

Complexities of Early Identification Using Screening Instruments

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Who am I?



Dr. Roald A. Øien, PhD

Professor of Special Education and Child Development – UiT The Arctic University of Norway

Assistant Professor Adjunct – Child Study Center, Yale University

- PhD – Psychology
- Research interests: early development, behavioral and temperamental traits in young children with neurodevelopmental disorders as they might affect how we identify and intervene.
- Research utilizing the Norwegian Mother and Child Study (MoBa) – A prospective general population study
- Associate editor in Journal of Autism and Developmental Disorders
- Father of four – 14-year-old daughter with ASD

Autism Spectrum Disorders (ASD)

- 01 Autism Spectrum Disorders (ASD) are:**
- Persistent deficits in social communication and social interaction
 - Restricted, repetitive patterns of behavior, interests, or activities
 - Symptoms must be present in the early developmental period (APA 2013)

- 02 Early identification of Autism Spectrum Disorders (ASD) is important because:**
- Access to benefits such as intervention (Mandell et al. 2005; Zwaigenbaum et al.2013)
 - It is considered a critical factor for improving future outcome.

- 03 Early Symptoms of Autism Spectrum Disorders (ASD) are:**
- Heterogeneous (Zwaigenbaum et al. 2015)
 - Different time and patterns of onset (Ozonoff et al. 2010, 2015; Chawarska et al. 2007)
 - Different symptoms in males and females

Time and Patterns of Onset

Knowledge

- Heterogeneity in e.g. behaviors, core symptoms, adaptive functioning, cognitive skills

(Zwaigenbaum et al. 2015)

- Increasing awareness of heterogeneity in time and patterns of onset

(Ozonoff et al. 2010, 2015;

Chawarska et al. 2007)

- Manifest differently depending on verbal and nonverbal skills

(Chawarska et al. 2015)

Challenges

- Elicits immense difficulties in detection and treatment planning
 - May need a greater social demand to become evident
- (Ozonoff et al. 2015)
- Symptoms might not be evident at 18-months

Screening

Knowledge

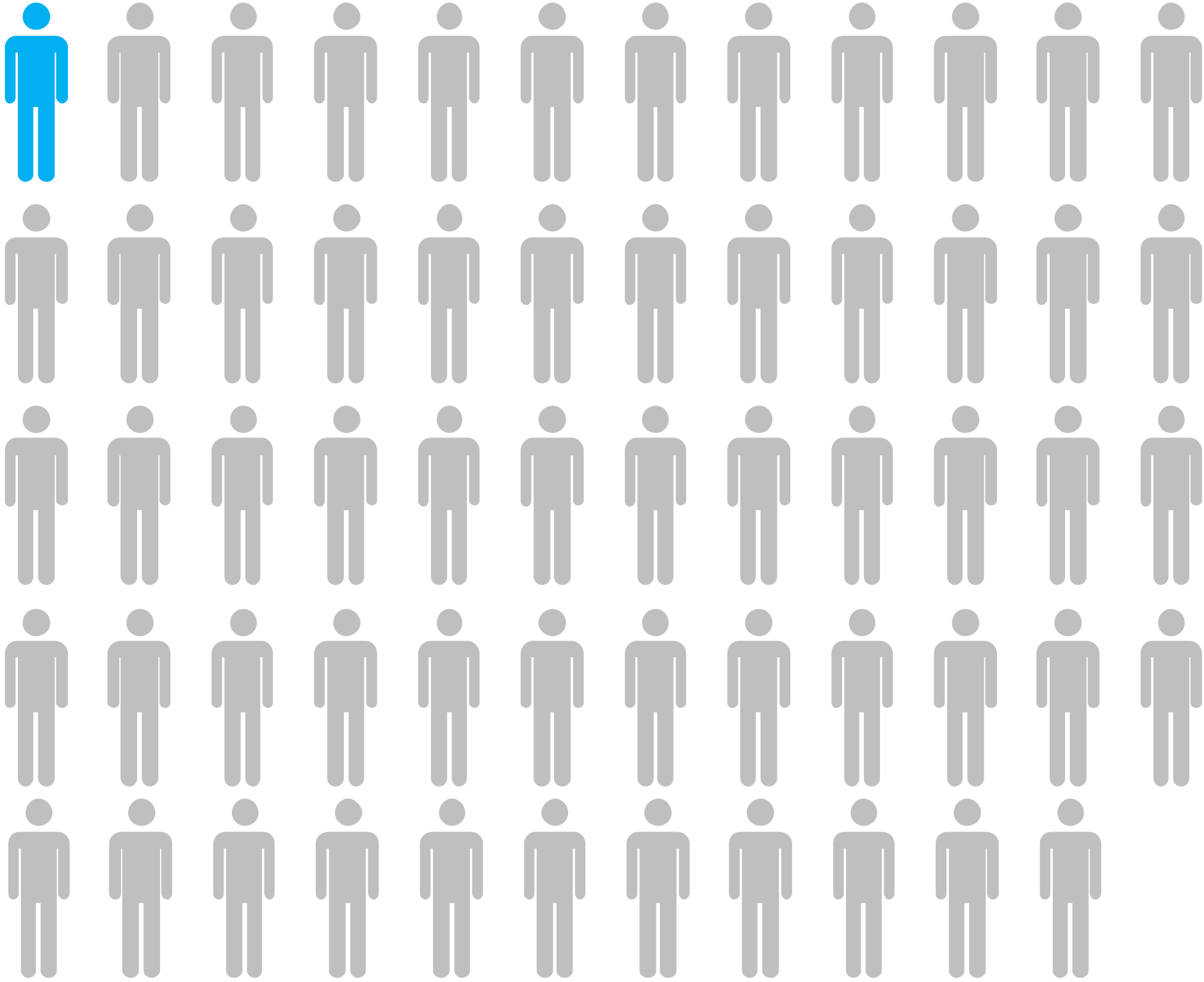
- Enhance early identification
- Early intervention
- Brief parent-endorsed questionnaires
- M-CHAT (R/F) most used (Robins 2001, Kleinmann 2008, Robins 2014)
- Lack of evidence for universal screening (Siu et al. 2016)
- AAP recommends screening at 18 and 24 months (AAP 2016)

Challenges

- The M-CHAT misses nearly most ASD cases at 18 months (False negatives) (Stenberg et al. 2014; Øien et al. 2018; Guthrie et al. 2019)
- M-CHAT identifies children with lower IQ and more language issues (Stenberg et al. 2020)
- Few prospective general population studies.
- Validation studies assessing screen positives with no prospective follow-up

