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Original Contribution

Advanced Parental Age and the Risk of Autism Spectrum Disorder

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This study evaluated independent effects of maternal and paternal age on risk of autism spectrum disorder. A case-cohort design was implemented using data from 10 US study sites participating in the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network. The 1994 birth cohort included 253,347 study-site births with complete parental age information. Cases included 1,251 children aged 8 years with complete parental age information from the same birth cohort and identified as having an autism spectrum disorder based on *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria. After adjustment for the other parent's age, birth order, maternal education, and other covariates, both maternal and paternal age were independently associated with autism (adjusted odds ratio for maternal age $\geq$35 vs. 25–29 years = 1.3, 95% confidence interval: 1.1, 1.6; adjusted odds ratio for paternal age $\geq$40 years vs. 25–29 years = 1.4, 95% confidence interval: 1.1, 1.8). Firstborn offspring of 2 older parents were 3 times more likely to develop autism than were third- or later-born offspring of mothers aged 20–34 years and fathers aged $<$40 years (odds ratio = 3.1, 95% confidence interval: 2.0, 4.7). The increase in autism risk with both maternal and paternal age has potential implications for public health planning and investigations of autism etiology.

autistic disorder; birth order; maternal age; paternal age

Abbreviations: ASD, autism spectrum disorder; PDD-NOS, pervasive developmental disorders-not otherwise specified.

This paper examines the relation between parental age at delivery and the prevalence of autism spectrum disorder (ASD). The possibility that autism is more common in offspring of older parents has generated considerable interest (1–6). Confirmation of such an association could have important public health implications in light of increasing trends in recent decades regarding both maternal and paternal age (7). In addition, evidence of paternal and maternal age effects on autism risk may provide clues to the etiology of a class of neurodevelopmental disorder that is still poorly understood and thought to be complex and multifactoral.

In evaluating the association between parental age and autism risk, it is important to account for other variables related to both parental age and autism or that may modify the association. Birth order is a potentially confounding factor because it is positively associated with parental age and has been reported in some studies to be associated with autism risk, with at least 3 studies reporting firstborn children to be at increased risk of autism (1, 2, 4). The goal of this study was to determine, in a large, population-based cohort of US children, whether advancing maternal and paternal age each independently increase a child's risk of developing autism after controlling for the other parent's age, birth order, and other risk factors.

MATERIALS AND METHODS

Study design and sample

We implemented a population-based, case-cohort design in which the comparison group was a cohort of all livebirths in 1994 in 10 geographically defined study areas participating in the Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network (8). The

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Table 1. Characteristics of the 1994 Birth Cohort and ASD Cases, 10 Study Sites From the US Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network

	Full Birth Cohort: All Livebirths in the 10 Study Areas	Birth Cohort With Complete Information on Parental Age	All Children Aged 8 Years With ASD Residing in the 10 Study Areas in 2002	ASD Cases With Any Birth Certificate Information	ASD Cases With Complete Information on Parental Age
No. (%)	326,785 (100)	253,347 (77.5)	2,142 (100)	1,517 (70.8)	1,251 (58.4)
Median maternal age, years	27	28		29	29
Median paternal age, years		30			31
Maternal age <20 years, %	13.8	8.5		8.0	5.4
Maternal age ≥35 years, %	10.9	12.6		16.2	17.2
Boys, %	51.2	51.4	81.2	81.7	81.8
White, %	60.1	67.6	63.1	65.5	69.0
Black, %	23.7	16.5	22.1	22.7	17.2
Hispanic, %	12.0	11.1	10.5	9.3	9.2
Gestational age <37 weeks, %	9.8	8.7		13.6	12.5
Gestational age <28 weeks, %	0.8	0.6		1.9	1.5
Autistic disorder, %			81.0	80.8	80.7
Confirmed intellectual impairment, %[a]			32.4	32.7	30.9
Confirmed normal intelligence, %[a]			43.2	42.1	43.2

Abbreviation: ASD, autism spectrum disorder.
[a] Information to confirm intellectual functioning was missing for approximately 25% of ASD cases.

