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CURRENT CHANGES IN THE OCCURRENCE OF AUTISM SPECTRUM DISORDERS IN STOCKHOLM

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*Current changes in the occurrence of
Autism Spectrum Disorders in Stockholm*
THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my beloved family

PROLOGUE

Halfway through my residency in child and youth psychiatry, I longed to obtain more insights into the determinants of mental health problems than my residency could provide.

Consequently, I was introduced to my current research supervisors Cecilia Magnusson, Christina Dalman and Clara Hellner-Gumpert. Our collaboration resulted in a project exploring mental health service use in a health care register in Stockholm. Eventually, this register was merged with a number of other health and administrative registers as part of the *Stockholm Youth Cohort*, on which the studies in the present thesis are based. At the same time, I enrolled as a Ph.D. student at Karolinska Institutet with a project plan focusing on neurodevelopmental disorders.

Thanks to endless support from my research and clinical supervisors as well as colleagues, I had the privilege of combining patient-oriented clinical practice with scientific training throughout my Ph.D. studies. My current clinical work involves diagnostic ascertainment of young children with suspected developmental disorders, such as autism spectrum disorders. Thus, my clinical work is closely related to the research domains of this thesis, i.e. ascertainment, recent prevalence changes of and risk factors for autism spectrum disorders.

I am grateful for the opportunity to work with patients as well as with colleagues who have always strived to achieve an interactive flow of ideas between clinical work and research domains. In light of the complexity of autism spectrum disorders, I believe that continuous communication between these domains is necessary for the generation of research hypotheses and the integration of new knowledge into clinical practice. Therefore, I hope that other clinicians as well as myself will have further possibilities to combine clinical work and research.

Stockholm, February 2015.

ABSTRACT

The overall objective of this thesis is to estimate recent changes in and current prevalence of autism spectrum disorders (ASD) among young people in Stockholm County. An additional objective is to explore potential risk factors for ASD in view of the increasing occurrence in the population. For this purpose, a register-based total population study was set up and ASD case ascertainment validated as a means and research model for achieving the overall objective.

All studies were based on the Stockholm Youth Cohort (SYC), a longitudinal total population study of 0-17 year olds resident in Stockholm County at any time since 2001. Prospectively compiled data for this population were merged from regional and national registers. In study I, we found that 96.0% of clinical case notes from randomly sampled ASD cases in the SYC were consistent with a diagnosis of ASD. Furthermore, we confirmed ASD in 82.5% of affected twins in the SYC by means of cross-validation against a twin study. In study II, we reported that ASD prevalence at the end of 2011 was 1.5% among 0-27 year olds (N=735,096), of whom 25.9% had a registered diagnosis of ID. The ASD prevalence was highest among teenagers at 2.4%. The male: female prevalence ratio for ASD decreased with age (from 3.3:1 among 0-12 year olds, to 1.9:1 among 18-27 year olds), particularly for ASD without ID. Between 2001 and 2011, the prevalence of ASD increased almost 3.5 fold among 2-17 year olds, mainly due to an eightfold increase of ASD without ID. In contrast, the prevalence of ASD with ID increased only slightly during this period.

The recent increase in ASD prevalence has attracted research interest toward risk factors for ASD that have increased in a parallel manner, such as parental age and weight. In study III, we found that higher parental age increased the risk of offspring ASD as well as stronger parental age effects for ASD with, than without, ID. We found the risk of ASD to be greater for offspring of older mothers than for those of older fathers. Furthermore, the paternal age effect on ASD risk was only evident among offspring to mothers aged 35 years or younger, while maternal age increased the risk of ASD regardless of paternal age. In the population-based analysis of study IV, we found that maternal overweight increased the risk of ASD, while no such effect was evident in the sibling analysis. In addition to the finding that too much weight gain during pregnancy increases the risk of offspring ASD, this study was the first to report that too little weight gain also constitutes a risk.

In conclusion, the prevalence of identified ASD without comorbid ID has increased substantially between 2001 and 2011 in Stockholm, and ASD currently affects more than 2% of teenagers, with important implications for the planning of health and educational services. Changes in diagnostic practice and awareness are likely to be the main drivers of the rise, but an actual true increase in ASD incidence cannot be ruled out. Collectively, these studies confirm the relevance of categorizing ASD according to ID. Finally, the SYC, with its extensive register-based data as well as a valid and thorough ASD case ascertainment constitutes an important resource for ASD research.

LIST OF SCIENTIFIC PAPERS

- I. **Idring Selma**, Rai Dheeraj, Dal Henrik, Dalman Christina, Sturm Harald, Zander Eric, Lee Brian K, Serlachius Eva, Magnusson Cecilia
Autism spectrum disorders in the Stockholm Youth Cohort: design, prevalence and validity.
PLoS One. 2012;7(7):e41280.
- II. **Idring Selma**, Lundberg Michael, Sturm Harald, Dalman Christina, Gumpert Clara, Rai Dheeraj, Lee Brian K, Magnusson Cecilia
Changes in prevalence of Autism Spectrum Disorders in 2001-2011: findings from the Stockholm Youth Cohort.
Journal of Autism and Developmental Disorders, 2014, Epub ahead of print.
- III. **Idring Selma**, Magnusson Cecilia, Lundberg Michael, Ek Mats, Rai Dheeraj, Svensson Anna C, Dalman Christina, Karlsson Håkan, Lee Brian K
Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort.
International Journal of Epidemiology, 2014, 43 (1), 107-115.
- IV. Gardner Renee M., Lee Brian K., Magnusson Cecilia, Rai Dheeraj, Frisell Thomas, Karlsson Håkan, **Idring Selma**, Dalman Christina
Maternal body mass index during early pregnancy, gestational weight gain, and risk of autism spectrum disorders: Results from a Swedish total population and discordant sibling study.
Manuscript submitted.

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ABBREVIATIONS

ASD	Autism Spectrum Disorders
BMI	Body Mass Index
CATSS	The Child and Adolescent Twin Study in Sweden
CDC	Centers for Disease Control and Prevention
DSM	Diagnostic and Statistical Manual of Psychiatric Disorders
GAM	General Additive Model
GWG	Gestational Weight Gain
ICD	International Classification of Diseases
ID	Intellectual Disability
IQR	Interquartile Range
MBR	Medical Birth Register
NPR	National Patient Register
PDD	Pervasive Developmental Disorders
PIN	Personal Identification Number
SYC	Stockholm Youth Cohort
TPR	Total Population Register

1 BACKGROUND

Autism spectrum disorders (ASD) are neurodevelopmental conditions characterized by impaired social interaction and communication, as well as restricted/ repetitive behaviours. As the name suggests, these core symptoms range on a spectrum from mild to severe. ASD are behaviourally defined, implying that a diagnosis is based on the symptoms presented by an individual, rather than on objective biological measures such as blood tests and radiological examinations. A diagnosis of ASD does not pertain to the cause or aetiological mechanism of the disorder. At present, such a diagnosis is defined by specific diagnostic criteria as set out in the International Classification of Diseases (ICD) (1) and the Diagnostic and Statistical Manual of Mental Disorders (DSM) (2, 3). To qualify for a diagnosis of ASD, an individual's daily functioning must be limited by her/ his symptoms. While the first signs of ASD commonly emerge early in early childhood and a reliable diagnosis can be made by the age of two years (4, 5), there is vast variability in the time of diagnosis (6). Early diagnosis is considered optimal as it enables early intervention, which has been found beneficial for younger children (7, 8). However, in many individuals impairments related to ASD – and hence the possibility of being diagnosed – first manifest when the demands of social interaction and communication exceed her/ his abilities.

In addition to the core symptoms of ASD, a substantial proportion of affected individuals present with comorbid conditions and/ or symptoms (9). Common comorbid conditions related to cognitive development and behaviour include intellectual disability (ID), attention problems, hyperactivity, aggression, depressive symptoms and sleep disorders (10). Furthermore, many individuals with ASD also present with comorbid medical conditions such as epilepsy and genetic disorders (11). The variable core symptoms of ASD, in combination with the range of comorbid conditions contribute to the heterogeneous manifestation. This presents an immense challenge in the field of ASD diagnostics, interventions and research.

1.1 DIAGNOSTIC CLASSIFICATION OF ASD

More than 70 years have elapsed since Dr. Kanner's milestone report on 11 children with deviating social development. In the following years, the field of classification of what is now known as ASD has undergone massive change. Initially considered a condition associated with schizophrenia, autism became an independent diagnostic entity in the ICD and DSM in 1977 and 1980, respectively. At that point, autism was narrowly defined as "infantile autism" in a class of disorders termed "pervasive developmental disorders" (PDD). In order to better describe the heterogeneous manifestation of autism, the diagnoses within the PDD diagnostic class have been progressively broadened in both the DSM and the ICD.

During the past two decades, the DSM-IV and the ICD-10 have been used to define PDD subdiagnoses, which are strongly related in both manuals. The DSM-IV and the ICD-10 include a diagnosis covering a fulminant triad of core symptoms of ASD (impairments in social interaction, communication, and restricted/ repetitive behaviours), entitled "Autistic

Disorder” in the DSM-IV and “Childhood Autism” in the ICD-10. Both also include the diagnosis “Asperger’s Disorder (DSM-IV)/ Syndrome (ICD-10)”. Individuals who qualify for the latter deviate in terms of social interaction and interests or behaviour but have neither significant language delays nor cognitive impairments. The DSM-IV diagnosis “PDD – not otherwise specified” encompasses individuals who do not meet the fulminant core symptoms of Autistic Disorder /Childhood Autism, nor the diagnostic criteria for Asperger’s Disorder. In the ICD-10 it corresponds to by several diagnoses with a more specific clinical presentation - “Atypical Autism”, “Other PDD” and “PDD – unspecified”. In addition, “Rett’s syndrome” and “Childhood Disintegrative disorder” are included in both manuals and pertain to individuals with normal initial development, followed by the loss of previously acquired skills within several developmental areas, including socio-communicative skills. The DSM-IV diagnostic criteria for Autistic Disorder, Asperger’s Disorder, and PDD not otherwise specified are listed in **Box 1**. While clinicians and researchers have used the diagnostic subcategories of the DSM-IV and ICD-10 for the past two decades, the distinctions between them have been found to be unreliable in several studies, providing little clinical information (12-14). The alternative approach of subtyping ASD in relation to comorbid ID is supported by recent clinical and population-based studies (12, 15, 16). Because IQ tends to remain stable over time and is a robust predictor of outcome in ASD (17), this method of ASD differentiation not only has practical implications for support and management, but may also be more useful for aetiological investigations than the DSM-IV and ICD-10 (15, 18).

In 2013, the most recent DSM revision, DSM-5, was published in the USA (3). At the time of writing it has not been translated into Swedish and is not yet clinically used in Sweden. A revised ICD-11 is due by 2017. The DSM 5 implies several major changes for the diagnosis of autism and related conditions. Amongst other, the subcategories of PDD have been replaced by a single, overarching category and ASD diagnosis. Because a distinct genetic aetiology has been found for Rett’s syndrome and Childhood disintegrative disorder, these are no longer listed under ASD. For a diagnosis of ASD in the DSM 5, an individual has to have, or have had, socio-communicative impairments as well as restricted, repetitive patterns of behaviour. Individuals with socio-communicative impairments but no repetitive and behavioural symptoms are listed under the new diagnosis of “Social Communication Disorder”. ASD is characterized by specifiers in the DSM 5, which relate to the presence of a wide range of comorbid conditions including ID, language impairment and medical or genetic factors (3).

DSM-IV Diagnostic Criteria for Autistic Disorder

I. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

(1) Qualitative impairment in social interaction, as manifested by at least two of the following:

(a) Marked impairment in the use of multiple nonverbal behaviors such as eye to-eye gaze, facial expression, body postures, and gestures to regulate social interaction .

