

# Advancing Paternal Age and Autism

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**Context:** Maternal and paternal ages are associated with neurodevelopmental disorders.

**Objective:** To examine the relationship between advancing paternal age at birth of offspring and their risk of autism spectrum disorder (ASD).

**Design:** Historical population-based cohort study.

**Setting:** Identification of ASD cases from the Israeli draft board medical registry.

**Participants:** We conducted a study of Jewish persons born in Israel during 6 consecutive years. Virtually all men and about three quarters of women in this cohort underwent draft board assessment at age 17 years. Paternal age at birth was obtained for most of the cohort; maternal age was obtained for a smaller subset. We used the smaller subset (n=132 271) with data on both paternal and maternal age for the primary analysis and the larger subset (n=318 506) with data on paternal but not maternal age for sensitivity analyses.

**Main Outcome Measures:** Information on persons

coded as having *International Classification of Diseases, 10th Revision* ASD was obtained from the registry. The registry identified 110 cases of ASD (incidence, 8.3 cases per 10 000 persons), mainly autism, in the smaller subset with complete parental age data.

**Results:** There was a significant monotonic association between advancing paternal age and risk of ASD. Offspring of men 40 years or older were 5.75 times (95% confidence interval, 2.65-12.46;  $P < .001$ ) more likely to have ASD compared with offspring of men younger than 30 years, after controlling for year of birth, socioeconomic status, and maternal age. Advancing maternal age showed no association with ASD after adjusting for paternal age. Sensitivity analyses indicated that these findings were not the result of bias due to missing data on maternal age.

**Conclusions:** Advanced paternal age was associated with increased risk of ASD. Possible biological mechanisms include de novo mutations associated with advancing age or alterations in genetic imprinting.

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**T**HIS STUDY INVESTIGATED whether advancing paternal age at birth of offspring is associated with an increased risk of autism spectrum disorder (ASD) in offspring. Autism is a chronic disorder with an onset by age 3 years, characterized by the following 3 main sets of behavioral disturbances: social abnormalities, language abnormalities, and stereotyped, repetitive patterns of behavior.<sup>1-4</sup> In the *International Classification of Diseases, 10th Revision (ICD-10)*, ASD also includes atypical autism, Asperger syndrome, Rett syndrome, overreactive disorder, childhood disintegrative disorder, and pervasive developmental disorders, which are believed to be etiologically related to autism. Prevalence estimates of ASD increased dramatically during the past 2 decades,<sup>5,6</sup> from approximately 5 cases to 50 cases per 10 000 children.<sup>5,6</sup> The increase

is partly artifactual, owing to improved diagnostic accuracy, changes in diagnostic criteria, earlier detection, and increased awareness of types of ASD other than autism.<sup>7</sup> However, it may also partly reflect a true increase in the incidence of ASD.<sup>8</sup>

Maternal and paternal ages have been associated with other neurodevelopmental disorders and have been considered in some previous studies of ASD. Advancing maternal age increases the risk of chromosomal abnormalities such as Down syndrome<sup>9</sup> and has been associated with the risk of brain damage during pregnancy,<sup>10</sup> dyslexia,<sup>11</sup> and mental retardation of unknown cause.<sup>12</sup> Studies<sup>13-20</sup> on the association between advancing maternal age and risk of ASD have reported mixed results. Among 5 recent epidemiological studies, 3 studies<sup>13,17,18</sup> did not find advancing maternal age to be a risk factor for ASD, while the other 2 studies<sup>19,20</sup> did (among the lat-

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ter 2 studies, only the study by Glasson et al<sup>19</sup> adjusted for paternal age).

Older age of the father at birth of offspring has been associated with several congenital disorders, including Apert syndrome,<sup>21</sup> craniosynostosis,<sup>22</sup> situs inversus,<sup>23</sup> syndactyly,<sup>24</sup> cleft lip or cleft palate,<sup>25,26</sup> and hydrocephalus.<sup>26</sup> Advancing paternal age has also been associated with an increased risk of schizophrenia<sup>27,28</sup> and with decreased intellectual capacity<sup>29,30</sup> in offspring. In some instances (eg, Apert syndrome), the association is explained by the increased risk of de novo genetic mutations in the germline of older fathers.<sup>31</sup> Therefore, one of the reasons for examining the relationship between paternal age and ASD is that it may provide clues to the biological pathways leading to ASD.

