ARTICLE

Maternal and Paternal Age and Risk of Autism Spectrum Disorders

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Objective: To explore the association between maternal and paternal age and risk of autism spectrum disorders (ASDs) in offspring.

Design: Historical birth cohort study.

Setting: Kaiser Permanente (KP) in Northern California.

Participants: All singleton children born at KP from January 1, 1995, to December 31, 1999, were included in the study. We identified 593 children who had ASD diagnoses (*International Classification of Diseases, Ninth Revision, Clinical Modification*, code 299.0 or 299.8) recorded 2 or more times in KP outpatient databases before May 2005. These children were compared with all 132 251 remaining singleton KP births.

Main Exposures: Maternal and paternal age at birth of offspring.

Main Outcome Measures: Relative risks (RRs) estimated from proportional hazards regression models. Risk of ASDs evaluated in relation to maternal and paternal age, adjusted for each other and for the sex, birth date, and birth order of the child, maternal and paternal educational level, and maternal and paternal race/ethnicity.

Results: Risk of ASDs increased significantly with each 10-year increase in maternal age (adjusted RR, 1.31; 95% confidence interval [CI], 1.07-1.62) and paternal age (RR, 1.28; 95% CI, 1.09-1.51). Adjusted RRs for both maternal and paternal age were elevated for children with autistic disorder (maternal age: RR, 1.18; 95% CI, 0.87-1.60; paternal age: RR, 1.34; 95% CI, 1.06-1.69) and children with Asperger disorder or pervasive developmental disorder not otherwise specified (maternal age: RR, 1.45; 95% CI, 1.09-1.93; paternal age: RR, 1.24; 95% CI, 0.99-1.55). Associations with parental age were somewhat stronger for girls than for boys, although sex differences were not statistically significant.

Conclusion: Advanced maternal and paternal ages are independently associated with ASD risk.

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THE CAUSE OF AUTISM SPECTRUM disorders (ASDs) is unknown; however, results from twin and family studies[1] provide evidence for a strong genetic contribution, with multiple loci potentially involved. Investigations of nonheritable factors suggest that environmental influences may also be etiologically important,[2] and neuropathologic and biomarker studies provide compelling evidence for a prenatal origin.[3,4] The reported prevalence of ASDs has increased significantly during the past few decades.[5] In this same period, the mean age at maternity and paternity has also increased.[6]

Advanced maternal age has been associated with risk of autism in several previous studies but not in all. Methodologic limitations, including lack of statistical control for paternal age, parity, or birth order and other potential confounding factors, have made these findings difficult to interpret. The role of paternal age in autism has been less frequently examined, although advanced paternal age has been associated with other adverse reproductive outcomes, including miscarriage,[7,8] fetal death,[9] childhood cancers,[10,11] autoimmune disorders,[12] schizophrenia,[13-19] and other neuropsychiatric disorders.[20] Associations with these diverse outcomes may be explained by the age-associated increase in de novo mutations in male germ cells.[21] In this study, we investigated the association between maternal and paternal age and childhood ASDs using data from a large California birth cohort while controlling for age of the other parent and several other demographic characteristics that are reliably recorded in medical records and birth certificates.

METHODS

STUDY PARTICIPANTS

The study participants in the present investigation were drawn from the cohort of single-

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ton children born in a Kaiser Permanente (KP) hospital in Northern California between January 1, 1995, and December 31, 1999 (n = 150 414). Kaiser Permanente is an integrated, group-model, nonprofit health plan that serves more than 3 million members in Northern California. The membership is demographically similar to the population of Californians who live in the counties served by KP, except that the very poor and very wealthy are underrepresented.[22]