(b) Failure to develop peer relationships appropriate to developmental level

(c) A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)

(d) Lack of social or emotional reciprocity

(2) Qualitative impairments in communication as manifested by at least one of the following:

(a) Delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures or mime)

(b) In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

(c) Stereotyped and repetitive use of language or idiosyncratic language

(d) Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(3) Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

(a) Encompassing preoccupation with one or more stereotyped patterns of interest that is abnormal either in intensity or focus

(b) Apparently inflexible adherence to specific, nonfunctional routines or rituals

(c) Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

(d) Persistent preoccupation with parts of objects

II. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:

(1) Social interaction

(2) Language as used in social communication

(3) Symbolic or imaginative play

III. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

DSM-IV Diagnostic Criteria for Asperger's Disorder

I. Qualitative impairment in social interaction, as manifested by at least two of the following:

- (a) Marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
- (b) Failure to develop peer relationships appropriate to developmental level
- (c) A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
- (d) Lack of social or emotional reciprocity

II. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

- (a) Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
- (b) Apparently inflexible adherence to specific, non-functional routines or rituals
- (c) Stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
- (d) Persistent preoccupation with parts of objects

III. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

IV. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years)

V. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

VI. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

DSM-IV Diagnostic Criteria for Pervasive Developmental Disorders – Not Otherwise Specified

This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interests, and activities are present, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant Personality Disorder. For example, this category includes "atypical autism"—presentations that do not meet the criteria for Autistic Disorder because of late age of onset, atypical symptomatology, or sub-threshold symptomatology, or all of these.

Box 1: DSM-IV diagnostic criteria for autistic disorder, Asperger's disorder and PDD- not otherwise specified

1.2 ASD CASE ASCERTAINMENT METHODOLOGY

Case ascertainment methodology is a central aspect of ASD research. Studies on, e.g., ASD prevalence, risk factors, treatment and outcomes should be compared in the light of how ASD cases are defined, identified and confirmed in each study.

1.2.1 Case definition

Studies on ASD have used various case definitions, commonly restricting cases to the diagnosis of autistic disorder/ childhood autism, or investigating various diagnostic subcategories of PDD in accordance with the DSM-IV and ICD-10 or earlier versions. Case definitions in other studies have encompassed a broader spectrum of ASD. A disadvantage with this strategy is that it does not cover the behavioural and comorbid heterogeneity of ASD unless cases are subcategorized.

1.2.2 Case identification

Two different principal strategies are used to identify individuals with ASD in a population; 1) the multistage approach, implying active screening of the study population with subsequent diagnostic evaluation of screen-positive individuals, and 2) locating previously identified cases.

1.2.2.1 The multistage approach

The first, population-screening phase of the multistage approach can involve administering questionnaires pertaining to ASD symptoms to parents or teachers (19-23), applying screening approaches at developmental follow-ups at paediatric units (24-27) or using health- (28, 29), school- (30) or multiple (31-34) data sources to identify individuals at risk of ASD. The second stage aims to assess whether the symptoms of at-risk individuals identified in the first screening phase correspond to a diagnosis of ASD. Although considered to provide the most accurate prevalence estimates, studies using the multistage approach may be hampered by non-complete coverage, e.g., screening that does not include the entire population. Many multistage studies have instead been directed towards populations with a higher probability of ASD such as individuals with special education needs, thus potentially introducing selection bias. Only a few studies based on the multistage approach have evaluated the sensitivity of the screening methodology, i.e. estimating the proportion of affected individuals in the general population identified by the screening procedure (20, 22, 23, 33, 35). Prevalence estimates from population screening approaches should therefore be considered as minimum ASD prevalence figures (19, 26).

1.2.2.2 Locating previously identified cases

This strategy identifies previously diagnosed ASD cases from various surveillance systems, databases and registers. Such studies frequently rely on healthcare registers (36-42) and/ or education registers (42-44). While more time and cost effective than studies using the multistage approach, the primary drawback of this strategy is that it underestimates the

prevalence among individuals not previously identified. Moreover, not all individuals with ASD receive a diagnosis in any one setting or are in touch with any given service at all times, indicating the need for thorough coverage of registers and surveillance systems with which an affected individual is likely to be in contact.

1.2.3 Case confirmation

This phase serves to confirm ASD in individuals identified as being at risk in the preceding screening phase of multistage studies as well as to examine the accuracy of a diagnosis in a sample of identified cases.

1.2.3.1 Case confirmation in multistage studies

In some multistage studies, at-risk individuals identified in the screening phase underwent diagnostic evaluation to confirm ASD case status using more or less structured methods (20, 21, 23, 25, 26, 28, 29, 32, 35). Diagnostic instruments used in this phase of multistage studies are of varying reliability and validity, while willingness on the part of the individual involved to participate in diagnostic evaluations may be limited (45). In contrast, a standardized review and scoring system based on case notes, rather than diagnostic evaluation, has been developed to determine ASD case status for data collected in the screening phase of US surveys of ASD prevalence (33).

1.2.3.2 Case confirmation in studies based on previously identified cases

According to a review of validity studies in psychiatric research, a uniform standard for assessing the accuracy of register data such as ASD diagnoses does not exist (Byrne et al 2005). To date, studies have confirmed previously identified ASD cases through clinical evaluation (40), diagnostic interviews with parents or caregivers (46), and clinical case-note reviews (47, 48).

1.3 ASD PREVALENCE

Early studies of ASD prevalence (the proportion of individuals with ASD at one point in time) focused primarily on the narrowly defined infantile autism, reporting it as a rare condition (45). However, recent reviews revealed that evidence from prevalence studies from different parts of the world indicates that the median estimated ASD prevalence is approximately 0.6% (45, 49), making ASD one of the most prevalent neurodevelopmental disorders. The range of ASD prevalence estimates reported by different studies is wide, likely contributed to by differences in case ascertainment methodology (45, 49). The range of ASD prevalence estimates reported by different studies is wide, likely due to differences in case ascertainment methodology (49). While the highest ASD prevalence estimates to date were reported by studies relying on the multistage approach, the lowest prevalence estimates came from studies locating previously identified cases from registers (45). Similarly, the proportion of ASD cases with intellectual impairment (IQ < 70) varies from 14.7% in a UK study based on previously identified cases (42) to 68.2% in a US study from Atlanta comprising a multistage case ascertainment approach (34).

1.3.1 ASD prevalence in relation to socio-demographic characteristics

The male predominance in ASD prevalence is one of the most consistent research findings with an average 4.2:1 male: female ratio (50). However, this ratio varies from 1.8: 1 in a Finnish study (51) to 15.7:1 in a UK study (Baird et al 2000), both of which employed multistage case ascertainment approaches. The mechanisms underlying the skewed sex ratio in ASD prevalence are unknown to date; underlying biological sex differences and / or ascertainment / diagnostic bias may contribute (52).

Multiple studies in the US have reported an association between offspring ASD and higher parental socio-economic status, indicated by e.g., parental education and household income (53-57). However, it has been suggested that this association is a result of socio-economic disparity in access to care (55, 58-62), suggesting that the association between socio-economic status and ASD is biased by such disparities. Such disparities are also thought to partly contribute to the lower ASD prevalence among certain racial / ethnic and immigrant populations observed in some studies (33, 54, 61, 63). However, evidence of an association between race/ ethnicity, migration and ASD prevalence has been inconsistent, with no strong proof of underlying biological causal pathways (45).

1.3.2 Time trends in ASD occurrence

Global prevalence estimates of ASD have increased over recent decades (49), even in studies examining prevalence over shorter, more recent time frames (33, 64, 65). For example, the ASD prevalence estimate among 8-year olds increased by 123% from 2002 to 2010 in the US (33). Increases in the identified prevalence of ASD have been noted at all levels of intellectual ability (Baird et al 2006), but have been more pronounced in those with an average or above-average IQ (Elsabbagh 2012, Samuendsen et al 2013, CDC 2014). Although evidence has been found for improved identification of specific subgroups such as Hispanic and black children during recent years, disparities in ASD prevalence across ethnic groups remain in the US (CDC 2014).

Both the incidence and the prevalence of ASD increases due to non-etiological factors that affect case ascertainment, such as increased public awareness (66), changes in diagnostic criteria and reporting practices (67), and younger age at diagnosis (68, 69). As these factors are problematic to control in surveys estimating time trends, it remains unclear which proportion of the increase in ASD occurrence is associated with non-etiological factors. Evidence to date indicates that an actual increase of ASD occurrence cannot be ruled out (Volkmar et al 2014).

1.4 RISK FACTORS FOR ASD

Similar to the field of classification, research on the aetiology of ASD has undergone principal development since Kanner's first publication on children with ASD symptoms. For several decades, autism was believed to be a result of poor parenting and more specifically the cold, destructive behaviour of "refrigerator mothers" (70). Bettelheim's causal theory

remained dominant until the 1970s when the pioneering twin study on ASD by Folstein and Rutter provided the first evidence of genetic influences in the aetiology of autism (71). Since then, the importance of the genetic contribution to ASD has been confirmed by multiple twin studies (72) as well as studies of familial recurrence (73-75). Early twin studies have suggested that genetic factors contribute to as much as 90% of the probability of autism (72). Accordingly, much research on the aetiology of ASD has focused on genetic factors. However, two recent large-scale studies based on twins in California (76) and extended families in Sweden (75) found a considerably lower contribution of genetic factors, 38% and 50%, respectively. Consequently, these studies suggest that non-genetic or environmental factors have a greater role in the risk of ASD than previously believed.

Because the first symptoms of ASD commonly appear during toddler years, environmental factors acting during the pre- and/ or perinatal period may be of particular interest for further aetiological research. The recent rise in ASD prevalence led researchers to focus on environmental risk factors for ASD that increase in a parallel manner, such as childbearing age in the Western world (77), and parental overweight (78).

1.4.1 Parental age

The association between parental age and risk of ASD in offspring has attracted much research attention. This is since the well-established demographic shift towards older first-time parenthood in developed countries (79) has been paralleled by trends of increasing ASD prevalence during recent decades. To date, approximately 40 studies have been published on the association between maternal and paternal age and ASD (80). While results of individual studies are mixed, recent meta-analyses integrating results from multiple studies report an independent association between offspring ASD and both paternal (81) and maternal age (82). According to these meta-analyses, mothers aged 35 years and over had a 1.5 fold (95% CI 1.1-1.9) higher odds of offspring ASD compared to mothers aged 25-29 years (82), while fathers aged 40-49 years had a 1.8 fold (95% CI 1.5-2.1) higher risk of offspring ASD compared with fathers under the age of 30 years (81). However, the mechanism underlying the association between maternal and paternal age and ASD remains unknown.

According to a recent review (80), evidence from epidemiological and animal studies suggests that different mechanisms may be responsible for maternal and paternal age effects on ASD risk. Current main hypotheses concerning paternal age effects on the risk of offspring ASD are related to higher rates of de novo mutations and epigenetic alternations with increasing paternal age. Similarly, structural and numerical genomic alternations with increasing maternal age may contribute to ASD risk. Mothers may also increase the ASD risk in offspring through age-related conditions such as perinatal and obstetrical complications (83, 84), medications (85) and cumulative exposure to toxins (86, 87) – all of which have been associated with greater ASD risk. Finally, ASD related personality traits and / or psychiatric illness in parents may confound the association between advancing parental age and offspring ASD through postponed parenting, an association which has been observed for schizophrenia (88, 89). In conclusion, complex pathways including both genetic and non-

genetic factors may underlie parental age effects on ASD risk, something that warrants further research (80).

The associations between parental age and ASD have mainly been reported for various diagnostic subtypes as presented in the DSM-IV or ICD-10 (82). However, as the diagnostic reliability of these subtypes has been questioned, further examination of how parental age affects different phenotypes of ASD is needed. For example, to date few studies have investigated whether the associations between parental age and ASD differ in relation to comorbid ID (90-93), and their results are inconsistent. Furthermore, there is a need for more studies on how maternal and paternal age in relation to co-parental age affect the ASD risk. For example, a recent Californian study indicated that the effect of advanced paternal age is only apparent in younger mothers, while the maternal age effect on ASD risk was independent of paternal age (94). Categorical parameterizations of parental age have been used in most previous studies, which limit the full exploration of age effects (82). Finally, most studies to date have provided relative risk estimates of parental age, which may be less informative to the general public than absolute risk estimates (95).

1.4.2 Maternal BMI and gestational weight gain

Due to the substantial worldwide increase in overweight and obesity among children and adults since the 1980s, obesity is currently a major global public health issue (78). In Sweden, the proportion of women who were overweight or obese (i.e., BMI of 25 or more) at the first antenatal visit increased from 25% in 1992 to more than 37% in 2009 (96). Maternal pre-pregnancy overweight or obesity and excessive gestational weight gain (GWG) have well-established associations with increased risk of several pregnancy-related and perinatal complications, such as preeclampsia (97), gestational diabetes (98) and perinatal adverse events (99). Moreover, associations between pre-pregnancy overweight and adverse outcomes in offspring have been found, including congenital anomalies (100), as well as cognitive and psychiatric problems (101).