10 areas are all sites with deidentified birth certificate information on parental age and other relevant variables included in the Network database and include sites in Alabama, Arizona, Arkansas, Colorado, Georgia, Maryland, Missouri, New Jersey, North Carolina, and Wisconsin.

The cohort serving as the comparison group includes all livebirths to mothers residing in any 1 of the study areas in 1994, with complete information available from birth certificates on maternal and paternal age, birth order, and other variables. We used 2 data sources to construct the cohort: 1994 deidentified birth records for the Wisconsin study area provided by the Wisconsin Department of Health and Family Services and, for the remaining sites, the National Center for Health Statistics public use natality data files (9). The public use file includes county of residence for births in densely populated counties, which enabled us to ascertain deidentified birth information for all births in most of the counties. We were unable to precisely obtain counts of births occurring in sparsely populated counties in which 13,043 (4.1%) of the study-area births occurred in 1994. For these counties, we obtained county-level aggregate information on the total number of births in 1994 and their distribution by variables such as maternal marital status, ethnicity, and age and selected a stratified random sample of deidentified birth records (equal in number and similar in distribution by maternal marital status, ethnicity, and age to all livebirths occurring in the respective counties in 1994) from sparsely populated counties of the state in which the study area was located. The full cohort included 326,785 livebirths, of which 73,438 (22.5%) were excluded because of missing paternal age. The cohort serving as the comparison group thus included the 253,347 livebirths with complete information on parental age and other key variables (Table 1).

The total number of children aged 8 years residing in the study areas in 2002 determined by the Autism and Developmental Disabilities Monitoring Network surveillance system to have an ASD was 2,142. Birth certificate information was available for 1,517 (70.8%) of these children, who were born in the same state as their state of residence in 2002. The remaining 29.2% of cases were excluded from this analysis because of missing birth certificate information. The case group for the present analysis was further restricted to the 1,251 children (58.4% of the total ASD case group) for whom information on both parents' age as well as birth order and gestational age was available. Our final sample was comparable to the total population of ASD cases regarding demographic factors and ASD case characteristics (Table 1).

Case definition

ASDs include behaviorally defined neurodevelopmental disorders diagnosed through clinical observation, and they encompass impairments in social, communicative, and behavioral development, often accompanied by abnormalities in intellectual functioning, learning, attention, and sensory processing. For this study, children with ASD included members of the birth cohort residing in the study area in 2002 who met *Diagnostic and Statistical Manual of Mental*

Disorders, Fourth Edition, Text Revision criteria for autistic disorder; pervasive developmental disorders-not otherwise specified (PDD-NOS (http://www.cdc.gov/ncbddd/autism/overview_diagnostic_criteria.htm), including atypical autism); or Asperger's disorder (10) based on a comprehensive review of educational and clinical records by trained clinicians. Children were classified by clinician reviewers as having an ASD if they had either a documented previous classification of ASD (65%) or an evaluation record from an educational or medical setting indicating unusual behaviors consistent with ASD (35%). For children previously identified as having an ASD, case status was confirmed on the basis of evaluation records. For children without a documented ASD classification, data were abstracted on all relevant ASD and developmental behaviors from education or medical evaluations to determine whether behaviors described in the evaluations by clinical reviewers were consistent with the diagnostic criteria. Because case status was determined solely on the basis of information contained in evaluation records, and because *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria are less well defined for PDD-NOS than for autistic disorder, the surveillance protocol for determining whether a child could be classified as having PDD-NOS required documentation of at least 1 behavior considered to be an ASD discriminator, such as being oblivious to others when there is a clear social opportunity or demonstrating atypical and persistent focus on sensory input (11).