To be eligible for inclusion, children were required to have at least 1 month of KP membership after birth and match to a California birth certificate (n = 139 419). Children with ASDs were identified from the computerized outpatient clinical database maintained for all KP members. This database contains all diagnoses recorded at each outpatient visit. Children with at least 2 diagnoses of an ASD (autism: *International Classification of Diseases, 9th Edition, Clinical Modification* [*ICD-9-CM*] code 299.0; Asperger disorder or pervasive developmental disorder not otherwise specified [PDD-NOS]: *ICD-9-CM* code 299.8), of which at least 1 was a definitive diagnosis (not "rule out," "possible," or "probable"), were designated as ASD cases. Children for whom all recorded diagnoses were *ICD-9-CM* code 299.0 were classified as having an autistic disorder (AD), whereas children for whom all recorded diagnoses were *ICD-9-CM* code 299.8 were classified as having PDD-NOS or Asperger disorder. Children with both types of diagnoses were classified according to the most recent specialist diagnosis or, lacking specialist diagnoses, according to the most recent nonspecialist diagnosis. A specialist was defined as a child psychiatrist, child neurologist, or developmental and behavioral pediatrician. Diagnostic data were retrieved from the computerized files on April 30, 2005; all study children were between 5 and 10 years of age. All children from the cohort who were not selected as cases based on these criteria were considered controls.

Maternal age, sex of child, and date of birth were extracted from KP data sources, whereas data on paternal age, birth order, and parental race/ethnicity and education were extracted from state birth certificate files. Only children with complete data on all covariates were included in the analyses (n = 132 844).

Maternal and paternal age at birth of the study child were examined as both continuous and categorical variables (<20, 20-24, 25-29, 30-34, 35-39, and ≥40 years). Variation in ASD risk based on parental age differences could be an important etiologic clue. To evaluate whether the amount of difference in the age of the parents influenced ASD risk, we created a 3-level categorical variable that represented the difference in the standardized maternal and paternal ages (>1 SD was defined as a large difference; 0.3 SD to 1 SD, a moderate difference; and <0.3 SD, a small difference).

Covariates included birth order (defined continuously), date of birth of child (from January 1, 1995, through December 31, 1999), sex of child, maternal and paternal educational level at birth of the study child (<high school, high school, college, or graduate school), and maternal and paternal race/ethnicity (white, non-Hispanic; white, Hispanic; African American; Asian; or other).

Since preliminary analyses showed that the mean number of vaccinations in the first 6 months of life and the mean number of well-child care visits in the second year of life were significantly higher for children with older parents and children with ASDs, we were concerned that differential health care–seeking behavior might confound our results. Thus, these variables were also included as covariates in multivariable models.

STATISTICAL ANALYSIS

Because many of the children in the birth cohort could not be followed up through the entire age range during which autism was diagnosed, we used statistical methods appropriate for data that is "right censored." Primarily, we used proportional hazards regression to examine the risk of autism in relation to maternal and paternal age, with adjustment for potential confounders, and also to estimate the cumulative incidence of ASD by the age of 10 years.[23] The timeline for our analyses was the age (in days) of the child. For each day of age (from the youngest age at diagnosis to the oldest), we compared the children who were diagnosed as having ASDs on that day vs all of the remaining children in the birth cohort who were still in follow-up and without an ASD diagnosis. Summarizing across all such comparisons, the fitted regression model yielded relative risk (RR) estimates for our predictor variables that could best predict who was diagnosed as having autism. The predictor variables included maternal and paternal age, educational attainment, and race ethnicity, as well as the child's sex, birth order, and birth year. A preliminary model examined autism risk in relation to 6 categories of maternal age and 6 categories of paternal age. After the risk of autism was found to increase rather steadily with maternal and paternal age in this preliminary analysis where age was categorized, we proceeded to fit a model that specified maternal and paternal age as continuous variables, scaled by decade of age.

The fit of the model was not significantly improved by including a measure of maternal age squared or paternal age squared or the product of maternal and paternal age. We also examined interactions between our timeline (the age of the child) and parental age, and we examined weighted Schoenfeld residuals to investigate whether autistic children tended to have older parents regardless of the age at which they were diagnosed as having autism. The associations of autism with parental age did not vary significantly by age at diagnosis (supporting the appropriateness of the proportionality assumption underlying our use of the regression model).

Cumulative incidence estimates were obtained using the proportional hazards model to determine what would have been the cumulative incidence by the age of 10 years in each of our subgroups defined by maternal and paternal age, if each subgroup had the same mean levels for the other covariates, as was found in the entire birth cohort.