Increased risk of offspring ASD has recently been associated with maternal pre-pregnancy overweight/ obesity (58, 102, 103) and GWG (58, 103, 104). Nevertheless, the underlying mechanisms of these associations remain unclear. Pregnancy-related and obstetric complications associated with obesity may present a potential causal pathway, as they are associated with offspring ASD (105-107). However, the association between maternal pre-pregnancy overweight/ obesity and GWG may also be confounded by environmental, lifestyle-related or genetic characteristics related to both these exposures, as well as offspring ASD. Because such confounding factors are difficult to identify and measure, other analytical approaches have been undertaken in recent studies in an attempt to untangle their role in the association between pre-pregnancy weight, GWG and offspring ASD. For example, individual associations between maternal and paternal BMI and offspring ASD can be compared. Associations that are stronger for maternal than paternal BMI would be indicative of causal intrauterine mechanisms. However, a recent study from Norway found paternal, rather than maternal obesity to be associated with certain diagnostic subtypes of offspring

ASD, which instead suggests a role of genetic factors (108). On the other hand, sibling comparison designs can be used to control for genetic factors, as well as environmental characteristics (e.g., socio-economic variables, rearing practices) that are similar among siblings. If an association found at a population-level is attenuated when comparing siblings with different exposures to pre-pregnancy BMI and GWG, it would indicate that there is an environmental or genetic factors shared by siblings that confounds the population level association. Only one study has examined the association between pre-pregnancy BMI and GWG using the sibling comparison design. This study found that ASD risk was significantly associated with GWG, but not pre-pregnancy BMI, both in a general population cohort and in a sibling comparison study, indicating that there may be a causal intrauterine mechanism related to GWG (104). All studies examining the association between pre-pregnancy BMI and/or GWG and offspring ASD to date have included less than 1000 ASD cases, limiting statistical power. In summary, the association between pre-pregnancy BMI, GWG and offspring ASD needs to be examined in other populations taking unmeasured confounding into account.

2 AIMS OF THE THESIS

The overall aims of this thesis were to 1) establish a valid ASD case ascertainment method using population registers 2) estimate recent changes in and current ASD prevalence, and 3) explore the effects of parental age, maternal BMI in early pregnancy and GWG on risk of offspring ASD with and without ID.

2.1 OVERALL HYPOTHESES

The overarching hypotheses tested in this thesis were:

- 1) That case ascertainment of individuals with ASD with and without ID would be valid in a large population-based study using prospectively collected register data (i.e. the Stockholm Youth Cohort)
- 2) That prevalence, changes in prevalence over time and risk factors and/ or the magnitude of their associations with ASD may differ depending on comorbid ID

An overview of the research framework is presented in **Figure 1**.

2.2 SPECIFIC AIMS

More specifically, the studies aimed to investigate:

2.2.1 Study I

1) How ASD cases are defined and identified in Stockholm using prospectively collected data from multiple registers, 2) whether ASD cases with and without comorbid ID in the Stockholm Youth Cohort could be confirmed and 3) whether prevalence estimates of ASD with and without comorbid ID in the SYC are similar to recent estimates from other population-based studies.

2.2.2 Study II

Whether prevalence estimates of ASD had increased during a recent time period, and whether the potential increase differed in relation to comorbid ID.

2.2.3 Study III

Whether greater maternal and paternal age had independent effects on the risk of offspring ASD with and without comorbid ID, and whether such effects differ depending on co-parental age.

2.2.4 Study IV

Whether maternal BMI in early pregnancy and GWG were associated with risk of offspring ASD with and without comorbid ID. Furthermore, the study explored whether these associations were affected by familial confounding.

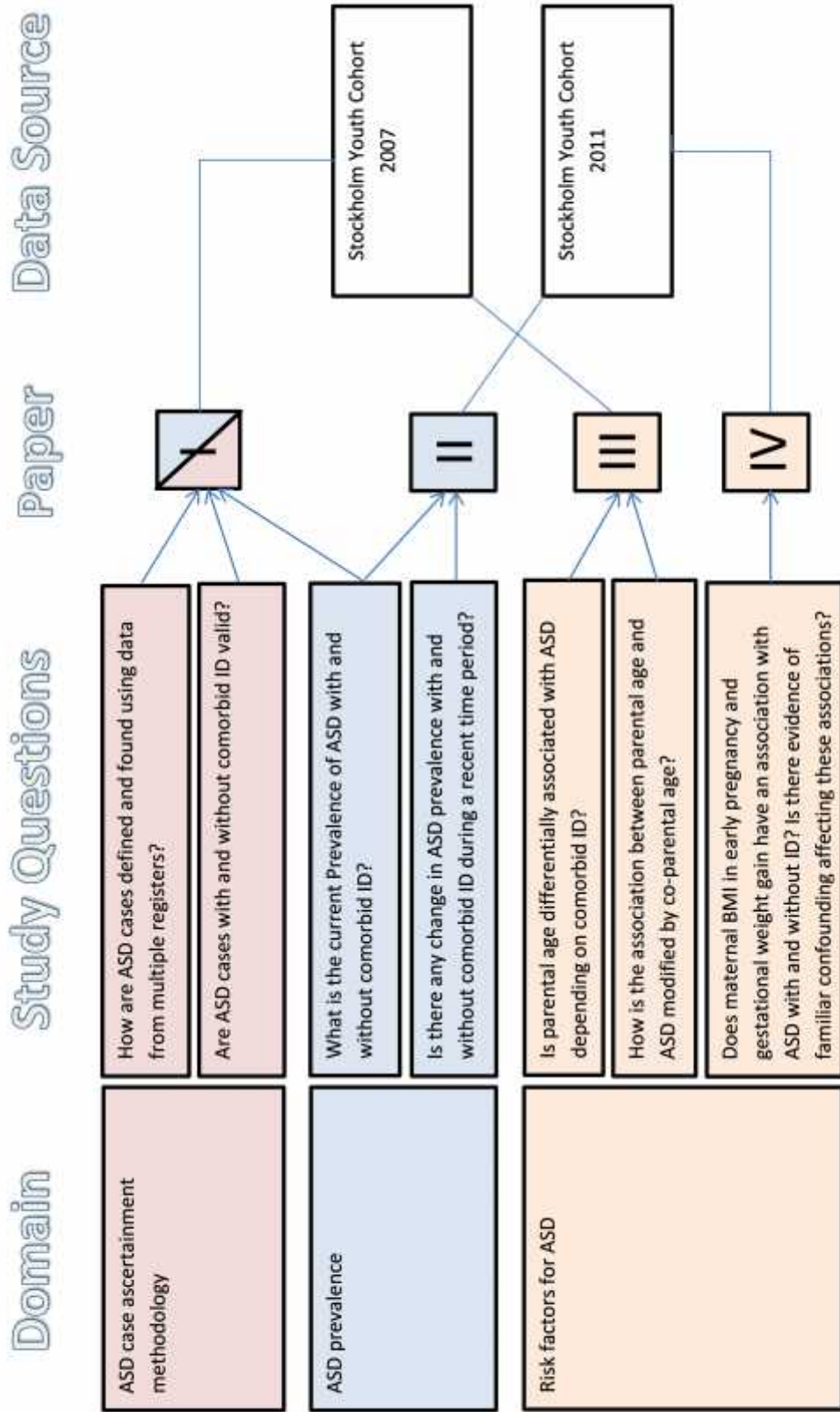


Figure 1. Overview of the research questions and overall research framework

ASD: Autism Spectrum Disorders ; ID: Intellectual Disability; BMI: Body Mass Index

3 MATERIALS AND METHODS

3.1 THE STOCKHOLM YOUTH COHORT

All studies were based on the Stockholm Youth Cohort (SYC); a longitudinal total population study of 0-17 year old individuals resident in Stockholm County at any time since 2001. Prospectively collected data pertaining to this population were merged from national and regional registers. On 31st December 2007 the SYC comprised 589,114 individuals (the population used for studies I and III), while on 31st December 2011 this figure was 735,096 individuals (the population used for studies II and IV).

3.2 REGISTER LINKAGE IN THE STOCKHOLM YOUTH COHORT

Individuals in the SYC were identified by means of the *Total Population Register*, maintained by Statistics Sweden (109). The unique identifier for an individual in this register is a 10-digit personal identity number (PIN) that all Swedish citizens receive at birth. All individuals who reside permanently in Sweden are also assigned a PIN. Immigrants without permanent residency are instead assigned a coordination number and not registered in the *Total Population Register* (110). The PIN is used in all contact with the public administration, e.g., health care, education, and social services. The PIN also enables national and regional registers to be merged, thus providing prospectively collected data on individual characteristics. The national and regional registers used in the SYC are described in **Table 1**.

Individuals in the SYC were linked to their first degree relatives (adoptive and biological parents and siblings) using the *Multigeneration Register* (111). Information on these relatives was also retrieved from the different registers that constitute the SYC.

For the purpose of this thesis, data on socio-economic status including highest level of educational attainment, occupational class and income were retrieved from the *Integrated database for Labour Market Research* (112), while some older data on employment and income were available from the *National Population and Housing census* (113). Individual prenatal, delivery and neonatal data were collected from the *Medical Birth Register* (114, 115). Data on somatic and psychiatric outcomes were gathered from national and regional health care registers, including the *National Inpatient Register* (116), *Stockholm Adult Psychiatric Care Register*, *Clinical Database for Child and Adolescent Psychiatry in Stockholm*, *Habilitation Register* and the *VAL Database*.

Additional register-based data from the SYC include information on prescribed drugs, sick-leave, academic achievements, illness and disability pensions and criminal convictions, which is available both for the index population and their first degree relatives.

Register source (web site)	Register (coverage period)	Register contents
Statistics Sweden (www.scb.se)	<i>Total Population Register</i> (1968-) (109)	Personal ID number, name, place of residence (region, address), sex, age, civil / marital status (never married, married, partner, divorced, widow/ widower), place of birth (country, county, parish), citizenship, immigration (date, country, ground for settlement), relations (married couples, child-parent).
	<i>Multi-Generation Register</i> (1932-) (111)	Linkages between individuals registered in Sweden at any time since 1961, and born 1932 or later (index persons), and their biological or adoptive parents. Enables identification of full siblings, maternal and paternal half siblings, children and cousins. Similar information is available for immigrants to Sweden who obtained Swedish citizenship before age 18 together with one, or both parents. Biological father of a child is assumed to be the husband of the mother at time of birth or is identified by acknowledgement for unwed mothers.
	<i>National Population and Housing census</i> (1960-1990) (113)	Individual and household data for all Swedish residents aged 16 years or older, e.g. employment, income, housing, household size and type of household, provided by the general public and real estate owners through questionnaires at 5-year intervals.
	<i>Integrated database for Labour Market Research (LOUISE/ LISA)</i> (1990-) (112)	Integrates socio-economic data from the social insurance, labour market and education sectors and is updated annually. Provides individual data such as level of education, employment including occupational class, alternative employment (studies, labour market activities, unemployment but also health insurance data such as parental leave), disposable income, country of birth, parental countries of birth, and latest year of immigration.
	<i>National School Registers</i> (1973-) (117)	Subject-specific school leaving grades from compulsory- (since 1988) and upper secondary school (since 1973) as well as scores on subject-specific national tests in compulsory school (since 2004)
The National Board of Health and Welfare (www.socialstyrelsen.se)	<i>Medical Birth Register</i> (1973-) (114, 115)	Data concerning prenatal-, delivery and neonatal care, originating from compulsory reports by health care providers. Includes prenatal characteristics recorded by midwives (e.g. maternal weight and height at beginning of the pregnancy, gestational weight gain, previous and current maternal health including smoking and snuffing habits, maternal medical drug use, diagnoses), delivery characteristics (e.g. mode of delivery, birth presentation, medication during delivery), and neonatal characteristics (e.g. live- or stillbirth, duration of pregnancy, weight, height, head circumference, APGAR score, birth weight for gestational age). Potential ante- and perinatal