Of the 1,251 ASD cases, 80.7% were determined to meet criteria for autistic disorder, while there was insufficient information for those remaining to distinguish between autistic disorder, Asperger's disorder, or PDD-NOS. Information from standardized intelligence tests was available for approximately 75% of the ASD cases. On the basis of this information, children with ASD were classified as having intellectual impairment (an IQ of <70) versus normal intelligence. Further details regarding the 2002 Autism and Developmental Disabilities Monitoring Network sample and methodology have been reported previously (8, 11).

Analytic strategy and statistical methods

Potential for confounding effects of birth order, gender, and other variables was evaluated by first examining unadjusted associations between each potential confounder and the independent variables of maternal and paternal age as well as the dependent variable, ASD case status. Variables were considered to be potentially confounding factors if they were associated with both parental age and ASD. Unadjusted odds ratios with confidence intervals were computed to evaluate the magnitude of these associations, and unconditional logistic regression models were fit to estimate adjusted odds ratios and 95% confidence intervals. Statistical significance was evaluated by using chi-square tests for categorical variables and analysis of variance for continuous variables.

To enhance the comparability of our findings with those from other studies, we fit 2 types of models, 1 with parental ages categorized into 6 categories: <20, 20–24, 25–29, 30–34, 35–39, ≥ 40 years; and the other with parental age as a continuous variable with the odds ratio scaled to reflect a 10-year difference in age (4). Although we found the association between parental age and autism risk to be similar across the 10 sites, to adjust for potential site-to-site variability we included site dummy variables in all multivariable models. To evaluate interaction or modifying effects of each covariate and of ASD subtypes on the associations between parental age and ASD, we performed stratified analyses. We also tested interaction terms for maternal age by paternal age and 2-way and 3-way interaction terms for each parent's age by the other covariates in the regression models, but we identified no significant interactions. SAS version 9.1.3 software (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

This research involved secondary analysis of deidentified data and was approved by the University of Wisconsin Institutional Review Board.

RESULTS

In unadjusted analyses, both mean maternal age and mean paternal age were significantly higher for ASD cases than for the birth cohort as a whole (Table 2). Table 2 also shows that mean parental ages differed significantly in unadjusted analyses across categories of birth order, maternal education, ethnicity, multiple birth, gestational age, and birth weight for gestational age, but not for gender. With parental age 25–29 years as the reference group, the odds of developing ASD was significantly reduced for parental age <20 years and increased for maternal age ≥ 35 and paternal age ≥ 40 years (Table 3, unadjusted odds ratios). We therefore used these age cutoffs (maternal age ≥ 35, paternal age ≥ 40 years) to classify each parent's age as "older" versus "younger." Other significant predictors of ASD in unadjusted analyses included low birth order, male gender, advanced maternal education, and preterm birth (Table 3).

Multivariable analysis of parental ages modeled as categorical variables

After we adjusted for the other parent's age and other covariates, the increases in ASD risk associated with maternal age ≥ 35 years and paternal age ≥ 40 years (relative to age 25–29 years) were slightly reduced compared with the unadjusted analysis (Table 3). In contrast, the results for birth order suggest that the decline in ASD risk associated with increasing birth order is somewhat stronger in the adjusted analysis than in the unadjusted analysis (Table 3). In addition, the apparent increase in ASD risk associated with higher levels of maternal education in the unadjusted analysis is no longer evident in the adjusted model, suggesting that the apparent maternal education effect is due to its association with parental age (Table 3).

