integration of the first stage of the screening into well-child visits at 30 months of age was successful overall, it remains to be seen whether the addition of the FUI to those services will require extra resources. This study provides limited information on the psychometric properties of the M-CHAT-R/F, but a follow-up of screen-negative children is underway, allowing for the validation of the tool in the present sample. A comparison of the screen population with a non-screen population is also being prepared.

This study has several strengths. The implementation process included the development of relationships with administrators at all levels, the identification of contact persons at each center who would encourage adherence to the screening protocol, and centralized assistance provided by the steering committee. This is consistent with key strategies that have been identified as facilitating success in the implementation of innovations in services for children with ASD (Broder-Fingert et al., 2019). There was no attrition between the screening stages, and all parents of the screen-positive children accepted diagnostic evaluation of their children. The first author conducted all FUIs in an attempt to ensure consistency of its implementation and to reduce a potential bias introduced by different observers. Diagnostic evaluation was conducted by an interdisciplinary team, in which experienced clinicians administered the ADOS-2 to all children. Referral pathways were well defined, and early intervention and diagnostic services were available.

5. Conclusion

The study shows that it is clinically feasible to implement screening for ASD with the M-CHAT-R into well-child care in Iceland. The M-CHAT-R/F detected some children with ASD who were missed by the usual developmental surveillance at 30 months of age. Identification of possible false negative cases awaits a follow-up of the participants after their next well-child visit at 48 months of age. The availability of services for screen-positive children contributed to the success of the early detection program, although the wait time for diagnostic evaluation, and in some cases for early intervention as well, needs to be shortened. Engaging immigrant families in screening for ASD also requires consideration. A gap that was identified in the ASD education of well-child care professionals highlights the need for regular courses on the topic. The findings contribute to the discussion about the usefulness of including screening for ASD in well-child care.

CRediT authorship contribution statement

All authors participated in designing the study. SLJ coordinated the project, collected and analyzed the data and wrote the first draft of the manuscript. All co-authors revised the manuscript and approved the final version.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Paper III

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ORIGINAL PAPER

Validation of the Modified Checklist for Autism in Toddlers, Revised with Follow-up in a Population Sample of 30-Month-Old Children in Iceland: A Prospective Approach

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Abstract
The Modified Checklist for Autism in Toddlers, Revised with Follow-up was validated on a population sample in Reykjavik, Iceland. The participants ($N = 1585$) were screened in well-child care at age 30 months and followed up for at least 2 years to identify autism cases. The sensitivity, specificity, positive and negative predictive values were 0.62, 0.99, 0.72, and 0.99, respectively. True-positive children were diagnosed 10 months earlier than false-negative children. Autism symptom severity and the proportions of children with verbal and performance IQs/DQs < 70 were similar between groups. Although the sensitivity was suboptimal, the screening contributed to lowering the age at diagnosis for many children. Adding autism-specific screening to the well-child care program should be considered.

Keywords Autism spectrum disorder · Screening · M-CHAT-R/F · Early detection

The detection of children with autism spectrum disorder (ASD) at the youngest age possible, followed by intervention services, is a major goal in the field of autism (Hyman et al., 2020; Interagency Autism Coordinating Committee, 2017). Both retrospective studies and prospective studies of high-risk infants have provided valuable knowledge about the emergence of early signs of ASD (Zwaigenbaum et al., 2013). Symptoms associated with ASD, i.e., impairment in social communication and stereotyped or repetitive behaviors, are not evident in the first half year of life (Landa et al., 2013; Ozonoff et al., 2010). However, a specific pattern of brain development has been documented in infancy (Piven et al., 2017), and prodromes have been identified during the presymptomatic period (Canu et al., 2020; Yirmiya & Charman, 2010). Symptoms of ASD emerge in variable patterns and with variable timing and become pronounced by the second birthday for most children (Goin-Kochel et al., 2015; Landa et al., 2013; Ozonoff et al., 2008, 2010; Pearson et al., 2018). Thus, a valid diagnosis can be made by experienced clinicians in the second or third year of life (Bacon et al., 2018; Charman & Baird, 2002; Chawarska et al., 2007; Ozonoff et al., 2008), but subtle cases may not be clinically detectable until later (Bacon et al., 2018; Davidovitch et al., 2015; Ozonoff et al., 2018).

Based on evidence from neuroscience (Johnson & Munakata, 2005), specialized early intervention programs have been developed for children with ASD to maximize developmental gains related to experience-dependent neural plasticity (Landa, 2018). ASD intervention studies indicate positive effects of these interventions on development in young children (Bejarano-Martín et al., 2020a, 2020b; Dawson et al., 2012; Fuller & Kaiser, 2019; Landa, 2018), potentially leading to better long-term outcomes in terms of independence and quality of life (Fernell et al., 2013; Jónsdóttir et al., 2018). In addition, the early detection and diagnosis of ASD may lessen the distress experienced by many parents, resulting in their greater satisfaction with services than that of parents of children who experience a delay in diagnosis (Bejarano-Martín et al., 2020a, 2020b; Crane et al., 2016). Furthermore, evidence-based services provided

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at a young age may reduce long-term costs and burden for families and communities caring for individuals with ASD (Peters-Scheffer et al., 2012). The challenge for service providers is intensified by the increasing prevalence of ASD, which has been estimated to be at least 1.5% in developed countries (Lyall et al., 2017) and as high as 2.7% in 7- to 9-year-old children in Iceland (Delobel-Ayoub et al., 2020).

Despite the presence of early symptoms and increased knowledge of how and when these symptoms emerge, there is still a considerable delay in the detection and diagnosis of ASD for many children, diminishing the full impact that early intervention may have. In an epidemiological study of 8-year-old children in the US, the median age at ASD diagnosis was 52 months, and 42% of the children received their first diagnostic evaluation by age 36 months (Baio et al., 2018). In a recent European epidemiological study including children of a similar age (Delobel-Ayoub et al., 2020), the median age at diagnosis for the Icelandic participants was 60 months. A small proportion of these participants (10%) received their ASD diagnosis by age 36 months, and 31% had received their diagnosis by age 48 months (Saemundsen, personal communication, June 26, 2020). Even when an 18-month wait time from detection/referral to diagnosis was accounted for, as found in our previous study (Jonsdottir et al., 2020), only a third of the children were detected to have suspected ASD before age 36 months. As in most countries, children in Iceland are offered regular developmental surveillance in well-child care, which is supplemented with broadband developmental screening instruments at ages 12, 18, 30, and 48 months. Screening for ASD has not been included in developmental surveillance, and no screening instruments for that purpose have previously been validated for use in the country.

Efforts to detect ASD earlier in other countries have included the development of screening models in primary care and ASD-specific screening instruments for toddlers (Garcia-Primo et al., 2014; Levy et al., 2020; Petrocchi et al., 2020). Universal screening for ASD, in conjunction with routine developmental surveillance and broad developmental screening, has repeatedly been recommended for children aged 18 and 24 months by the American Academy of Pediatrics (Hyman et al., 2020; Johnson et al., 2007). There is evidence that this approach may assist in the early detection of ASD in children between 16 and 40 months of age (Levy et al., 2020). Thus, studies showed that compared with the usual procedures, screening for ASD contributed to lowering the age at diagnosis by 14 to 24 months (Li et al., 2018; Oosterling et al., 2010; Robins et al., 2014) and significantly increased the proportion of children diagnosed before age 36 months (Nygren et al., 2012; Oosterling et al., 2010).

Other agencies, such as the US Preventive Services Task Force (USPSTF), do not recommend universal screening for ASD in children aged 18 to 30 months, partly because of the limited accuracy of the available screening instruments. However, the USPSTF found the strongest evidence for two versions of the same instrument, i.e., the Modified Checklist for Autism in Toddlers (M-CHAT) and the Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F) (McPheeters et al., 2016; Siu et al., 2016). The M-CHAT evolved from a one-stage parent-report questionnaire to a two-stage screening instrument (Kleinman et al., 2008; Robins et al., 2001). The second stage, which became an integral part of the revised version of the checklist, the M-CHAT-R/F, consists of a follow-up interview (FUI) with parents to verify the failed items for children who screened positive. The added value of the FUI is the reduction in the number of false-positive cases. Compared with the earlier version of the instrument, the M-CHAT-R/F has demonstrated improvements in detecting children with ASD in low-risk samples. These improvements were achieved by a significant reduction in the screen-positive rate in the first screening stage as well as an increase in the rate of detection of ASD (Robins et al., 2014).

An acceptable sensitivity of developmental screening instruments has been estimated to be 0.70 to 0.80, while an acceptable specificity has been estimated to be closer to 0.80 (Glascoe, 2005). The original validation study of the M-CHAT-R/F in the US (Robins et al., 2014), as well as some subsequent validation studies of this revised instrument in low-risk populations in other countries, have reported acceptable sensitivity and specificity (Guo et al., 2019; Magán-Maganto et al., 2020; Windiani et al., 2016). In one study, the specificity was just below the acceptable level (Oner & Munir, 2020), and in another study, the sensitivity was as low as 0.50 (Sangare et al., 2019). The above studies reported different positive predictive values (PPVs), which ranged from 0.26 to 1.00 (Guo et al., 2019; Magán-Maganto et al., 2020; Oner & Munir, 2020; Robins et al., 2014; Sangare et al., 2019; Windiani et al., 2016). PPV is largely dependent on the prevalence of the disorder, which may provide some explanation for the differences in this value when the same instrument is used across settings and contexts. In addition, the age of the participants, the presence of developmental concerns, and the quality of a given study affect the interpretation of the psychometric properties reported (Levy et al., 2020; Yuen et al., 2018).

A limitation of most screening studies identified by the USPSTF (McPheeters et al., 2016) and a recent systematic evidence review (Levy et al., 2020) is a significant loss to follow-up between the initial screening and diagnosis and insufficient follow-up of screen-negative children to identify those with ASD (false negatives). Another concern is insufficient evidence to determine if certain factors, such as the age at screening or other characteristics of the child or family, modify the performance characteristics of the screening instruments. Thus, further research with diverse populations

and thorough follow-up is needed to ascertain the true psychometric properties of the M-CHAT-R/F.

The adaptation of a screening instrument to the culture and language of the population for which it is intended is an integral part of establishing validity. This adaptation process is ideally based on established guidelines (Soto et al., 2015). Accordingly, the M-CHAT-R/F was adapted for use in Iceland as a part of the first phase of an early detection project, where the focus was on the implementation of universal screening in well-child care (Jonsdottir et al., 2020). The current study is the second phase of the project. Its aim is to validate the M-CHAT-R/F on a population sample of 30-month-old children and to examine the association of screening status with age at diagnosis and clinical measures.