Suggestions of an association between paternal age and ASD can be traced back to the 1970s,<sup>32,33</sup> and studies<sup>15,18,19,34,35</sup> of ASD have reported paternal age frequencies among numerous other variables. However, few studies have systematically examined this association in rigorous designs that included adjustment for maternal age. The results of 3 recent case-control studies were mixed: 2 studies<sup>15,18</sup> found advancing paternal age to be a risk factor for ASD, while the other study<sup>19</sup> did not.

The present investigation was a historical population-based cohort study specifically designed for a rigorous test of the hypothesis that advancing paternal age is associated with increased risk of ASD in offspring. The cohort members were born in Israel during 6 consecutive years and were assessed by the Israeli draft board at age 17 years. To our knowledge, this is the first epidemiological study using an entire cohort and focusing on the paternal age hypothesis. Our analyses included adjustment for maternal age and other potential confounders.

## METHODS

This study is based on a cohort of Jewish persons born in Israel during 6 consecutive years in the 1980s. A total of 378 891 individuals in this 6-year birth cohort were assessed by the Israeli draft board at age 17 years. Linkage to the Israeli Bureau of Statistics indicated that 98% of the boys and 75% of the girls in the cohort who had survived the first year of life were included in the draft board registry. The proportion is lower among women because orthodox Jewish women (about 25% of women) are exempted from military induction. The draft board determines intellectual, medical, and psychiatric eligibility for compulsory military service. The draft board registry data were used in this study to obtain data on parental age at birth and to obtain the diagnostic outcomes among the cohort at age 17 years, as described herein.

After receiving local human subjects committee approval, a data file of the full cohort was created by the managers of the draft board registry database. The data file was stripped of identifiers; only deidentified data were used by the investigators.

### PARENTAL AGE AT BIRTH

Israeli citizens are given a unique identification number at birth or at award of Israeli citizenship. The draft board data for an inductee often include the identification numbers of the inductee's parents. In these instances, the identification numbers of the parents were linked to the parents' draft board assessments at age

17 years and, when applicable, to the parents' military service files. With the inductee's date of birth and the maternal and paternal dates of birth, it is possible to compute the paternal and maternal age at the time of birth of the inductee.

Of 378 891 cohort members assessed by the draft board, 318 506 (84.1%) had data on paternal age at birth (hereafter, the larger cohort). There were 2 reasons for missing data on paternal age. First, individuals emigrating to Israel after age 35 years are not required to report to the draft board. Second, the draft board initiated computerized databases only in the 1960s. In light of these reasons, we suspect that paternal age data were more likely to be missing for cohort members with older fathers than for those with younger fathers.

Data on maternal age at birth were obtained for 132 271 (41.5%) of the cohort members with paternal age data (hereafter, the smaller cohort). There were 2 main reasons why it was much more difficult to obtain data on maternal age than on paternal age at birth. First, when draft board data on parents were unavailable, the parental data could be obtained from the files kept on individuals in active military service (through the reserve forces), but this pertained mainly to men because most women were not in active service. Second, as noted earlier, orthodox Jewish women (about 25% of women) are exempt from military service and are unassessed by the draft board.

### ASD OUTCOMES

The draft board assigns *ICD-10* diagnoses. Psychiatric diagnoses are assigned by a board-certified psychiatrist experienced in treating adolescents. The standard procedure for psychiatric diagnosis includes a face-to-face assessment as described in detail elsewhere.<sup>36</sup> For individuals with developmental disabilities (including ASD), the standard procedure is modified. At age 17 years, their medical status is reported in detail to the draft board by government agencies and other organizations responsible for their care and protection. Such reports include the current diagnosis according to contemporary criteria. The original childhood diagnosis and subsequent clinical history up to age 17 years are also commonly reported. The draft board generally assigns a diagnosis based on review of these materials rather than a face-to-face assessment.