Parental ages modeled as continuous variables

In unadjusted analyses, the risk of developing ASD increased significantly with each 10-year increase in both maternal age and paternal age. After adjustment for age of the

Table 2. Unadjusted Mean Maternal and Paternal Ages at Delivery for ASD Cases Compared With the Cohort as a Whole, and in the Cohort as a Whole Stratified by Covariate Categories, 1994 Birth Cohort From 10 Study Sites From the US Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network

	No.	%	Mean Age, years	
			Maternal	Paternal
ASD case status				
ASD cases	1,251		29.0[a]	31.4[a]
Birth cohort (comparison group)	253,347		28.0[a]	30.1[a]
Birth order				
1st	105,140	41.3	26.1[a]	28.3[a]
2nd	88,065	34.6	28.5[a]	30.7[a]
3rd	39,902	15.7	30.0[a]	32.0[a]
≥4th	21,491	8.4	31.5[a]	33.5[a]
Gender				
Boys	131,258	51.6	28.0	30.2
Girls	123,340	48.4	28.0	30.1
Maternal education				
<High school	37,377	14.7	23.1[a]	26.2[a]
High school graduate	83,093	32.8	26.8[a]	29.1[a]
Some college	60,105	23.7	28.5[a]	30.6[a]
≥4-year college graduate	73,302	29.0	31.4[a]	33.0[a]
Child's race/ethnicity				
Non-Hispanic white	172,148	67.6	28.7[a]	30.7[a]
Non-Hispanic black	42,133	16.6	26.2[a]	28.6[a]
Hispanic	28,309	11.1	26.3[a]	28.6[a]
Other and mixed	12,008	4.7	28.3[a]	31.1[a]
Multiple birth				
Singleton	247,329	97.1	27.9[a]	30.1[a]
Multiple	7,269	2.9	29.5[a]	31.5[a]
Gestational age, weeks				
<28	1,566	0.6	27.7[a]	29.7[a]
28–36	20,652	8.1	27.9[a]	30.0[a]
37–41	226,128	88.8	28.0[a]	30.2[a]
>41	6,252	2.5	27.4[a]	29.6[a]
Birth weight for gestational age[b]				
>2 SDs below the mean	4,245	1.7	27.3[a]	29.8[a]
1–2 SDs below the mean	30,325	11.9	27.1[a]	29.5[a]
Within 1 SD of the mean	180,919	71.1	27.9[a]	30.1[a]
1–2 SDs above the mean	31,855	12.5	28.9[a]	30.9[a]
>2 SDs above the mean	7,254	2.9	29.5[a]	31.6[a]

Abbreviations: ASD, autism spectrum disorder; SD, standard deviation.
[a] Analysis of variance across all strata for this variable $P < 0.0001$.
[b] Number of standard deviations from the mean birth weight at a given gestational age for each gender based on all 1994 US births.

other parent and other covariates, each 10-year increase in maternal age was associated with a 20% increase in ASD risk (odds ratio = 1.2, 95% confidence interval: 1.1, 1.4) while each 10-year increase in paternal age was associated with a 30% increase in ASD risk (odds ratio = 1.3, 95% confidence interval: 1.1, 1.5).

Combined effects of parental age and birth order

The risk of ASD within each of 3 parental age categories (both parents "younger," 1 parent "older," and both parents "older") was highest among firstborn children and declined with increasing birth order (Table 4). Considering the

Table 3. Distribution of ASD Cases and Birth Cohort Comparison Group by Parental Age Categories and Other Independent Variables, and Unadjusted and Adjusted Odds Ratios With 95% Confidence Intervals, 1994 Birth Cohort From 10 Study Sites From the US Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network

