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Detection of autism in childhood

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Chapter 7

General discussion

The objective of this thesis was to identify factors to enhance the detection of autism spectrum disorder (ASD) in childhood. Three aspects of detection of ASD were addressed:

- Age at ASD diagnosis: *what is the current global age at ASD diagnosis?*
- Early detection of ASD by preventive care physicians: *can we improve early detection by healthcare professionals?*
- Eating problems and ASD: *can the assessment of eating behavior potentially be useful in the (early) detection of ASD?*

The strengths and shortcomings of the individual studies have been discussed in chapters 2-6. This final chapter offers a broader overview of the early detection of ASD and suggestions for future research.

AGE AT ASD DIAGNOSIS

In chapter 2 we discussed the results of a meta-analysis on data from 2012–2019 that indicated a mean age at ASD diagnosis of 60.5 months (range 30.9–234.6 months).[1] Map presentations of the meta-analysis results are provided in figures 7.1 and 7.2. This update was needed as the previous literature review used studies up to 2012.[2] However, the ultimate objective is to convert these results into healthcare measures to improve the early detection of ASD.

For people with ASD, early detection and a younger age at diagnosis can lead to earlier treatment,[3] which has been shown to improve later language and cognitive abilities, and help improve the core symptoms in children and adults with ASD.[4,5] Although an ASD diagnosis can be established as early at age 18 months,[6] the current global mean age at diagnosis is 43 months for children up to 10 years old;[1] this makes a huge difference, especially for young children – at age 18 months they are in the toddler development phase, while at age 43 months they are in the late early-childhood development phase. A solid and comprehensive evaluation of the age at diagnosis can contribute to reducing the local or national age at ASD diagnosis and thereby increasing the quality of healthcare offered to children with potential ASD. Such an evaluation can: 1) indicate factors affecting age at ASD diagnosis, and 2) refine and evaluate the efficacy of a national/local healthcare system in detecting and diagnosing ASD (and evaluate the effects of policy changes).

Our literature review and meta-analysis identified several limitations that make it difficult to compare the different studies and guide policy-making effectively. The largest limitations in the current literature are: 1) study heterogeneity (large variation in study characteristics, e.g. type of study sample, sample size, age of study sample, location of study), 2) an insufficient evaluation of factors affecting age at ASD diagnosis (e.g. ASD type or severity), and 3) incomplete reports on study results (e.g. missing SD, gender ratio).