RESULTS

Of the 132 844 children in the study cohort, 593 met the study criteria for ASDs and were defined as cases; the 132 251 remaining children were defined as controls. Of the 593 ASD cases, 277 (47%) were classified as AD cases and 316 (53%) as PDD-NOS or Asperger disorder cases. Sixty-five percent of all study participants had 1 period of continuous KP enrollment beginning sometime after birth, and 35% had multiple periods (range, 1-12; mean, 1.5). The total number of months of KP membership per participant ranged from 1 to 123 (mean, 67.5 months).

Maternal age ranged from 12 to 53 years (mean, 28.8 ± 5.9 years), and paternal age ranged from 13 to 70 years (mean, 31.5 ± 6.8 years). The correlation between maternal and paternal age was 0.74 ($P<.001$). Children with ASDs were more likely than controls to be male and to have older, more highly educated, and white, non-Hispanic parents (**Table 1**).

MATERNAL AND PATERNAL AGE MODELED AS CATEGORICAL VARIABLES

Crude and adjusted hazard ratios and 95% confidence intervals (CIs) for maternal and paternal age defined as

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Table 1. Characteristics of Children With and Without ASDs, 1995-1999, Singleton Births, Kaiser Permanente*

Characteristic	Children With ASDs (n = 593)	Control Children (n = 132 251)
Maternal age, y		
Mean (SD)	30.8 (5.5)	28.8 (5.9)
<20	12 (2)	8588 (6)
20-24	68 (11)	23 454 (18)
25-29	162 (27)	39 009 (29)
30-34	193 (33)	37 607 (28)
35-39	127 (21)	19 347 (15)
≥40	31 (5)	4246 (3)
Paternal age, y		
Mean (SD)	33.8 (6.6)	31.5 (6.8)
<20	4 (1)	4210 (3)
20-24	39 (7)	15 994 (12)
25-29	112 (19)	31 952 (24)
30-34	178 (30)	39 126 (30)
35-39	154 (26)	25 990 (20)
≥40	106 (18)	14 979 (11)
Parity		
1	271 (46)	55 317 (42)
2	225 (38)	45 165 (34)
3	70 (12)	20 957 (16)
4	19 (3)	7077 (5)
≥5	8 (1)	3735 (3)
Birth year		
1995	145 (24)	25 481 (19)
1996	121 (20)	25 412 (19)
1997	108 (18)	26 109 (20)
1998	122 (21)	27 197 (21)
1999	97 (16)	28 052 (21)
Sex of child		
Male	501 (84)	67 489 (51)
Female	92 (16)	64 762 (49)
Maternal educational level		
<High school graduate	30 (5)	15 020 (11)
High school graduate	133 (22)	41 825 (32)
Undergraduate college	323 (54)	59 918 (45)
Postgraduate	107 (18)	15 488 (12)
Paternal educational level		
<High school graduate	35 (6)	14 568 (11)
High school graduate	163 (27)	45 365 (34)
Undergraduate college	284 (48)	54 443 (41)
Postgraduate	111 (19)	17 875 (14)
Maternal race/ethnicity		
White, non-Hispanic	291 (49)	60 260 (46)
White, Hispanic	108 (18)	31 735 (24)
Black	54 (9)	11 869 (9)
Asian	57 (10)	11 751 (9)
Other	83 (14)	16 636 (13)
Paternal race/ethnicity		
White, non-Hispanic	300 (51)	59 897 (45)
White, Hispanic	113 (19)	31 952 (24)
Black	63 (10)	14 505 (11)
Asian	53 (9)	10 658 (8)
Other	64 (11)	15 239 (12)

Abbreviation: ASDs, autism spectrum disorders.
*Data are presented as number (percentage) of children unless otherwise indicated.