For individuals with ASD, the responsible agency is the not-for-profit Israeli Society for Autistic Children (ISAC). The ISAC was established in 1974, and its services receive wide publicity and media coverage, emphasizing their nonselective availability. Eligibility for specialized health services or for any other form of federal support, including tax credits, depends on reporting to the ISAC. Consequently, virtually all children and adolescents diagnosed as having ASD are registered with the ISAC. Individuals are generally referred to the ISAC by specialists at a child development center. Israel has universal health insurance coverage that guarantees equal access to health services, regardless of employment status or socioeconomic status. All infants and preschool children are regularly seen at well-child care clinics and undergo routine medical and developmental screening. Those with suspected developmental disabilities are referred for assessment at a child development center where children with suspected ASD are evaluated by board-certified clinicians specializing in childhood developmental disorders. Diagnosis is typically made by a team that includes a psychiatrist, clinical psychologist, and speech pathologist or occupational therapist, depending on clinical manifestations. The instruments include parental interviews, direct testing of the child, and observations in naturalistic settings, including the home or educational location. At the time of initial diagnosis of cases in the present cohort, the standard instrument for diagnosis in use in Israel was the Childhood Autism Rating Scale.<sup>37</sup> Individuals who are diagnosed as having ASD are then registered with the ISAC for on-

going care and evaluation. At age 17 years their medical status is reported to the draft board.

The draft board registry does not differentiate the specific *ICD-10* diagnoses within ASD, which include autism, atypical autism, Asperger syndrome, Rett syndrome, overreactive disorder, childhood disintegrative disorder, and pervasive developmental disorders. For 2 reasons, however, it is safe to assume that most individuals with ASD diagnoses met *ICD-10* criteria for a diagnosis of autism per se. First, these individuals were originally diagnosed and followed up during the 1980s and early 1990s, when the diagnosis of autism was narrow and uncommon, and diagnoses of ASD such as Asperger syndrome were rare (Asperger syndrome was assigned a unique *ICD-10* diagnostic classification code only in 1992). The ISAC records of individuals registered during the childhood years of the cohort almost exclusively indicate a diagnosis of autism. Second, although we were unable to reassess subjects in our cohort because cohort members in this study are anonymous, we have been ascertaining subjects with autism from the ISAC registry as part of another study. The Autism Diagnostic Interview–Revised is administered to these subjects. Twenty-two such subjects were born during the years of the present study cohort, and diagnostic criteria for autism according to the Autism Diagnostic Interview–Revised algorithm were upheld for all 22 subjects.

### PATTERN OF MISSING DATA

Paternal age was more likely to be missing for ASD than non-ASD cohort members (35% vs 16%;  $\chi^2=84.75$ ,  $P<.001$ ). This would be expected if (as suggested earlier) individuals with older fathers were more likely to be missing data on paternal age and if (as suggested by our results) individuals with older fathers were also more likely to have ASD. If, for some reason, the combination of having both ASD and an older father was associated with having missing data on paternal age, this would bias results toward the null of no association between paternal age and ASD. Maternal age was similarly missing for ASD and non-ASD cohort members (39% vs 38%;  $\chi^2=0.02$ ,  $P=.89$ ). Linkage to the Israeli Bureau of Statistics indicated that the distribution of maternal age in our cohort was similar to the distribution of maternal age in the entire cohort born during the relevant years, with minimal underrepresentation of older mothers.

### DATA ANALYSIS

The primary data analysis was conducted in the smaller subset ( $n=132\,271$ ). Logistic regression analysis was used to examine the associations between parental age and risk of ASD. When adjusting paternal age for maternal age, or vice versa, paternal age and maternal age were consistently defined (ie, both were treated as continuous or categorical variables in the regression models). Odds ratios (ORs) and 95% confidence intervals (CIs) were computed.  $P$  values were calculated using Wald  $\chi^2$ , and the significance level was set at  $P<.05$  (2-sided). All analyses were conducted using SAS statistical software (SAS Institute, Cary, NC) at the Department of Mental Health of the Medical Corps, Israel Defense Forces.