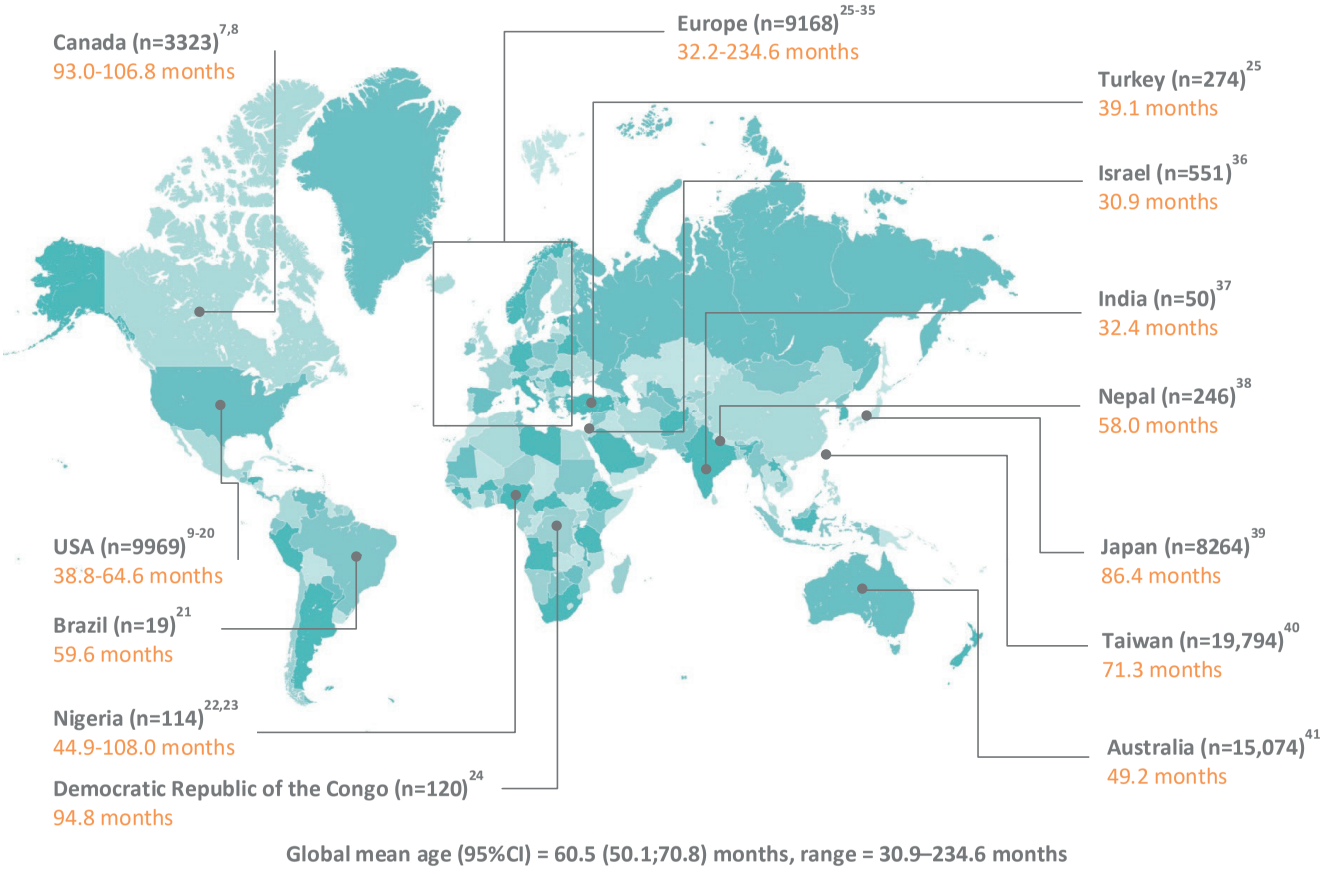

Figure 7.1 Global mean age at ASD diagnosis.