Prevalence

US Centers for Disease Control and Prevention



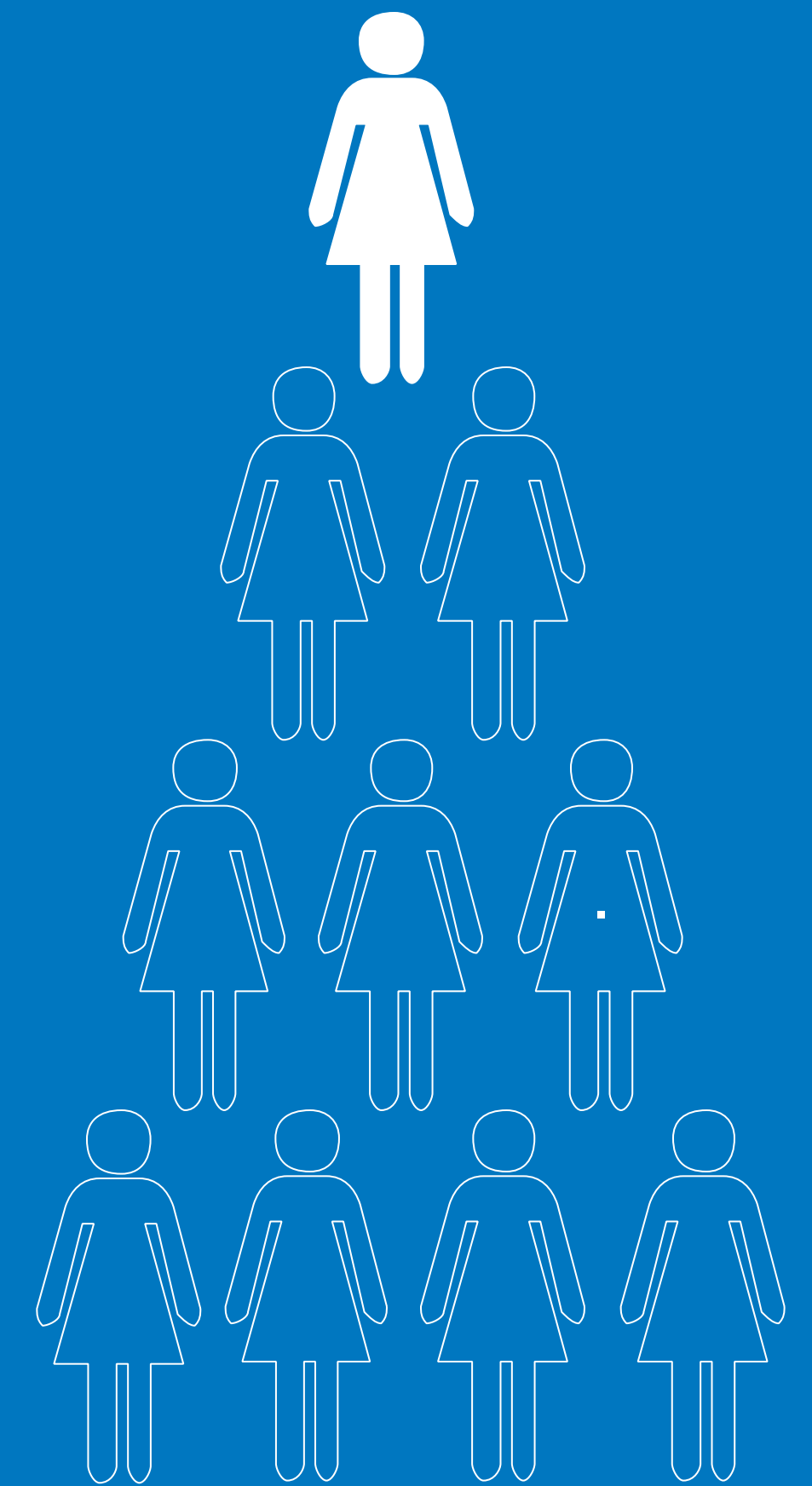
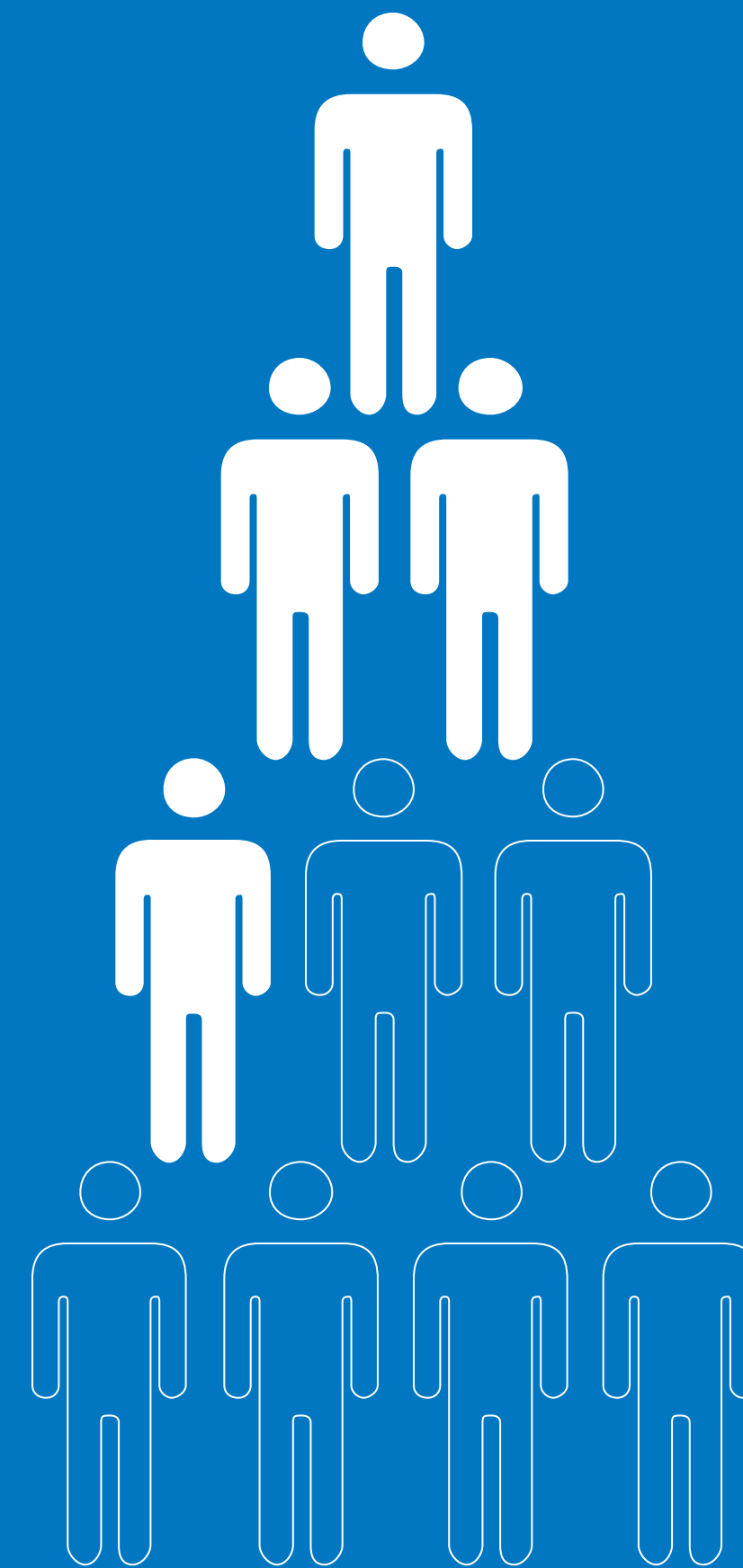
2016: 1 in 54 1.85%

