Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort

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Abstract

Background: The objectives of this study were to examine the independent and dependent associations of maternal and paternal age and risk of offspring autism spectrum disorders (ASD), with and without intellectual disability (ID).

Methods: The sample consisted of 417,303 Swedish children born 1984–2003. ASD case status (N=47,46) was ascertained using national and regional registers. Smoothing splines in generalized additive models were used to estimate associations of parental age with ASD.

Results: Whereas advancing parental age increased the risk of child ASD, maternal age effects were non-linear and paternal age effects were linear. Compared with mothers at the median age 29 years, those <29 had similar risk, whereas risk increased after age 30, with an odds ratio (OR) of 1.75 (95% CI: 1.63–1.89) at ages 40–45. For fathers, compared with the median age of 32 years, the OR for ages 55–59 was 1.39 (1.29–1.50).

The risk of ASD was greater for older mothers as compared with older fathers. For example, mothers aged 40–45 (≥97.2th percentile) had an estimated 18.63 (95% CI: 17.25–20.01) ASD cases per 1000 births, whereas fathers aged 55–59 (≥99.7th percentile) had 16.35 (95% CI: 15.11–17.58) ASD cases per 1000 births. In analyses stratified by...
co-parental age, increased risk due to advancing paternal age was evident only with mothers ≤35 years. In contrast, advancing maternal age increased risk regardless of paternal age. Advancing parental age was more strongly associated with ASD with ID, compared with ASD without ID.

Conclusions: We confirm prior findings that advancing parental age increases risk of ASD, particularly for ASD with ID, in a manner dependent on co-parental age. Although recent attention has emphasized the effects of older fathers on ASD risk, an increase of n years in maternal age has greater implications for ASD risk than a similar increase in paternal age.

Key words: Autism spectrum disorders, intellectual disability, risk factors, parental age

Key Messages
- Advancing parental age increased the risk of offspring autism spectrum disorders (ASD). Maternal age effects were non-linear whereas paternal age effects were linear.
- The risk of ASD was greater for older mothers, as compared with older fathers.
- In analyses stratified by co-parental age, increased risk of offspring ASD due to advancing paternal age was evident only in mothers aged ≤35 years. Advancing maternal age increased risk of offspring ASD regardless of paternal age.
- Advancing parental age was more strongly associated with ASD with intellectual disability, compared to ASD without intellectual disability.

Introduction
Parental age has attracted considerable attention as a potential risk factor for autism spectrum disorders (ASD) in offspring, since parental age at childbearing has increased in the Western world during latter decades. To date, over 30 epidemiological studies have examined parental age in relation to ASD, including recent meta-analyses of paternal age, maternal age or both maternal and paternal age. These meta-analyses suggest that both maternal and paternal advanced age are independently associated with increased risk for ASD. However, as it is increasingly apparent that ASD represent a heterogeneous group of disorders with potentially different aetiologies, there is a need of studies of parental age effects on different phenotypes of ASD. To date, few studies have examined whether associations between parental age and ASD differ by intellectual disability (ID), which is the most frequent co-occurring condition in ASD and is associated with poor outcome. Studies published to date have had contradictory results, which may be due to small numbers of ASD cases with the exception of a recent large study from Finland showing an association between maternal, but not paternal age and ASD in cases without ID. Similarly, in the two studies to date exploring the potential interaction between maternal and paternal age, no results are presented by ID, but rather by current ICD classification codes, which have questionable diagnostic reliability.

The majority of previous studies of parental age and ASD have used categorical parameterizations of parental age. Whereas categorical parameterizations allow for easily interpretable results, continuous parameterizations of age allow for flexible, non-linear associations that are frequently less biased and more efficient. We used penalized cubic regression smoothing splines implemented in generalized additive models (GAMs) to model the independent and dependent associations of maternal and paternal age and risk of offspring ASD, subtyped by co-morbid ID, using a large, Swedish total-population-based cohort.

Methods
Study population
The Stockholm Youth Cohort (SYC) is a longitudinal register-based cohort of the total child population aged 0–17 years and resident in Stockholm County, Sweden, between 1 January 2001 and 31 December 2007. The register comprises prospectively compiled data on children and their
first-degree relatives through record linkage with a range of Swedish national and regional health and administrative registers. The primary key to record linkage was the unique personal identification number assigned to each Swedish citizen at birth, or upon arrival in Sweden for immigrants. A full description of the SYC and the national and regional registers used to characterize the SYC is available elsewhere. Ethical approval was obtained from the research ethics committee at Karolinska Institutet.