Methods

Study Design and Setting

This prospective population-based screening study was integrated into the existing services. The investigators were not able to influence the time interval from the referral of screen-positive children to diagnostic assessment, which took place up to 18 months later. A further prospective case confirmation was undertaken 2 years after completion of the screening period.

The healthcare system in Iceland is state-centered, is mostly publicly funded, and provides universal coverage. During the first 4 years of life, children are offered 11 well-child visits to a primary healthcare center (PHC). The main emphasis is on developmental surveillance, parents' education in child rearing, and children's participation in a comprehensive vaccination program. Developmental screening with the Parents' Evaluation of Developmental Status (PEDS; Glascoe, 2009) is performed at child ages 12, 18, 30, and 48 months as well as the Brigance Early Preschool Screen II (Brigance, 2017) at 30 and 48 months of age (Development Center for Primary Healthcare in Iceland, 2020). The present study was conducted during regular well-child visits at child age 30 months in nine randomly selected PHCs in the capital area of Reykjavik.

Participants

A total of 2531 children were registered at the nine PHCs for their 30-month well-child visits during the screening period from March 2016 through October 2017. Of these children, 2201 (87%) attended the visits, and the parents of 1588 children (63% of the population) gave informed consent to participate in the study. The reasons for nonparticipation among those who attended the visits were described in a previous paper (Jonsdottir et al., 2020). Two children were excluded from the study since they had already been referred for assessment for possible ASD. Thus, 1586 children were eligible to participate. Their mean age at screening was 31.66 months (standard deviation (*SD*) = 1.72). Table 1 shows the demographic characteristics for the total sample and for the subsamples of screen-positive and screen-negative children who received diagnostic assessment.

Measures

Screening Instrument

The M-CHAT-R/F is a two-stage parent-report screening instrument that is used to identify children who may be at risk for ASD. It was originally validated in children between

Table 1 Demographic characteristics of all participants and of subsamples of those who screened positive and negative and received diagnostic assessment

	All participants (*N* = 1586)	Screen positive, to diagnostic assessment (*n* = 25)	Screen negative, to diagnostic assessment (*n* = 17)
Age at screening, mean (*SD*)[a]	31.66 (1.72)	32.08 (2.14)	30.94 (1.20)
Gender, *n* (%)			
Male	801 (50.5)	20 (80.0)	14 (83.4)
Female	785 (49.5)	5 (20.0)	3 (17.6)
Nationality of parents, *n* (%)			
Both Icelandic	1469 (92.6)	22 (88.0)	12 (70.6)
One or both non-Icelandic	116 (7.4)	3 (12.0)	5 (29.4)
M-CHAT-R respondent, *n* (%)			
Mother	1325 (83.5)	23 (92.0)	13 (76.4)
Father	219 (13.8)	1 (4.0)	2 (11.8)
Both parents	42 (2.7)	1 (4.0)	2 (11.8)

[a]Age in months

M-CHAT-R Modified Checklist for Autism in Toddlers, Revised

16 and 30 months of age in the US (Robins et al., 2014). The first stage (the M-CHAT-R) consists of 20 yes/no questions on behavior-related items. The total score defines a child's risk level for ASD, i.e., low risk (total score 0–2), moderate risk (total score 3–7), and high risk (total score 8 or higher). If a child's total score is in the low-risk range, the child screens negative in the first stage, and no action needs to be taken. If the child's total score is in the moderate-risk range, it is recommended that the second stage, the M-CHAT-R/F, which consists of an FUI, be administered. The FUI focuses on the items that were failed, and the parent is asked to provide more detailed information and examples of behaviors related to these items. A score of 2 or higher after the FUI has been completed is considered positive and a referral for diagnostic assessment and early intervention is recommended. If a score is initially in the high-risk range, the FUI can be bypassed, and the appropriate referrals can be made immediately (Robins et al., 2009, 2014). An Icelandic version of the M-CHAT-R/F (Jonsdottir et al., 2020), as well as translations of the instrument into other languages for nonnative Icelandic parents, was used in this study.

Clinical Assessment Instruments

The Autism Diagnostic Observation Schedule, Second Edition (ADOS-2; Lord et al., 2012) is a semistructured standardized assessment. It is based on the direct observation of communication, social interaction, play, and restricted and repetitive behaviors. The ADOS-2 includes five modules (the Toddler Module and Modules 1–4), each of which is tailored to the individual's age and expressive language ability from age 12 months to adulthood. Modules 1 and 2 were used in this study. The observed behaviors are coded, and the total score is compared with autism, autism spectrum, and non-spectrum cutoff scores. A comparison score is obtained, which allows for a comparison of the child's level of ASD-related symptoms to that of children with ASD who have similar language skills and are of the same age. Based on the comparison score, the severity of ASD-related symptoms can be classified as minimal to no evidence (score 1–2), low (score 3–4), moderate (score 5–7), or high (score 8–10).

Two tests were used to measure intellectual functioning, depending on the child's developmental level. The Icelandic translation, adaptation and standardization of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989), referred to as the WPPSI-RIS (Gudmundsson & Olafsdottir, 2003), was used in most cases (81%). The WPSSI-R was designed for children in the age range from 2 years and 11 months to 7 years and 3 months. It consists of subtests of cognitive functioning in two domains, i.e., verbal and performance, with a mean subscale score of 100 and an SD of 15. A composite score for the child's general intellectual ability and cognitive functioning can also be obtained, but this score is not reported in this study. A study on the WPPSI-RIS showed the adequate reliability and validity of the test (Gudmundsson, 2008).

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III; Bayley, 2006) was used for children who were not able to complete the WPPSI-RIS (19%). The BSID-III assesses the development of children between 1 and 42 months of age. It has five subtests, two of which were used in this study, i.e., the cognitive and language scales. The composite scores for the scales are standardized, with a mean of 100 and an SD of 15. Age equivalent developmental levels can also be obtained, and these levels were used in this study to compute ratio developmental quotients (DQs) for each scale. DQs were calculated to obtain comparable BSID-III measures across children since some of the children scored below the standardized values and some of the children's chronological age was higher than the age-specific norms. US norms were used for this test since it has not been standardized in Iceland.

Procedure

Screening

The nine participating PHCs were randomly selected from the 17 PHCs in the capital area of Reykjavik. Shortly before a scheduled well-child visit at child age 30 months, the parents were sent an introductory letter about the study and an invitation to participate. To reach not only native Icelandic parents but also the minority nonnative Icelandic parents, the letter and a consent form were available in six languages in addition to Icelandic. The parents were invited to sign an informed consent form during the visit, and those who did were then asked to complete the M-CHAT-R after they had filled out the PEDS. If the M-CHAT-R was needed in a language other than Icelandic, it was printed from the instrument web page (https://mchatscreen.com/). The completed M-CHAT-R questionnaires were sent to the first author (SLJ) for scoring. The original scoring criteria for the M-CHAT-R/F (Robins et al., 2014) was used in this study. The first author conducted all FUIs by phone for children who screened positive in the first stage, i.e. with a total score of 3 and higher. This author has more than 40 years of clinical experiences in the field of ASD among which is assessment of young children suspected of ASD. If the child's score remained positive after the FUI, i.e. a total score of 2 and higher, the parent was informed about the result and asked for permission to refer the child for diagnostic assessment and early intervention.

Assessment

All screen-positive children were referred by SLJ to the State Diagnostic and Counseling Center (SDCC) for assessment. This tertiary institution serves children from age 0 to 17 years across the whole country. The SDCC receives referrals from the secondary level of services when there are concerns regarding serious neurodevelopmental disorders. It provides an interdisciplinary evaluation, which results in an ICD-10 diagnosis (World Health Organization, 1993). The diagnosis is based on all available information and includes the following: (a) a physical and neurological examination and the review of the developmental and medical history obtained from the child's parents by a pediatrician; (b) an assessment with the ADOS-2 by a trained psychologist; (c) the review of results from cognitive tests; (d) a parent interview with a social worker involving the assessment of family circumstances and support needs; and (e) a review of written reports from the child's preschool and video clips of the child in the preschool environment. In this study, the evaluation team was not blind to the screening results. Clinical data were gathered from the medical records at the SDCC for use in this study.

Follow-up Period

The participants were followed-up to identify those with ASD, including both true positives and false negatives. The closing date for the follow-up period was 2 years after the completion of the screening period, i.e., 31. October 2019. The follow-up period ranged from 2 to 3 years and 8 months for individual children. The identification of children with ASD was accomplished by examining the SDCC database. To ensure that we had not missed any of the participants who had been referred for diagnostic assessment at other institutions, the database of the Center for Child Development and Behavior (CCDB) was also explored. The CCDB is a secondary diagnostic institution related to PHCs. This search did not reveal any new children with ASD.

Data Analysis

Descriptive statistics were used to summarize the demographic data and screening results. The prevalence of ASD was estimated, where the denominator was all children in the targeted age group who were registered at the participating PHCs during the screening period. The 95% confidence interval (CI) was computed using continuity correction. The clinical validity of the instrument in terms of sensitivity, specificity, predictive values, and likelihood ratios were calculated on three levels, i.e., the results from the first screening stage only, the results from the second screening stage, and the results from both screening stages. Area under the receiver operator characteristic (AUC) curves were computed for the M-CHAT-R, i.e., the first screening stage, and the M-CHAT-R/F, and the optimal cutoff values were identified. The effect of failing an item on the M-CHAT-R on the odds of an ASD diagnosis was estimated with univariate logistic regression. The item responses on the M-CHAT-R were compared between children with ASD and all other participants, as well as between children with ASD and children with other neurodevelopmental disorders, using Fisher's exact tests. The internal consistency of both the M-CHAT-R and the M-CHAT-R/F was examined using Cronbach's alpha, where a level greater than 0.70 was considered adequate (Cortina, 1993). Since the clinical data of the children who were evaluated did not meet the assumptions for normality and homogeneity of variance, the Kruskal–Wallis nonparametric test was conducted to examine the association of screening status with the clinical measures. The findings of interest were followed-up with pairwise comparisons using the Mann–Whitney test. Fisher's exact test was used to compare the proportions of true-positive and false-negative children with verbal and performance IQs/DQs that indicated intellectual disability (< 70). Kaplan–Meier survival curves were generated to compare the cumulative probability of an ASD diagnosis by age for true-positive and false-negative children. A log-rank test was used to compare survival curves between the groups. The significance threshold was set at 0.05 (two-tailed). The data were analyzed using SPSS 26.0 for Windows and R version 4.00.