Table 2. Parental Age Modeled as a Categorical Variable for Autism Spectrum Disorders

Parental Age	RR (95% CI)	Adjusted RR (95% CI)*
Maternal age, y		
<20	0.37 (0.21-0.67)	0.62 (0.30-1.27)
20-24	0.76 (0.57-1.01)	0.86 (0.62-1.18)
25-29	1 [Reference]	1 [Reference]
30-34	1.15 (0.93-1.41)	1.04 (0.83-1.31)
35-39	1.41 (1.12-1.78)	1.20 (0.91-1.58)
≥40	1.53 (1.04-2.24)	1.27 (0.83-1.95)
Paternal age, y		
<20	0.29 (0.11-0.78)	0.45 (0.15-1.41)
20-24	0.74 (0.52-1.07)	0.86 (0.57-1.30)
25-29	1 [Reference]	1 [Reference]
30-34	1.20 (0.95-1.52)	1.14 (0.89-1.48)
35-39	1.51 (1.18-1.92)	1.38 (1.04-1.84)
≥40	1.73 (1.32-2.25)	1.52 (1.10-2.10)

Abbreviations: CI, confidence interval; RR, relative risk.
*Adjusted for other parent's age, birth order, date of birth, sex of the child, maternal and paternal educational level, and maternal and paternal race/ethnicity.

categorical variables are given in **Table 2**. In unadjusted analyses, maternal and paternal age older than 34 years was significantly associated with increased risk of ASDs. After adjusting for the other parent's age and sex of the child, parity, maternal and paternal educational level, and maternal and paternal race/ethnicity, only paternal age older than 34 years remained significantly associated with increased risk. However, after adjustment for the other parent's age and all other covariates, the trend of increasing risk with increasing age was statistically significant for both maternal age (adjusted RR for linear trend across age categories, 1.11; 95% CI, 1.01-1.23; $P=.04$) and paternal age (adjusted RR, 1.17; 95% CI, 1.07-1.29; $P=.001$).

MATERNAL AND PATERNAL AGE MODELED AS CONTINUOUS VARIABLES

Adjusted RRs and 95% CIs for maternal and paternal age modeled as continuous variables are given in **Table 3**. Risk of ASDs increased significantly with each 10-year increase in maternal age (adjusted RR, 1.31; 95% CI, 1.07-1.62) and paternal age (adjusted RR, 1.28; 95% CI, 1.09-1.51). The RR estimates were unchanged after adjustment for parental health care–seeking behavior.

Proportional hazards regression models were run separately for the 2 ASD diagnostic strata (Table 3). The adjusted RRs for maternal and paternal age remained elevated for children with AD and for children with PDD-NOS and Asperger disorder. The maternal age effect was stronger for PDD-NOS and Asperger than AD, and the paternal age effect was stronger for AD than PDD-NOS or Asperger disorder, but these differences were not statistically significant and disappeared when children with both an AD and a PDD-NOS or Asperger disorder diagnosis (for whom final ASD severity was imputed, n=187 [31%]) were excluded from the analysis (data not shown).

We estimated RRs separately for boys and girls and observed a trend toward a higher ASD risk associated with increasing maternal and paternal age in girls than in boys, although the differences in risk estimates for girls and boys were not statistically significant. The RRs for maternal age were 1.27 (95% CI, 1.01-1.60) for boys and

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Table 3. Parental Age Modeled as a Continuous Variable for ASDs