### MODELING OF PATERNAL AGE

We first examined paternal age using a categorical measure to allow for a nonlinear effect of paternal age on the risk of ASD. Paternal age was divided into the following 4 age categories: 15 to 29 years (referent category), 30 to 39 years, 40 to 49 years, and 50 years or older. For the unadjusted result, we fitted paternal age as the only predictor of ASD. For the adjusted result, we also included in the model the following 3 variables

found to be associated with both paternal age and risk of ASD (ie, potential confounders): year of birth,<sup>5</sup> socioeconomic status,<sup>38</sup> and maternal age.<sup>13,19,20</sup> Socioeconomic status was based on paternal years of educational achievement which was available from the draft board. Because of statistical power considerations, the oldest paternal age categories (40–49 and  $\geq 50$  years) were combined in the adjusted analysis. We used the Cochran–Armitage trend test to examine linear trend in the relationship between paternal age and risk of ASD. We then examined paternal age as a continuous variable. For ease of interpretation, results for age as a continuous variable are presented in terms of a 10-year increase in paternal age.

### MODELING OF MATERNAL AGE

The same procedures were repeated to assess the association between maternal age and ASD. Therefore, maternal age was modeled first as a categorical variable. We divided maternal age into the following 3 age groups consistent with the paternal age categories: 15 to 29 years, 30 to 39 years, and 40 years or older. Maternal age was then analyzed as a continuous variable.

### OFFSPRING SEX

We then examined results for male and female offspring separately. This was done in part because different etiologies may pertain to male and female subjects with ASD. It was also done as a safeguard against bias due to loss to follow-up. As noted earlier, almost all men but only about three quarters of women in the birth cohort were ascertained by the draft board at age 17 years. An analysis restricted to male offspring would be unaffected by bias due to loss to follow-up.

### SENSITIVITY ANALYSES

For 2 sensitivity analyses, we used the larger subset ( $n=318\,506$ ). These analyses were designed to gauge potential bias in the primary analysis due to the exclusion of individuals missing data on maternal age.<sup>39</sup> First, in a categorical data analysis, we imputed missing maternal age with values obtained by means of linear interpolation based on paternal age. We regressed maternal age on paternal age in the cohort with complete parental age data; predicted maternal age values were based on this linear regression model. Second, as a further safeguard, we simulated an extreme scenario of confounding by maternal age, although the pattern of missing data on maternal age does not suggest differential loss for ASD cases. All non-ASD cohort members with missing data on maternal age were randomly assigned to maternal age categories in rates that ensured that the distribution of maternal age in the subset with paternal age data was equivalent to the census bureau distribution of maternal age at birth in the cohort years. The ASD cohort members with missing data on maternal age were then assigned to maternal age categories based on the (unlikely) premise that maternal age was much more likely to be missing for the oldest maternal age group ( $\geq 40$  years). For this analysis, we assumed a 10-fold higher rate of ASD in this group than that observed in the cohort used for the primary analysis. The remaining subjects with ASD with missing data on maternal age were assigned in equal proportions to the other 2 maternal age categories.

## RESULTS

The risk of ASD was 8.4 cases per 10 000 persons (319 cases) among all individuals in the cohort who were assessed by the draft board, 8.3 cases per 10 000 persons (110 cases)

**Table 1. Associations Between Paternal Age and Risk of Autism Spectrum Disorder (ASD) in the Smaller Subset With Data on Both Paternal and Maternal Age**

Paternal Age Group, y	Non-ASD Cohort (n = 132 161)	ASD Cases (n = 110)	Risk	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)*	P Value
15-29†	60 654	34	6:10 000	1.00	...	1.00	...
30-39	67 211	62	9:10 000	1.64 (1.08-2.50)	.02	1.62 (0.99-2.65)	.06
40-49	4106	13	32:10 000	5.65 (2.98-10.71)	<.001	5.75 (2.65-12.46)‡	<.001
≥50	190	1	52:10 000	9.39 (1.28-68.94)	.03	...	...

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Adjusted for year of birth, socioeconomic status, and maternal age.

†Reference group.

‡Includes oldest age group.