2014: 1 in 59 (1.7%)

2012: 1 in 68 (1.5%)

Prevalence & male-to-female ratio

- Prevalence: 1:59 (1.7%) (CDC, 2018)
- Skewed since the seminal studies (Kanner 1943; Asperger 1944)
- Frequently reported as 4.3 – 5.5:1 (Fombonne 2003;2005)
- Loomes (2017) reported a «true» male-to-female ratio closer to 3.1:1 due to missing females with ASD
- IQ and Intellectual disability (ID) affect the male-to female ratio
- 5.75:1 in the normal range IQ
- 1.9:1 in individuals with comorbid ID (Baird 2006; Fombonne 2009; Kim 2011)



Sex Differences

Knowledge

- Females more oriented towards social stimuli (Chawarska et al. 2016)
- Males tend to score higher on externalizing behaviors than females (Bölte et al. 2011 Mandy et al. 2012; Szatmari et al. 2011)
- Later identified than males (Salamone et al. 2016)
- Lower levels of RRBs (Frazier et al. 2014; Charman et al. 2017, Supekar & Menon 2015)

Challenges

- Females with less externalizing behaviors (Dworzynski et al. 2013) might be missed
- Females might require a greater genetic load to be identified (Robinson 2013)
- Small samples of females might complicate the search of the female phenotype
- Camouflaging (Bargiela et al. 2016)

Papers

Journal of Autism and Developmental Disorders
<https://doi.org/10.1007/s10803-018-3488-y>

ORIGINAL PAPER



Sex-Differences in Children Referred for Assessment: An Exploratory Analysis of the Autism Mental Status Exam (AMSE)

Roald A. Øien^{1,2} · Sara M. Vambheim¹ · Logan Hart^{1,2} · Anders Nordahl-Hansen³ · Craig Erickson⁵ · Logan Wink⁵ · Martin R. Eisemann¹ · Frederick Shic⁴ · Fred R. Volkmar² · David Grodberg²

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Abstract

The autism mental status exam is an eight-item observational assessment that structures the way we observe and document signs and symptoms of ASD. Investigations of test performance indicate strong sensitivity and specificity using gold-standard assessment as reference standard. This study aims to explore potential sex differences in AMSE test performance and observations of 123 children referred for autism assessment. Results indicates more language deficits in females with ASD than in males with ASD and less sensory symptoms in females compared to males with ASD. The AMSE performance is similar in identifying ASD and non-ASD in females compared to males. Less disruptive behaviors in females, might cause a need for a bigger hit to other areas of development to raise concern.

Keywords Sex differences · Gender differences · Behavior · Autistic traits · Autism-related symptoms

Introduction

Prevalence studies consistently indicate that ASD is over-represented in boys compared to girls (Elsabbagh et al. 2012; Fombonne 2003; Fombonne et al. 2011; Loomes

differences between typically developing males and females (Halpern 1997; Zahn-Waxler et al. 2006), with ASD representing an extreme expression of male traits (Baron-Cohen 2002, 2009). The difference in prevalence could also reflect a genetic protective factor in females (Robinson et al. 2013).

J Autism Dev Disord (2017) 47:126–134
 DOI 10.1007/s10803-016-2945-8



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Parent-Endorsed Sex Differences in Toddlers with and Without ASD: Utilizing the M-CHAT

Roald A. Øien^{1,2} · Logan Hart^{1,2} · Synnve Schjølberg³ · Carla A. Wall² · Elizabeth S. Kim⁴ · Anders Nordahl-Hansen³ · Martin R. Eisemann¹ · Katarzyna Chawarska² · Fred R. Volkmar² · Frederick Shic²

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Abstract Sex differences in typical development can provide context for understanding ASD. Baron-Cohen (Trends Cogn Sci 6(6):248–254, 2002) suggested ASD could be considered an extreme expression of normal male, compared to female, phenotypic profiles. In this paper, sex-specific M-CHAT scores from N=53,728 18-month-old toddlers, including n=185 (32 females) with ASD, were examined. Results suggest a nuanced view of the “extreme male brain theory of autism”. At an item level, almost every male versus female disadvantage in the broader population was consistent with M-CHAT vulnerabilities in ASD.

Keywords Sex differences · Gender differences · Behavior · Autistic traits · m-Chat · Identification

Introduction

Studies examining gender differences in typically developing infants and toddlers show sex-specific patterns in behavior and development. Differences include higher activity level in males, while social orienting, reciprocity, eye-contact and language development tend to represent

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<http://pediatrics.aappublications.org/content/early/2018/05/17/peds.2017-3596>

Paper I

Sex-Differences in Children Referred for Assessment: An Exploratory Analysis of the Autism Mental Status Exam (AMSE)

Paper I aimed to examine sex differences at the item level in clinician-endorsed symptoms of the AMSE.

Paper II

Parent-Endorsed Sex Differences in Toddlers with and Without ASD: Utilizing the M-CHAT

Paper II examined sex differences in ASD and Non-ASD children at 18 months of age and whether there was proof for the extreme male brain theory.

Paper III

Clinical Features of Children with Autism Who Passed 18-Month Screening

Paper III examined development and temperament in false-negative male and female toddlers.

Paper I: Sex-Differences in Children Referred for Assessment: An Exploratory Analysis of the Autism Mental Status Exam (AMSE)

Aims

- Explore sex differences in observed/reported behaviors in children with ASD
- Measure the diagnostic ability of the AMSE in males and females suspected of ASD.