Characteristic	Adjusted RR (95% CI)*		
	ASD (n = 593)	Autistic Disorder (n = 277)	PDD-NOS or Asperger Disorder (n = 316)
Maternal age†	1.31 (1.07-1.62)	1.18 (0.87-1.60)	1.45 (1.09-1.93)
Paternal age†	1.28 (1.09-1.51)	1.34 (1.06-1.69)	1.24 (0.99-1.55)
Birth order	0.78 (0.71-0.85)	0.83 (0.73-0.94)	0.73 (0.64-0.83)
Date of birth	1.09 (1.03-1.16)	1.02 (0.94-1.12)	1.17 (1.07-1.28)
Sex of child			
Male	5.27 (4.22-6.58)	4.1 (3.04-5.53)	6.88 (4.92-9.63)
Female	1 [Reference]	1 [Reference]	1 [Reference]
Maternal educational level			
<High school graduate	0.81 (0.52-1.26)	0.75 (0.40-1.39)	0.88 (0.47-1.63)
High school graduate	1 [Reference]	1 [Reference]	1 [Reference]
Undergraduate college	1.36 (1.08-1.69)	1.22 (0.89-1.69)	1.49 (1.08-2.04)
Postgraduate	1.44 (1.06-1.95)	1.21 (0.77-1.90)	1.68 (1.11-2.53)
Paternal educational level			
<High school graduate	0.92 (0.61-1.37)	1.02 (0.58-1.81)	0.83 (0.47-1.48)
High school graduate	1 [Reference]	1 [Reference]	1 [Reference]
Undergraduate college	1.06 (0.86-1.31)	1.16 (0.85-1.59)	0.98 (0.73-1.31)
Postgraduate	1.09 (0.82-1.45)	1.09 (0.71-1.68)	1.08 (0.74-1.59)
Maternal race/ethnicity			
White, non-Hispanic	1 [Reference]	1 [Reference]	1 [Reference]
White, Hispanic	0.98 (0.74-1.30)	1.34 (0.89-2.01)	0.76 (0.52-1.12)
Black	1.15 (0.70-1.88)	2.55 (1.31-4.97)	0.46 (0.22-0.96)
Asian	0.88 (0.57-1.35)	1.08 (0.58-2.03)	0.74 (0.41-1.34)
Other	1.27 (0.90-1.80)	1.39 (0.82-2.34)	1.20 (0.75-1.90)
Paternal race/ethnicity			
White, non-Hispanic	1 [Reference]	1 [Reference]	1 [Reference]
White, Hispanic	1.09 (0.83-1.44)	0.84 (0.55-1.28)	1.34 (0.93-1.94)
Black	0.91 (0.57-1.44)	0.65 (0.33-1.26)	1.22 (0.67-2.23)
Asian	1.00 (0.64-1.55)	1.02 (0.54-1.92)	0.97 (0.53-1.78)
Other	0.73 (0.49-1.06)	0.75 (0.43-1.31)	0.71 (0.42-1.19)

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; PDD-NOS, pervasive developmental disorder not otherwise specified; RR, relative risk.
*Adjusted for maternal and paternal age, birth order, date of birth, sex of the child, maternal and paternal educational level, and maternal and paternal race/ethnicity.
†A 10-year age difference.

1.55 (95% CI, 0.93-2.59) for girls. The RRs for paternal age were 1.27 (95% CI, 1.06-1.52) for boys and 1.38 (0.93-2.05) for girls. All RRs were adjusted for the other parent's age, birth order, date of birth, sex of the child, maternal and paternal educational level, and maternal and paternal race/ethnicity.

DIFFERENCES BETWEEN MATERNAL AND PATERNAL AGE

The difference in parental age was not significantly associated with ASD risk after adjusting for all covariates (large vs small difference: RR, 0.83; 95% CI, 0.51-1.35; moderate vs small difference: RR, 1.13; 95% CI, 0.87-1.47).

RISK ASSOCIATED WITH COVARIATES

Risk of ASDs was inversely correlated with birth order, positively correlated with date of birth, and significantly elevated for boys and children whose mothers had a college or postgraduate education, independent of parental age and all other covariates (Table 3). These increased risks were more pronounced in children classified as having PDD-NOS or Asperger disorder, especially after children with imputed ASD severity were removed (data not shown). Although no overall differences in ASD risk were associated with maternal race/ethnicity, children whose mothers were black were more likely to be diagnosed as having AD and less likely to be diagnosed as having PDD-NOS or Asperger disorder compared with children whose mothers were white, non-Hispanic (Table 3). These differences were also more pronounced after children with imputed severity were removed from the analyses (data not shown). Risk did not vary by paternal educational level or paternal race/ethnicity, either for the total group or for subgroups defined by diagnostic strata.

CUMULATIVE INCIDENCE

The cumulative incidence of ASD by the age of 10 years increased nearly 2-fold from the youngest (<20 years: 1 in 251) to the oldest mothers (≥40 years: 1 in 123) and more than 3-fold from the youngest (<20 years: 1 in 387) to the oldest fathers (≥40 years: 1 in 116), independent of the other parent's age and all other covariates (**Table 4**).