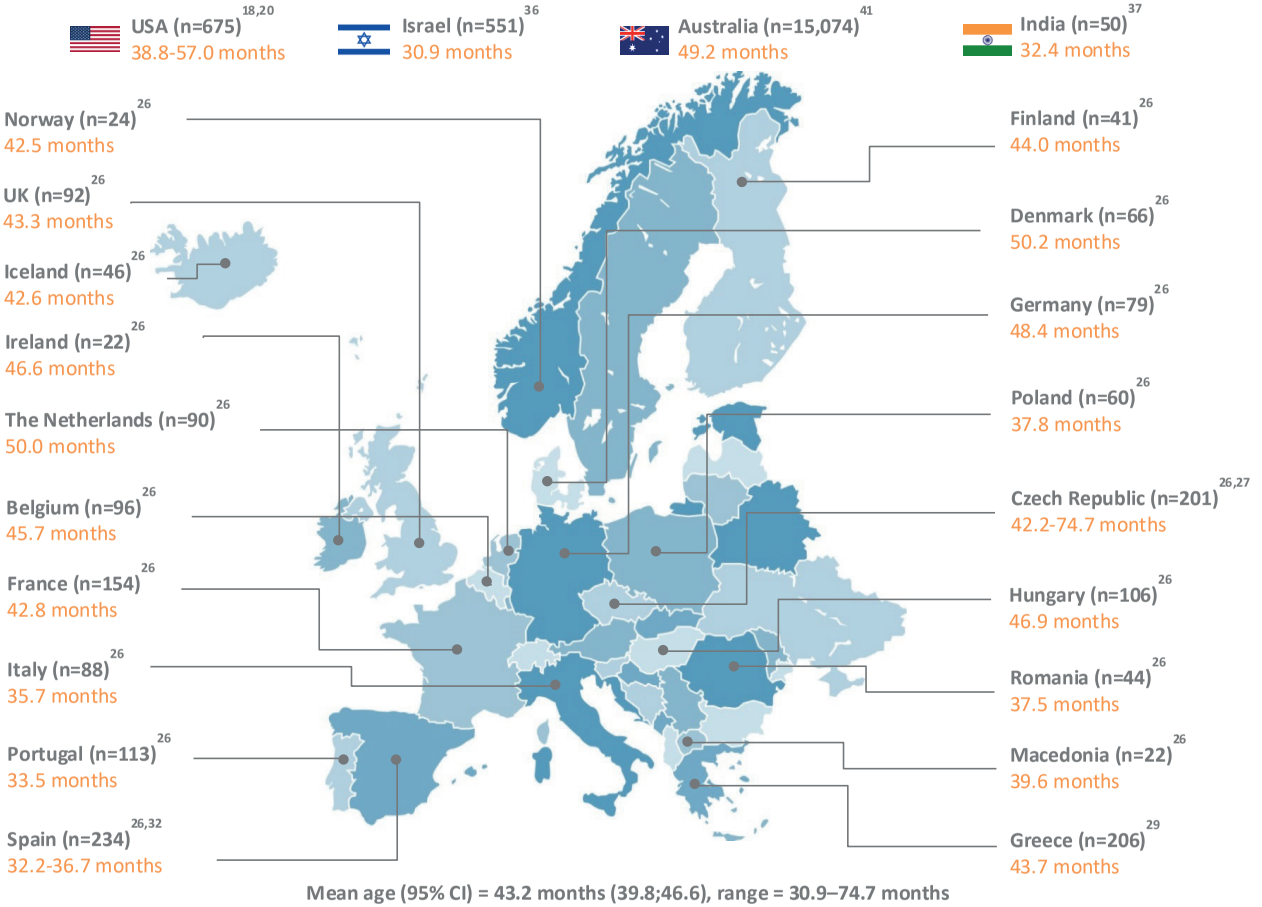

Figure 7.2 Global mean age at ASD diagnosis for children up to 10 years of age.

Factors affecting age at ASD diagnosis: the need for an integral perspective

One challenge in putting the age at ASD diagnosis literature into practice and policy change is in defining the concept of age at diagnosis. Research has indicated that a multitude of clinical, sociodemographic, parental, healthcare, educational, geographical, cohort and period factors affect the reported age at ASD diagnosis.[1,2] These factors must therefore be included in evaluating age at diagnosis.

The effect of some factors on age at diagnosis appears to be clear. For example, including a large sample with Asperger's Disorder (AD) increases the age at diagnosis, as children with AD were diagnosed 8 to 80 months later than children with ASD in general.[34,41–46] Including children with more severe ASD symptoms lowers the reported age at diagnosis[10] by 1.9–4.1 years,[47] while using a younger study sample lowers the reported age at diagnosis.[10,17,32,48] However, numerous factors have conflicting effects on the age at ASD diagnosis (e.g. co-morbid disorders, gender, parental age), and national or regional differences in age at diagnosis are also found,[23,41,46] raising questions about the accessibility to healthcare in different countries.

Another challenge is that many influencing factors are intertwined. For example, conflicting results are found for the effect of ethnicity on the age at ASD diagnosis.[9,18,46,49] However, research indicates that cultural and contextual factors affect the identification and diagnosis of ASD and whether parents seek help[50]: i.e. ethnic minority families with a child with (possible) ASD experience more difficulties in gaining access to healthcare and an ASD diagnosis and they are less likely to contact a healthcare provider with their concerns.[51] A major challenge is that ethnicity is also related to other characteristics like parental education, poverty status and residential area,[51] which all affect access to healthcare services and increase the age at ASD diagnosis. Ethnicity is therefore not an isolated construct, but a factor intertwined with several other factors.

A more integral perspective towards the age at diagnosis and influencing factors is needed to standardize future research and enable inter-study comparisons. Figure 7.3 displays a proposal for a multi-level model providing an integral perspective on age at ASD diagnosis.