Results

Screening and Diagnostic Results

Of the 1586 participants, 63 (4%) screened positive during the first stage and moved onto the second screening stage when the FUI was completed. Among these 63 children were nine children who failed eight or more items. As shown in Fig. 1, 26 children (41.3% of those who initially screened positive and 1.6% of the total sample) still screened positive in the second stage and were referred to diagnostic assessment and early intervention. One child moved abroad with his family before assessment was initiated. Of the remaining 25 children, 18 (72%) were diagnosed with ASD (true positives), and seven (28%) were false positives. Six of the false-positive children were diagnosed with other ICD-10 neurodevelopmental disorders, and speech and language disorders and intellectual disability were the most common. One child did not meet the criteria for any clinical diagnosis. All nine children who initially scored in the high-risk range (a total score of 8 and higher) still screened positive after the FUI. Eight

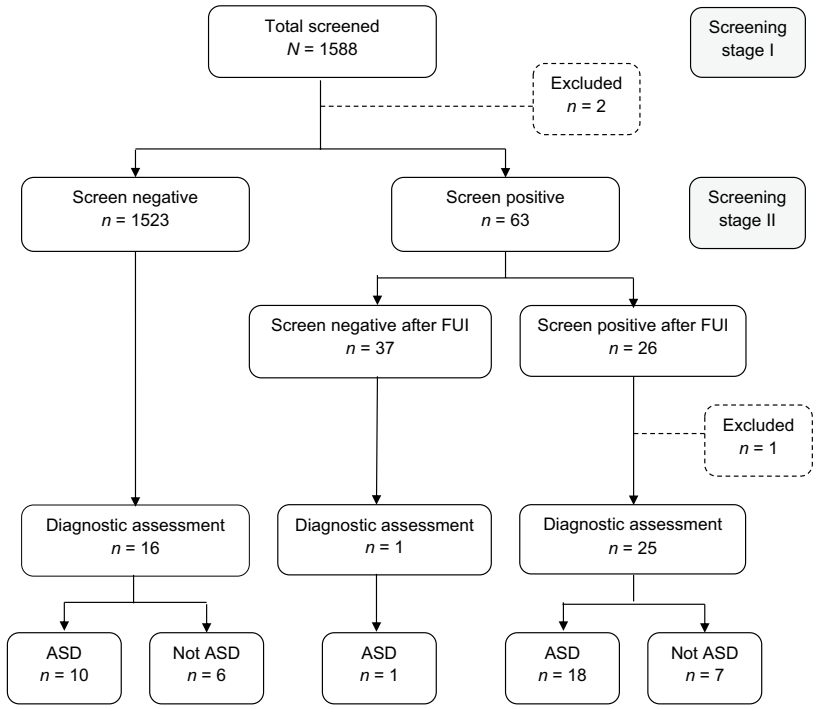

Fig. 1 Flowchart of the screening and assessment results

of these children were diagnosed with ASD, and one was diagnosed with another neurodevelopmental disorder.

Seventeen of the screen-negative children from the first and second screening stages were identified during the follow-up period, which was terminated when they were between 54 and 79 months of age. These children were referred by health or educational services to the SDCC for diagnostic assessment. Among these children, 11 were diagnosed with ASD (false negatives), including one child who passed both screening stages. Of the six participants who were true negatives, five were diagnosed with other neurodevelopmental disorders, and one did not receive a clinical diagnosis (see Fig. 1).

Prevalence

Of the 2531 children in the targeted age group who were registered at the participating PHCs, 29 were diagnosed with ASD, for an estimated ASD prevalence of 1.15%, 95% CI [0.79, 1.67]. When the two children who had been detected prior to the screening and were thus excluded from other analysis were considered, the prevalence estimate was 1.22, 95% CI [0.84, 1.75]. The male-to-female ratio was 7.8:1.

Attributes of the Screening Instrument

Clinical Validity

The sensitivity, specificity, predictive values, and likelihood ratios for detecting ASD are shown in Table 2. Calculations based on screening status for all 1585 participants yielded a similar sensitivity and specificity for the first screening stage (0.66 and 0.97, respectively) and for both screening stages combined (0.62 and 0.99, respectively). The table also shows that when calculations were based only on the screening status of the 62 participants who entered the second screening stage and received a diagnostic assessment, the sensitivity was 0.95, and the specificity was 0.84. The FUI was effective in reducing the number of false-positive cases: the PPV was 0.31 without the FUI and 0.72 with the FUI. The PPV of all neurodevelopmental disorders was 0.96.

The AUC for the first screening stage, using 3 as the total score cutoff, was 0.865, 95% CI [0.779, 0.950]. Lowering the total score cutoff to 2 did not improve the accuracy of the screening; the sensitivity remained at 0.66, and the specificity was similar (0.92). However, lowering the total score cutoff to 1 instead of 3 increased the sensitivity from 0.66 to 0.86, but this increase occurred at the cost of specificity, which then dropped from 0.97 to 0.69. The AUC for the

Table 2 Sensitivity, specificity, predictive values, and likelihood ratios of the M-CHAT-R and the M-CHAT-R/F

	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	LR+	LR−
M-CHAT-R[a]	19	10	43	1513	0.66 (0.48–0.83)	0.97 (0.96–0.98)	0.31	0.99	23.71	0.35
M-CHAT-R/F[b]	18	1	7	36	0.95 (0.85–1.00)	0.84 (0.73–0.95)	0.72	0.97	5.82	0.06
M-CHAT-R/F[c]	18	11	7	1549	0.62 (0.44–0.80)	0.99 (0.99–1.00)	0.72	0.99	137.97	0.38

TP true-positive, *FN* false-negative, *FP* false-positive, *TN* true-negative, *CI* confidence interval, *PPV* positive predictive value, *NPV* negative predictive value, *LR+* likelihood ratio positive, *LR-* likelihood ratio negative, *M-CHAT-R* Modified Checklist for Autism in Toddlers, Revised, *M-CHAT-R/F* Modified Checklist for Autism in Toddlers, Revised with Follow-up

[a]Screening status after the first screening stage

[b]Screening status after the second screening stage

[c]Screening status after the first and second screening stages

second screening stage was 0.927, 95% CI [0.859, 0.994]. The optimal cutoff for the total score for the highest sensitivity (0.95) while maintaining high specificity (0.84) for the second screening stage was 2, which was the cutoff used in this study.

Internal Consistency

The internal consistency of the 20 items on the M-CHAT-R was inadequate (Cronbach's $\alpha = 0.677$). Three of the items related to motor activities (4, 13, and 20) were created as foils. Deleting these items, however, resulted in a similar internal consistency (Cronbach's $\alpha = 0.678$). In the whole sample, the items with the highest percentage of fails were two of the auditory items, i.e., item 2, wondering if the child might be deaf, with 9.3% fails, and item 12, child is upset by everyday noises, with 15.7% fails. Deleting these two items increased the internal consistency to an adequate level (Cronbach's $\alpha = 0.745$). The internal consistency of the M-CHAT-R/F, i.e., after the FUI, was good (Cronbach's $\alpha = 0.831$).

Predictive Power

Table 3 shows the effect of failing an item on the M-CHAT-R on the odds of an ASD diagnosis.

The items were arranged in descending order based on their predictive power, as measured by their standardized coefficients, and based on their standard errors. All but two of the 20 items on the M-CHAT-R significantly predicted ASD classification. Six of the 10 items that had the greatest contribution in classifying children as either having or not having ASD were related to the child's failure to initiate social interaction (items 17, 9, 19, 14, 8, and 7), and four were related to the child's failure to respond to social stimuli (items 16, 2, 10, and 1), whereas item 2 (wondering if the child might be deaf) may assess a lack of response to both social and nonsocial stimuli. Table 3 also shows the failure rates for each of the 20 items for children diagnosed with ASD and for all other participants. The Fisher's test analysis indicated that 17 of the 20 items were more frequently failed by children diagnosed with ASD than by all other participants. The three items that were not significantly different between the groups (i.e., item 4, likes climbing ($p = 0.131$); item 12, upset by everyday noises ($p = 0.245$); and item 13, walks ($p = 1.000$) were also the items that had the least predictive power for ASD. There were no significant differences in any of the items between children diagnosed with ASD and children diagnosed with other neurodevelopmental disorders.

Changes in Responses

The analysis of the item responses of the 63 children who participated in both screening stages showed that the largest changes in the proportion of failed responses were for item 12, upset by everyday noises (the failed response rate changed from 44 to 16%); item 16, follows gaze (the failed response rate changed from 55 to 27%); and item 6, points to get help (the failed response rate changed from 37 to 16%).

Clinical Data

Clinical data for the 42 children who received diagnostic assessment are presented in Table 4 based on screening status.

Age at Referral and Diagnosis

The Kruskal–Wallis test indicated significant associations of screening status with age at referral and age at diagnosis (Table 4). Pairwise comparisons between the true-positive and false-negative groups showed that age at referral ($Mdn = 32.00$, $M = 33.28$, $SD = 2.56$) and age at diagnosis ($Mdn = 51.00$, $M = 51.22$, $SD = 2.39$) for the true-positive children were lower than age at referral ($Mdn = 39.00$, $M = 41.00$, $SD = 5.42$) and age at diagnosis ($Mdn = 60.00$, $M = 61.36$, $SD = 3.75$) for the false-negative children

Table 3 Effect of failing an item on the M-CHAT-R on the odds of an ASD diagnosis arranged in decending order and failure rates of each item on the M-CHAT-R by group