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Table 4. Estimated Cumulative Incidence of Autism Spectrum Disorders per 1000 Live Births

Parental Age, y	Cumulative Incidence (95% CI)*	
	Maternal Age	Paternal Age
<20	3.98 (1.21-6.74)	2.58 (0-5.45)
20-24	5.49 (3.74-7.25)	4.92 (2.93-6.90)
25-29	6.41 (4.86-7.95)	5.69 (4.18-7.19)
30-34	6.69 (5.07-8.30)	6.50 (4.95-8.05)
35-39	7.69 (5.54-9.83)	7.84 (5.84-9.84)
≥40	8.13 (4.63-11.61)	8.65 (6.13-11.17)

Abbreviation: CI, confidence interval.
*Adjusted for other parent's age, birth order, date of birth, sex of the child, maternal and paternal educational level, and maternal and paternal race/ethnicity.

COMMENT

We found that risk of ASD was independently associated with advanced maternal and paternal age in a contemporary cohort of California-born children. Major strengths of this study include a large population-based sample and prospective collection of autism diagnoses and covariates, thus avoiding biases due to differential reporting and recall by parents of affected and unaffected children. We examined parental age–associated risks using both categorically and continuously defined age variables while statistically adjusting for characteristics of the parents, such as race, educational level, parity, and health care–seeking behavior, which could potentially confound the association.

Although some degree of underascertainment of ASDs may be present in this population, the observed ASD prevalence of 4.5 in 1000 approximates recent figures from multisource surveillance systems and community-based surveys.[24,25] Diagnoses were obtained from clinical diagnoses recorded in KP databases, without clinical validation for this study. Previous validation studies conducted by the investigators have demonstrated that approximately 90% of children identified as ASD cases from the KP electronic files meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[26] criteria with full review of diagnostic information from medical records. In a current study within the KP system, children are being evaluated with the Autism Diagnostic Interview–Revised[27] and Autism Diagnostic Observation Schedule–Generic[28] to confirm diagnoses. Of the 92 children evaluated to date who were included as cases in this analysis, 84% met criteria for ASD on both the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule–Generic, and 100% met criteria on at least 1 instrument.

Although the association between autism and maternal age has been evaluated in multiple clinical and epidemiologic samples, some studies have reported a positive association[29-36] and others no association.[37-43] The association of ASD risk with paternal age has been less frequently investigated.[35,36,42,44-48] The 4 large population-based epidemiologic studies that simultaneously adjusted for the ages of both parents in the same model have produced inconsistent results. In an Australian population, Glasson et al[45] found that increased maternal age, but not paternal age, was significantly associated with autism risk independent of other perinatal factors. In a Danish population, Lauritsen et al[46] found that the risk of autism was associated with increasing paternal but not maternal age, independent of the child's age, child's sex, parental psychiatric history, sibling autism status, parental country of birth, and degree of urbanization. A second Danish study by Larsson et al[47] reported no statistically significant association between risk of autism and either maternal or paternal age after adjusting for other perinatal factors and parental psychiatric history. In an Israeli population, Reichenberg et al[48] found that increased paternal age, but not maternal age, was associated with autism risk after adjustment for year of birth and socioeconomic status.

Inconsistencies between our results and those of the previous studies may be due to differences in study methods. In our study, although a clear trend of increasing risk with increasing maternal age was observed when age was modeled categorically, the maternal age association achieved statistical significance only when age was modeled continuously. The Australian and Danish studies treated parental age as a categorical variable only. Although the Israeli study examined parental age both categorically and continuously, the small sample size resulted in imprecise risk estimates, and the authors concluded that a small effect in the oldest mothers could not be ruled out. Children across the entire autism spectrum were included in our study, whereas the previously published samples were skewed toward children on the more severe end of the spectrum. In addition, the covariates included in the adjusted analyses differed to some extent across the studies.

In all 4 previous studies, a significant association was observed with both advanced maternal and paternal age in unadjusted analyses. Other studies[29,45] that examined maternal age without adjusting for paternal age may have overstated the maternal age effect. In the current investigation, the RRs for both maternal age and paternal age were higher before adjusting for age of the other parent.