Based on results from this thesis, we recommend that future research on age at ASD diagnosis should: 1) include more general population samples instead of localized and/or specific population studies (e.g. tertiary mental healthcare clinics), 2) include more influencing factors in their study design, 3) report more completely the study results, so that data can be used in meta-analyses, and 4) use meta-analyses to adjust for a wide range of influencing factors.

A more comprehensive meta-analysis that adjusts for a wide variety of personal, socio-environmental, and national or local influencing factors would yield a more standardized current age at ASD diagnosis. This could then be used to compare results and identify weak points in local or national healthcare systems and improve the early detection of ASD.

Figure 7.3 Multi-level model for gaining an integral perspective on the age at ASD diagnosis

EARLY DETECTION OF ASD BY PREVENTIVE CARE PHYSICIANS

It is necessary to establish the current global mean age at ASD diagnosis to evaluate the barriers to and possible facilitators of an earlier detection of ASD. The current burden on healthcare makes it important to create an efficient system and develop methods to identify children at risk for ASD.[52] Such a system should include developmental surveillance and screening to identify conditions that affect children's development and achievements.[53] As preventive care professionals hold a key position in child healthcare systems, one way of facilitating earlier detection would be to optimize the knowledge and skills of this group of professionals. In chapters 3 and 4 we have evaluated the early detection of ASD by preventive care physicians working in Dutch Youth and Family Healthcare Centers (YFC).

Educational program to enhance early detection of ASD

Chapter 3 indicated that Dutch preventive care physicians have low levels of specific ASD knowledge. These results are in line with previous studies indicating misconceptions about ASD held by Iranian healthcare workers and paediatricians[54] and low levels of ASD training in well-child care professionals in Iceland.[55] Our results in chapter 3 show that we should be aware that some healthcare

professionals who screen for ASD in the general population may not have sufficient knowledge about ASD. In agreement with our findings, the literature emphasizes the need for global ASD-specific training in African healthcare workers,[56] Iranian healthcare workers and paediatricians,[54] and Canadian physicians.[57] In chapter 4 we describe how a live online educational program can be used to increase the level of ASD knowledge and self-confidence in detecting ASD among preventive care physicians, highlighting the importance of such educational programs.

Live online educational program

Face-to-face educational programs are traditionally used to enhance the early detection of ASD by well-child care professionals.[55] However, online inter-professional learning offers multiple benefits in enhancing the educational experience: it is time-efficient, overcomes geographic limitations, and offers greater flexibility than face-to-face programs.[58] Online programs can be especially beneficial in low-resource countries, in which the high cost of training is one of the largest barriers in ASD diagnosis and healthcare,[59] or in a context where face-to-face training is not feasible, for example, in conflict areas or in the current COVID-19 pandemic.

Training materials for ASD detection are mostly standardized but do not include advice, practical cases, or supervision that can offer advice and tips based on specific local issues (e.g. cultural differences or available materials). Yet the method used for the educational program described in this thesis made it possible to hold live video-based sessions between tutor and students in an online school platform. This online live contact enabled not only knowledge transfer, but also discussion of case studies and responses to students' questions. The relevance of this type of interaction is supported by the results of a study on ASD distance learning for parents and professionals that showed the efficacy of a self-directed online educational program.[60] However, Wainer and Ingersoll[60] also mentioned that the added value of a more supportive and interactive educational program, including feedback and coaching, may be beneficial for some trainees.

To increase ASD knowledge and reduce stigma in low- and middle-income countries, a basic, easy-to-implement, live online ASD educational program needs to be developed for healthcare professionals who screen children. It should be implemented worldwide and made freely available for countries and organizations to use, just like the *Caregiver Skill Training* developed by WHO and *Autism Speaks* for carers of children with developmental delays and disorders.[61,62] The program developed for this thesis could be the basis for a generic global training program that could be made accessible for everyone to use. For a good uptake of the training program in a new setting, it is important to collaborate and engage with local stakeholders and experts to ensure buy-in and that the program's contents and delivery strategy fits into the local culture and context.[63,64] Implementing such a program might also reduce the higher level of stigma towards ASD and other mental illnesses that is

seen in non-Western countries.[65] The level of stigma towards autism could be evaluated internationally with the Autism Stigma and Knowledge Questionnaire (ASK-Q), which was developed by Harrison et al.[66,67] during the writing of this thesis.