In the present study we examined the 1984 to 2003 birth cohorts of the SYC, with a total of 442,848 non-adopted children who had resided in Stockholm County for at least 4 years. All children with missing data on either maternal or paternal age were excluded (N = 25,545), resulting in a final analytical sample of 417,303 individuals.

ASD diagnosis and validity

ASD case status as of 31 December 2007, was ascertained using national and regional registers covering all known pathways of ASD diagnosis and care in Stockholm County. Intellectual disability was ascertained as a recorded diagnosis of 317-319 or F70-79 according to the ICD-9 and ICD-10, respectively, and 317-319 according to the DSM-IV diagnostic classification manual. The validation of ASD case ascertainment through review of medical records found that 96.0% of cases with ASD were consistent with an ASD diagnosis.

Covariate description

Biological parents and their dates of birth were identified from the Multi-generation Register. Parity was identified from the Medical Birth Register. Sociodemographic data were extracted from the Integrated Database for Labour Market Research for the year before birth of the child, or as close as possible. Maternal and paternal educational attainment, i.e. completed degree of education, was categorized as primary school (including 9 years of schooling), secondary school (2–3 more years of schooling) or higher education. Occupational class (the higher of the mother or father) was categorized as: unskilled manual worker, skilled manual worker, lower-level non-manual employee, intermediate level non-manual employee, high level non-manual employee, self-employed and unclassified (those without a formal occupation). Family income was calculated after deductions of taxes and is adjusted for family size. To account for inflation, family income was categorized into quintiles according to birth year. From the Social Insurance Agency, we extracted data on whether the mother and father were receiving social subsidies and disability pensions at time of childbirth. History of parental psychiatric care was obtained from the National Patient Register, Stockholm Adult Psychiatric Register, VAL database (including public healthcare services in Stockholm County) and the Clinical Database for Child- and Adolescent Psychiatry in Stockholm, and dichotomized into outcomes of maternal and paternal history of in- or outpatient psychiatric use, respectively. Data on maternal country of birth were obtained from the Register of Total Population, and categorized as mother born in Sweden, mother born in Europe outside Sweden and mother born outside Europe.

Data analysis

We used penalized cubic regression smoothing splines implemented in GAMs to model the associations of parental age with ASD. Models were adjusted for potential confounders a priori identified by literature or in our analyses as predictive of ASD. Model covariates included offspring sex, birth year, co-parental age, parity, maternal and paternal psychiatric history, occupational class, family income and maternal country of birth. To account for clustering in sibships, random effects modelling was used. Random effects for the birth mother were implemented in the GAMs as penalized regression terms, with smoothing parameter estimation by maximum likelihood. Marginal estimates of odds ratios (ORs) and age-specific prevalence rates were estimated from the GAMs using a G-computation approach. These estimates can be interpreted as relevant for a sample assuming the covariate pattern of the sample in the study (e.g. 51.3% male children, 74.9% of mothers from Sweden, see Table 1). For computational efficiency, 95% confidence intervals (CIs) were estimated from posterior simulation of model parameters. To minimize instability in estimates at extreme parental ages (i.e. beyond the 0.1% and 99.9%; fathers <18 years or >59 years of age, mothers <16 years or >45 years of age), GAMs were fit excluding these observations.

To examine possible interaction between maternal and paternal age, parental ages were parameterized with main effects smooths as well as a tensor product smooth interaction of maternal and paternal ages. Statistical significance of the maternal and paternal age interaction was examined using likelihood ratio testing comparing nested models. To further explore the maternal and paternal age interaction, we conducted stratified analyses. In selected strata of maternal and paternal ages, we examined GAMs with a linear or linear-spline basis for the parental age term of interest, the co-parental age smoothed with penalized cubic regression splines, and the aforementioned covariates.

To estimate categorical age effects from the GAMs, we pooled specific age estimates obtained from the GAMs via
the generalized invariance method, using a model with maternal and paternal age main effects smooths, tensor product smooth interaction of maternal and paternal age, and the aforementioned covariates.20

All analyses were conducted using SAS version 9.227 and R 2.15.28 GAMs were implemented using the mgcv package in R.

### Results

#### Sample characteristics

Our final sample included 417,303 individuals of whom 4746 (1.1%) had an ASD. These included 1994 (42.0%) cases with a recorded intellectual disability (ID) and 2752 (58.0%) cases without ID. Compared with non-ASD cases, ASD cases had slightly older mothers and fathers (Table 1). As previously reported,22,23 ASD cases were more likely to be male, firstborn, have less family income, be of manual occupational class and have a parent with a history of psychiatric care utilization, as compared with individuals without ASD.