Items		Coeficient	*SE*	95% CI		*p*	ASD (*n* = 29) %	Not ASD (*n* = 1556) %	*p*
				LL	UL				
17	Gains parent's attention	3.992	0.439	3.113	4.870	< 0.001	41.4	1.3	< 0.001
9	Shows things	4.398	0.503	3.392	5.405	< 0.001	34.5	0.6	< 0.001
16	Follows gaze	3.434	0.420	2.594	4.274	< 0.001	41.4	2.5	< 0.001
19	Social referencing	3.468	0.426	2.616	4.320	< 0.001	37.9	1.9	< 0.001
14	Makes eye contact	3.784	0.497	2.790	4.778	< 0.001	27.6	0.9	< 0.001
2	Wondering if child is deaf	2.889	0.394	2.102	3.676	< 0.001	62.1	8.3	< 0.001
10	Responds to name	4.617	0.679	3.260	5.975	< 0.001	20.7	0.3	< 0.001
1	Follows a point	3.920	0.579	2.761	5.079	< 0.001	20.7	0.5	< 0.001
8	Interested in other children	3.646	0.551	2.543	4.748	< 0.001	20.7	0.7	< 0.001
7	Points to show	2.997	0.456	2.086	3.909	< 0.001	27.6	1.9	< 0.001
18	Understands commands	4.254	0.668	2.919	5.590	< 0.001	17.2	0.3	< 0.001
15	Imitates actions	3.433	0.735	1.962	4.903	< 0.001	10.3	0.4	< 0.001
11	Responds to a smile	3.357	0.888	1.582	5.132	< 0.001	6.9	0.3	0.008
20	Likes movement activities	2.950	0.839	1.272	4.629	< 0.001	6.9	0.4	0.013
3	Pretend play	2.288	0.654	0.980	3.597	< 0.001	10.3	1.2	0.006
5	Unusual finger movements	2.437	0.799	0.840	4.034	0.002	6.9	0.6	0.026
6	Points to get help	1.491	0.556	0.379	2.603	0.007	13.8	3.5	0.034
4	Likes climbing	1.285	0.627	0.031	2.539	0.04	10.3	3.1	0.131
12	Upset by everyday noises	0.544	0.440	− 0.335	1.424	0.215	24.1	15.6	0.245
13	Walks	− 12.592	665.514	− 1343.620	1318.436	0.985	0	0.8	1.000

M-CHAT-R Modified Checklist for Autism in Toddlers, Revised, *ASD* autism spectrum disorder, *SE* standard error, *CI* confidence interval, *LL* lower limit, *UL* upper limit

Table 4 Clinical data by screening status of children who received diagnostic assessment

	True-positive (*n* = 18)		False-negative (*n* = 11)		False-positive (*n* = 7)		True-negative (*n* = 6)		*H*	*p*
	Mean (*SD*)		Mean (*SD*)		Mean (*SD*)		Mean (*SD*)			
Age at screening (months)	32.50	(2.20)	30.64	(1.12)	31.00	(1.63)	31.50	(1.23)	7.37	0.061
Age at referral (months)	33.28	(2.56)	41.00	(5.42)	32.14	(1.46)	42.67	(5.96)	22.47	0.000
Age at diagnosis (months)	51.22	(2.39)	61.36	(3.75)	50.43	(1.72)	63.17	(5.35)	29.33	0.000
M-CHAT-R total	6.83	(3.66)	0.82	(0.87)	5.86	(2.55)	0.83	(0.41)	29.81	0.000
M-CHAT-R/F total[a]	6.00	(3.61)	1.00	-	4.29	(2.87)	–	–	–	–
ADOS-2 comparison	5.33	(2.00)	5.55	(1.70)	1.00	(0.00)	2.20	(0.84)	23.55	.000
IQ/DQ verbal	65.44	(25.34)	79.91	(25.25)	80.86	(13.89)	70.50	(13.32)	3.17	.366
IQ/DQ performance	81.00	(21.22)	92.82	(20.18)	92.57	(12.80)	84.67	(26.93)	2.61	.456

M-CHAT-R Modified Checklist for Autism in Toddlers, Revised, *M-CHAT-R/F* Modified Checklist for Autism in Toddlers, Revised with Follow-up, *ADOS-2* Autism Diagnostic Schedule, Second Edition, *IQ/DQ* intelligence quotient/developmental quotient

[a]The follow-up interview was only administered to parents of one of the false-negative participants, see Fig. 1. The Mann–Whitney test indicated a non-significant difference between the true-positive group and the false-positive group, $U = 42.00$, $z = -1.282$, $p = 0.200$

($U = 20.00$, $z = -3.58$, $p = 0.000$ and $U = 1.00$, $z = -4.43$, $p = 0.000$, respectively).

Figure 2 shows the Kaplan–Meier survival curves for the children, where the y-axis illustrates the cumulative probability of an ASD diagnosis and the x-axis illustrates the age of the children in months. A visual inspection of the curves shows that the true-positive children received an earlier diagnosis than the false-negative children, with an overlap of only one child in each group. Both of these children were diagnosed at 57 months, which was the oldest age at the

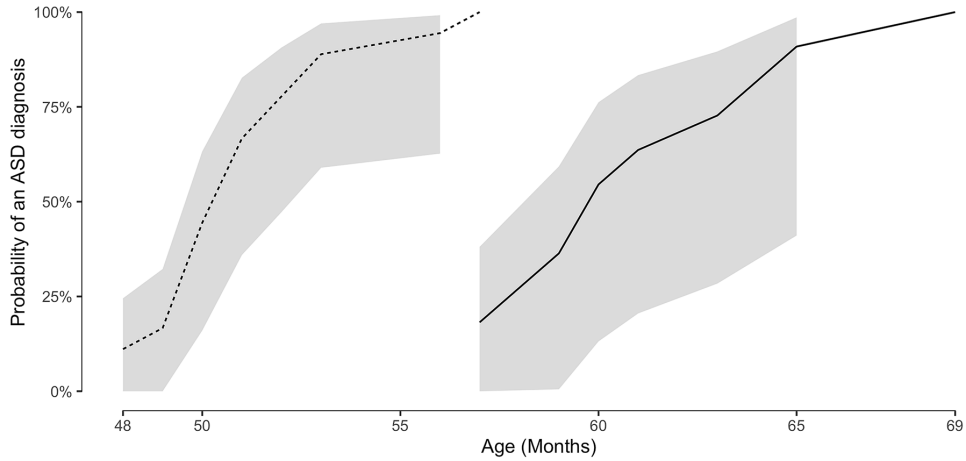

Fig. 2 Kaplan–Meier survival curves for the cumulative probability of an ASD diagnosis by age in months for true-positive (dotted line) and false-negative (continuous line) children

time of diagnosis in the true-positive group and the youngest age at diagnosis in the false-negative group. A log-rank test confirmed the difference between the two survival groups (X^2 (1, $N = 1585$) = 26.6, $p = 3e{-}07$).

Autism Symptoms

The main association of screening status with the severity of autism symptoms, as measured by the ADOS-2, was significant (Table 4). However, a pairwise follow-up comparison indicated a nonsignificant difference between the true-positive group ($Mdn = 5.50$, $M = 5.33$, $SD = 2.00$) and the false-negative group ($Mdn = 5.00$, $M = 5.55$, $SD = 1.70$) ($U = 94.50$, $z = -0.205$, $p = 0.837$).

Intellectual Functioning

The associations of screening status with verbal IQ/DQ and performance IQ/DQ were not significant for any of the four categories of participants (Table 4). A pairwise comparison of the true-positive and false-negative groups revealed the following results for verbal and performance IQ/DQs: $U = 70.5$, $z = -1.281$, $p = 0.200$ and $U = 69.50$, $z = -1.327$, $p = 0.185$, respectively. Regarding intellectual disability, similar proportions of true-positive (50%) and false-negative (45.5%) children had a verbal IQ/DQ < 70 ($p = 1.000$). A somewhat higher proportion of true-positive children (27.8%) than false-negative children (18.2%) had a performance IQ/DQ < 70, but this difference was not significant ($p = 0.677$).

Discussion

This is the first study to validate the M-CHAT-R/F in an Icelandic population sample. The participants were screened when they attended routine well-child care at age 30 months and were followed-up for at least 2 years to identify missed cases. Of the 1586 children who were screened, 29 were diagnosed with ASD, of whom 18 were identified as true positives with the M-CHAT-R/F, and 11 were missed, i.e., were false negatives. True-positive children were on average 10 months younger at the time of diagnosis than false-negative children. There were no significant differences between these groups regarding symptoms of autism or cognitive measures. In terms of the measures of diagnostic accuracy, the sensitivity was 0.62 for the two-stage screening, which is below the acceptable level estimated in the range of 0.70–0.80, while the specificity was high (0.99).

The sensitivity found in the present study is lower than that reported in most population-based screening studies using the M-CHAT-R/F and with no or short follow-up time in order to identify false-negative cases (Guo et al., 2019; Magán-Maganto et al., 2020; Oner & Munir, 2020; Robins et al., 2014; Windiani et al., 2016). A limitation of many screening studies is the use of inadequate methods to identify potential missed cases (Levy et al., 2020; McPheeters et al., 2016), which may then inflate the estimated sensitivity of the screening instrument. The sensitivity in the present study is considerably higher than reported in population-based studies using the M-CHAT or the M-CHAT-R (0.33–0.39) and with several years of follow-up for detecting false-negative cases (Carbone et al., 2020; Guthrie et al., 2019; Stenberg et al., 2014). In the present study, we were able to conduct a

thorough follow-up of screen-negative children by reviewing the records of institutions that diagnose children with autism and other neurodevelopmental disabilities. We are confident that we were able to capture all children in our sample who had been diagnosed with ASD by the closing date of the follow-up period, when the children were up to 79 months old. However, this approach did not rule out the possibility that more cases would be detected later at a higher age, resulting in further weakening of the sensitivity. Because of variability in how and when the symptoms of ASD emerge (Landa et al., 2013; Pearson et al., 2018; Zwaigenbaum et al., 2013), these symptoms have not been detected in a large proportion of children in young screening populations (Carbone et al., 2020; Guthrie et al., 2019; Øien et al., 2018; Stenberg et al., 2014, 2020). Efforts to minimize the number of false-negative cases in prospective validation screening studies have included a combination of different tools and strategies in the screening process and repeated screenings for ASD (Magán-Maganto et al., 2017; Robins, 2020). The comparison of the sensitivity between different screening studies for ASD are complicated because of differences in the execution of the studies. Most important are the different lengths of follow-up and methods used to detect cases among those who initially screened negative. Also of importance are the different ages of the children in the screen populations, different versions of the screening instrument used (M-CHAT, M-CHAT-R, and MCHAT-R/F), different race and ethnicity in each study and between studies, as well as different prevalences of ASD in the screen populations. Moreover, the studies have been performed at different times.