		complications are coded according to ICD 9–10.
	<i>National Patient Register</i> (1964–) (116)	Data on admission / visit to health care service including diagnoses coded according to ICD 7-10, and admission date. Data covers inpatient care (with complete coverage from psychiatric clinics from 1973, and complete national coverage since 1987), and outpatient visits to specialist doctors since 1997. Degree of coverage and content varies depending on speciality.
	<i>Cancer Register</i> (1958–) (118)	Data concerning cancer site, histological type, stage, date and basis of diagnosis, originating from compulsory reports by health care providers. Classification and site of tumors are coded according to ICD 7–10.
	<i>Cause of Death Register</i> (1952–; 1952-1960 of varying quality; (119, 120)	Includes data on primary and contributory causes of death for all individuals who at the time of death were registered Swedish residents. Causes of death are coded according to ICD 7–10 and originate from the death certificate, the reporting of which is compulsory for health care providers. Primary and contributory causes of death and date of death.
	<i>Prescribed Drug Register</i> (2005–) (121)	Data on prescribed and administered drugs e.g. dosage. Drugs are coded according to the national substance classification system.
Stockholm County Council (www.sll.se)	<i>Stockholm Adult Psychiatric Care Register</i> (1997–)	Adult psychiatric out- and inpatient care within Stockholm County, including diagnosis and global assessment of functioning ratings (GAF). Diagnoses are coded according to DSM-IV groupings until 2004, and according to the ICD 10 since 2005.
	<i>Clinical Database for Child and Adolescent Psychiatry in Stockholm</i> (2001–)	Child and adolescent psychiatric in – and outpatient care within Stockholm County, including diagnosis and ratings of general functioning according to the Children’s Global Assessment Scale. Diagnoses are coded according to DSM-IV groupings until 2008, and according to ICD-10 since 2009.
	<i>Habilitation Register</i> (1997–)	Utilization of Stockholm County Habilitation Services according to type of disability (ID, PDD, mobility, vision or hearing impairments).
	<i>VAL database</i> (1997–) <i>Public health</i>	Public health care services in Stockholm County, including diagnostic (coded according to ICD 10, available since 2006) and service provider (clinic) information.
Swedish Social Insurance Agency (www.fk.se)	<i>Social Insurance Registers</i> (1994–)	Social insurance benefits including periods of sick leave (with diagnostic information according to ICD 10 since 2005), disability pension (with diagnostic information

		according to ICD 9–10 since 1994), occupational injury annuity, disability allowance, old age pension and parental leave.
The Swedish Tax Agency (www.skatteverket.se)	<i>The Register of Income and Wealth</i> (1968-1989)	Annual taxation data for the Swedish population
Swedish Defence Recruitment Agency	<i>The Conscription Register</i>	Data on physical and psychological characteristics for all individuals born 1946 or later who enrolled or conducted an entrance assessment at the Armed Forces' Enrolment Board or the National Service Administration. The archive contains information on more than 3 million individuals. Conscription at age 18-20 was mandatory for all Swedish men until 2007; absence was punishable offence. In the 1990s, less than 5% did not enlist, usually due to somatic illness or mental retardation.
The Swedish National Council for Crime Prevention (www.bra.se)	<i>National Convictions Register</i> (1973–) (122)	Data on timing, nature and number of all offences that lead to court convictions for individuals aged 15 or older.

Table 1: Overview of record-linkages to national and regional registers in the Stockholm Youth Cohort.

3.3 SERVICES FOR INDIVIDUALS WITH ASD IN STOCKHOLM

All services related to diagnostic ascertainment and follow-up, health care, special education and social care are provided by services run or contracted by Stockholm County Council. Individuals younger than 18 years are entitled to free non-emergency medical care (123). Virtually all preschool children in Stockholm County are enrolled in the health- and developmental surveillance programme provided by child healthcare centres in Stockholm County (124), aimed at timely detection of developmental deviation such as cerebral palsy, ID, ASD, and attention deficit/ hyperactivity disorder (125). As part of this programme, all children are offered regular surveillance of social, motor, language and cognitive development by specially trained nurses at 1, 2, 6, 10-12, 18, 36, 48 and 60 months of age. Supplementary examinations by a medical doctor are provided at specific age points (2, 6, 10-12 months) and according to need or in cases of developmental deviation (124, 125).

In cases of suspected developmental deviation, children are referred to multi-professional teams, typically including a psychologist and a medical doctor from the paediatric or child mental health services (126). Children may also be referred to such teams by general practitioners, child psychiatrists, speech therapists, school doctors as well as other health and social agencies. Regional guidelines for diagnostic evaluation of neurodevelopmental disorders, including ASD, ADHD, ID and borderline ID, were published by the Stockholm County Council in 2010 (126) and diagnoses are in accordance with the DSM or ICD classification system.

If the diagnostic ascertainment results in a diagnosis of ASD, families are offered Habilitation services for their child, usually at specialized Habilitation centres for children with ASD (127). These services are not mandatory. Within the Habilitation services, various interventions are offered according to individual need, including parental/ school staff education, social care, intervention programmes and communication therapy.

3.4 ASD CASES IN THE STOCKHOLM YOUTH COHORT

The cases of ASD as of December 31st 2011 were collected from four national and regional registers, covering all pathways of diagnosis and care related to ASD in Stockholm County. The registers were (with the proportion of cases from each source in 2011 in parenthesis): 1) the *VAL database*, a regional register providing data on public health care services in Stockholm County (80.4%), 2) the *Habilitation Register* (69.4%), 3) the *Clinical database for Child and Adolescent Psychiatry in Stockholm* (60.7%), and 4) the *National Patient Register* (13.3%). A detailed description of the registers can be found in **Table 1**.

ASD was defined as a diagnosis of ICD-9 (299) or ICD-10 (F84) in the *VAL database* and the *National Patient Register* and as a diagnosis of DSM-IV (299) in the *Clinical database from Child and Adolescent Psychiatry in Stockholm*, while in the case of the *Habilitation Register*, it was ascertained on the basis of registration as a service recipient in specialist ASD centres, in which a formal ASD diagnosis is a prerequisite for referral. As information on DSM or ICD diagnostic subcategories was not available in all registers, individuals with ASD were divided into two groups based on the presence of comorbid ID (defined as IQ 70 and functional impairment according to international and Swedish norms). ID was defined as a recorded diagnosis of 317–319 or F70-79 based on the ICD-9 and ICD-10, respectively, or 317–319 according to the DSM-IV(1, 2), and supplemented by the *Habilitation Register*, which categorizes service recipients as having autism with or without ID. Information about the age at first diagnosis of an ASD was not available in these registers.

3.5 EXPOSURE VARIABLES

3.5.1 Maternal and paternal age

Maternal and paternal age was defined as the age of the biological mother and father at the birth of the child. Parental age was retrieved from the MGR (111).

3.5.2 Maternal and paternal BMI, gestational weight gain and metabolic conditions

Maternal BMI was derived from maternal weight and height data in the MBR recorded by midwives at the first visit to a maternal health clinic at median 10.6 weeks of pregnancy (IQR 9.0-12.6) (115). Paternal BMI data were derived from the time of conscription in the Swedish military at the age of 18-20 years, objectively measured by conscription personnel as part of the physical examination. A weight below 40 kg and above 140 kg and a height under 140 cm and over 200 cm were censored. BMI values were categorized by standard convention

(128): underweight (BMI<18.5), normal (18.5 BMI<25), overweight (25 BMI<30), and obese (BMI 30).

GWG was calculated for the mother/ child pairs for whom data on maternal weight was available both at the first antenatal visit as well as at the time of delivery. GWG categories were defined as “ideal”, “insufficient” or “excessive” for each BMI category (underweight: 12.5-18 kg, normal weight 11.5-16 kg, overweight 7-11.5 kg and obese 5.9 kg) as recommended by the Institute of Medicine (129).

Maternal metabolic conditions (pre-gestational hypertension, pre-gestational diabetes, pre-eclampsia, and gestational diabetes) were identified from the MBR or the NPR. Statistical analysis

3.6 STATISTICAL ANALYSES

3.6.1 Inferential statistics

Inferential statistics are used to estimate the likelihood that chance alone accounts for the observed results. One way of assessing the role of chance in observational studies is to estimate the range of values likely to include the “true” value, i.e., the confidence interval. The Clopper-Pearson method, based on cumulative probabilities of the binomial distribution, was used to calculate the 95% confidence interval (CI) of the obtained proportion of ASD in the study populations in studies I and II. In study III, a 95% CI was estimated from posterior simulation of model parameters. Another way of assessing the role of chance in observational studies is to use statistical tests to obtain a p-value, which is used to determine whether or not results are accounted for by chance. To test the statistical significance of a difference in ASD prevalence by sex and age in study I, the Chi square statistic was used, together with its associated degrees of freedom, to derive a p-value. In study II, the 95% CIs of proportions were compared to determine whether there were significant differences between different groups from the study population.

3.6.2 Estimation of inter-rater agreement

In the case-note validation procedure in study I, Cohen’s kappa (K) coefficient was used as a statistical measure of final case status concordance between the two reviewers. Cohen’s kappa values are considered poor when < 0.0, slight at 0.0-0.2, fair at 0.21-0.4, moderate at 0.41-0.60, substantial at 0.61-0.8, and almost perfect to perfect at 0.81-1.00 (130).

3.6.3 Regression methods

Regression analysis includes all techniques for modelling and analysing the relationship between a dependent (i.e., outcome) and an independent (i.e., predictor or exposure) variable. The simplest form of regression analysis is linear regression, in which the relationship between the outcome and predictor variables is linear. In this thesis, regression analyses were used in Studies III and IV. Different types of regression analysis were applied depending on the type of data.

3.6.3.1 *Logistic regression*

Logistic regression is commonly used to analyse the relationship between a dichotomous outcome (i.e., binary, meaning that it only has two outcomes, such as ASD yes /no) and a number of exposures, while controlling for other confounding variables. Conditional logistic regression is used when investigating this relationship in matched pairs, such as siblings in Study IV. Logistic regression results in estimates of Odds Ratios (OR) with a 95% CI (the odds of being affected by an outcome when exposed to a predictor, compared to those of being affected by an outcome when not exposed to a predictor). Logistic regression is based on an adaptation of ordinary linear regression.

3.6.3.2 *General additive modelling (GAM)*

While linear models offer a well-established framework for describing the relationship between an exposure and outcome in epidemiological studies, they are limited by their assumption of a linear correlation between these variables. In studies III and IV, we wished to capture the shape of the association between the variables of interest and ASD without suggesting that the relationship had a particular form prior to analysis. Cubic regression splines in GAM provide such a framework, which is useful for modeling non-linear relationships between variables. In short, an independent variable is divided into intervals (cubic regression splines), which are used to obtain the best fit to the data. To avoid overfitting the data, which weakens the predictive performance of a model, cubic regression splines were penalized. Parental age, BMI and GWG estimates for the risk of ASD with and without ID were presented as both continuous and categorical terms.

3.6.3.3 *Accounting for clustered data*

Individuals in the same family, e.g. siblings, are more similar to each other than individuals from different family because of shared genetic and environmental factors. Consequently, data collected on individuals from the same family (i.e., a cluster) are also more similar than data on individuals from different families. Analysis of data consisting of multiple observations on a cluster is complicated by within-cluster correlation. Within-cluster correlation between exposures implies that disentangling individual contributions of an exposure to an outcome may be impossible. Several methods can be used to account for clustered data. In study III, GAM was adapted to account for clustering via random effects. Hence, random effects for the birth mother were implemented in GAMs as penalized regression terms, with smoothing parameter estimation by maximum likelihood. However, in study IV, we used general estimating equation (GEE) models specifically developed for clustered data, with the logit link clustered on the maternal identification number to provide robust standard errors.

3.7 ETHICAL APPROVAL

Ethical approval for the record linkages and studies included in this thesis was provided by the Research Ethics Committee at Karolinska Institutet. Informed consent was not required

for the analysis of anonymized register data. Prior to researcher access to register data, individual PINs are replaced by a unique identification code, which protects the personal integrity of the individuals. For the clinical case-note review (Study I), randomly selected individuals with ASD were de-identified by Statistics Sweden and their case notes scrutinized by healthcare professionals bound by professional secrecy. Retrieved data were returned to Statistics Sweden and the PINs replaced by unique identification codes. The results are presented at group level.

3.8 STUDY I METHODS

The register linkage and ASD case ascertainment in the SYC was described in this paper. Furthermore, the prevalence of ASD with and without ID in the year 2007 was estimated for the study population (0-17 year olds resident in Stockholm County at some time between 2001 and 2007, N=589,114) as well as 95% confidence intervals for proportions. In order to maximize the possibility of detecting an ASD diagnosis in the registers, only children resident in Stockholm County for at least 4 years were included, resulting in a final study population of 444,154 individuals. The overall prevalence of ASD as well as ASD with and without ID was estimated for sex and age. These results were compared using the chi-square statistic, while its associated degrees of freedom were employed to calculate the p-value.

ASD case ascertainment in the SYC was validated by means of two different approaches: case-note review and cross-validation against the Child and Adolescent Twin Study in Sweden (CATSS).