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Date _____ Rater _____ Subject # _____

EYE CONTACT <small>(observed)</small>	<input type="checkbox"/> ≥ 3 seconds	<input type="checkbox"/> Fleeting	<input type="checkbox"/> None
INTEREST IN OTHERS <small>(observed)</small>	<input type="checkbox"/> Initiates Interaction with Examiner	<input type="checkbox"/> Only Passively Responds	<input type="checkbox"/> No Interest
POINTING SKILLS <small>(observed)</small>	<input type="checkbox"/> Can Point/ Gesture to Object	<input type="checkbox"/> Only Follows Point	<input type="checkbox"/> None
LANGUAGE <small>(reported and/or observed)</small>	<input type="checkbox"/> Can Speak About Another Time Or Place	<input type="checkbox"/> Single Words <input type="checkbox"/> Phrases (≤ 3 words) <input type="checkbox"/> Undeveloped Sentences	<input type="checkbox"/> Nonverbal
<input type="checkbox"/> Articulation Problem			
PRAGMATICS OF LANGUAGE	<input type="checkbox"/> Not impaired <input type="checkbox"/> Not applicable	<input type="checkbox"/> Cannot manage turns or topics <input type="checkbox"/> Unvaried or odd intonation	<input type="checkbox"/> reported <input type="checkbox"/> observed
REPETITIVE BEHAVIORS/ STEREOTYPY <small>(reported and/or observed)</small>	<input type="checkbox"/> None	<input type="checkbox"/> Insists on Routines/ Compulsive-like behaviors	<input type="checkbox"/> Motor stereotypy or vocal stereotypy <input type="checkbox"/> Echolalia <input type="checkbox"/> Stereotyped speech
UNUSUAL OR ENCOMPASSING PREOCCUPATIONS	<input type="checkbox"/> None	<input type="checkbox"/> Present--describe:	<input type="checkbox"/> reported <input type="checkbox"/> observed
UNUSUAL SENSITIVITIES	<input type="checkbox"/> None	<input type="checkbox"/> Heightened Sensitivity <input type="checkbox"/> High Pain Threshold	<input type="checkbox"/> reported <input type="checkbox"/> observed

Paper I: Methods

Sample

- 123 (28.5% females) children were included
- Mean age of 5.74 years (S.D.= 2.88).
- 85 (23 females) received an ASD diagnosis
- No differences between ASD males and females on AMSE or ADOS score or rates of ID.

Measures

- Autism Mental Status Exam (AMSE)
- An 8-item direct observational tool
- Social, Communication, Behavioral domains

Statistical analyses

- ROC curve analyses to examine performance
- Ordinal regression analyses on item level

Table 1 Participants characteristics

	Total	Non-ASD	ASD
N	123	38	85
Male	88	26	62
Female	35	12	23
Mean age (SD)	5.74 (2.88)	5.68 (2.55)	5.77 (3.03)
Mean of total ASME score (SD)	6.43 (2.63)	3.63 (1.56)	7.68 (1.95)
Mean of ADOS-2 comparison score (SD)	6.74 (4.03)	3.34 (1.81)	8.21 (3.84)
ADOS classification for ASD	92	10	82
Comorbid intellectual disability (ID)	23	3	20

Paper I: Results

Results

- Differences in AMSE score ($p < .001$, $d = 2.29$) Non-ASD vs ASD
- Differences in rates of ID (ID) ($p = .046$, $d = .439$) Non-ASD vs ASD
- No differences in AMSE score, rates of ID, and age between males and females with ASD
- ASD females had more language deficits ($p = .005$, $d = 0.784$)
- ASD females had less oversensitivity issues ($p = .017$, $d = 0.220$)
- ROC curve analyses revealed equal discriminative performance in males vs females

	M	SD	(2a) Main effect sex		
			β	SE	p
1. Eye contact (observed)	.85	.362	0.85	.545	.120
2. Interest in others (observed)	.73	.497	0.20	.454	.646
3. Pointing skills (observed)	.49	.570	-0.35	.462	.455
4. Language (observed/reported)	.72	.526	-1.42	.501	.005*
5. Pragmatic (observed/reported)	.36	.531	1.08	.596	.069
6. RRBs/stereotypy (observed/reported)	1.01	.422	0.35	.643	.588
7. Unusual or preoccupations (observed/reported)	.76	.527	-0.53	.459	.250
8. Unusual sensitivities (observed/reported)	.79	.465	1.23	.516	.017*

β Negative values indicate females score higher than males, positive values indicate female score lower than males

*Significant $p < .050$

Paper I: Summary

- ✔ Comparable performance in girls referred for ASD assessment compared to boys referred for ASD assessment
- ✔ Higher rates of severity and rates of ID in ASD vs Non-ASD
- ✔ Less sensitivity issues in ASD females than ASD males
- ✔ More language deficits in ASD females than ASD males



Paper II: Parent-Endorsed Sex Differences In Toddlers With and Without ASD: Utilizing the M-CHAT

Aims

- To examine differences in overall endorsement of autistic symptoms associated with sex and diagnosis
- To examine individual behavioral symptoms associated with a diagnosis of ASD versus non-ASD
- To examine if non-ASD children differ by sex in symptoms endorsed at an M-CHAT item level
- To examine if ASD children differ by sex in symptoms endorsed at an M-CHAT item level.

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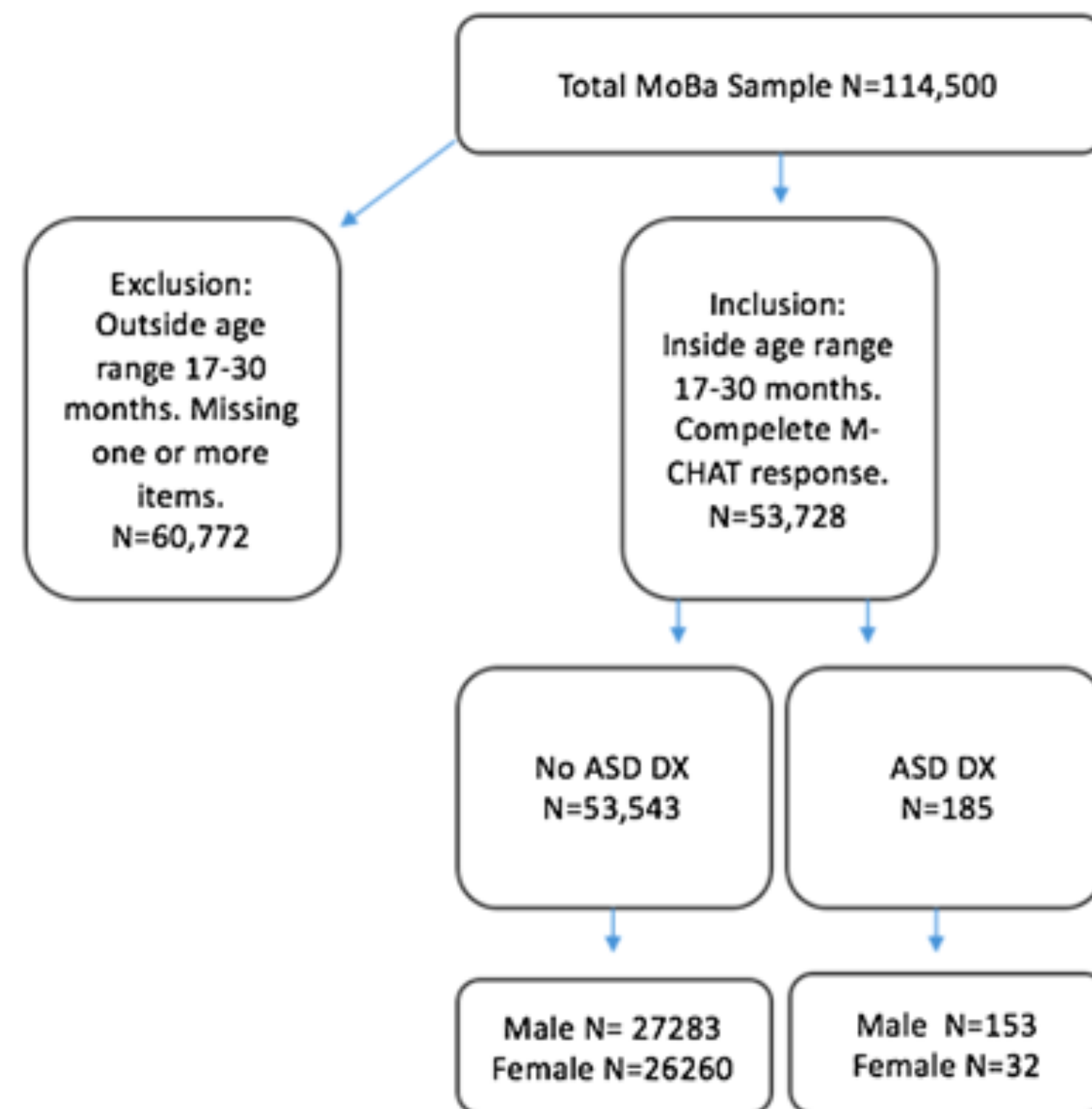
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Paper II: Methods