Given that a positive screening result leads to an immediate referral to diagnosis and intervention, a major challenge of false negatives is a delay in children benefiting from these services. True-positive children in the present study were considerably younger at the time of diagnosis than false-negative children, with a mean difference in age of 10 months. Our previous study of this population showed that, in accordance with the practices in Iceland, intervention services were initiated for all screen-positive children before diagnosis was confirmed or at a mean age of 35.64 ($SD = 4.44$) months (Jonsdottir et al., 2020). Another Icelandic study of 145 children receiving their first diagnostic assessment at the SDCC in 2018 included 13 of the screen-positive children in the present study. A comparison of these 13 children with the other 132 participants showed that the mean time from referral to the start of intervention was similar for both groups. However, the screen-positive children were 10 months younger than the other participants at the time of referral, resulting in a similar difference in age at the start of intervention and diagnosis (Gunnarsdottir, 2020). This finding is in line with the difference in age at diagnosis found in the present study between the true-positive and false-negative participants, which provides further support for the benefits that screening for ASD has for those who screened positive.

Seven of the screen-positive children were false positives, of whom six were diagnosed with other neurodevelopmental disorders. Although referral for diagnostic assessment and intervention was justified for these six children, consideration needs to be given to a sensible use of time and resources that best meets their needs. One approach that has been found to reduce the false-positive rate after the FUI is a two-tiered screening, where a positive screen result on the M-CHAT-R/F is followed by an interactive level 2 screener. The results from the second screen help to determine whether an ASD-specific or more general developmental assessment and intervention should be prioritized (Khowaja et al., 2017). This strategy may prevent some children and parents from undergoing unnecessary and time-consuming assessment procedures with ASD diagnostic instruments, shorten waiting lists for these assessments, and be more cost effective than referring all screen-positive children to ASD-specific services.

Only one of the screen-positive children did not meet any criteria for a clinical diagnosis. This issue has been observed not only among children who are referred for assessment based on screening for ASD but also among children referred after the usual developmental surveillance. Hence, among the 17 screen-negative children in this study who were referred for assessment by health or educational services, one was found to be typically developing. This was also the case for five of the 145 children who were referred by these service providers to the SDCC and had their first diagnostic assessment in 2018 (Gunnarsdottir, 2020). Since variability in autism symptom trajectories over time has been documented in young children referred for possible ASD (Kim et al., 2018), it is likely that some of these children actually presented with developmental challenges at the time of referral that were no longer observable 18 months later when the diagnostic assessment took place owing to maturation and intervention.

Sensitivity and specificity indicate how well a test discriminates between those who have and those who do not have the condition (in this study, ASD), and these measures are helpful in health policy decisions (Eusebi, 2013). The moderate sensitivity obtained in this study supports recommendations that a single screening for ASD in low-risk populations is insufficient and that other early detection strategies should be used in conjunction with screening in developmental surveillance programs (Hyman et al., 2020). Once a screening test result is known, measures that predict the probability of having the condition are useful in clinical practice (Eusebi, 2013). The PPV for ASD was 0.31 after the first screening stage and 0.72 after both screening stages, supporting the use of the FUI to rule out as many

false positives as possible. The PPV for any developmental disorder was 0.96, meaning that a child with a positive screen result will almost always present with a condition that warrants referral to diagnostic and intervention services. This is in line with findings in other validation studies using the M-CHAT-R/F in low-risk populations (Guo et al., 2019; Magán-Maganto et al., 2020; Robins et al., 2014); however, the limitation of the use of predictive values for comparisons between studies must be considered since these values vary based on the study population and the prevalence. Unlike predictive values, likelihood ratios are not dependent on prevalence. They are based on the sensitivity and specificity of the test and have been recommended as an optimal choice in reporting diagnostic accuracy (Eusebi, 2013). The positive likelihood ratio (LR+) in the present study showed that a positive test result was 138 times more likely to occur in children who had ASD than in those who did not have ASD. This LR+ was within the 95% CI of the LR+ in the original validation study of the M-CHAT-R/F in the US (Robins et al., 2014) and a more recent validation study of this instrument in Spain (Magán-Maganto et al., 2020).

An analysis of the predictive power of individual items, as well as an examination of items that were problematic, may contribute to the development of a shorter version of the instrument (Brennan et al., 2016; Kamio et al., 2014). Such data could also contribute to the examination of alternative scoring methods, for example, weighting the items based on their predictive association with an ASD diagnosis instead of giving each item an equal weight (Roberts et al., 2019). Sixteen of the 17 items on the M-CHAT-R that were significant in predicting an ASD classification were related to the child's lack of social communication behaviors, and one was related to the presence of restrictive repetitive behavior (unusual finger movements). Of the three items that were least predictive of an ASD diagnosis, not surprisingly, two were foil items that pertained to motor activities, i.e., item 4 (likes climbing) and item 13 (walks), and one, i.e., item 12 (upset by everyday noises), was a sensory/auditory item. A comparison of the predictive ability of the individual items on the M-CHAT-R between studies reveals some variations. For example, the three abovementioned items (4, 12, and 13) were among those with the least predictive power in a study of the M-CHAT-R in Albania (Brennan et al., 2016). The same applied to item 12 in a study in China, but interestingly, items 14 (makes eye contact) and 19 (social referencing) were also among the least predictive items (Guo et al., 2019). This difference in the ability of individual items to predict an ASD diagnosis may be due to cultural norms pertaining to how parents perceive a lack of certain behaviors, such as eye contact (Akechi et al., 2013).

The shift from fail to pass between the two screening stages was greatest for items 6 (points to get help), 12 (upset by everyday noises), and 16 (follows gaze). Many parents reported during the FUI that they had not paid considerable attention to whether the child was showing the particular behaviors that pertained to items 6 and 16 but were able to recollect instances when prompted by the questions and examples in the FUI. Item 16 was also the item that parents most often (1.4%) left blank. The initial failure rate for item 12 may have been based on a misunderstanding of its meaning, similar to what other studies have reported regarding this item (e.g., Canal-Bedia et al., 2011; Guo et al., 2019; Seung et al., 2015). Brennan et al., (2016) found the largest change in failure rates between the screening stages for items 2 (wondering if deaf), 5 (unusual finger movements), and 12 (upset by everyday noises). These items are the only reversed scored items, where a "yes" response indicates at-risk behavior, unlike the other items, where a "yes" response indicates the presence of developmentally appropriate behavior. High failure rates for the reversed scored items have been found in many studies using translated versions of the M-CHAT or the M-CHAT-R, suggesting a positive response bias (DuBay, 2020). Such a bias may have affected the responses to items 2 and 12 in the present study, but not item 5, as 14 of the other items were endorsed more frequently than item 5. Deleting items 2 and 12 increased the internal consistency to an adequate level (>0.70), and the same was found when items 2, 5 and 12 were deleted in the study of Brennan et al., (2016). Different findings in the response patterns for the translated versions of these instruments may be related not only to cultural norms but also to linguistic influences, as the meaning of some concepts has been found to be lost in the traditional forward-back translation process (DuBay, 2020).

The symptoms of autism, as assessed with the ADOS-2, did not differ between true-positive and false-negative children, which is consistent with other studies (Kamio et al., 2014; Robins et al., 2014). This lack of difference highlights the limitations of prospective screening studies relying on parent-report questionnaires. Thus, it is impossible to know if early signs indicating risk for ASD were not yet clinically detectable in the false-negative children at the time of screening or if they were indeed present but the parents were unable or unwilling to report them (Petrocchi et al., 2020; Robins, 2020).

The proportion of children with a verbal IQ/DQ <70 was similar in both groups. Although a higher proportion of true-positive children had a performance IQ/DQ <70, the difference between the groups was not statistically significant. This finding is comparable to that of Eaves et al., (2006), whereas other researchers found that a significantly greater proportion of true-positive children had intellectual disability than false-negative children (Dereu et al., 2010; Kamio et al., 2014). Age at screening may have contributed to the different results. Approximately half of the participants in the study of Eaves et al. (2006) were the same age as the participants in the present study, while the others were older;

in the other two studies, the mean ages of the participants were 17 months (Dereu et al., 2010) and 18 months (Kamio et al., 2014). Thus, Kamio et al. (2014) noted that screening at such a young age may identify more low-functioning children with ASD than high-functioning children with ASD, which is also consistent with the findings of Stenberg et al. (2020).

Extending the follow-up period for the participants in this study would probably have allowed us to identify more children with ASD. These children would presumably have been less impaired than those who had already been identified in the study sample, which agrees with findings on the higher age at ASD diagnosis (Jónsdóttir et al., 2011; Mazurek et al., 2014; Oosterling et al., 2010; Wiggins et al., 2006). The estimated prevalence of ASD in our study was 1.15%, with diagnosis occurring during the follow-up period when the participants were between 54 and 79 months of age. This prevalence is lower than the 2.7% prevalence rate found in a recent epidemiological study of 7- to 9-year-old children in Iceland (Delobel-Ayoub et al., 2020). This discrepancy in the estimated prevalence between age groups supports the notion that there were still some missed cases of ASD among our participants. The male–female ratio (7.8:1) of the children diagnosed with ASD in the present study exceeded the often cited ratio of 4:1 and the estimated true ratio, which is close to 3:1 (Loomes et al., 2017). Thus, it is not unlikely that some of the missed children with ASD were females, which is in accordance with the findings that ASD is diagnosed at a later age in females than males (Lai & Baron-Cohen, 2015; Rutherford et al., 2016). Continued follow-up of the participants to detect those with ASD and an analysis of the factors that contributed to their cases being missed will be beneficial in a future study, which will then also allow the true psychometric properties of the M-CHAT-R/F in the study population to be established.

Limitations

The attendance rate (87%) of the 30-month well-child visits was suboptimal. The reason may be that no vaccination is scheduled during this visit, unlike the previous (at 18 months) and subsequent (at 48 months) visits. Of the parents who brought their child to the 30-month visit, 72% participated in the ASD screening. No information was available to us about the characteristics of the parents and their children who did not participate. However, as discussed in our previous study, there were indications that children of nonnative parents were underrepresented, even though efforts were made to have all material pertaining to the study available in numerous languages and to offer translation services if needed (Jonsdottir et al., 2020). Blinding between the screening and the diagnostic stages was not possible for the screen-positive children who were referred for assessment, as their screening results were stated in a letter accompanying the referral. As has been suggested, it is possible that knowledge about a positive screening result could incline clinicians to diagnose a child with ASD, leading to an overestimation of the accuracy measures (Yuen et al., 2018). Interestingly, however, one of the children who scored in the high-risk range on the M-CHAT-R and whose score remained unchanged after the FUI was not diagnosed with ASD. Contrary to the screen-positive children, for the screen-negative children, no information was available to the diagnostic teams regarding the children's participation in the ASD screening since they were not referred by those performing the study. Only 11 children were identified as false negatives. Hence, the comparison of clinical measures between false-negative and true-positive children should be interpreted with caution. However, a 10-month delay in diagnosis for false-negative children compared with that of true-positive children was supported by data from another study (Gunnarsdottir, 2020). The relatively long time from referral to diagnosis was in accordance with the current practices in this field in Iceland. As a consequence of this delay in diagnosis, the study was affected by limitations inherent in prospective validation studies of screening instruments targeting behaviors in young children that often change over time (Marks et al., 2008; Robins, 2020).