In our study, the age effects were somewhat different according to the severity of autism, but differences between diagnostic groups were not statistically significant and should be interpreted with caution until replicated in future studies using more rigorous criteria to determine case type. Our finding that advanced paternal age was more strongly correlated with AD is consistent with the Danish findings of a stronger paternal age effect among the more severely affected children. Of note, in 3 previous schizophrenia studies, the association with advanced paternal age was significant only for persons who met criteria for schizophrenia and not the broader spectrum of schizophrenia disorders,[49] related nonaffective psychoses,[13] or other psychoses.[17] Differences in maternal and paternal age and maternal educational level effects across ASD severity categories, although not significant, raise the possibility that the underlying biological and sociological risk profiles may differ according to ASD severity. Larger samples with better phenotypic characterization are needed to study this phenomenon further.

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Our data suggest that increased risk of ASDs associated with advanced maternal and paternal age may be somewhat stronger in girls than in boys. This finding could be a statistical artifact, since the same parental age–related effect could result in a higher multiplicative effect in girls given that the baseline prevalence of ASDs is lower in girls than in boys. Alternatively, our finding may be a possible etiologic clue. Increased paternal age has been documented in the inheritance of *MeCP2* mutations in girls with Rett syndrome.[50] Of note, the association between advanced paternal age and schizophrenia was stronger in girls than in boys in 1 study,[14] but not in 2 others.[13,15] The stronger association with paternal age in girls might suggest that a de novo mutation in a gene on the X chromosome may play a role. Many genes expressed in the central nervous system and associated with cognitive impairment are located on the X chromosome.[51] Evidence from recent family-based association[52] and linkage studies[53,54] suggests the presence of autism risk loci on the X chromosome.

The increased risk of ASDs observed with advanced maternal age could be explained by uncontrolled confounding due to increased risk of pregnancy complications in older mothers[45,47] or advanced birth order.[41,45] Although we did not control for pregnancy complications, we observed independent associations with maternal age and birth order.

Our observation of increased ASD risk in older fathers is consistent with the hypothesis that new point mutations may contribute in part to the cause of autism. In men, spermatogonia constantly divide during the lifespan, accumulating new mutations as men age.[55] Evidence suggests that several genetic loci may be involved in the vulnerability to autism[1]; some may be arising de novo. The biological mechanism underlying our observation of increased ASD risk in older fathers could be de novo mutations introduced in aging fathers. If this is the case, we would expect to see a stronger association with paternal age in sporadic rather than familial cases of autism. Epigenetic effects, such as age-related methylation changes, could be an alternative biological explanation for our findings. Evidence is increasing that epigenetic factors may contribute to ASD risk. For example, several chromosomal regions subject to imprinting (eg, 7q, 15q, and X) have been linked to ASDs.[56] Attributes of the parents that lead to older age at childbearing and that are related to autism risk might also explain the association we observed with advancing parental age.[57] Psychosocial traits that are related to the autism phenotype, including social deficits, may influence age at childbearing. In some studies, such traits have been shown to be more prevalent in parents of autistic children than in the general population.[58] Increased risk with increasing age could also be explained by lack of control for nongenetic exposures that increase with advancing age and that are associated with autism risk. Finally, our findings might be a result of more complete ascertainment of children with ASDs among older parents, who may be more attuned to deviances in the expected developmental trajectory of their young children. Although we found no evidence of confounding by health care–seeking behavior measured in the first few years of life, the stronger associations with older maternal age and higher maternal educational level we observed for children with PDD-NOS or Asperger disorder lend some support to this hypothesis.

CONCLUSION

These data suggest that advanced maternal and paternal age are independently associated with ASD risk. Age effects were independent of birth year and thus not explained by the increasing age of parents that has been observed in recent years. If the relationship between parental age and ASD is causal, the fraction of autism in this sample attributable to having a mother or father older than 35 years is 4% to 13%. Future investigations focused on the identification of both genetic and environmental factors that correlate with advanced parental age are warranted.

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