	Non ASD total	Non ASD male	Non ASD female	ASD total*	ASD male	ASD female
N	53,543	27,283	26,260	185	153	32
Mean age	18.53	18.53	18.53	18.55	18.57	18.48
Mean age (S.D.)	0.58	0.58	0.58	0.66	0.68	0.49
Mean of total failed items	0.80	0.84	0.74	3.11	2.68	5.16
Mean of total failed items (S.D.)	1.17	1.22	1.11	4.00	3.54	5.34
Mean critical items	0.15	0.17	0.13	0.96	0.84	1.50
Mean critical items (S.D.)	0.44	0.47	0.40	1.38	1.26	1.76



Sample

- 53,738 children from the Norwegian Mother and Child Cohort Study (MoBa) completed the M-CHAT

- 185 (32 females) later received an ASD diagnosis

Measures

- M-CHAT (A 23-item yes/no parent-endorsed ASD-specific screening instrument administered at 18 months.
- Diagnoses retrieved from the ABC study clinic and National patient registry (NPR)

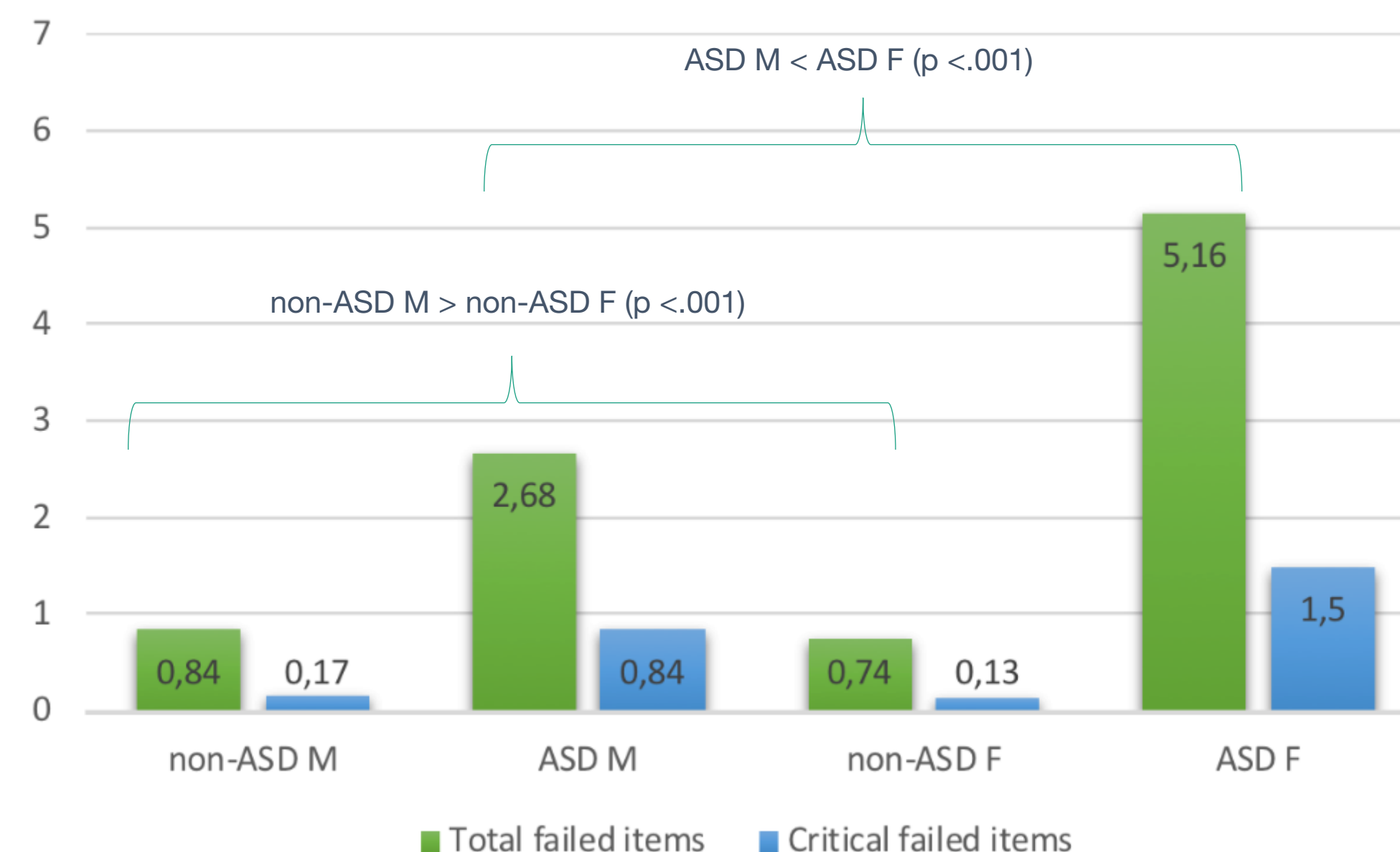
Statistical analyses

- Two-way ANOVA (sex by diagnosis) was conducted to ascertain between-group differences.
- Logistic regression to explore differences through an individual M-CHAT item analysis