3.8.1 Case-note review

For the case-note review, a random sample of 100 ASD cases without, and 100 cases with, comorbid ID was drawn from the SYC. Following ethical approval these individuals were de-identified by Statistics Sweden, and their clinical case notes requested from the clinical units responsible for their care. Using this process, clinical notes of 177 (88.5%) ASD cases were retrieved, while the case notes of the remaining 23 ASD cases were either missing or could not be retrieved due to lack of a response from the clinical units. Two clinical experts, a child psychiatrist (Selma Idring) and a neuro-paediatrician (Anna Shchokina), reviewed the case notes. A case note review survey was designed by a child psychiatrist (Selma Idring), a neuro-paediatrician (Harald Sturm) and a medical doctor specialized in learning disabilities (Dheeraj Rai), to be used during the review process. The survey covered documented diagnoses, age at diagnosis and the diagnostic evaluation procedures used (in accordance with regional guidelines published to date (126)). The latter included parental interviews, child observation, psychometric and diagnostic tests and interviews, medical examination, and complementary assessments. Moreover, all information on referrals to health and / or community services related to ASD was retrieved. Of the 177 retrieved case notes, 74 were reviewed independently by both assessors, blinded to each other. Inter-rater agreement was calculated as Cohen's kappa coefficient of the concordance of the final case status (overall and by the presence of comorbid ID) between the reviewers. The criteria used to determine

final case status were 1) a case-note documented diagnosis of ASD with or without ID in accordance with ICD-9, ICD-10 or DSM-IV and at least one of the following, 2) documented evidence of a structured diagnostic process, 3) evidence of referral to health- and/or community services related to ASD with or without ID.

3.8.2 Cross-validation against a twin study

In the second approach, ASD cases from the SYC were compared with information from a national population-based study of twins born since 1992 (the Child and Adolescent Twin Study in Sweden- CATSS) (131). In CATSS, ASD was assessed via parental report, and a comprehensive screening interview for a broad range of neurodevelopmental disorders was conducted with the parents at the children's 9th or 12th birthday (A-TAC), which is considered a reliable and valid screening tool for ASD (132-134). All twins co-occurring in the SYC and the CATSS were first identified, after which the proportion of SYC twins confirmed as ASD cases in the CATSS was estimated.

3.9 STUDY II METHODS

In 2011 the ASD prevalence by comorbid ID and socio-demographic characteristics (age, sex, country of origin, disposable family income at time of birth, highest level of parental education) was estimated for the entire study population (0-17 year olds resident in Stockholm County at some time between 2001 and 2011, N=735,096). The annual proportion of ASD with and without ID among 2-17 year olds during the study period from 2001 up to and including 2011 by birth year, sex, country of origin, disposable family income at time of birth and highest level of parental education was calculated by dividing the number of cases identified by the total number of residents at the follow-up at the end of 2011. The 95% confidence intervals (CI) were calculated using the Clopper-Pearson method. The age range of 2-17 years was selected because no cases were discovered among 0 to 1 year olds, while estimates for adults during initial years of surveillance might be deflated by truncation, i.e., key registers for case ascertainment started in 1997 and 2001 could have deflated the observed prevalence among older children.

3.10 STUDY III METHODS

Smoothing splines in GAMs were used to estimate the association between parental age and ASD with and without ID in a sample of non-adopted individuals born between 1984 and 2003 who had resided in Stockholm County for at least four years and for whom there was available data on maternal and paternal age (N=417,303). Models were adjusted for offspring sex, birth year, co-parental age, parity, history of parental psychiatric care, occupational class, family income and maternal country of birth. To account for clustering in sibships, random effects for the birth mother were implemented in GAMs as penalized regression terms, with smoothing parameter estimation by maximum likelihood. Maternal and paternal age estimates of the risk of ASD with and without ID were presented as both continuous and categorical terms. The prevalence of ASD with and without ID was also estimated for maternal and paternal age categories.

An interaction term for maternal and paternal age was introduced into the GAMs and the statistical significance of the interaction tested using likelihood ratio to compare the models. Furthermore, we conducted stratified analyses of maternal and paternal age in selected strata of co-parental age.

3.11 STUDY IV METHODS

In this paper, the study population consisted of all 0-17 year olds in the SYC who had resided in Stockholm for at least 4 years as of December 31, 2011 (N=735,096). Children who were adopted (N=7,266), from a multiple birth (N=13,919) or born outside Sweden (N=60,020) were excluded because no individual level data for maternal BMI and GWG were available for them.

3.11.1 Maternal and paternal BMI, maternal metabolic conditions

Both categorical and continuous analyses were used to model the relationship between maternal and paternal BMI and ASD. Restricted cubic spline models with 5 knots and xbrcspline post-estimation were employed for continuous analyses, with BMI =21 as the referent. General Estimating Equation (GEE) models with the logit link clustered on the maternal identification number to provide standard errors were used to account for clustered data. The models were adjusted for covariates chosen à priori, based on reported associations with ASD including sex, birth year, parity, maternal age, paternal age, maternal country of birth, parental education, income and parental psychiatric history (62, 81, 82, 85, 106) . Maternal and paternal BMI were included separately and in a mutually adjusted model. Analyses were performed for ASD, as well as for ASD with and without ID. GEE models were used to estimate the relationship between maternal metabolic conditions and ASD. The analyses were repeated including adjustment for each maternal BMI category.

3.11.2 Gestational weight gain

GWG was analysed as a categorical and continuous variable using GEE. Categorical analyses employed ideal GWG as the referent category, while continuous analyses used restricted cubic spline models with five knots and GWG=14 kg as the referent. In addition to adjusting for sex, birth year, parity, maternal age, paternal age, maternal country of birth, parental education, income and parental psychiatric history, the models were also adjusted for maternal BMI category and gestational age at birth. Analyses were performed for ASD, as well as for ASD with and without ID. The analysis was repeated in a restricted sample of mothers who had a normal BMI at the start of pregnancy in order to distinguish potential effects of GWG from BMI at the beginning of pregnancy.

3.11.3 Sibling analyses

The relationship between maternal BMI and ASD was analysed in matched sibling comparisons using conditional logistic regression models, grouped on the maternal identification number, and adjusted for sex, birth year, sibling birth order, as well as maternal

and paternal age at time of birth. Maternal BMI was analysed both as a categorical and a continuous variable for BMI values ≥ 21 .

3.11.4 Sensitivity analyses

Sensitivity analyses were performed to examine the robustness of maternal and paternal BMI effects. Maternal BMI was examined 1) in the full cohort with maternal BMI measures, 2) in a sub-cohort with data on gestational week at the first visit 3) while controlling for a more inclusive indicator of parental psychiatric illness including both in- and outpatient psychiatric history and 4) while stratifying the sample on the median birth year 1997 in order to examine cohort effects. For paternal BMI measures, sensitivity analyses included additional adjustment for paternal IQ measured at the time of conscription, parental psychiatric service use (in- or outpatient) and stratification on the median birth year (1997).

4 RESULTS

4.1 STUDY I: YEAR 2007 ASD PREVALENCE AND VALIDATION OF ASD CASE ASCERTAINMENT

A total of 5,100 cases of ASD (1.2%) were found in the study population of 4-23 year olds by the end of 2007 (N=444,154). Of these, 42.6% (95% CI 41.0-44.2) also had a registered diagnosis of ID. The prevalence of ASD increased with age, being lowest among 4-6 year olds (0.7%; 0.6-0.7) and highest among 13-17 year olds (1.5%; 1.4-1.5). Among young adults (18-23 years), ASD prevalence was 1.1% (1.0-1.1). (**Fig. 2A**).

The male: female prevalence ratio for ASD overall was 2.6:1, which was similar for ASD with and without ID (2.7:1 versus 2.5:1). The sex ratio decreased with age (from 5.1:1 at age 8, to 1.9:1 at age 18), especially for ASD without ID (**Fig. 2B, C**).

The key findings of the validation studies of ASD case ascertainment in the SYC were that:

- A higher proportion of ASD cases without comorbid ID (77 out of 87, 88.5%) than with comorbid ID (68 out of 90, 75.6%) was confirmed. Inter rater agreement on ASD status was achieved in 71 of the 74 cases reviewed by both raters (corresponding to a K of 0.91).
- From 148 clinical case notes providing detailed information about diagnostic ascertainment, the median age at diagnosis was found to be 8.0 years for ASD overall (range 1–19, interquartile range [IQR] 8.0), 11.5 years for ASD without ID (range 4–19, IQR 6.0) and 6.0 years for ASD with ID (range 1–17, IQR 4.0) years. Girls were older than boys at diagnostic assessment (median age 11.0 compared to 8.0 years). The majority of cases had been evaluated by multidisciplinary teams in accordance with current regional practice guidelines (126).
- Of the 27 twins with ASD identified in the SYC, 23 (85.2%, 66.2–95.8) had ASD confirmed according to diagnostic information in the CATSS. Of the 2721 twins who had not been identified with ASD in the SYC, a total of 27 (1.0%, 0.7–1.4) received an ASD diagnosis in the CATSS.

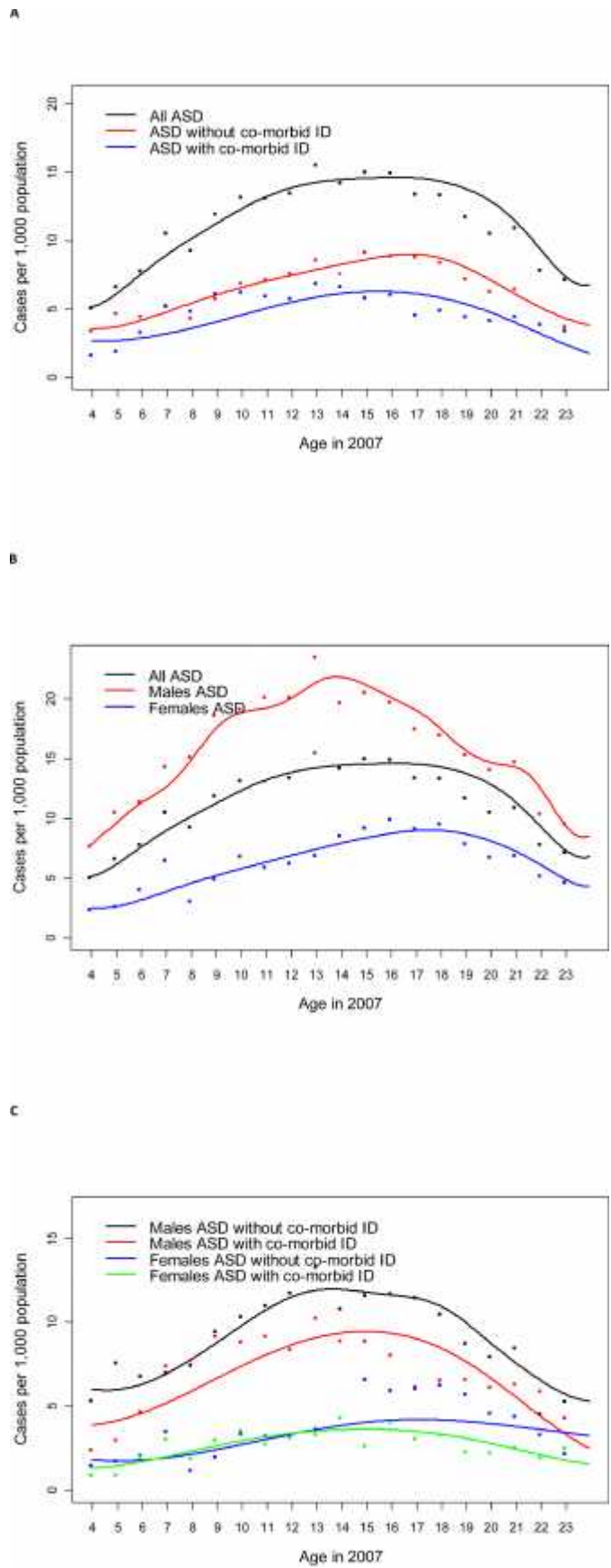


Figure 2. The prevalence of ASD in the Stockholm Youth Cohort in 2007.

Points indicate the observed prevalence (cases per 1,000) for each age (4-23 years). An empirical mode decomposition smoothing curve is superimposed. A) ASD prevalence with or without comorbid ID B) ASD prevalence according to sex C) ASD prevalence by sex with and without comorbid ID.