Other methods to enhance global ASD training should also be further explored, such as the remote machine-learning models for detecting developmental delays and autism that showed promising results in US[68] and Bangali[69] settings.

Preventive healthcare systems

Besides evaluating individual factors that could decrease the age at ASD diagnosis, health system factors should also be considered. Preventive healthcare (e.g. well-baby/child clinics) plays a vital role in the national and local healthcare system and in detecting ASD. There is consensus that early identification of children with ASD and appropriate intervention are a public health priority and that universal screening is an essential tool for the early detection of ASD.[70] However, the accessibility and efficiency of well-baby clinics depend on a variety of factors, such as professionals' level of ASD knowledge, availability of ASD screening questionnaires, national/local presence of well-baby clinics, and financial consequences.

Differences in the various healthcare systems can also explain possible barriers to earlier detection or facilitators. Well-baby clinics are the core of public health services for infants and preschool children; they are present in several European countries (Sweden, Norway, Finland, Belgium, Iceland, United Kingdom, Italy and the Netherlands),[71,72] and in the United States,[73] Australia,[72] Taiwan,[74] Turkey,[75] Nigeria,[76] Ghana,[77] and South Africa.[78] However, there are major differences in the purpose and activities of well-child/well-baby visits amongst countries.[79] Where some clinics offer universal surveillance of the complete child population, others provide well-child checks that are driven by parental request. The differences between clinic surveillance and well-child checks is summarized by The European Observatory on Health Systems and Policies[80] and described in Table 7.1.

There is a limited amount of information regarding the specific details (e.g. presence, procedures) of national well-child clinics and their role in the national system of infant and child healthcare.

Table 7.1 Differences between surveillance and well-child check[80]

Surveillance	Well-child checks
Clinician driven	Parent or caregiver driven
Occurs at regular or routine intervals	At the parent or caregiver's initiative
Expensive in health care provider time	Less costly
Early detection of disease or risk factors	Promoting a healthy lifestyle to prevent disease or risk factors
Universal for all children	May exclude the children most in need
May pick up too many false positives	May pick up fewer deviations from normal (false negatives)
Provides support for parents (including those with normal children)	Puts responsibility with parents and may widen inequalities

Table 7.2 provides an overview of well-child clinics and screening capacities in several counties, based on literature/internet searches and personal inquiry among international colleagues. The results are similar to a 2010 study that indicated a wide range in the number of preventive child health examinations between European countries.[79]

Table 7.2 Screening capacities of well-child clinics in selected countries around the world

	Well-child clinics present	Surveillance or well-child check	Screening for developmental delays	Additional costs	National coverage	Number of visits
The Netherlands[65]	Yes	Surveillance	Yes	No	Yes	22 (first 18 years)[a]
Iceland[55]	Yes	Surveillance	Yes	No	Yes	11 (first 4 years)
Belgium[81]	Yes	Surveillance	Yes	No	Yes	10 (first 2.5 years)
Germany[82]	No[b]	Surveillance	Yes	No[c]	Yes	13 (first 18 years)
Norway[83]	Yes	Surveillance	Yes	No	Yes	14 (first 5 years)[d]

[a] 13 individual-, 6 collective-, and 3 optional individual consultations (programs vary slightly between centers)
[b] provided by pediatrician
[c] covered by German health insurance
[d] After the 5th year, health surveillance is organized by the schooling system.