Paper II: Results

- Children with ASD failed more items than children without ASD ($p < .001$, $d = .783$).
- Non-ASD males failed more items than non-ASD females ($p < .001$, $d = .086$)
- ASD males failed fewer items than ASD females ($p < .001$, $d = .547$)
- ASD females showed strength in joint attention (following a pointing gesture) ($p = .011$, $d = 1.327$)
- ASD females showed a weakness in imitation (facial expressions) ($p = .036$, $d = 0.605$)

Table 1. Number of failed items M-CHAT groupwise



Paper II: Results

- Nuanced support for the Extreme Male Brain Theory (Baron-Cohen 2002)
- Most weaknesses in ASD similar to non-ASD male weaknesses
- At an item level, almost every male versus female disadvantage in the broader population was consistent with M-CHAT vulnerabilities in ASD
- Controlling for total M-CHAT failures, this male disadvantage was more equivocal and many classically ASD-associated features were found more common in non-ASD

Paper II: Summary

- ✔ 18-month-old females later diagnosed with ASD show greater impairments as measured by MCHAT than 18-month-old males with ASD
- ✔ In the Non-ASD sample, this effect is reversed (males scoring higher than females)
- ✔ Follow to point emerged as especially strong for females with ASD, while imitation was a weakness compared to ASD males.
- ✔ Nuanced support for the EMB Theory (ASD females maintained strengths in JA as seen in non-ASD females)

Paper III: Clinical Features of Children with Autism Who Passed 18-Month Screening

Aims

- To examine developmental and temperamental profiles at 18 months in false negative cases.
- This focus represents a novel approach towards identifying early characteristics that potentially can lead to identification of new critical markers relevant to early identification and diagnosis of ASD.

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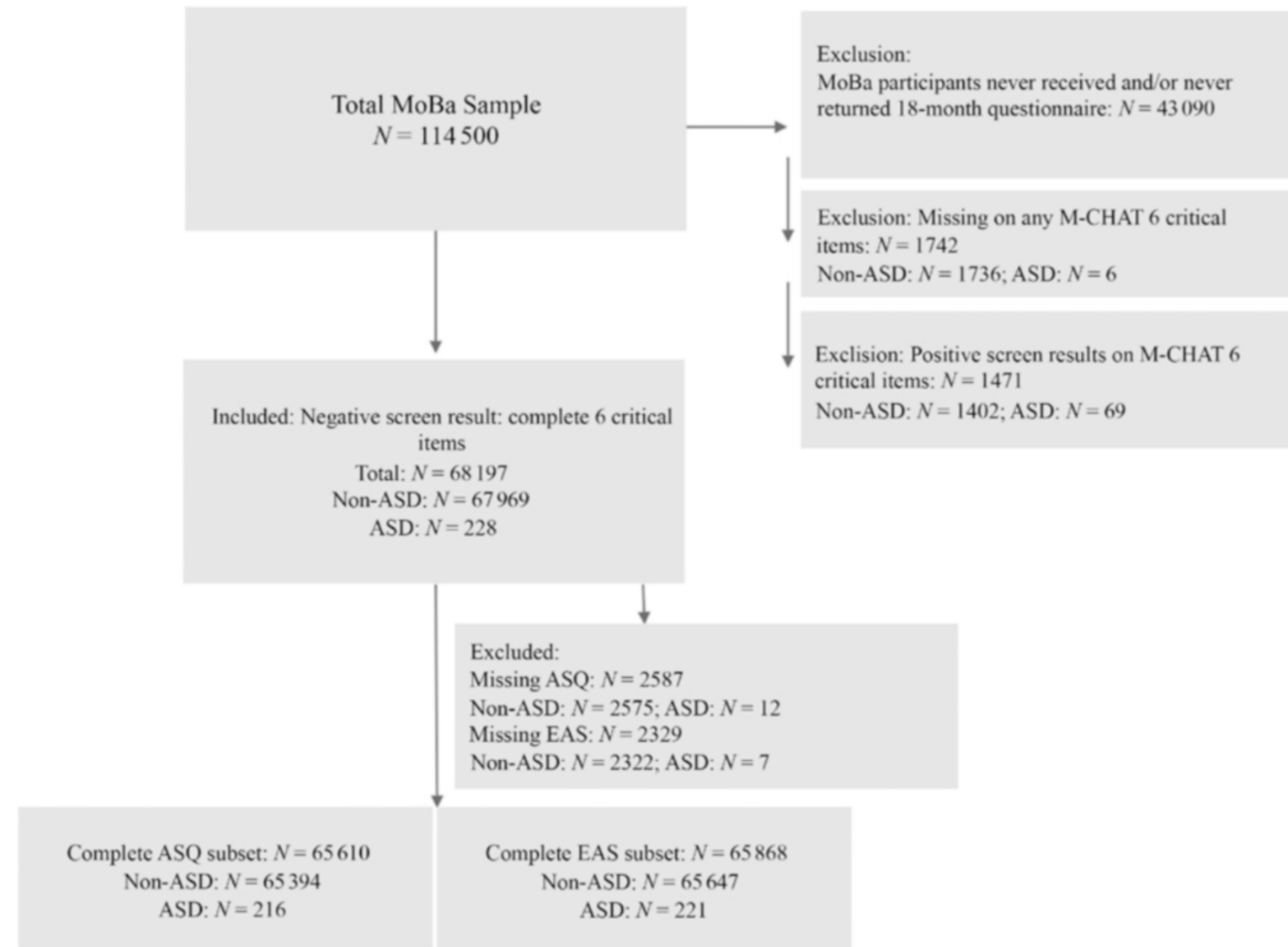


FIGURE 1
Sample inclusion and exclusion information.

TABLE 1 Number of Cases and Mean (SD) of Participant’s Age at Time of Screening and of Failed M-CHAT 6 Critical Items

	Total True-Negative Cases	True-Negative Boys	True-Negative Girls	Total False-Negative Cases	False-Negative Boys	False-Negative Girls
No. cases	67 969	34 502	33 467	228	192	36
Age at time of screening, mo	18.53 (0.62)	18.53 (0.64)	18.53 (0.60)	18.51 (0.55)	18.51 (0.56)	18.53 (0.48)
Failed M-CHAT 6 critical items	0.10 (0.30)	0.12 (0.32)	0.08 (0.28)	0.27 (0.44)	0.25 (0.43)	0.41 (0.50)

Sample

- 68,197 screen-negative children from the MoBa
- 228 (36 females) false-negative children (76.8%) of all children with a later dx).