**Table 2. Offspring Sex-Specific Associations Between Paternal Age and Risk of Autism Spectrum Disorder (ASD) in the Smaller Subset With Data on Both Paternal and Maternal Age**

Paternal Age Group, y	Non-ASD Cohort (n = 132 161)	ASD Cases (n = 110)	Risk	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)*	P Value
<b>Male Offspring</b>							
15-29†	32 101	31	10:10 000	1.00	...	1.00	...
30-39	35 072	52	15:10 000	1.54 (0.98-2.39)	.06	1.62 (0.95-2.78)	.08
40-49	2139	9	42:10 000	4.36 (2.07-9.16)	<.001	5.35 (2.26-12.67)‡	<.001
≥50	92	1	107:10 000	11.25 (1.52-83.32)	.02	...	...
<b>Female Offspring</b>							
15-29†	28 553	3	1:10 000	1.00	...	1.00	...
30-39	32 139	10	3:10 000	2.96 (0.82-10.76)	.10	3.28 (0.83-13.05)	.54
40-49	1967	4	20:10 000	18.43 (4.12-82.42)	<.001	17.25 (2.64-112.58)‡	.003
≥50	98	0	...	...	...	...	...

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Adjusted for year of birth, socioeconomic status, and maternal age.

†Reference group.

‡Includes oldest age group.

in the smaller subset used for the primary analysis, and 6.5 cases per 10 000 persons (208 cases) in the smaller subset used for the sensitivity analysis. The risk is somewhat lower in the latter subset because paternal age data were more likely to be missing for ASD than non-ASD cohort members (see the “Methods” section).

#### PATERNAL AGE AS A CATEGORICAL VARIABLE

We first examined the effect of paternal age on ASD risk using the aforementioned 10-year age categories. The unadjusted ORs for each of these categories, relative to the group aged 15 to 29 years, are given in **Table 1**. There was a significant increase in the risk of ASD with advancing categories of paternal age. This association persisted after adjustment for year of birth, socioeconomic status, and maternal age.

Inspection of these data suggested that the relationship between paternal age and risk of ASD is monotonic. In particular, there was no indication of increased risk of ASD in offspring of the youngest fathers, as fathers 20 years or younger had no offspring with ASD. This monotonic relationship was also supported by the result of the test for linear trend in the logistic model ( $z=4.22$ ,  $P<.001$  for linearity).

There seems to be an especially strong effect in the oldest paternal age group. Therefore, it is possible that the relationship is monotonic but nonlinear. However, we did not conduct a formal analysis of a nonlinear monotonic association because the numbers are too small to allow for a reliable statistical test.

The association between paternal age and ASD risk is evident in male and female offspring (**Table 2**). However, the male-female sex ratio in the offspring with ASD of fathers younger than 40 years (5.6:1.0) was noticeably higher than the sex ratio in the offspring with ASD of fathers 40 years or older (2.3:1.0). These numbers are too small for a sound statistical analysis but are intriguing nevertheless as they suggest the possibility of a distinct etiology for ASD that is more prominent among offspring of older fathers and that pertains equally to both sexes.

#### PATERNAL AGE AS A CONTINUOUS VARIABLE

Having demonstrated a positive monotonic association between ASD and increasing paternal age on a categorical scale, we then examined the effect of paternal age on ASD modeled as a continuous variable. We found an association between advancing paternal age and ASD (unadjusted OR, 1.07; 95% CI, 1.04-1.11;  $\chi^2=15.71$ ,  $P<.001$ ).

**Table 3. Associations Between Maternal Age and Risk of Autism Spectrum Disorder (ASD) in the Smaller Subset With Data on Both Paternal and Maternal Age**

Maternal Age Group, y	Non-ASD Cohort (n = 132 161)	ASD Cases (n = 110)	Risk	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)*	P Value
15-29†	90 457	64	7:10 000	1.00	...	1.00	...
30-39	41 120	42	10:10 000	1.44 (0.98-2.13)	.06	0.87 (0.54-1.41)	.57
≥40	584	4	68:10 000	9.68 (3.51-26.67)	<.001	2.68 (0.81-8.96)	.11

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Adjusted for year of birth, socioeconomic status, and maternal age.

†Reference group.

**Table 4. Associations Between Paternal Age and Risk of Autism Spectrum Disorder (ASD) in the Larger Subset With Data on Paternal but Not Complete Maternal Age Based on the Sensitivity Analyses\***

Maternal Age Group, y	Adjusted Model Linear Interpolation OR (95% CI)†	P Value	Adjusted Model Extreme Scenario OR (95% CI)‡	P Value
15-29§	1.00	...	1.00	...
30-39	1.27 (0.87-1.88)	.21	1.05 (0.76-1.45)	.77
≥40	2.76 (1.51-5.06)	.001	1.89 (1.22-2.93)	.004

Abbreviations: CI, confidence interval; OR, odds ratio.