Although there are reports of the early detection of ASD in well-baby clinics[84] or by related professionals[85] (e.g. pediatricians), the number of studies is limited and their results are difficult to compare because the healthcare systems differ and the precise role of the professionals is uncertain. In general, although an international report stated that most countries (91%) provided some child preventive care, this was only seen in 64% of low-income countries.[86] A 2019 report on the International Child Neurology Association Meeting on ASD in Africa indicated a huge variation in available services amongst 14 African countries, with only small numbers of specialists assessing and managing ASD compared to the size of population served.[56]

Evaluating local and national healthcare systems: development of an international rating scale

Certain healthcare system factors are known to improve the early detection of ASD. For example, the availability of suitable ASD screening questionnaires has a significant effect on the early detection of ASD. However, although a review in 2019 identified 37 different ASD screening tools, many of these are not freely available, nor available in multiple languages.[87] But another 2019 study identified ten ASD screening tools that show promise for effective use in low- and middle-income countries; the ten tools are brief, low-cost and can be administered by paraprofessionals or community health workers.[88] The literature thus highlights the importance of identifying such universal tools for more general use in national healthcare systems to enhance the early detection of ASD.

In order to expand the facilities to detect and diagnose ASD at an early age, the accessibility and efficiency of many (child) healthcare systems needs to be improved. This means it is first necessary to assess the current situation to see what is needed in a specific context. A global rating tool to perform such an assessment would be very helpful and we feel future research should focus on its development. The tool should cover the factors that affect the quality of an early detection system for ASD but that are often not evaluated or reported in the literature (see below). A study on vaccination coverage has already demonstrated the relevance of rating healthcare systems; it categorized European and Australian healthcare systems based on freedom of primary care provider (hierarchical vs non-hierarchical organization) and whether preventive care services were provided by a separate organization (e.g. well-baby clinics).[72]

Box 7.1 Factors in a healthcare system that have a positive effect on the (early) detection and diagnosis of ASD[2,89,90]

- (free) well-baby/child healthcare centers with multiple screening moments early in life
- national guidelines on the early detection of ASD
- training for professionals on the early signs of ASD
- availability of validated (translated) screening tools for ASD
- availability of validated (translated) diagnostic tools for ASD
- availability of an early intervention service/referral options for ASD cases
- working in multidisciplinary teams, adopting appropriate working procedures

The above items (Box 7.1) can be used to develop a rating system, which would make it easier to compare regional and national differences in the early detection and age at ASD diagnosis, and the rating could then serve to highlight points needing improvement.

Box 7.2 How could Bram have benefited from these insights?

The general introduction of this thesis described the case histories of Bram and Mara. What could the insights in this thesis offer them?

Bram
Bram's signs of ASD were recognized by when he was 6 years old and adequate steps were taken to establish a diagnosis. However, it is likely that more subtle, early signs were present but missed during previous visits to the well-child clinic. An educational program on the early signs of ASD could probably have given the preventive care professional more knowledge, potentially leading to earlier detection, improving treatment outcome, and sparing child and parental distress.

EATING PROBLEMS AND ASD

Identifying the early signs of ASD can enhance the timely detection of ASD in a child. This thesis (chapters 5 and 6) has explored eating problems as an early ASD sign. Many children (and adults) with ASD struggle with eating-related problems, but the general public and many healthcare professionals are unaware of the association between ASD and eating problems. This illustrates a big gap in useful knowledge that would aid the detection of ASD in infancy and middle childhood.