Measures

- Completed at least the six-critical item criterion
- Ages and Stages Questionnaire (ASQ) (Developmental)
- Emotionality, Activity, Sociability (EAS) (Temperament)

Statistical analyses

- A set of univariate ANOVAs with diagnosis and sex on domain scores.
- Post-hoc analyses were conducted for between- and within-group differences.

Paper III: Results

TABLE 2 Mean (SD) of the ASQ Scores for Boys and Girls in the True-Negative and False-Negative Groups

	<i>N</i>	ASQ Social	ASQ Communication	ASQ Fine Motor	ASQ Gross Motor
Boys: true-negative	33 163	9.32 (1.18)	7.51 (2.64)	9.39 (1.27)	9.49 (1.40)
Girls: true-negative	32 231	9.59 (0.94)	8.44 (2.21)	9.28 (1.37)	9.46 (1.49)
Boys: false-negative	183	8.88 (1.66)	5.71 (3.26)	8.76 (1.78)	8.83 (2.29)
Girls: false-negative	33	8.48 (2.18)	5.20 (3.40)	8.28 (2.34)	6.36 (3.85)

TABLE 3 Mean (SD) of the EAS Scores for Boys and Girls in the True-Negative and False-Negative Groups

	<i>N</i>	EAS Sociability	EAS Shyness	EAS Emotionality	EAS Activity
Boys: true-negative	33 300	3.95 (0.55)	3.99 (0.62)	3.25 (0.75)	4.08 (0.64)
Girls: true-negative	32 347	3.96 (0.55)	3.91 (0.65)	3.27 (0.76)	3.96 (0.64)
Boys: false-negative	185	3.96 (0.59)	3.84 (0.71)	3.18 (0.79)	4.05 (0.71)
Girls: false-negative	36	3.83 (0.63)	4.14 (0.59)	3.09 (0.79)	3.75 (0.86)

Paper III: Results

Developmental domains (ASQ)

- Atypicalities in false negative children across all domains
- Weaknesses appeared to be more pronounced in females

Temperamental domains (EAS)

- False negative females were rated as less social fearful than false-negative males ($p = .017, d = .463$)

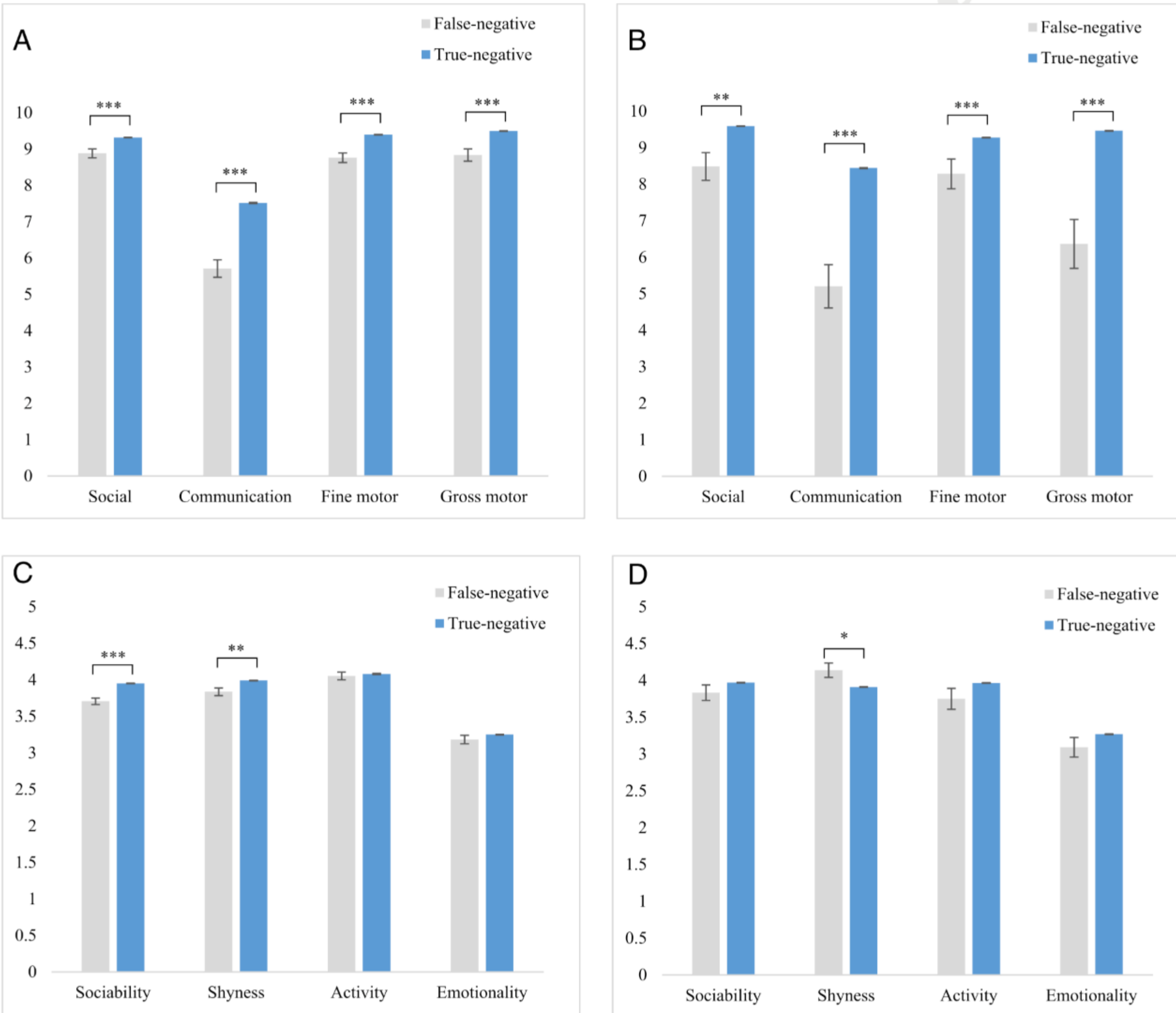


FIGURE 2
 A, Mean (± 1 SE) of the ASQ scores for false-negative and true-negative boys. *** $P < .001$. B, Mean (± 1 SE) of the ASQ scores for false-negative and true-negative girls. *** $P < .001$; ** $P < .010$. C, Mean (± 1 SE) of the EAS scores for false-negative and true-negative boys. *** $P < .001$; ** $P < .010$. Higher scores on the shyness and emotionality scales indicate less shy and emotional presentation; higher sociability and activity scores indicate more pronounced characteristics in this domain. D, Mean (± 1 SE) of the EAS scores for false-negative and true-negative girls. * $P < .050$. Higher scores on the shyness and emotionality scales indicate less shy and emotional presentation; higher sociability and activity scores indicate more pronounced characteristics in this domain.