4.2 STUDY II: ASD PREVALENCE IN 2011 AND CHANGES IN ASD PREVALENCE 2001-2011

A total of 11,330 cases of ASD (1.5%) were found in the study population of 0- 27 year olds by the end of 2011 (N=735,096). Of these, 25.9% had a recorded diagnosis of ID. The ASD prevalence in 2011 was found to be 0.4% (0.4-0.4), 1.7% (1.7-1.8), 2.4% (2.4-2.6), and 1.8% (1.7-1.8) among 0-5, 6-12, 13-17, and 18-27 year olds, respectively. The corresponding proportion of cases with a recorded diagnosis of ID was 17.4, 22.1, 26.1 and 29.4%.

The proportion of children identified as having ASD by the end of 2011 differed in terms of the following socio-demographic characteristics:

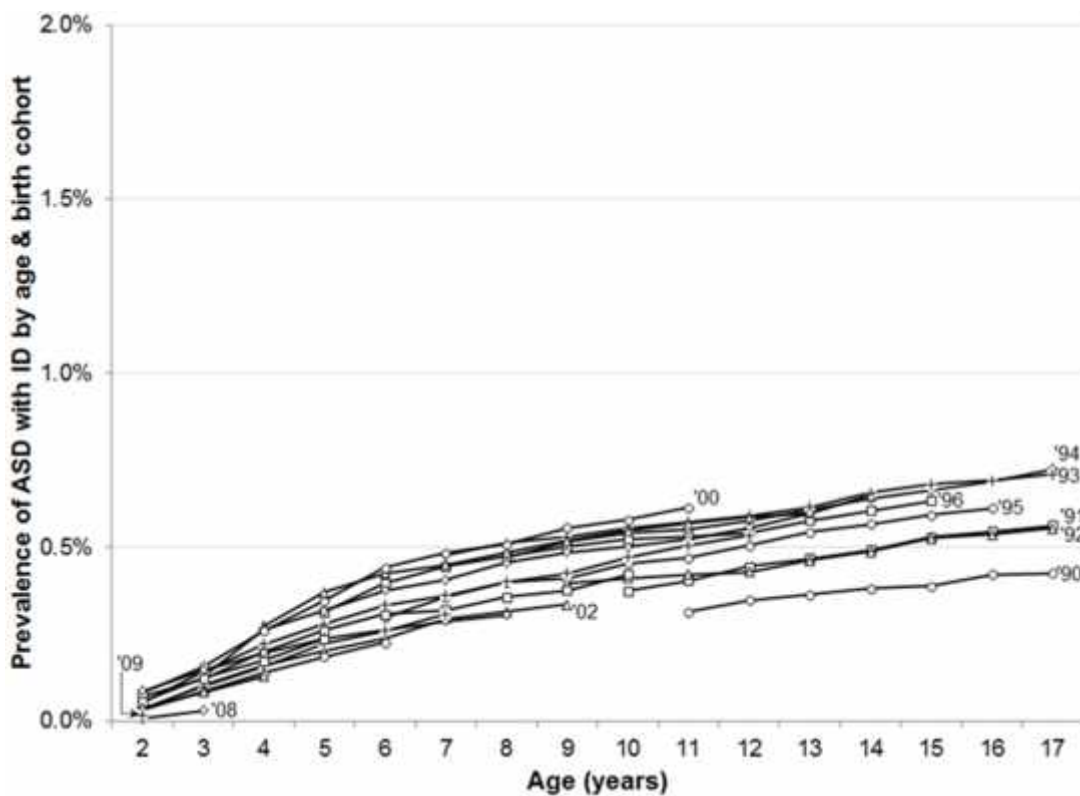
- The male: female prevalence ratio for ASD overall was 2.3:1, which was similar for ASD with and without ID. The sex ratio decreased with age (from 3.3:1 among 0-12 year olds, to 2.4:1 and 1.9:1 in teenagers and adults, respectively). This was particularly evident for ASD without comorbid ID.
- ASD with ID was significantly more prevalent among 2nd generation immigrants (implying that a Swedish-born individual's mother was born abroad), compared to individuals born in Sweden and 1st generation immigrants (implying that the individual was born abroad).
- ASD without ID was significantly less prevalent among 2nd generation immigrants from countries with a low human developmental index, and 1st generation immigrants, compared to individuals born in Sweden and 2nd generation immigrants from countries with a high human developmental index
- The prevalence of ASD overall - and particularly ASD with ID- decreased with increasing familial levels of income
- ASD prevalence decreased with increasing level of parental education, regardless of comorbid ID.

The key findings on changes in ASD prevalence among 0-17 year olds between 2001 and 2011 were as follows:

- ASD prevalence increased almost 3.5 fold among children aged 2-17 years. The increase was mainly accounted for by an approximately 8-fold increase of ASD without ID (from 1.4/ 1000 to 11.0/ 1000), while the prevalence of ASD with ID increased only slightly (from 2.8/ 1000 to 3.4 /1000).
- A consistent increase of ASD without, but not with, ID was observed with subsequent (younger) birth cohorts (**Fig. 3 A, B**). The occurrence of diagnosed ASD did not appear to level off with increasing age within birth cohorts, regardless of ID (**Fig. 3 A, B**).
- Increases in ASD prevalence across birth cohorts were more prominent with increasing age. For example, among 8, 14 and 16-year olds, ASD prevalence increased approximately three, four and sixfold.

- The proportion of ASD cases without ID steadily increased; from 21.7 to 80.6% among 8-year olds, from 45.8 to 75.8 % among 14-year olds and from 33.3 to 74.3 % among 16-year olds.
- No significant differences in changes of ASD prevalence with and without ID were observed across birth cohorts in relation to sex, country of origin, and parental education.

A.



B.

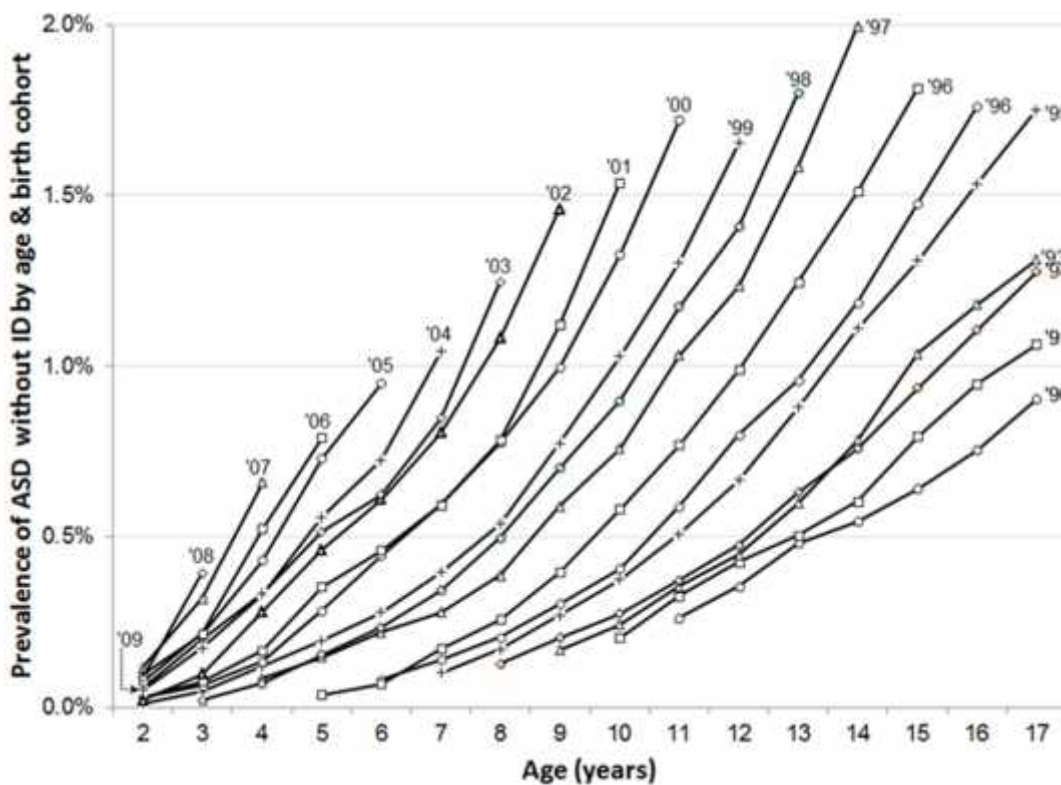


Fig. 3 Prevalence of ASD with (A) and without ID (B) among 2–17 year olds in the Stockholm Youth Cohort in 2001–2011, by age and birth cohort. Note: Although birth cohorts from 1990 to 2009 are displayed, only certain cohort curves are labelled due to overlapping curves.

4.3 STUDY III: PARENTAL AGE AND RISK OF OFFSPRING ASD

A total of 4,746 cases of ASD (of whom 42% had comorbid ID, $n=1,994$) were found in the study population ($N=417,303$).

The key findings of study III were as follows:

- Both higher maternal and paternal age increased the risk of ASD in offspring. While maternal age effects were non-linear with increased risk beyond 30 years (OR 1.07; 95% CI 1.04-1.11 for mothers aged 30-34 years and OR 1.75, 95% CI 1.63-1.89 for mothers aged 40-45 years compared to median maternal age of 29 years), paternal age effects were linear (OR 0.9, 95% CI 0.90-0.96 for fathers aged 25-28 years and OR 1.14, 95% CI 1.10-1.18 for fathers aged 40-44 years compared to a median paternal age of 32 years).
- The absolute risk of ASD was greater for older mothers as compared to older fathers, e.g. mothers aged 40-45 years had an estimated 18.63 (95% CI 17.25-20.01) ASD cases per 1,000 births whereas fathers aged 55-59 years had 16.35 (95% CI 15.11-17.58) ASD cases per 1,000 births.
- In analyses stratified by co-parental age, increased risk of offspring ASD due to advancing paternal age was only seen in mothers aged 35 years or younger. In contrast, higher maternal age increased the risk of offspring ASD regardless of paternal age.
- Advancing parental age was more strongly associated with ASD with, than without, comorbid ID.

4.4 STUDY IV: MATERNAL BMI, GESTATIONAL WEIGHT GAIN AND RISK OF OFFSPRING ASD

A total of 6420 cases of ASD were found in the study population consisting of 333,057 individuals aged 4-27 years, born to 176 850 mothers. The key findings were as follows:

- In the population-level analysis, maternal overweight and obesity were associated with a greater ASD risk (OR_{25 BMI<30} 1.31, 95% CI 1.21-1.41; OR_{BMI 30} 1.94; 1.72-2.17), as were paternal underweight and obesity (OR_{BMI<18.5} 1.19, 95% CI 1.06-1.33; OR_{BMI 30} 1.47; 1.12-1.92)
- In a matched sibling analysis, the association between maternal overweight/ obesity and ASD risk was not evident
- In both population-level and matched sibling analyses, GWG was found to have a U-shaped association with offspring ASD risk (OR_{insufficient GWG} 1.26; 1.10-1.43; OR_{excessive GWG} 1.22; 1.08-1.43 and OR_{insufficient GWG} 1.26; 0.78-2.03; OR_{excessive GWG} 1.58; 1.00-2.48, respectively)
- Similar associations were observed regardless of ID

5 DISCUSSION

5.1 KEY FINDINGS IN RELATION TO CURRENT KNOWLEDGE

5.1.1 Case definition

The ASD DSM-IV and ICD-10 diagnostic categories could not be employed in the studies included in the present thesis because they were not recorded in all the registers from which case ascertainment was drawn. However, as mentioned in the Introduction, the boundaries between these diagnostic subtypes are not considered reliable (12-14). While our ability to make comparisons with other studies that report these diagnostic categories is limited, our strategy of subtyping ASD according to comorbid ID is more consistent with the DSM-5, the most recent DSM revision which uses ID as a specifier (3).

5.1.2 Case identification

Our approach was to identify previously diagnosed cases in the SYC. In general, this strategy is more likely to under-ascertain the prevalence among individuals not identified by services, and the lowest ASD prevalence rates have been reported by epidemiological studies using this strategy (45). However, we found that in both 2007 and 2011, the ASD prevalence in studies I and II, respectively, corresponded to ASD prevalence estimates among comparable age groups from large epidemiological studies based on active population screening and subsequent diagnostic tests from the US (31, 33, 135), the UK (19, 23) and South Korea (20). Factors likely to contribute to this result are described below.