\*Larger subset comprised 318 506 subjects that included 208 ASD cases.

†Missing maternal age was estimated using linear regression analysis based on corresponding paternal age. The model was adjusted for year of birth, socioeconomic status, and maternal age.

‡Non-ASD cohort members with missing data on maternal age were placed based on the census bureau population distribution; ASD cases with missing data on maternal age were placed assuming a 10-fold higher rate of ASD in the oldest maternal age group than that observed in the cohort used for the primary analysis. The model was adjusted for year of birth, socioeconomic status, and maternal age.

§Reference group.

The change in the OR associated with each 10-year increase in paternal age in this model was 2.11 (95% CI, 1.55-2.89;  $\chi^2=22.11$ ,  $P<.001$ ). In the analysis that adjusted for year of birth, socioeconomic status, and maternal age, the adjusted OR associated with each 10-year increase in paternal age was 2.14 (95% CI, 1.44-3.16;  $\chi^2=14.34$ ,  $P=.001$ ), indicating more than twice the risk of ASD in children of men who were 10 years older, holding year of birth, socioeconomic status, and maternal age constant.

#### MATERNAL AGE

When analyzed as a categorical variable, maternal age was associated with ASD in the unadjusted model but not after adjustment for paternal age (**Table 3**). Similarly, when analyzed as a continuous variable, maternal age was associated with ASD in the unadjusted model (unadjusted OR, 1.09; 95% CI, 1.05-1.14;  $\chi^2=17.96$ ,  $P<.001$ ) but not after adjustment for paternal age (adjusted OR, 1.01; 95% CI, 0.65-1.56;  $\chi^2=0.001$ ,  $P=.98$ ). Although we found no evidence of a maternal age effect in the adjusted models, because of the sample size we cannot completely rule out a possible small effect in the oldest mothers ( $\geq 40$  years).

#### SENSITIVITY ANALYSES

Using the larger subset, we conducted the 2 sensitivity analyses described in the "Methods" section. First, we repeated the categorical data analysis using an imputa-

tion approach, which was based on the high correlation between paternal and maternal age. The OR was reduced but not close to unity, and a monotonic relationship was still apparent (**Table 4**). Second, we repeated this analysis using an extreme scenario of bias due to confounding. The OR was again reduced but not close to unity. These results indicate that the association between paternal age and ASD observed in the primary data analysis is unexplained by the exclusion from that analysis of individuals with missing data on maternal age.

#### COMMENT

In a historical population-based cohort study, we demonstrated a relationship between increasing paternal age at birth of offspring and risk of ASD in offspring. The effect persisted after adjustment for year of birth, socioeconomic status, and maternal age. These results are similar to findings from 2 recent case-control studies.<sup>15,18</sup> In our cohort, most individuals diagnosed as having ASD had autism; the finding is not necessarily generalizable to other ASD diagnoses such as Asperger syndrome.

One possible mechanism for the paternal age effect is mutagenesis, originally put forward as the "copy error" hypothesis by Penrose.<sup>40</sup> According to this hypothesis, de novo spontaneous mutations could arise, propagate, and accumulate in successive generations of sperm-producing cells (spermatogonia). These could be point mutations or structural chromosomal abnormalities<sup>41-43</sup>

that might account for the association between paternal age and autism.

An alternative mechanism that might mediate the paternal age effect is imprinting.<sup>44</sup> Imprinting is a form of gene regulation in which gene expression depends on whether the allele was inherited from the male or female parent in the prior generation. When imprinted genes are paternally expressed, the maternal genes are reciprocally silenced, and the contrary is true for maternally expressed genes. Therefore, only one parental allele is expressed, and the other one is silenced. One of the mechanisms for gene silencing is DNA methylation. The inherited methylation pattern is maintained in somatic cells but is erased and re-established late in spermatogenesis for paternally imprinted genes, a process that could become impaired as age advances. Although our understanding of genetic imprinting is nascent, it merits consideration in autism. Imprinted genes play a key role in brain development,<sup>45,46</sup> investigations of Turner syndrome suggest a role for imprinted genes in language development and social functioning,<sup>47</sup> and parent-of-origin effects have been reported in Angelman syndrome<sup>48</sup> and in at least some autism studies.<sup>49,50</sup>

These hypothesized mechanisms for paternal age effects on risk of ASD are genetic. It is important to keep in mind, however, that age at paternity is influenced by the sociocultural environment and varies across societies and over time. In a given population, a change in the sociocultural environment could produce a change in paternal age at birth. In theory, it could thereby lead to a change in the incidence of genetic causes of autism.