	ASD Cases		Birth Cohort Comparison Group		Unadjusted OR	95% CI	Maternal Age at Delivery, years	Adjusted OR[a]	95% CI
	No.	%	No.	%					
Maternal age at delivery, years									
<20	67	5.4	21,507	8.5	0.6[b]	0.5, 0.8		0.7[b]	0.5, 1.0
20–24	238	19.0	55,583	21.9	0.9	0.7, 1.0		0.9	0.8, 1.1
25–29	366	29.3	75,053	29.6	1.0	Reference		1.0	Reference
30–34	365	29.2	69,357	27.4	1.1	0.9, 1.2		1.1	0.9, 1.3
35–39	185	14.8	27,330	10.8	1.4[b]	1.2, 1.7	≥35[c]	1.3[b]	1.1, 1.6
≥40	30	2.4	4,517	1.8	1.4	0.9, 2.0			
Paternal age at delivery, years									
<20	26	2.1	9,734	3.8	0.6[b]	0.4, 0.8		0.6	0.4, 1.0
20–24	162	13.0	42,020	16.6	0.8	0.7, 1.0		0.9	0.7, 1.1
25–29	322	25.7	67,080	26.5	1.0	Reference		1.0	Reference
30–34	379	30.3	75,179	29.7	1.1	0.9, 1.2		1.0	0.9, 1.2
35–39	219	17.5	40,283	15.9	1.1	1.0, 1.4		1.0	0.9, 1.3
≥40	143	11.4	19,051	7.5	1.6[b]	1.3, 1.9		1.4[b]	1.1, 1.8
Birth order									
1st	588	47.0	104,552	41.2	1.0	Reference		1.0	Reference
2nd	425	34.0	87,640	34.6	0.9	0.8, 1.0		0.8[b]	0.7, 0.9
3rd	168	13.4	39,734	15.7	0.8[b]	0.6, 0.9		0.6[b]	0.5, 0.8
≥4th	70	5.6	21,421	8.5	0.6[b]	0.5, 0.7		0.5[b]	0.4, 0.6
Gender									
Boys	1,023	81.8	130,235	51.4	4.2[b]	3.7, 4.9		4.2[b]	3.7, 4.9
Girls	228	18.2	123,112	48.6	1.0	Reference		1.0	Reference
Maternal education									
<High school	136	10.9	37,241	14.7	0.8[b]	0.6, 0.9		1.0	0.8, 1.2
High school graduate	394	31.5	82,699	32.6	1.0	Reference		1.0	Reference
Some college	303	24.2	60,105	23.7	1.1	0.9, 1.2		1.0	0.9, 1.2
≥4-year college graduate	418	33.4	73,302	28.9	1.2[b]	1.0, 1.4		1.0	0.9, 1.2
Child's race/ethnicity									
Non-Hispanic white	863	69.0	171,285	67.6	1.0	Reference		1.0	Reference
Non-Hispanic black	215	17.2	41,918	16.5	1.0	0.9, 1.2		1.0	0.9, 1.2
Hispanic	115	9.2	28,194	11.1	0.8	0.7, 1.0		0.9	0.7, 1.2
Other and mixed	58	4.6	11,950	4.7	1.0	0.7, 1.3		0.9	0.7, 1.1
Multiple birth									
Singleton	1,209	96.6	246,120	97.2	1.0	Reference		1.0	Reference
Multiple	42	3.3	7,227	2.8	1.2	0.9, 1.6		1.0	0.7, 1.4
Gestational age, weeks									
<28	19	1.5	1,547	0.6	2.6[b]	1.7, 4.1		2.5[b]	1.6, 3.9
28–36	137	11.0	20,515	8.1	1.4[b]	1.2, 1.7		1.4[b]	1.2, 1.7
37–41	1,061	84.8	225,067	88.8	1.0	Reference		1.0	Reference
>41	34	2.7	6,218	2.5	1.2	0.8, 1.6		1.1	0.8, 1.5
Birth weight for gestational age									
2 SDs below the mean	22	1.8	4,223	1.7	1.1	0.7, 1.6		1.1	0.7, 1.6
1–2 SDs below the mean	153	12.3	30,172	11.9	1.1	0.9, 1.2		1.1	0.9, 1.3
Within 1 SD of the mean	874	69.9	180,045	71.1	1.0	Reference		1.0	Reference
1–2 SDs above the mean	161	12.9	31,694	12.5	1.0	0.8, 1.2		1.0	0.9, 1.3
>2 SDs above the mean	41	3.3	7,213	2.9	1.2	0.9, 1.6		1.3	0.9, 1.6

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio; SD, standard deviation.