The mean age at delivery for mothers delivering in 1984 was 28.6 years [standard deviation (SD) 5.3] and increased to 31.2 years (SD 4.9) by 2003 (Figure 1). For fathers, the mean age at delivery increased from 31.6 years (SD 6.2) in 1984 to 34.0 years in 2003 (SD 6.0).

#### Maternal and paternal age effects

The odds of ASD were unaffected by maternal ages younger than 29 years, but thereafter increased in a nonlinear fashion with each advancing year of maternal age (Figure 2). Pooled ORs were 1.07 (95% CI: 1.04–1.11) for

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Table 1. Selected characteristics of the Stockholm Youth Cohort birth cohorts from 1984 to 2003, by ASD category; mean (SD) provided for continuous covariates

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No ASD (N = 412,557)</th>
<th>Any ASD (N = 4746)</th>
<th>ASD without ID (N = 2752)</th>
<th>ASD with ID (N = 1994)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)a</td>
<td>51.1</td>
<td>72.8</td>
<td>72.1</td>
<td>73.8</td>
</tr>
<tr>
<td>Maternal age at delivery, yearsa</td>
<td>29.5 (5.1)</td>
<td>29.7 (5.5)</td>
<td>29.5 (5.5)</td>
<td>30.0 (5.6)</td>
</tr>
<tr>
<td>Paternal age at delivery, yearsa</td>
<td>32.5 (6.3)</td>
<td>32.8 (6.7)</td>
<td>32.3 (6.5)</td>
<td>33.4 (6.8)</td>
</tr>
<tr>
<td>Parity (%)a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>45.8</td>
<td>48.4</td>
<td>51.9</td>
<td>43.5</td>
</tr>
<tr>
<td>2</td>
<td>36.3</td>
<td>34.0</td>
<td>32.0</td>
<td>36.8</td>
</tr>
<tr>
<td>≥3</td>
<td>17.9</td>
<td>17.6</td>
<td>16.1</td>
<td>19.7</td>
</tr>
<tr>
<td>Multiple births (%)</td>
<td>2.7</td>
<td>2.9</td>
<td>2.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Family income (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (lowest)</td>
<td>20.2</td>
<td>20.0</td>
<td>17.1</td>
<td>23.9</td>
</tr>
<tr>
<td>Q2</td>
<td>20.0</td>
<td>23.3</td>
<td>22.9</td>
<td>23.9</td>
</tr>
<tr>
<td>Q3</td>
<td>19.9</td>
<td>21.6</td>
<td>23.5</td>
<td>19.1</td>
</tr>
<tr>
<td>Q4</td>
<td>20.0</td>
<td>18.0</td>
<td>19.0</td>
<td>16.6</td>
</tr>
<tr>
<td>Q5 (highest)</td>
<td>19.9</td>
<td>17.1</td>
<td>17.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Occupational class (%)a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unskilled manual</td>
<td>13.5</td>
<td>17.4</td>
<td>17.6</td>
<td>17.2</td>
</tr>
<tr>
<td>Skilled manual</td>
<td>13.6</td>
<td>15.3</td>
<td>15.6</td>
<td>14.9</td>
</tr>
<tr>
<td>Non-manual low-level</td>
<td>13.8</td>
<td>13.3</td>
<td>14.1</td>
<td>12.0</td>
</tr>
<tr>
<td>Non-manual intermediate</td>
<td>19.1</td>
<td>17.8</td>
<td>19.4</td>
<td>15.5</td>
</tr>
<tr>
<td>Non-manual high-level</td>
<td>17.4</td>
<td>17.2</td>
<td>16.8</td>
<td>17.8</td>
</tr>
<tr>
<td>Self-employed</td>
<td>4.7</td>
<td>3.8</td>
<td>3.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Unclassified</td>
<td>17.9</td>
<td>15.3</td>
<td>13.2</td>
<td>18.3</td>
</tr>
<tr>
<td>Maternal psychiatric history (%)a</td>
<td>30.6</td>
<td>46.3</td>
<td>49.6</td>
<td>41.8</td>
</tr>
<tr>
<td>Paternal psychiatric history (%)a</td>
<td>19.5</td>
<td>27.5</td>
<td>28.0</td>
<td>26.7</td>
</tr>
<tr>
<td>Maternal region of origin (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Born in Sweden</td>
<td>74.9</td>
<td>75.4</td>
<td>81.2</td>
<td>67.3</td>
</tr>
<tr>
<td>Born in Europe outside Sweden</td>
<td>9.3</td>
<td>10.1</td>
<td>9.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Born outside Europe</td>
<td>15.9</td>
<td>14.5</td>
<td>8.8</td>
<td>22.3</td>
</tr>
</tbody>
</table>

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*aIndicates that P-value <0.05 from t test (continuous variables) or chi-square test (categorical variables) comparing no ASD and any ASD groups.