Our study had limitations. First, the modest number of subjects with ASD in the smaller subset limited the statistical power. The association between advancing paternal age and ASD was strong, however, so the sample was sufficient to yield reasonably narrow CIs and statistically significant results. In addition, we extended the sensitivity analyses to the larger subset, and the result for paternal age was sustained.

Second, there is some potential for bias due to loss to follow-up, because not all individuals in this 6-year birth cohort were assessed by the draft board at age 17 years. However, almost all men in this birth cohort were in the draft board registry. The association between paternal age and offspring ASD was evident in an analysis restricted to male offspring, and it is unlikely that bias due to loss to follow-up could explain this association among men. Furthermore, most subjects with ASD are male.

Third, we could not examine whether paternal age was related to the specific diagnoses within ASD or to the specific dimensions of ASD psychopathologic features. The draft board registry does not distinguish between subjects with autism and subjects with other types of ASD. It also provides no information about clinical features such as severity of mental retardation and language level. Based on ancillary evidence, we believe that most of our subjects with ASD had autism rather than other ASD diagnoses. Therefore, the finding may not be generalizable to spectrum disorders such as Asperger syndrome, and the relationship of paternal age to these disorders should be specifically examined in more contemporary cohorts.

Fourth, the diagnoses of subjects with ASD are assigned by the draft board at age 17 years. These diagnoses,

however, are in some ways superior to diagnoses based on a clinical assessment at a single point in childhood. They are based on the full clinical history from the time of first assessment up to age 17 years. Individuals with ASD received a comprehensive diagnostic evaluation at a child development center and were then eligible to receive services and treatments from well-trained clinicians and were often followed up for long periods. Therefore, by the time information is sent to the draft board (at age 17 years), it is likely that most of these subjects with ASD have been well diagnosed. Furthermore, as noted earlier, our ascertainment from the ISAC registry of subjects with autism born during the years of the present study has yielded excellent diagnostic consistency against the Autism Diagnostic Interview-Revised algorithm.

Fifth, we had no information about autistic traits in parents of cohort members. Consequently, we cannot rule out the possibility that parental constitutional factors, such as traits related to the autism phenotype, explain the observed association between paternal age and ASD. Such traits, especially social deficits, have been described in parents of autistic children<sup>51</sup> and could result in an older age of fatherhood as a result of a reduced ability for social integration.<sup>52</sup> However, the plausibility of such an argument in accounting for advancing paternal age effect in developmental disorders has been disputed.<sup>53</sup>

Sixth, information about birth order was also unavailable in our data, but birth order is closely associated with maternal age. Furthermore, although some studies<sup>17,19</sup> found an association between birth order and autism, another study<sup>54</sup> did not. Therefore, we find it unlikely that also adjusting for birth order would notably reduce the association between paternal age and risk of autism.

Seventh, data on prenatal and childhood environmental exposures were unavailable. Although evidence for a role of such exposures in autism is scarce and inconclusive,<sup>15,19,55,56</sup> it would be interesting to explore whether these exposures may interact with paternal age.

Eighth, advancing paternal age is associated with several congenital and psychiatric disorders. The lack of complete specificity does not, however, diminish the importance of our findings. Advancing paternal age may well be associated with various genetic mutations, each associated with a different disorder.

## CONCLUSIONS

These data suggest a significant association between advancing paternal age and risk of ASD. The findings persisted after adjustment for maternal age and other potential confounders. De novo germline mutations or alterations in genetic imprinting may be responsible, at least in part, for the observed association. Although further work is necessary to confirm this interpretation, we believe that our study provides the first convincing evidence that advanced paternal age is a risk factor for ASD.

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