Infant eating behavior as an early sign of ASD

The results reported in this thesis (chapter 5) indicate an association between infant eating behavior (formula feeding and eating problems) and later autistic traits. Our results are in line with previous studies suggesting that children with ASD are less likely to have been breastfeed than their non-ASD peers.[91] We hypothesize that a child's ASD characteristics complicate breastfeeding, for example, sensory problems[92–94] (e.g. elevated oral stimuli due to flavors in breastmilk[95]), skin-to-skin contact,[96] or dysregulated breastfeeding patterns[97] could negatively affect the duration of breastfeeding. It is also possible that maternal factors (general maternal psychopathology,[98,99] elevated depressive symptomology[100], socio-affective impairment[101] related to the broader autism phenotype,[102,103] and under- or over-responsiveness to sensory stimuli[104–106]) could negatively affect breastfeeding.
Our work also indicated an association between infant eating problems (drinking only small quantities and being hungry/not satisfied) and later autistic traits. The literature shows multiple associations between infant feeding practices and later health issues, for example, an increased risk of obesity.[107] An evaluation of childhood eating trajectories indicated associations between overeating and later binge eating/binge eating disorder, and between persistent undereating (in girls only) and fussy eating and later anorexia nervosa.[108] In addition, previous research in the same general population sample that we studied found that persistent picky eating during childhood (1.5-6 years) predicted more autistic traits at 7 years old.[109] Studies often focus on how caregivers affect their infants eating behavior, but it has also been suggested that infant eating behavior can be seen as a dyadic model in which the behavior is modified by the relational dynamics between an infant's characteristics (e.g. temperament) and its parents (e.g. food type choice, frequency, duration, amount, method, response to feeding cues).[110]
Although further studies are needed, our results indicate that evaluation of infant eating behavior could improve the early detection of ASD.

Sex-specific association between eating behavior in middle childhood

The results reported in chapter 6 show an association between autistic traits and eating behavior

problems (picky eating and food responsiveness) in middle childhood. Our results are in line with previous studies indicating an association between eating behavior and autistic traits.[109] However, we were also able to show that autistic traits were associated with girls' emotionally based eating problems (emotional over- and undereating).

The literature emphasizes the need for girl-specific ASD screening to prevent under- or misdiagnosis in females.[111] Although it is still being debated, the girl-specific ASD phenotype likely includes social imitation or the camouflaging of social difficulties with less evident impairments.[112] A recent report indicated that girls and women with ASD are not only significantly underdiagnosed but they also often struggle with internalizing problems such as anxiety, depression, and eating disorders, and in addition, they are regularly mislabeled and criticized in a social context.[113]

A recent study by Wallace et al.[114] partly confirms our results as they found that children (4-17 years) with ASD exhibited more emotional over- and undereating than their non-ASD peers. In addition, girls were more inclined towards emotional overeating than boys with ASD, resulting in a higher consumption of sweet foods and fewer vegetables. This study found no differences in the emotional eating behavior of non-ASD children,[114] although it included children with only an ASD diagnosis so that girls with high autistic traits and another diagnosis – e.g. anorexia nervosa, often showing high levels of emotional undereating – were excluded, which would explain the lack of gender difference. Although much about the underlying mechanisms is unknown, this thesis indicates that emotional eating problems may complement the girl-specific ASD phenotype.

Eating behavior as an (early) sign of ASD: from research to clinical practice and future research

This thesis has made several recommendations on improving the (early) detection of ASD in clinical practice and the aims of future research into associations between ASD and eating behavior.

Future research: adding eating behavior to ASD screening tools

The reported association between infant eating behavior and later autistic traits indicates that the inclusion of eating behavior in ASD screening tools could enhance the early detection of ASD. Widely used screening instruments like the Modified Checklist for Autism in Toddlers (M-CHAT(R/F),[115,116] the Social Communication Questionnaire (SCQ)[117] and the Early Screening of Autistic Traits Questionnaire (ESAT/CoSoS in Dutch)[118] often include items specific to ASD-related deficiencies, such as having an unusual response to sensory stimuli,[115,117,118] but none of them evaluates eating behavior specifically. Yet problems with sensory stimuli may well appear while eating; if healthcare professionals are more aware of the relationship between eating behavior and ASD they will notice this when problems are being reported by parents. Indeed, the Copenhagen Infant Mental Health

Screening (CIMHS), used at age 9-10 months, includes eating behavior and shows potential for infant mental health screening based on community health nurses.[119]
Future research should evaluate if the sensitivity and/or specificity of ASD screening questionnaires increases when eating behavior questions are included. We recommend a study be performed in collaboration with well-child clinics (e.g. Youth and Family Centre in the Netherlands), in which children who are suspected of ASD are screened by the ESAT with additional questions on eating behavior. These children should be followed through their diagnostic process to confirm ESAT screening results and evaluate whether the results improve when eating behavior is included.