*bParental psychiatric history is defined as maternal and paternal history of in- or outpatient psychiatric care utilization according to healthcare registers, respectively.
mothers aged 30–34 and 1.32 (95% CI: 1.27–1.38) for ages 35–39, increasing to 1.75 (95% CI: 1.63–1.89) for ages 40–45 compared with the 29-year-old reference group (Table 2). Maternal ages beyond 30 years were associated with a greater risk of ASD with ID, compared with without ID, such that the pooled OR was 2.04 (95% CI: 1.82–2.30) for mothers aged 40–45 and 1.54 (95% CI: 1.41–1.68) for these subtypes, respectively.

In contrast, advancing paternal age was associated with an increasing risk of ASD in an approximately linear fashion, such that the youngest fathers had the lowest risk (Figure 2). Compared with 32-year-old fathers, 18–19- and 25–28-year-old fathers had a 0.84 (95% CI: 0.78–0.90) and 0.93 (95% CI: 0.90–0.96) odds of a child with ASD, whereas 40–44- and 55–59-year-old fathers had a 1.14 (95% CI: 1.10–1.18) and 1.39 (95% CI: 1.29–1.50) odds of a child with ASD. Advancing paternal age was associated with a greater risk of ASD with, than without, ID, such that the oldest fathers aged 55–59 had 1.52 (95% CI: 1.36–1.70) and 1.19 (95% CI: 1.08–1.31) odds of a child with these subcategories, respectively.

The absolute risk at a given maternal age was greater than the absolute risk at that same paternal age; for example, mothers aged 35–39 were estimated to have 14.06 (95% CI: 13.54–14.59) ASD cases per 1000 births (Table 2), whereas similarly aged fathers were estimated to have 12.36 (95% CI: 12.11–12.62) ASD cases per 1000 births. This increased risk for maternal age was more evident among the oldest parents. Mothers aged 40–45 (≥97.2th percentile) were estimated to have 18.63 (95% CI: 17.25–20.01) ASD cases per 1000 births, which was higher than the absolute risk for fathers aged 55–59 (≥99.7th percentile) estimated at 16.35 (95% CI: 15.11–17.58) ASD cases per 1000 births.

### Interaction of maternal age and paternal age

In GAMs of ASD and ASD with ID, inclusion of a maternal and paternal age interaction significantly improved model fit over models without the interaction (P-values = 0.014 and 0.003, respectively), but not for ASD without ID (P-value: 0.275). To explore the nature of the interaction, we conducted stratified analyses at parental ages typically recognized as older (mothers: ≤35 vs >35 years; fathers: ≤40 vs >40 years). In mothers ≤35 years, 1-year and 5-year increases in paternal age linearly increased the odds of a child with ASD by 1.02 (95% CI: 1.01–1.02) and 1.08 (95% CI: 1.05–1.12) times, respectively (Figure 3a). In contrast, in mothers >35, paternal age did not appear to influence the odds of ASD (Figure 3b). In fathers ≤40 years, a 1-year increase in maternal age prior to 30 years had no impact on ASD risk (OR: 1.00; 95% CI: 0.99–1.01). However, maternal age above 30 years increased the odds of ASD among fathers ≤40 years, such
that 1-year and 5-year increases in maternal age affected the odds of a child with ASD by 1.04 (95% CI: 1.02–1.07) and 1.23 (95% CI: 1.11–1.37) times, respectively (Figure 3c). In fathers >40 years, 1-year and 5-year increases in maternal age increased the odds of a child with ASD by 1.02 (95% CI: 1.00–1.04) and 1.12 (95% CI: 1.02–1.23), respectively (Figure 3d).

**Discussion**

In this large population-based study, we demonstrated that whereas advancing maternal and paternal ages are associated with increased risk of ASD, the nature of the associations was different. Whereas the maternal age effect was non-linear with the sharpest increase in risk after age 30, the paternal age effect was linear. Comparatively speaking, the risk of offspring ASD was greater for a given maternal age than for the same paternal age. Furthermore, advancing maternal age increased the risk of ASD regardless of paternal age, whereas advancing paternal age linearly increased risk of offspring ASD only in mothers younger than 35 years. Finally, we found that advancing maternal and paternal age imposed greater risk of ASD with, than without, ID.