[a] Adjusted for all other variables in this column in addition to site indicators.

[b] Odds ratios with confidence intervals that exclude 1.0.

[c] Because the increased risk was similar for ages 35–39 and ≥40 years, the high-risk maternal age category was defined as ≥35 years.

Table 4. Adjusted Odds Ratios[a] With 95% Confidence Intervals Indicating Increasing Risk of ASD With Parental Age[b] and Decreasing Risk With Birth Order, 1994 Birth Cohort From 10 Study Sites From the US Centers for Disease Control and Prevention's Autism and Developmental Disabilities Monitoring Network

Birth Order	Both Parents Younger (Mother Aged 20–34 and Father Aged <40 Years)				Only 1 Parent Older (Mother Aged ≥35 or Father Aged ≥40 Years)				Both Parents Older (Mother Aged ≥35 and Father Aged ≥40 Years)			
	No.	% of Total Cohort	OR	95% CI	No.	% of Total Cohort	OR	95% CI	No.	% of Total Cohort	OR	95% CI
1st	77, 883	33.4	1.7[c]	1.4, 2.1	8,102	13.4	2.3[c]	1.7, 3.2	2,462	1.1	3.1[c]	2.0, 4.7
2nd	70, 123	30.1	1.4[c]	1.2, 1.8	10,796	4.6	2.0[c]	1.5, 2.7	3,234	1.4	2.3[c]	1.7, 3.2
≥3rd	44, 329	19.0	1.0	Reference	11,619	5.0	1.7[c]	1.3, 2.3	4,666	2.0	1.8[c]	1.2, 2.7

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; OR, odds ratio.
[a] Adjusted for gender, gestational age, birth weight for gestational age, multiple birth, maternal ethnicity and education, and site indicators.
[b] Births to mothers aged <20 years were excluded.
[c] Odds ratios with confidence intervals that exclude 1.0.

combined effects of parental age and birth order, we excluded from the analysis births to mothers aged <20 years and found the lowest risk group to be third- or later-born offspring of mothers aged 20–34 years and fathers aged <40 years. Compared with that for this group, the risk of ASD increased with both declining birth order and increasing number of older parents. The highest risk group included firstborn offspring of mothers aged ≥35 years and fathers aged ≥40 years, with a risk 3 times that of the reference group (Table 4).

DISCUSSION

Our findings are consistent with those recently reported from a large study of members of a California health maintenance organization (4) that found the risk of ASD to be positively and independently associated with both maternal and paternal age, with adjusted odds ratios nearly identical to those reported here. These findings contrast somewhat with 5 other recent epidemiologic studies that found only 1 or neither parent's age to be associated with ASD risk after controlling for the other parent's age (2, 3, 12–14).

The lack of consistency across studies could be due to limitations of sample size and of population representation of previous studies as well as other methodological differences, including autism case definitions and inclusion criteria and the ability to control for important variables. The present study included a large sample of children with sufficient information to enable evaluation of separate and combined effects of each parent's age as well as birth order and other variables. With more than 1,200 cases, it included over 50% more cases and thus more statistical power than any of the previous studies examining independent effects of maternal and paternal age on ASD risk.

Another advantage of this study is the population-based nature and diversity of the cohort, allowing control for factors that may confound the association between parental age and ASD. Maternal education is 1 variable we considered to be a potentially confounding factor because it is associated with maternal age and has been observed to be related to ASD risk (15). Our results, however, suggest that the association between advanced maternal education and ASD risk observed in unadjusted analysis may be spurious and due to confounding by parental age.

The results of this study also demonstrate the importance of controlling for birth order in evaluating independent effects of parental age on ASD risk. Because birth order increases with parental age and, in this and other studies, has been found to be negatively associated with ASD risk, failure to control for birth order may mask a positive association between parental age and ASD risk. Two of the previous studies reporting an association between advancing maternal age and ASD (2, 4) also had adjusted for birth order and, similar to the present study, found birth order to be negatively associated with ASD.