Health care service systems in Stockholm are general, well-developed and free of charge for children. All children are offered regular surveillance of social, motor, language and cognitive development at child healthcare centres (124). Furthermore, there are regional guidelines for diagnostic evaluation of neurodevelopmental disorders, and our validation study (study I) confirmed that a majority of diagnostic evaluations had been performed in line with these guidelines (126). While similar free healthcare services for children also exist in other parts of Sweden as well as in the UK, Norway, Denmark, and Finland, recent studies from these countries have reported lower ASD estimates in comparable age groups (40, 136, 137) than the SYC. A reason might be that the studies in question were only based on case identification from medical registers, illustrating the advantage of the multisource case identification strategy employed in the SYC. However, as previous studies suggest that a substantial proportion of ASD cases remain unidentified (23, 33) ASD prevalence estimates based on cases identified in the SYC should be considered conservative.

5.1.3 Validation of ASD case ascertainment

The clinical case-note review revealed that 96.0% of the scrutinized case notes were consistent with a diagnosis of ASD, which is in line from other case-note reviews from the UK (47) and Denmark (48). In our clinical case-note review, a lower proportion of ASD cases with than without ID was confirmed. However, it is possible that children with ASD

and severe ID did not undergo the structured intelligence tests required as part of the ASD subtype confirmation in the validation study.

In the clinical case-note review, it was not possible to investigate whether the original source of information (i.e. the clinical case notes) was in fact representative of a diagnosis of ASD. Individual clinical evaluation by means of standardized, validated diagnostic instruments was used to confirm 94% of ASD cases identified in the Norwegian Patient Register (40). Alternatively, a standardized diagnostic interview with parents or caregivers was conducted to confirm 96% of identified cases of childhood autism from the Finnish Hospital Discharge Register (46). However, results from these studies are limited by small sample size and low participation rate. Although measures such as data abstraction and calculation of inter-rater reliability were undertaken in the present clinical case-note review to make the data abstraction from case notes more objective, the subjectivity of the original recording clinicians is still evident. Moreover, there is a possibility that when abstracting data, researchers may be biased towards obtaining data in support of a diagnosis. In contrast, cross-validation against the CATSS relied on parental interviews. Besides generating a high ASD confirmation rate (85.2%), this approach also provided evidence that very few non-case twins in the SYC received an ASD diagnosis in the CATSS. However, a drawback was the small number of individuals eligible for cross-validation and that no cross-validation according to comorbid ID could be made. Nevertheless, in combination, the two validation approaches used in study I indicate high sensitivity and specificity of the ASD case ascertainment in the SYC.

5.1.4 Current ASD prevalence

As discussed above, the universal healthcare system in Sweden and the thorough, multisource case identification approach provided up to date ASD prevalence estimates in the SYC comparable to studies comprising general population screening procedures. For example, the overall 1.5% prevalence of ASD among 8-year olds from the 2010 surveillance in the US (33), based on active screening and diagnostic evaluations in populations with identified special education needs, symptoms associated with ASD or comorbid conditions, is comparable to the 1.6% ASD prevalence among 8-year olds in 2011 in the SYC. In a study from South Korea, a multistage approach including screening of a general population sample yielded the highest ASD prevalence estimate to date, 2.6% among 6-12 year olds (20), which is similar to ASD prevalence estimates among teenagers in the SYC.

Some studies using a multistage case ascertainment approach reported a higher proportion of ASD cases with ID (19, 25, 33) than our study. However, in the general population sample of a recent study from South Korea, an even lower proportion of cases with ID were identified, indicating that ASD cases with a normal IQ are likely to remain unidentified.

5.1.4.1 Current ASD prevalence by socio-demographic characteristics

The most recent overall male: female ASD prevalence ratio of 2.3:1 among children and young adults in the SYC is lower than the commonly reported 4:1 ratio (50). Furthermore,

there was no difference between the male: female ratio in terms of comorbid ID, in contrast to previous epidemiological studies reporting a lower male: female ratio with an increasing proportion of ID (50). Results from several recent epidemiological studies using a multistage ascertainment approach were in line with the male: female ASD prevalence ratio observed in comparable age groups in the SYC (19, 20, 25, 51), while two Japanese studies reported an even lower ratio (25, 138). Although biological mechanisms may contribute to the sex differences in prevalence (52), our findings from the case-note review indicate that later diagnosis of ASD in girls likely contributes to the comparatively lower male: female ratio in ASD prevalence observed in our studies. In other words, it is likely that young girls with ASD are under-ascertained in the SYC.

Besides young girls, other groups are likely to be under-ascertained in the SYC, despite advantages of the free and universal health care offered to child residents in Stockholm. Differences in access to healthcare may contribute to the lower prevalence of ASD without ID among individuals with a migrant background from developing countries previously reported in Sweden (63, 139) and the Netherlands (140) - a finding also observed in the SYC. In contrast, ASD was found to be significantly more prevalent among 2nd generation immigrants in the SYC, a finding which may be affected by factors associated with migration (63). Under-ascertainment among pre-school children with ASD is probable, as indicated by the high median age at diagnostic evaluation found in the clinical case-note review (study I). Considering that children can be reliably diagnosed with ASD by 2 years of age (4, 5) and the potential benefits of early intervention at the individual (7, 8) and familiar/ societal level (141, 142), a median age of 8 year at diagnosis is alarmingly high. Compared to the SYC, studies from Sweden (26) and Japan (25) in which active ASD screening procedures were applied reported substantially higher ASD prevalence estimates of 0.8% and 1.8% among 2 year olds and preschool children, respectively. Finally, prevalence estimates in our adult population may have been underestimated due to truncation, i.e., key registers for case identification being started in 1997 and 2001, respectively. However, the most recent estimate of a 1.8% ASD prevalence among 18-27 year olds in the SYC is higher than the 1% identified in a UK adult population (35).

A socio-economic gradient in ASD prevalence was found in the SYC, in that higher prevalence corresponded with lower familial levels of income and parental education. In contrast, US studies report an association between offspring ASD and higher parental socio-economic status (53-57), while our findings are in agreement with studies from countries with universal healthcare systems (58-62). Together with our results, the latter findings indicate that when disparities in access to healthcare are minimized, the observed socio-economic gradient resembles previously observed associations between low parental socio-economic status and negative developmental outcomes in children (143, 144).

5.1.5 Recent changes in ASD prevalence

The recent increase in ASD prevalence observed in the SYC is paralleled by findings from the US (33, 145), Canada (64), Iceland (11), Denmark, Finland, Sweden, Western Australia

(136) and Japan (25). According to a recent review, ASD prevalence increases have become more pronounced for cases without ID, which is also in line with our findings from SYC (49). In fact, the prevalence of ASD with ID increased only marginally between 2001 and 2011 in the SYC. In contrast to the U.S. where improved ASD identification in specific ethnic subgroups was noted over time (33), no significant differences in ASD prevalence with and without ID were observed across birth cohorts in relation to sex, country of origin or parental education.

Which factors drive the substantial increase of identified ASD without ID in the SYC? Identical case ascertainment methodology was applied throughout the study period, thus, the increase in ASD prevalence is unlikely explained by changes in internal measurement. Nor were the diagnostic boundaries of ASD widened during the study period, which would contribute to increasing ASD prevalence. However, there were regional changes in the healthcare services leading to enhanced detection, which are likely to have contributed to the largest proportion of the ASD prevalence increase. Specifically, the considerably increased rate of diagnostic evaluations between 2007-2011 among children in Stockholm County (146) may have contributed to identification of ASD cases without ID, which are generally less likely to be detected by healthcare, educational and social support services than cases with ID (20). This is supported by the pronounced ASD prevalence increase in the older age groups in the SYC, as a substantially higher median age at diagnosis was found for ASD cases without compared to with ID in the case-note review in study I. It has been speculated in previous studies (6, 147) that the younger age at ASD diagnoses in recent years has contributed to increased ASD prevalence (39, 68, 148, 149), a factor that is unfortunately not possible to examine empirically in the SYC. There may also be a growing acceptance that ASD can co-exist with other conditions such as attention deficit/hyperactivity disorder or learning disabilities. In fact, it has been hypothesized that comorbid conditions with autistic features are increasingly diagnosed as ASD, contributing to the recent increase in ASD prevalence (150). A reason for this may be that in Sweden, a diagnosis of ASD is more likely to result in school and community support, than other diagnoses.

Collectively, this evidence points to factors related to identification as the primary driver of the increased prevalence of ASD without ID in the SYC. In a recent multi-national study (136) it was speculated that similar mechanisms underlie recent prevalence increases of other neuropsychiatric disorders besides ASD. However, a true increase in ASD incidence cannot be ruled out. Similarly, a considerable share of the increase of ASD prevalence in Denmark could not be explained by factors related to improved identification (67), emphasizing the need for further exploration of aetiological factors that potentially contribute to the increased prevalence.

5.1.6 Parental age and risk of offspring ASD

Our finding that higher maternal and paternal age increases the risk of ASD in offspring is in line with results from previous meta-analyses (81, 82). However, there was variation in the shape of maternal and paternal age effects on ASD risk, indicating that different mechanisms

may underlie these effects. While paternal age effects were linear, we found a non-linear maternal age effect, which increased sharply after the maternal age of 30 years. Moreover, the paternal age effect on offspring ASD risk was only evident in mothers aged 35 years or younger, which is in line with two previous studies (94, 151). In contrast, higher maternal age increased the risk of ASD in offspring ASD, irrespective of paternal age. When combined, these findings may indicate that paternal age effects are evident among younger women who are at less risk of obstetrical complications (84). The linear paternal age effects on offspring ASD risk found in the SYC resemble the linear increase in de novo mutations with increasing paternal age observed in recent family-based studies (152, 153), thus supporting the hypothesis of age-related mutagenesis of male germ cells as the underlying mechanism. When the risks of perinatal and obstetric complications – or some other age-related risk - increase among mothers older than 35 years, they may overpower paternal age effects. Although much recent research attention has focused on paternal age effects on offspring ASD risk (80), our study indicates that attention also needs to be devoted to potential mechanisms and moderating factors of maternal age effects.

We found higher parental age to be more strongly associated with ASD with as opposed to without ID. This may be due to previously demonstrated associations between decreased offspring intelligence and advanced maternal (154, 155) and paternal (154, 156) age, although results are inconsistent. Direct comparison with other studies is difficult due to small samples in some studies as well as presentation of results based on the ICD / DSM classification of ASD.

5.1.7 Maternal BMI, gestational weight gain and risk of offspring ASD

In line with previous studies (58, 102), an association was found between maternal pre-pregnancy obesity and offspring ASD risk at the population-level analysis of the SYC. Maternal obesity at age 18, although not for the period closer to pregnancy, was related to offspring ASD in a US study of nurses (103). Moreover, the effect size of the association reported by these studies is in line with the effect size found in the population-level analysis of the SYC.

However, further findings in our study indicate that the association between maternal pre-pregnancy overweight and offspring ASD may be ascribed to unmeasured familial confounding. First, we found that paternal underweight and obesity were associated with increased risk of offspring ASD, which suggests a contribution of genetic factors to the relationship between parental BMI and offspring ASD. A link between paternal obesity and certain diagnostic subtypes of ASD was recently found in a Norwegian study. However, interpretations of the latter result may be limited due to the self-reported exposure data, and substantial under-ascertainment of ASD cases (108). Moreover, no relationship with maternal overweight or obesity was found in the sibling analysis in the SYC, further suggesting that this association may be ascribed to unmeasured familial confounders.

Excess GWG was associated with offspring ASD risk in the population level analysis of the SYC, which is in line with previous reports (58, 104). Moreover, excess GWG was also associated with offspring ASD in the sibling analysis, which agrees with the results of a previous study with a substantially smaller sample size (104). Although caution is required when interpreting the findings due to the wide 95% CI in the sibling analysis, our study is the first to report an increased risk of offspring ASD associated by insufficient weight gain during pregnancy. The latter indicates the possibility that maternal under-nutrition during pregnancy may contribute to ASD risk.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Study design

The most powerful way to study risk factors is to conduct a randomized controlled trial in which the researcher selects risk factors of interest and applies them to study groups that are otherwise similar in their susceptibility to a disease. However, an experimental study design is seldom considered ethically justifiable in human research as well as taking a long time and being very expensive. Therefore, most epidemiological studies of risk factors are observational, meaning that the researcher observes events in relation to exposure, rather than actively assigning individuals to different exposures of interest. A problem with observational studies is that individuals who are exposed to a risk factor of interest differ from unexposed individuals in terms of factors other than the exposure itself. This makes it difficult to infer whether outcomes in exposed and unexposed groups differ due to exposure to the risk factor of interest, or other factors. In other words, differences between exposed and unexposed individuals can confound the association between the risk factor and outcome. While confounding can be minimized in an experimental study, they need to be carefully accounted for in observational studies.