Conclusion

This study demonstrated that the early detection of ASD can be enhanced in Iceland by adding screening with the M-CHAT-R/F to the well-child care program at age 30 months. A positive screening result contributed to an earlier age at diagnosis and the start of early intervention, which have the potential to improve outcomes. The moderate sensitivity of the M-CHAT-R/F in this study encourages the use of additional strategies, such as a focused ASD observation, to reduce the number of false-negative cases. Methods that have proven effective in reducing false-positive cases beyond the FUI may help to streamline referrals to diagnostic and intervention services. Although the results suggest that the screening enhanced the early identification of ASD and was beneficial for the true-positive children, the public health benefits of universal screening cannot be fully estimated until data are available on the long-term outcomes of children with ASD identified through screening compared to those of unscreened children with ASD.

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Author Contributions SLJ contributed to the conception and design of the study; coordinated the project; collected, analyzed, and interpreted the data; and wrote the first draft of the manuscript. ES and VR contributed to the conception and design of the study, interpreted the data, and helped draft the manuscript. BG provided a statistical consultation and participated in the data analysis and interpretation. All authors read and revised earlier drafts of the manuscript and approved the final version.

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Declarations

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical Approval Ethical approval for the study was granted by the National Bioethics Committee of Iceland (VSNb2015110029/03.01), the Scientific Committee of the Healthcare of the Capital Area and the University of Iceland, and the Scientific Committee at the SDCC. The study was approved by the Icelandic Data Protection Authority.

Informed Consent Written informed consent was obtained from the parents.

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Paper IV

Evaluating Screening for Autism Spectrum Disorder: Outcome in an Invited Group Compared with Outcomes in two Control Groups Using Cluster Randomization

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Abstract

We evaluated the rate of autism spectrum disorder (ASD) in a group invited to a screening program compared to the rates in two groups who received usual care. The population eligible for screening was all children in Iceland registered for their 30-month well-child visits at primary healthcare centers (PHCs) from March 1, 2016, to October 31, 2017 (N = 7173). The PHCs in the capital area of Reykjavik were the units of cluster randomization. Nine PHCs were selected for intervention (invited group), while eight PHCs received usual care (control group 1). PHCs outside the capital area were without randomization (control group 2). Children in the population were followed up for at least two years and 119 cases were identified. The overall cumulative incidence of ASD was 1.66 (95% confidence interval (CI): 1.37, 1.99). In the invited group incidence rate was 2.13 (95% CI: 1.60, 2.78); in control group 1, the rate was 1.83 (95% CI: 1.31, 2.50); and in control group 2, the rate was 1.02 (95% CI: 0.66, 1.50). Although the rate of ASD was higher in the invited group than in the control groups, the wide confidence intervals prevent us to conclude definitively that the screening detected ASD more readily than did usual care.

Key Words: autism spectrum disorder; screening; M-CHAT-R/F; usual care; cluster randomization

Appendix A

Parental evaluation of first concerns about their child's development

A questionnaire used in a telephone interview with parents to obtain information about their first concerns about their child's development, and some familial and social characteristics

Númer þátttakanda:_____

Mat á fyrstum áhyggjum foreldra af þroska barna sinna

Góðan dag. Ég heiti …… og hringi vegna rannsóknar á vegum Greiningar- og ráðgjafarstöðvar ríkisins. Við sendum kynningarbréf vegna rannsókarinnar í síðustu viku, hefur það borist þér?

Hefur þú náð að kynna þér bréfið?
Má ég biðja þig að taka þátt í rannsókninni með því að svara nokkrum spurningum?

Ef bréfið hefur ekki borist þá ber að bjóðast til þess að senda það og athuga hvort að heimilisfang viðtakanda sé rétt.

Má ég senda þér eintak af bréfinu og hringja að viku liðinni til þess að athuga hvort þú viljir taka þátt í rannsókninni?

Ef þátttakandi hefur ekki náð að kynna sér bréfið þá ber að athuga hvort megi kynna honum það símleiðis eða hringja aftur síðar.

Má ég segja þér frá rannsókninni símleiðis eða viltu að ég hringi aftur síðar?

Áður en við vindum okkur í spurningalistann þá vil ég benda þér á þú getur hætt þátttöku hvenær sem er án útskýringa og að þér er ekki skylt að svara einstökum spurningum kjósir þú að hafna þeim.

Fyrst langar mig að spyrja þig um almennar áhyggjur af þroska barnsins

1. Hvað olli þér fyrst áhyggjum í þroska barnsins? Var það t.d. [lesa upp valmöguleika. Ef fólk segir fl. en eitt atriði biðja þá um að nefna það sem mest var áberandi. Sá möguleiki er merktur 1 en hinir x]

- ☐ Seinkaður málþroski
- ☐ Seinkaður almennur þroski
- ☐ Læknisfræðileg vandmál
- ☐ Svefnftruflanir
- ☐ Matarvandamál
- ☐ Órói
- ☐ Annað, hvað?_____

2. Hver hafði fyrst orð á hugsanlegum frávikum (vandkvæðum) í þroska barnsins?

- ☐ Móðir
- ☐ Faðir
- ☐ Ættingi
- ☐ Vinur/vinkona
- ☐ Fagaðili, hver?_____
- ☐ Annar; hver? _____

3. Hvað var barnið u.þ.b. gamalt þegar áhyggjur af þroska þess vöknuðu fyrst?

Nú langar mig að spyrja þig nokkurra spurninga um hugsanlegar áhyggjur af hegðun barnsins sem tengjast einkennum einhverfu sérstaklega.

x. Manstu hvaða einkenni í hegðun barnsins vakti fyrst grun um að barnið hefði einkenni einhverfu? Var það t.d. [lesa upp valmöguleika. Ef fólk segir fl. en eitt atriði biðja þá um að nefna það sem mest var áberandi. Sá möguleiki er merktur 1 en hinir með x]

- ☐ Seinkaður málþorski
- ☐ Svaraði ekki nafni/kalli
- ☐ Skortur á augnsambandi
- ☐ Afturför í þroska
- ☐ Lítill áhugi á samskiptum við aðra
- ☐ Skortur á svipbrigðum
- ☐ Erfiðleikar með að þola breytingar
- ☐ Virtist ekki njóta snertingar eða sækja í faðmlög
- ☐ Notaði líkama annarra til tjáskipta
- ☐ Sérkennileg og/eða áráttukennd hegðun
- ☐ Annað, hvað?_____

x. Hjá hverjum vaknaði fyrst grunur um að barnið hefði einkenni einhverfu?

- ☐ Móður
- ☐ Föður
- ☐ Ættingja
- ☐ Vini
- ☐ Fagaðila, hverjum?_____
- ☐ Öðrum, hverjum?_____

Þó nokkrir foreldrar hafa greint frá því að eftir að þeir fái að kynnast einkennum einhverfu betur þá sjái þeir fyrstu æviár barns síns í öðru ljósi. Þeir muna eftir ákveðnum þáttum í fari barnsins sem þeir mundu í dag flokka undir einkenni einhverfu.

x. Þegar þú lítur til baka, telur þú að barnið þitt hafi á fyrstu árum sýnt einhver einkenni einhverfu sem vöktu á þeim tíma ekki áhyggjur þínar? Var það t.d. [lesa upp valmöguleika. Ef fólk segir fl. en eitt atriði biðja þá um að nefna það sem mest var áberandi. Það atriði er merkt 1 en hin atriðin sem foreldri nefnir með x]

- ☐ Svaraði ekki nafni/kalli
- ☐ Skortur á augnsambandi
- ☐ Lítill áhugi á samskiptum við önnur börn
- ☐ Lék sér ekki í þykjustuleik
- ☐ Hermdi ekki eða illa eftir svipbrigðum
- ☐ Virtist ekki njóta snertingar eða sækja í faðmlög
- ☐ Benti ekki með vísifingri til að sýna áhuga á einhverju
- ☐ Erfiðleikar með að þola breytingar

- ☐ Notaði líkama annarra til tjáskipta
- ☐ Sérkennileg og/eða áráttukennd hegðun
- ☐ Annað, hvað?_____

(Ef foreldri svara játandi við einhverjum af eftirfarandi möguleikum þá ber að spyrja næstu spurningar. Ef foreldri svara nei þá ber að sleppa næstu spurningu)

x. Þegar þú lítur til baka, hvað telur þú að barnið hafi verið gamalt þegar fyrstu einkenna einhverfu varð vart?_____

Næst langar mig að spyrja þig nokkurra spurninga um leið ykkar að greiningu.

x. Hvaða einkenni var fyrst og fremst ástæðan fyrir því að þið leituðuð ykkur aðstoðar?

_____

x. Til hvers leituðuð þið fyrst? [Ef foreldri man það ekki ber að lesa upp valmöguleika]

- ☐ Heimilislæknis/heilsugæslulæknis
- ☐ Barnalæknis
- ☐ Sálfræðings
- ☐ Talmeinafræðings
- ☐ Leikskólakennara
- ☐ Grunnskólakennara
- ☐ Annað, hvert?_____

x. Hvað var barnið gamalt þegar fyrst var leitað aðstoðar?_____

x. Hver voru svör þeirra sem fyrst var leitað til?

_____

x. Hver var það sem vísaði ykkur til Greiningarstöðvar?

_____

Að lokum vil ég biðja þig um að svara nokkrum almennum spurningum.

x) Hvar á landinu býrð þú?

a) Staður:_____

b) Póstnúmer:_____

x) Hefur þú flutt síðan að barnið fékk greiningu a) Nei b) já

Ef já

x) Hvar á landinu bjóst þú áður?

a) Staður:_____

b) Póstnúmer:_____

x) Hefur þú lokið einhverju námi eftir skyldunám?

[*ATHUGIÐ: Ef eitthvað er óljóst í tengslum við þau próf/menntun sem svarendur hafa lokið, skrifið þá athugasemdir við spurninguna.]*

01. **Nei, hef engu námi lokið eftir skyldunám**.