Paper III: Summary

- ✔ Boys and girls who later receive a diagnosis of ASD show delays and atypical features in social, communication, and motor domains.
- ✔ False-negative females have similar, but more pronounced difficulties than false-negative males. Possibly greater severity.
- ✔ False-negative females show less social inhibition or social fearfulness as represented by Shyness domain

What do screening
instruments pick up?

Functional outcomes

What do we know about children identified?

- Identifies a great proportion of children with intellectual disability, not specific to ASD.
- Identifies children (false positives) that might need access to the same services or interventions.
- Identifies ASD children with greater symptom severity, decreased functional language and lower IQ (Stenberg et al. 2020).
- Children within normal range IQ seems to be missed.

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S.I. : EARLY DETECTION IN AUTISM SPECTRUM DISORDER



Functional Outcomes of Children Identified Early in the Developmental Period as at Risk for ASD Utilizing the The Norwegian Mother, Father and Child Cohort Study (MoBa)

Nina Stenberg¹ · Synnve Schjølberg² · Frederick Shic^{5,6} · Fred Volkmar⁴ · Anne-Siri Øyen^{2,8} · Michaeline Bresnahan⁷ · Britt Kveim Svendsen¹ · Stephen von Tetzchner⁹ · Nina Torheim Thronæs³ · Suzanne Macari⁴ · Domenic V. Cicchetti⁴ · Katarzyna Chawarska⁴ · Pål Suren² · Roald A. Øien^{3,4}

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Abstract

Early identification of autism spectrum disorder (ASD) is regarded as crucial for swift access to early intervention and, subsequently, better outcomes later in life. However, current instruments miss large proportions of children who later go on to be diagnosed with ASD, raising a question of what these instruments measure. The present study utilized data from the Norwegian Mother, Father, and Child Cohort Study and the Autism Birth Cohort study to explore the subsequent developmental and diagnostic characteristics of children raising developmental concern on the six-critical discriminative item criterion of the M-CHAT (DFA6) at 18 months of age (N = 834). The DFA6 identified 28.8% of children diagnosed with ASD (N = 163), but 4.4% with language disorder (N = 188) and 81.3% with intellectual disability (N = 32) without ASD. Scoring in the «at-risk» range was associated with lower IQ, impaired functional language, and greater severity of autism symptoms whether children had ASD or not.

N (%)	Below cut-off	Cut-off or higher	Total
No Dx or ClinProbl	288	3 (1.0%)	291
Autistic disorder	65	28 (30.1%)	93
PDD-Nos	49	14 (22.2%)	63
Syndrome ASD or loss of skills	2	5 (71.4%)	7
Intellectual disability (ID) no ASD	6	26 (81.3%)	32
Language disorder (LD) noASD noID	165	23 (4.4%)	188
Other Dx or ClinProbl	153	7 (4.4%)	160
Total	728	106	834

Conclusions

Early identification and screening

- Majority of cases (76.8%) are false-negatives at 18 months (even when showing atypicalities)
- High rates of false positives likely resulting from heterogeneity in symptoms, time of and patterns of onset as well as properties of current screeners.
- Symptoms might need a greater demand to be evident for parents.
- False-negative children show parent-endorsed atypicalities in development at 18 months.
- More often identifies children with intellectual disability and other disorders.

Sex differences

- Marked sex differences in both high-risk and low-risk samples related to joint attention, oversensitivity, shyness/social fearfulness
- Strengths in pro-social behavior in females with ASD might make them less socially avoidant (Paper I, II, and III)
- There is a need for
 - Improving current or designing new screening instruments sensitive to sex differences in expression of ASD
 - Improving understanding of parental interpretation of questions and effect on endorsement of autistic symptoms

Implications

- Examine if new items, sex sensitive questions and different graded responses can improve screening
- Combination of screening and developmental surveillance at various timepoints
- Many ASD-specific behaviors might not be evident until the social demands exceeds abilities
- Other developmental markers might provide more general signs that are not ASD-specific.
- Methodological issue that screening instruments are only validated on screen positives
- Most children missed at 18 months, question the fundamental drive for universal screening?
- Identifies other cases more often than ASD. What are the implications?
- Sex-stratified temperamental markers as a valuable addition to screening
- Females might have somewhat different symptom patterns than males, not necessarily more
- M-CHAT versus M-CHAT-R: Not much difference in terms of false negatives
- Developmental surveillance and parental concern important tools for early identification

Theoretical model of ASD identification in females

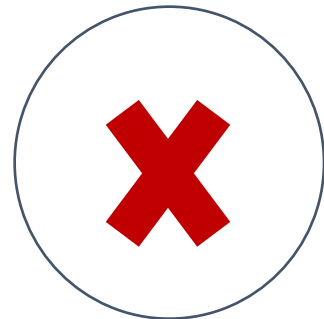


Better joint attention (Øien et al. 2017)

Less oversensitivity (Øien et al 2018)

Less social fearfulness (Øien et al. 2018)

Less RRBs (Frazier et al. 2014; Charman et al. 2017; Supekar & Menon 2015)



Sociability (Chawarska et al. 2016)

Severity of symptoms (Øien et al. 2017; Volkmar et al. 1993; Robinson 2013)

Language difficulties (Øien et al. 2018; Volkmar et al. 1993; Salamone et al. 2016)

False negative

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Thank you

In memoriam Domenic V. Cicchetti,
Ph.D



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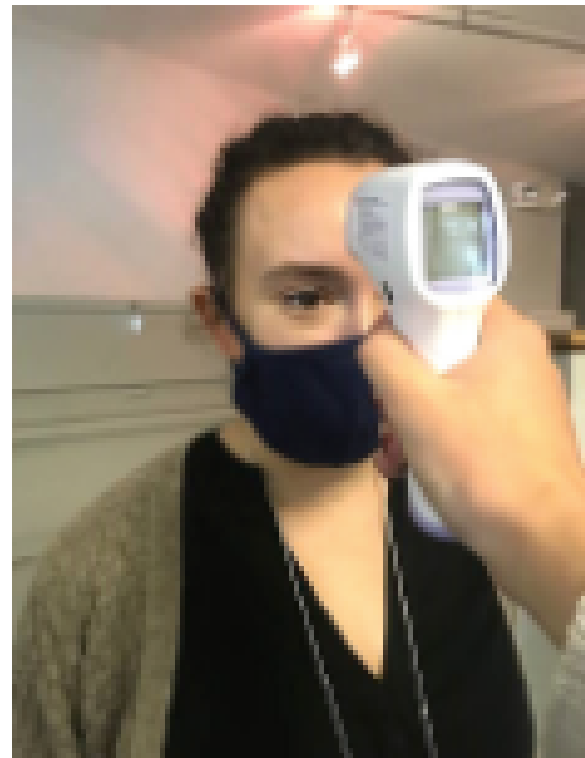


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