As a total population study with prospective data collection, the SYC provides an opportunity to study a range of risk factors and outcomes using extensive register-based data not only on the index population but also on their relatives. Such a study also enables calculation of absolute risk, for example, the risk of offspring ASD in various maternal and paternal age groups in study III. The SYC also permits cross-sectional examination of outcomes, such as ASD prevalence at selected time points (studies I and II), which is of public health interest for the allocation and planning of resources. The largest drawback of the register based study design is that only those exposures, outcomes and covariates available in the registers can be examined. Although the registers provide a wide range of individual and contextual level data of very high quality and completeness, they are designed for administrative purposes and do not necessarily provide data that suit the research questions focused upon. However, the alternative approach of prospectively collecting data specifically adapted for the research questions would require extensive resources and time.

5.2.2 Random error

Random errors result from chance findings. As described in the Methods section, they are described by confidence intervals and p-values. The risk of random errors in large epidemiological studies is small, because it is reduced with increasing sample size. However, the confidence intervals in the sibling comparison in study IV were wide, indicating greater uncertainty about the results.

5.2.3 Systematic error

Ideally, study populations are similar to the target populations they make inferences about, which implies high applicability or external validity of the results. Furthermore, in ideal conditions the characteristics of exposed and non-exposed groups are identical, apart from the exposure. However, most studies are biased as a result of systematic errors in the study design, which can involve selection of the study sample (selection bias) and how information is obtained or classified (misclassification bias). These two types of bias can be addressed at the planning stage of a study but not controlled in the analytical stage. The association between an exposure and an outcome can also be affected by the presence of another variable, i.e., mixing or confounding of the effects. In contrast to selection and misclassification bias, confounders can be controlled for in the analytical stage of a study.

5.2.3.1 Selection bias

Selection bias occurs if the association between an exposure and outcome differs for cases in the study when compared to cases who do not participate in the study. In general, selection bias in the SYC is minimized by the virtually complete coverage of the total population through mandatory registers. Furthermore, the majority of diagnosed ASD cases are likely to have been captured in the SYC due to case identification from multiple sources.

Selection bias can also result from missing data for variables, which may lead to exclusion of individuals from the study. Although the completeness of the SYC registers is generally high, adopted children were excluded in studies III and IV as exposure data were not available for them. For similar reasons, children born outside Sweden and from multiple births were excluded in study IV. There was limited availability of exposure data (parental BMI and GWG) in study IV; for example, maternal weight at time of delivery, which enables calculation of GWG, was only available for 34% of the study population. However, no notable differences were found between women with and without BMI and GWG data in the eligible population. This suggests that BMI data were missing at random and thus did not introduce selection bias into the results.

In study IV it was found that fathers for whom BMI data were available were less likely to be immigrants and to have a child with a mother of immigrant origin. However, these factors were adjusted for in the multivariate analyses and are unlikely to have influenced the internal validity of the study.

5.2.3.2 *Misclassification bias*

This type of bias results when recorded information about exposure and/ or outcome in the study participants is incorrect. Misclassification bias can be non-differential, implying that it is equally likely to occur in both study groups (e.g. exposed and non-exposed), which results in an underestimate of the true association. It can also be differential, implying that it occurs to a greater extent in one study group than the other (i.e., exposed or non-exposed individuals). Differential misclassification results in either an underestimate of the true associations, or false positive findings.

Exposure misclassification

By using prospectively collected data, the risk of recall bias in relation to exposure status is avoided in the SYC. The accuracy of maternal age is considered high in the MGR, which was used as a data source. In the MGR, the biological father of a child is assumed to be the husband of the mother at time of birth or is identified by acknowledgement by unwed mothers. However, the accuracy of paternity in the MGR has not been examined, implying a theoretical possibility of misclassification regarding paternal age in study II.

Outcome misclassification

Although most diagnosed ASD cases are likely to have been captured by the multisource case ascertainment methodology, there is a possibility of undiagnosed cases among individuals not registered as having ASD in the SYC (i.e., false negatives). As previously discussed, there is risk of outcome misclassification among young children, adults, and individuals of immigrant background. Similarly, some misclassification of outcome status with regard to exposure may be possible in the SYC despite a universal health care system for children and thorough data collection. For example, it may be so that identification of ASD in a child is influenced by parental age.

To maximize the likelihood of an affected individual being registered with a diagnosis of ASD, and hence minimize outcome misclassification, in studies I, III, and IV we restricted the population to individuals who were resident in Stockholm County for at least 4 years. However, because we wished to estimate the prevalence of ASD among children under 4 years, we did not include this restriction in study II.

In study I, we assessed the extent to which the outcome variable ASD with and without ID corresponded with an accurate data entry into the SYC. Because case-note reviews may be biased by the subjectivity of the originally recording clinicians well as abstracters being more likely to abstract data in favour of confirming a diagnosis, outcome misclassification was assessed by cross-validation against the CATSS. However, since outcome misclassification cannot be ruled out, findings from the SYC should be interpreted bearing this potential bias in mind. However, outcome misclassification is likely to affect both exposed and unexposed groups in the same way, and thus lead to underestimations of associations rather than false positive findings.

5.2.3.3 *Confounding*

Confounding may distort the association focused upon in a study. Confounding variables are determinants of both the outcome and exposure, in addition to constituting an important source of bias in epidemiological studies. There are several methods for addressing confounding. In the population-based analyses in studies III and IV, a range of confounders were chosen à priori based on reported associations with ASD (62, 63, 106), and adjusted for in multivariable regression models. However, residual confounding due to factors that are unknown, or unavailable from the data, is still possible. Most important, it is difficult to address confounding caused by genetic factors in register-based studies such as the SYC because the data do not include a diagnosis of ASD or related traits in relatives of the study population.

Two different family study approaches were used in study IV in order to better address confounding by unmeasured familial factors. First, the association between both maternal and paternal BMI and offspring ASD was examined, to test the hypothesis that stronger associations for maternal, than paternal BMI would be indicative of causal intrauterine mechanisms. While exposure data in the SYC is prospectively collected and paternal conscription BMI data are considered of high quality (157), no paternal BMI data were available for the period closer to the birth of the child. However, an advantage of using conscript BMI data is that factors that increase with paternal age and might confound the association between paternal BMI and offspring ASD are unlikely to be introduced into the model. In other words, using paternal BMI data from a period long before the birth may be better for testing the hypothesis that genetic factors underlie the association between parental BMI and offspring ASD. Second, a sibling comparison analysis was used to control for both genetic and environmental characteristics shared by siblings. However, sibling comparison estimates are more severely biased by non-shared confounders such as birth order and parental age, than standard comparisons (158). Although non-shared confounders such as sex, birth year, sibling birth order, and maternal and paternal age at the time of birth were adjusted for in our sibling analysis, there might be residual non-shared confounders among offspring of women whose weight changes substantially between pregnancies.

5.2.4 Power

Because the SYC is a large total population study, relatively rare exposures and outcomes can be examined with sufficient power (i.e., the ability of a study to find a true difference). However, the population size is reduced in the sibling analysis in study IV, which weakens its power.

5.2.5 External validity / generalizability

This thesis comprises population studies based on regional and national registers. It should be noted that the multisource ASD case ascertainment used in the SYC only applies to Stockholm County. Therefore, the prevalence estimates of diagnosed ASD found in the SYC may not pertain to other parts of Sweden, unless similar services are available or targeted

ASD screening is applied. When such screening was carried out at child healthcare centres in the Swedish city of Gothenburg, it resulted in even higher ASD prevalence estimates among toddlers than in the SYC (26). Furthermore, similar proportions of ASD cases in comparable age groups were found in recent studies in several developed countries using combined population screening and diagnostic procedures (20, 33, 135, 159). Interestingly, results from other studies using these procedures were also similar to our results concerning the proportion of ASD cases with comorbid ID (33) and the male: female ratio (20, 25). Taken together, these results demonstrate that the proportion of children with ASD in the SYC is in line with studies from other countries in which thorough, multistage case ascertainment methodology was employed, indicating that studies on ASD from the SYC are likely to have good external validity and that the results can thus be generalized to other developed countries.

The limited availability of parental BMI and GWG data potentially limits the generalizability of the study IV, despite the fact that measures were undertaken to maximize the internal validity of the findings. Furthermore, the sample used in the sibling analysis may produce biased results that limit generalizability, because only certain kinds of families can be included by this design.

6 CONCLUDING REMARKS AND FUTURE DIRECTIONS

Data from Swedish national and regional registers indicate a substantial increase in the prevalence of identified ASD cases without comorbid ID in Stockholm over recent years. At present, more individuals are affected by ASD than was previously believed to be the case, with more than 2% of teenagers registered with ASD. While findings from Stockholm suggest that factors related to improved identification of ASD are likely to have contributed to the observed increase in ASD prevalence, an actual increase in ASD cannot be ruled out, emphasizing the need for further exploration of risk factors that potentially contribute to the increased prevalence.

Is it possible to attribute any of the ASD prevalence increase to current trends of deferred parenthood, maternal obesity or other non-genetic risk factors? While higher parental age does increase the ASD risk by a yet unknown mechanism, its contribution to the increase in ASD prevalence has been estimated as small (94). Due to methodological limitations, we cannot rule out an association between maternal pre-pregnancy overweight and offspring ASD risk. However, results from our study indicate that this association may be confounded by familiar factors, which needs to be examined further using other study designs. While observed changes in pre, peri, and neonatal risk factors for ASD over time may theoretically contribute to increased ASD prevalence, their impact has been estimated as minimal (160). Similarly, in a study conducted in California, broad environmental factors and younger age at diagnosis were less likely to explain age, period and cohort effects than changes in diagnostic practices and increased awareness (161). However, empirically identifying and quantifying factors that contribute to changes in ASD prevalence is challenging as these factors are likely to be multiple and overlapping.

Despite the challenges involved in identifying the causes of increasing ASD prevalence, recent changes in identified prevalence of ASD with ID are not unique to Stockholm and highlight the importance of providing adequate services. It is hypothesized that recent increases in ASD prevalence are a result of a greater tendency to diagnose comorbid conditions with autistic features as ASD (150), possibly because such a diagnosis enables more extensive support at school or in the community. Nevertheless, affected individuals need support adapted to their specific symptom presentation. It is important to bear in mind that ASD are generally life-long conditions, thus population-based, longitudinal studies related to various outcomes of ASD among adults are required for service planning (17).

Results from studies included in this thesis as well as other studies from the SYC suggest that subtyping of ASD by ID is useful, as epidemiological and genetic evidence indicates that different aetiological mechanisms may underlie these subtypes (15, 18). However, additional methods of subtyping should be employed in future studies to better represent the phenotypic variability of ASD. Future studies may have an advantage in the subtyping of ASD, because the DSM 5 allows comorbidity unlike the DSM IV and ICD 10.

Although the advantages of the general Swedish healthcare system and the thorough case ascertainment design used in our study provide ASD prevalence estimates comparable to more detailed studies that also include general population screening procedures, there are indications that ASD is currently under-ascertained among girls, preschool children, adults and individuals of immigrant background. Further studies of potential aetiological implications that contribute to differences in prevalence among girls and individuals of migrant background are also warranted. More importantly, because diagnostic barriers may delay intervention, it is important to examine impact of factors determining timely identification of children with developmental problems.

7 CONCLUSIONS

The prevalence of identified ASD without comorbid ID has increased substantially between 2001 and 2011 in Stockholm County, and ASD currently affects more than 2% of teenagers, with important implications for the planning of health and educational services. Changes in diagnostic practice and awareness are likely to be the main drivers of the rise, but an actual true increase in ASD incidence cannot be ruled out.

As ASD implies a considerable burden for the individual, family and society, it is important to identify potentially modifiable risk factors. Our study on parental age and ASD suggests that both maternal and paternal age increase the risk of offspring ASD, possibly through different mechanisms. Nevertheless, the absolute risk of offspring ASD with higher parental age is modest and probably does not contribute vastly to the observed increase in ASD prevalence. The family study approaches we used to investigate the relationship between maternal overweight and offspring ASD risk suggest that this association may be ascribed to unmeasured familial confounding. In addition, evidence of a too small or large weight gain during pregnancy increasing ASD risk in offspring was found. These findings need to be examined further in further studies.

The prevalence of ASD, its changes over time and the magnitude of parental age effects on risk of offspring ASD varied according to comorbid ID, emphasizing the value of subtyping ASD according to ID. Finally, the SYC, with its extensive data from Swedish registers as well as valid and thorough ASD case ascertainment constitutes an important resource for ASD research.

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