Future research: association of ASD with eating behavior
We recommend that the association between infant eating behavior and later ASD is further evaluated. More specific evaluation of infant eating behaviors with the Baby Eating Behaviour Questionnaire (BEBQ)[120] and the Child Eating Behaviour Questionnaire (CEBQ)[121] in a general population cohort would provide insight into which type(s) of infant eating behavior is associated with ASD. It would be beneficial to evaluate eating behavior at multiple moments throughout infancy and early childhood (e.g. 2 months, 6 months, 1 year, 2 years) to see if specific eating behavior trajectories are associated with later diagnosis of ASD and if any gender differences are present.

Future research: gender differences and overlap with other disorders
Firstly, although our work found gender differences were present in the association between eating behavior and ASD in early childhood,[122] we did not find any in infancy.[123] This may be due to the fact that gender differences were found in emotional eating – these behaviors are shaped by shared environmental factors rather than genetic risk,[124] and may develop only later during childhood. Nonetheless, previous research has demonstrated an association between the parental use of food to soothe (emotional feeding strategies) and the later development of emotional eating problems,[125] indicating that eating-related behavior is already being shaped as early as infancy and suggesting it can be observed during infancy. However, there were no gender differences found in the effects of parental use of food to soothe during infancy.[126] More precise and repeated evaluations of eating behaviors in infancy may reveal any gender differences.
Secondly, we must continue to follow the Generation R population to evaluate how eating behavior and ASD traits develop into pre-adolescence and adolescence, the period in which most eating disorders start to manifest.[127] Studies should focus especially on the development of eating behavior (especially emotional eating) in girls with ASD and the possible overlap with anorexia nervosa,[128–134] to enhance early identification and referral to suitable treatment.

Finally, future research should evaluate how the inclusion of (emotional) eating behavior can enhance the diagnosis of ASD in girls. There is ongoing debate and research on the girl-specific ASD phenotype but there is a clinical relevance to enhancing the detection/diagnosis of ASD in girls to ensure they have appropriate support and treatment.

Box 7.3 How could Mara have benefited from these insights?

The general introduction of this thesis described the case histories of Bram and Mara. How could Mara have benefited from the insights provided in this thesis?

Mara
Although Mara had some early signs of ASD at age 4 years, e.g. playing alone and butterflying in the nursery school yard, her eating problems were the main cause of concern at that time and not linked to her ASD. If the preventive care professional had had more knowledge of eating problems as an early sign of ASD and, in Mara's case, of emotional eating problems (not eating after getting upset), this would have raised the possibility of her having ASD and led to further screening and an earlier ASD diagnosis.

CONCLUSIONS

The objective of this thesis was to identify factors which can enhance the detection of autism spectrum disorder (ASD) in childhood. Three aspects of the detection of ASD were addressed:

- Age at ASD diagnosis: *what is the current global age at ASD diagnosis?* (Chapter 2)
  We found that the current global mean age at ASD diagnosis is 60.48 months (range 30.9–234 months). Efforts are needed to evaluate the age at ASD diagnosis by a meta-analysis that includes a wide variety of influencing factors in order to advance early detection of ASD in healthcare systems.
- Early detection of ASD by preventive care physicians: *can we improve early detection by healthcare professionals?* (Chapters 3 & 4)
  Our work indicates that a live online ASD educational program for preventive care professionals contributes to the early detection of ASD. Efforts are needed to evaluate global well-baby facilities and to implement ASD educational programs to enhance the early detection by healthcare professionals screening for ASD in the child population.
- Eating problems and ASD: *can the assessment of eating behavior potentially be useful in the (early) detection of ASD?* (Chapters 5 & 6)
  Our work indicates an association between eating behavior and ASD in early and middle childhood; it could therefore be beneficial to include questions on eating behavior in ASD

screening tools. Future research should further specify the association between eating behavior and ASD, and determine its usefulness as a screening item.

This thesis describes improvements that can be made to improve global ASD preventive healthcare. We want to encourage researchers and clinicians to further explore the possibilities of detecting ASD at a younger age in order to enhance the quality of care and life for children with ASD.

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