02. **Já** → Hvaða námi hefur þú lokið? _____

10. Starfsnámi, s.s. tölvu-, viðskipta-, bókhalds-, trygginga-, ritara-, sjúkraliða-, póst-, banka-, lögreglu-, fiskvinnslu-, hússtjórnarnámi eða öðru starfsnámi.
20. Bóklegu framhaldsnámi, s.s. verslunarprófi, samvinnuskólaprófi, stúdentsprófi.
30. Verklegu framhaldsnámi – iðnmenntun, s.s. sveins- og/eða meistaraprófi, vélstjóra- og stýrimannaprófi, búfræði, garðyrkjufræði eða tækniteiknun.
40. Prófi úr sérskólum á eða við háskólastig, s.s. myndlistarnámi, fósturnámi, tæknínámi o.fl.
50. Háskólanámi (3 ára háskólanám eða lengra: BA, BS, kandídatsnám, MA, MS, doktorsnám).

98. Veit ekki
99. Neitar að svara

x) Hefur faðir/móðir (fer eftir hver svarar) lokið einhverju námi eftir skyldunám?

[*ATHUGIÐ: Ef eitthvað er óljóst í tengslum við þau próf/menntun sem svarendur hafa lokið, skrifið þá athugasemdir við spurninguna.]*

01. **Nei, hef engu námi lokið eftir skyldunám**.

02. **Já** → Hvaða námi hefur þú lokið? _____

10. Starfsnámi, s.s. tölvu-, viðskipta-, bókhalds-, trygginga-, ritara-, sjúkraliða-, póst-, banka-, lögreglu-, fiskvinnslu-, hússtjórnarnámi eða öðru starfsnámi.
20. Bóklegu framhaldsnámi, s.s. verslunarprófi, samvinnuskólaprófi, stúdentsprófi.
30. Verklegu framhaldsnámi – iðnmenntun, s.s. sveins- og/eða meistaraprófi, vélstjóra- og stýrimannaprófi, búfræði, garðyrkjufræði eða tækniteiknun.
40. Prófi úr sérskólum á eða við háskólastig, s.s. myndlistarnámi, fósturnámi, tæknínámi o.fl.
50. Háskólanámi (3 ára háskólanám eða lengra: BA, BS, kandídatsnám, MA, MS, doktorsnám).

98. Veit ekki
99. Neitar að svara

x) Hvert er megin starf þitt? _____
(*Miða skal við aðalstarf, ef svarandi er í fleiru en einu starfi og það starf sem unnið er með námi sé um slíkt að ræða. Ef viðkomandi er heimavinnandi, í námi eða atvinnulaus er nóg að skrá það hér að ofan. Annars skrá að ofan og flokka starfið í réttan flokk hér að neðan*)

10. Kjörnir fulltrúar og æðstu embættismenn
- 11. Kjörnir fulltrúar, æðstu embættismenn og æðstu stjórnendur hagsmunasamtaka.
- 12. Forstjórar og stjórnendur stærri fyrirtækja og stofnana. Atvinnurekendur. Yfirmenn stórra deilda t.d. verkstjórar (undirmenn fleiri en 10).
- 13. Framkvæmdastjórar og forstöðumenn lítilla fyrirtækja/stofnana/deilda, t.d. verslunarstjórar og atvinnurekendur (undirmenn 10 eða færri).
- 14. Yfirmenn á skipum (skipstjórar, stýrimenn, vélstjórar) - Ekki yfirmenn á bátum, t.d. trillubátum.

20. Sérfræðingar
- 21. Sérfræðingar í raunvísindum, stærðfræði, verkfræði, arkitektar, tölvunarfræðingar o.þ.h.
- 22. Sérfræðingar í náttúruvísindum og heilbrigðisgreinum, læknar, hjúkrunarfræðingar, líffræðingar.
- 23. Framhaldsskólakennarar eða grunnskólakennarar. Leikskólakennarar og þroskaþjálfar.
- 24. Háskólakennarar og sérfræðingar í félagsvísindum, hugvísindum, opinberri stjórnsýslu, lögfræðingar, viðskiptafræðingar, frétta- og blaðamenn.
- 25. Rithöfundar og listamenn.

30. Tæknar eða sérmenntað starfsfólk
- 31. Tæknar í raunvísindum, læknisfræði, stærðfræði, verkfræði o.þ.h. Vélstjórar og flugmenn.
- 32. Tæknar í náttúrufræðum og heilbrigðisgreinum, sjúkraliðar, tannfræðingar, sjúkranuddarar.
- 33. Fóstrur, uppeldisfulltrúar o.þ.h.
- 34. Fulltrúar, miðlarar, lögreglumenn, skemmtikraftar, íþróttamenn/þjálfarar, fatahönnuðir.
- 35. Kokkar, þjónar, hárgreiðslu- eða snyrtifræðingar.

40. Skrifstofufólk
- 41. Almennt starfsfólk á skrifstofu, bréfberar.
- 42. Skrifstofufólk við afgreiðslu, gjaldkerar, innheimtufólk, símaverðir.

50. Þjónustu-, sölu- og afgreiðslufólk
- 51. Starfsfólk við þjónustu- og gæslu. Umönnunarstörf. Brunaverðir.
- 52. Afgreiðslufólk, sölufólk, sýningarfólk.

60. Bændur eða sjómenn
- 61. Bændur
- 62. Sjómenn

70. Iðnaðarmenn og sérhæft starfsfólk við iðnað
- 71. Byggingariðnaðarmenn, (húsasmiðir, múrarar, pípulagningamenn, o.fl.)
- 72. Málmiðnaðarmenn, vélsmiðir, vélvirkjar, bifvélavirkjar, o.fl.
- 73. Rafiðnaðarmenn (rafvirkjar, rafeindavirkjar, símsmiðir).
- 74. Aðrir iðnaðarmenn (matvæla-, leður-, húsgagna-, fínsmíði, bókagerð).
- 75. Verkstjórar og sérhæft starfsfólk í iðnaði.

80. Véla- og vélgæslufólk. Bifreiðastjórar
- 81. Vélgæslufólk í iðjuverum og verksmiðjum.
- 82. Vélafólk, t.d. í efnavöru- og matvælaframleiðslu.
- 83. Bifreiðastjórar og stjórnendur vinnuvéla og annarra vélknúinna ökutækja.

90. Ósérhæft starfsfólk
- 91. Verkafólk við sölu- og þjónustustörf (ræstingu/sorphreinsun/sendlar/ dyraverðir).
- 92. Verkafólk í iðnaði, fiskvinnslu, landbúnaði.

99. Neitar að svara

x) Hvert er megin starf föður/móður (fer eftir hver svarar)?

_____

(*Miða skal við aðalstarf, ef svarandi er í fleiru en einu starfi og það starf sem unnið er með námi sé um slíkt að ræða. Ef viðkomandi er heimavinnandi, í námi eða atvinnulaus er nóg að skrá það hér að ofan. Annars skrá að ofan og flokka starfið í réttan flokk hér að neðan*)

10. Kjörnir fulltrúar og æðstu embættismenn
- 11. Kjörnir fulltrúar, æðstu embættismenn og æðstu stjórnendur hagsmunasamtaka.
- 12. Forstjórar og stjórnendur stærri fyrirtækja og stofnana. Atvinnurekendur. Yfirmenn stórra deilda t.d. verkstjórar (undirmenn fleiri en 10).
- 13. Framkvæmdastjórar og forstöðumenn lítilla fyrirtækja/stofnana/deilda, t.d. verslunarstjórar og atvinnurekendur (undirmenn 10 eða færri).
- 14. Yfirmenn á skipum (skipstjórar, stýrimenn, vélstjórar) - Ekki yfirmenn á bátum, t.d. trillubátum.

20. Sérfræðingar
- 21. Sérfræðingar í raunvísindum, stærðfræði, verkfræði, arkitektar, tölvunarfræðingar o.þ.h.
- 22. Sérfræðingar í náttúruvísindum og heilbrigðisgreinum, læknar, hjúkrunarfræðingar, líffræðingar.
- 23. Framhaldsskólakennarar eða grunnskólakennarar. Leikskólakennarar og þroskaþjálfar.
- 24. Háskólakennarar og sérfræðingar í félagsvísindum, hugvísindum, opinberri stjórnsýslu, lögfræðingar, viðskiptafræðingar, frétta- og blaðamenn.
- 25. Rithöfundar og listamenn.

30. Tæknar eða sérmenntað starfsfólk
- 31. Tæknar í raunvísindum, læknisfræði, stærðfræði, verkfræði o.þ.h. Vélstjórar og flugmenn.
- 36. Tæknar í náttúrufræðum og heilbrigðisgreinum, sjúkraliðar, tannfræðingar, sjúkranuddarar.
- 37. Fóstrur, uppeldisfulltrúar o.þ.h.
- 38. Fulltrúar, miðlarar, lögreglumenn, skemmtikraftar, íþróttamenn/þjálfarar, fatahönnuðir.
- 39. Kokkar, þjónar, hárgreiðslu- eða snyrtifræðingar.

40. Skrifstofufólk
- 43. Almennt starfsfólk á skrifstofu, bréfberar.
- 44. Skrifstofufólk við afgreiðslu, gjaldkerar, innheimtufólk, símaverðir.

50. Þjónustu-, sölu- og afgreiðslufólk
- 51. Starfsfólk við þjónustu- og gæslu. Umönnunarstörf. Brunaverðir.
- 52. Afgreiðslufólk, sölufólk, sýningarfólk.

60. Bændur eða sjómenn
- 61. Bændur
- 62. Sjómenn

70. Iðnaðarmenn og sérhæft starfsfólk við iðnað
- 71. Byggingariðnaðarmenn, (húsasmiðir, múrarar, pípulagningamenn, o.fl.)
- 72. Málmiðnaðarmenn, vélsmiðir, vélvirkjar, bifvélavirkjar, o.fl.
- 73. Rafiðnaðarmenn (rafvirkjar, rafeindavirkjar, símsmiðir).
- 74. Aðrir iðnaðarmenn (matvæla-, leður-, húsgagna-, fínsmíði, bókagerð).
- 75. Verkstjórar og sérhæft starfsfólk í iðnaði.

80. Véla- og vélgæslufólk. Bifreiðastjórar
- 81. Vélgæslufólk í iðjuverum og verksmiðjum.
- 82. Vélafólk, t.d. í efnavöru- og matvælaframleiðslu.
- 83. Bifreiðastjórar og stjórnendur vinnuvéla og annarra vélknúinna ökutækja.

90. Ósérhæft starfsfólk
- 91. Verkafólk við sölu- og þjónustustörf (ræstingu/sorphreinsun/sendlar/ dyraverðir).
- 92. Verkafólk í iðnaði, fiskvinnslu, landbúnaði.