To our knowledge, this is the first population-based study with a large sample of ASD cases, based on an exhaustive case ascertainment methodology relying on valid register-based diagnoses, which provides sufficient power to study ASD according to ID. Although we confirmed a lower proportion of cases ASD with ID, than without ID, in our validation study, it is plausible that many children with severe autistic symptoms have not been eligible for structured intelligence tests, which were required as part of ASD subtype confirmation.

A number of mechanisms underlying the association between parental age and offspring ASD have been proposed; however, mechanisms underlying maternal and paternal age effects are likely different, although the differences are difficult to disentangle due to high correlation between maternal and paternal age. The mechanisms most frequently proposed to underlie paternal age effects are increased rates of de novo mutations and epigenetic alternations with increasing age. In addition to the increased rates of genomic alternations with increasing maternal age proposed to underlie maternal age effects,
increasing maternal age is associated with increased exposure to environmental factors such as cumulative exposure to air pollution or medications, reported to increase risk of ASD. Furthermore, perinatal and obstetric complications that present at a much higher rate in older mothers have been shown to increase risk of ASD. With increasing age, mothers may be increasingly subjected to other factors associated with ASD, such as autoimmunity, metabolic conditions or nutritional deficiencies. Finally, it has been suggested that parental age effects on risk of neurodevelopmental disorders are the result of unmeasured confounding by mental disorders or personality traits related to these which defer parenthood among fathers or psychosocial environmental characteristics related to having older parents.

Our findings of a linear paternal age effect support the hypothesis of increased genomic alternations with increasing paternal age; in fact the linear effect bears striking resemblance to the linear increase in de novo mutations with increasing paternal age observed in a recent Icelandic study. In contrast, the non-linear maternal age effects found in our study support the inference that multiple mechanisms may be at play. Whereas increased rates of genomic alternations may play a role, the sharp increase in ASD risk after age 30 is consistent with well-established knowledge of riskier pregnancies and perinatal outcomes in mothers aged above 35. Interestingly, although both maternal and paternal age increase the rate of de novo mutations in offspring, the same increase in maternal vs paternal age resulted in 60% larger number of mutations in a recent study. In line with our results, two recent studies examining effects of interactions of maternal and paternal age on ASD risk, found increasing paternal age to increase ASD risk primarily in mothers younger than 30, and only in mothers younger than 35 years, respectively. We speculate that this finding may be related to a lower risk of pregnancy complications and other non-heritable risk factors in mothers younger than 35, in whom the paternal age effect is consequently most evident. When risk of perinatal and obstetric complications increases among mothers older

Figure 3. Generalized additive model estimates of probability of ASD by maternal and paternal age (years) in the Stockholm Youth Cohort, stratified by co-parental age category. The 95% CIs are indicated by dashed lines.
than 35, such risk may overwhelm the risk conferred by advancing paternal age. Thus, our results suggest that among parents older than 35 years, an age typically recognized by the medical community as associated with riskier pregnancy outcomes, an increase of n years in maternal age has greater implications for ASD risk than a similar increase in paternal age.

Although evidence is inconsistent, advanced maternal age has been associated with decreased offspring intelligence, which may contribute to the stronger association with ASD with ID observed in our study. Similarly, advanced paternal age has been associated with decreased offspring intelligence in some studies but not all studies. Direct comparison of our results with previous studies is obstructed by the variable proportion of ASD cases with ID included in previous studies. However, our findings contrast recent meta-analytical reports on the lack of variation of maternal age effects on the risk of ASD by the proportion of cases diagnosed with autistic disorder, which is associated with some degree of intellectual disability in a majority (70%) of cases. Similarly, the association between paternal age and autism was unaltered by removal of studies including high rates of ASD in a meta-analysis of paternal age. In more agreement with our results, maternal age had a slightly stronger association with ASD and risk of autism spectrum disorders in a Finnish national birth cohort. 6

In conclusion, while our results support the conclusion that advancing parental age increases risk of ASD, maternal age appears to be a more important risk factor for ASD than paternal age, contrasting recent emphasis on paternal or even grandpaternal age and indicating that further research on identifying the mechanisms contributing to the effects of maternal and paternal age is needed.

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Conflict of interest: None declared.

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