99. Neitar að svara

Appendix B

Modified Checklist for Autism in Toddlers, Revised with Follow-Up, Icelandic translation and adaptation

This appendix includes the parent-report questionnaire, the M-CHAT-R, which constitutes the first screening stage. The questionnaire and the follow-up interview (the second screening stage) can be accessed on the M-CHAT website, https://mchatscreen.com/

M-CHAT-R™

Vinsamlega svaraðu eftirfarandi spurningum um barnið þitt. Hafðu í huga hvernig barnið hegðar sér venjulega. Ef þú hefur séð tiltekna hegðun hjá barninu í nokkur skipti, en það sýnir hana ekki venjulega, svaraðu þá **nei**. Vinsamlega gerðu hring um **já** eða **nei** fyrir hverja spurningu. Takk fyrir.

1.	Þegar þú bendir á eitthvað hinum megin í herberginu, horfir barnið á það? (**TIL DÆMIS**, þegar þú bendir á leikfang eða dýr, horfir barnið á leikfangið eða dýrið?)	Já	Nei
2.	Hefur þú einhvern tíma velt fyrir þér hvort barnið gæti verið heyrnarskert?	Já	Nei
3.	Leikur barnið þykjustu- eða ímyndunarleiki? (**TIL DÆMIS**, þykjast drekka úr tómum bolla, þykjast tala í síma eða þykjast mata dúkku eða tuskudýr?)	Já	Nei
4.	Finnst barninu gaman að klifra? (**TIL DÆMIS**, á húsgögnum, í útileiktækum eða í stigum)	Já	Nei
5.	Sýnir barnið óvenjulegar fingrahreyfingar nálægt augunum? (**TIL DÆMIS**, hristir barnið fingurna hratt upp og niður nálægt augunum?)	Já	Nei
6.	Bendir barnið með einum fingri til að biðja um eitthvað eða til að fá hjálp? (**TIL DÆMIS**, að benda á snakk/nammi eða leikfang sem er utan seilingar)	Já	Nei
7.	Bendir barnið með einum fingri til þess að sýna þér eitthvað áhugavert? (**TIL DÆMIS**, að benda á flugvél á lofti eða stóran vörubíl á veginum)	Já	Nei
8.	Hefur barnið áhuga á öðrum börnum? (**TIL DÆMIS**, horfir barnið á önnur börn, brosir til þeirra eða fer til þeirra?)	Já	Nei
9.	Sýnir barnið þér hluti með því að koma með þá til þín eða að halda þeim á lofti svo þú getir séð þá – ekki til að fá hjálp, bara til að deila með þér? (**TIL DÆMIS**, að sýna þér blóm, tuskudýr, eða leikfangabíl)	Já	Nei
10.	Bregst barnið við nafninu sínu þegar þú kallar? (**TIL DÆMIS**, lítur það upp, talar, bablar, eða hættir því sem það er að gera þegar þú kallar á það með nafni?)	Já	Nei
11.	Þegar þú brosir til barnsins, brosir það til baka?	Já	Nei
12.	Kemur hversdagslegur hávaði barninu í uppnám? (**TIL DÆMIS**, öskrar barnið eða grætur vegna hávaða í ryksugu eða háværrar tónlistar?)	Já	Nei
13.	Gengur barnið óstutt?	Já	Nei
14.	Horfir barnið í augun á þér þegar þú talar við það, leikur við það eða klæðir það?	Já	Nei
15.	Reynir barnið að herma eftir því sem þú gerir? (**TIL DÆMIS**, vinka bless, klappa, eða framkalla skemmtileg/sniðug hljóð þegar þú gerir það)	Já	Nei
16.	Þegar þú snýrð höfðinu til þess að horfa á eitthvað, horfir barnið í kringum sig til þess að sjá hvað þú ert að horfa á?	Já	Nei
17.	Reynir barnið að fá þig til að horfa á sig? (**TIL DÆMIS**, horfir barnið á þig til að fá hrós eða segir „sjáðu“ eða „sjáðu mig“?)	Já	Nei
18.	Skilur barnið þegar þú segir því að gera eitthvað? (**TIL DÆMIS**, ef þú bendir ekki, getur barnið skilið „settu bókina á stólinn“ eða „komdu með teppið til mín“?)	Já	Nei
19.	Þegar eitthvað nýtt gerist, horfir barnið framan í þig til þess að sjá hvað þér finnst um það? (**TIL DÆMIS**, þegar það heyrir skrýtin eða skemmtileg hljóð eða sér nýtt leikfang, horfir það þá framan í þig?)	Já	Nei
20.	Finnst barninu hreyfileikir skemmtilegir? (**TIL DÆMIS**, að láta sveifla sér eða vera hossað á hnjánum þínum)	Já	Nei

Íslensk þýðing 2015: Sigríður Lóa Jónsdóttir, Evald Sæmundsen, & Gyða Haraldsdóttir.

Appendix C

Detection of autism in well-child care

A pre- and post-course self-assessment on autism knowledge, skill, and confidence in detecting signs of autism, and a general assessment of the course

Greiningar- og ráðgjafarstöð ríkisins

HEILSUGÆSLAN

Að bera kennsl á einhverfu í ung- og smábarnavernd

Matsblað

Ath. Hér á eftir er hugtakið „einhverfa“ notað í víðri merkingu, eða fyrir allt einhverfurófið

Hve lengi hefur þú starfað í ung- og smábarnavernd? _____

Hefur þú áður fengið sérstaka fræðslu um einhverfu? Já____ Nei____

Ef „já“ – hvar fékkstu fræðsluna og hve umfangsmikil var hún? _____

_____

Þú ert beðin/n um að meta þekkingu þína og viðhorf á eftirtöldum sviðum (gerðu hring um viðeigandi svar)

	Fyrir þetta námskeið				**Eftir þetta námskeið**			
Þekking á alþjóðlegum skilgreiningum á einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Þekking á einkennum hjá ungum börnum sem geta bent til einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Þekking á orsökum einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Þekking á meðröskunum einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Þekking á algengi einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð

Framhald á bakhlið

	Fyrir þetta námskeið				Eftir þetta námskeið			
Þekking á helstu áhyggjum foreldra barna sem síðar greinast með einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Þekking á helstu áhættuþáttum fyrir einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Þekking á gildi snemmtækrar íhlutunar	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Færni og öryggi sem þú telur þig búa yfir til að taka afstöðu til þess hvort tiltekin einkenni gefi tilefni til nánari athugunar vegna hugsanlegrar einhverfu	Mjög góð	Góð	Sæmileg	Takmörkuð	Mjög góð	Góð	Sæmileg	Takmörkuð
Hversu vel mun námskeiðið nýtast þér í starfi					Mjög vel	Vel	Sæmilega	Lítið
Heildarmat þitt á námskeiðinu					Mjög gott	Gott	Sæmilegt	Lélegt

Annað sem þú vilt koma á framfæri:

Appendix D

A survey on experiences with and attitudes toward screening for autism

This questionnaire was completed by the contact nurses from the participating PHCs at the end of the screening period

Könnun á reynslu og viðhorfi til skimunar fyrir einhverfu

1. Ég tók þátt í að afhenda foreldrum skimunarlista fyrir einhverfu í tengslum við rannsóknina: *Að bera kennsl á einhverfu snemma*, eða tengdist rannsókninni á annan hátt vegna starfa minna í heilsugæslunni

Já _____ Nei_____

Ef svar þitt við spurningu nr. 1 er „nei“, slepptu þá spurningum nr. 2 og 3 og farðu beint yfir á spurningu nr. 4.

2. Mér fannst foreldrar almennt taka jákvætt í það að svara listanum

Algerlega sammála	Nokkuð sammála	Hlutlaus	Nokkuð ósammála	Algerlega ósammála
___	___	___	___	___

3. Foreldrar gátu almennt svarað listanum án aðstoðar

Algerlega sammála	Nokkuð sammála	Hlutlaus	Nokkuð ósammála	Algerlega ósammála
___	___	___	___	___

4. Ég er hlynnt/ur því að leitað sé kerfisbundið að einkennum einhverfu hjá ungum börnum með því að biðja foreldra þeirra um að svara þar til gerðum spurningum/skimunarlista

Algerlega sammála	Nokkuð sammála	Hlutlaus	Nokkuð ósammála	Algerlega ósammála
___	___	___	___	___

Ef svar þitt við spurningu nr. 4 er neikvætt (nokkuð ósammála eða algerlega ósammála) slepptu þá spurningum nr. 5, 6 og 7 og farðu beint yfir á spurningu nr. 8.

5. Ég er hlynnt/ur því að skimað verði fyrir einhverfu (merkja má við fleiri en einn svarmöguleika):

___ Hjá öllum börnum í tólf mánaða skoðun
___ Hjá öllum börnum í átján mánaða skoðun
___ Hjá öllum börnum í tveggja og hálfs árs skoðun
___ Hjá öllum börnum í fjögurra ára skoðun
___ Eingöngu hjá börnum sem eru í skilgreindum áhættuhópum fyrir einhverfu
___ Þegar áhyggjur vakna hjá foreldrum
___ Þegar áhyggjur vakna hjá fagaðilum
___ Annað: .....

Framhald á bakhlið

6. Ég tel að æskilegt sé að skimun fyrir einhverfu fari fram með því að:

___ Foreldrar fylli út spurningalista í pappírsformi
___ Foreldrar fylli út spurningalista í rafrænu formi
___ Fagmaður leggi spurningar skimunarlista fyrir foreldra í viðtalsformi

7. Ég tel að besti vettvangurinn til þess að skima fyrir einhverfu sé:

___ Í tengslum við reglubundið eftirlit með þroska í ung- og smábarnavernd
___ Á leikskóla barnsins
___ Á báðum stöðum

8. Ég tel mig þekkja nokkuð vel til einkenna einhverfu hjá ungum börnum

Algerlega	Nokkuð		Nokkuð	Algerlega
___ sammála	___sammála	___Hlutlaus	___ósammála	___ósammála

9. Ég myndi vilja fá meiri fræðslu um einhverfu

Algerlega	Nokkuð		Nokkuð	Algerlega
___ sammála	___sammála	___Hlutlaus	___ósammála	___ósammála

10. Er eitthvað annað sem þú vilt koma á framfæri og tengist ofangreindum spurningum eða þátttöku í rannsókninni *Að bera kennsl á einhverfu snemma*?

Takk fyrir!