An additional advantage of this study is its restriction to a single birth year, thereby controlling for temporal trends in recent decades in both ASD prevalence and parental ages at the birth of their children. This feature of the study allows estimation of the association between parental age and ASD risk independently of temporal trends in diagnostic practices or other factors.

Public health implications

The strength of the independent associations between maternal and paternal age and ASD risk, as indicated by the odds ratios in the range of 1.2–1.4 reported here, is modest. However, the observation that these effects are independent of each other and of low birth order raises the likelihood that the combined effects of parental age and birth order may have important public health implications. Mean maternal age in the United States has increased steadily since the 1970s, particularly for firstborn children, for whom mean maternal age at delivery increased by 3.8 years between 1970 and 2004 (16). In addition, the proportion of births to women aged ≥35 years began increasing in the United States after 1980, when it was 5%; by 2004, it had increased to 14.2% (17, 18). During this same period, fertility rates for men aged ≥40 years also increased each year, while fertility among men aged <30 years declined (16). With the decline in average family size in recent decades, we would also expect the proportion of children who are firstborn to have increased. Similar trends are occurring in other developed countries (7). The results of this study raise the question of whether some portion of the recent rise in ASD prevalence (19) may be linked to recent trends in

parental age and family size. A further question is whether a modest increase in prevalence associated with advancing parental age and low birth order may have contributed to a greater awareness of ASD and, in turn, increases in measured prevalence. The tendency for older parents of firstborn children to have higher levels of educational achievement and resources than other parents could further contribute to increased awareness and an expansion of the diagnosis of ASD.

Potential etiologic implications of parental age effects

Because we observed independent effects of the age of each parent on ASD risk, the possible mechanisms for these effects could include a broad range of processes associated with either or both maternal and paternal age. The observed paternal age effect independent of maternal age could point to a causal role of gene mutations in male germ cells, because the probability or selection of these mutations increases as men age (20, 21). The independent effect of maternal age, on the other hand, may point to age-related chromosome changes, pregnancy complications, or environmental exposures during pregnancy. Independent effects of 1 or both parents' ages also could point to a role of accumulated environmental exposures that may have mutagenic effects on gametes or could result from a combination of mechanisms (21, 22).

The association between advanced maternal and paternal age and ASD is also consistent with a potential role of infertility treatments or assisted reproductive technologies, the uses of which have increased in the past decade, especially by women and men of advanced reproductive age (23). Numerous studies have found associations between these technologies and adverse pregnancy outcomes, including those due to epigenetic effects (24–27), although a recent review found no evidence of elevated rates of autism among children born after in vitro fertilization techniques (28). Even though we have no information about exposure to these treatments in our cohort, the observation that firstborn children of older parents had the highest ASD risk is consistent with a possible infertility treatment effect because women who give birth after infertility treatment are more likely to be primiparous than those represented in the general birth cohort. However, the association between multiple birth and ASD in this study was weak and not statistically significant (Table 3, unadjusted odds ratio), whereas assisted reproduction technologies are strongly associated with multiple birth (23).

Another unmeasured factor in the present study potentially associated with both advanced parental age and ASD risk in offspring is psychopathology or behavioral traits of parents that may result in both delayed parenthood and genetic susceptibility to autism in offspring (14).

Birth-order effects

The observation in this and at least 2 previous studies (2, 4) that the risk of developing ASD was highest for firstborn children and declined with increasing birth order is a pattern also observed for other childhood disorders, including type I diabetes and atopy, and is cited as support for the "hygiene hypothesis." According to this hypothesis, firstborn children are exposed to fewer infections from other children early in childhood and, because of delayed immunologic challenge, may be more likely to develop autoimmune responses including those that may adversely affect neurodevelopment (29). Another possible factor that could lead to the observed birth-order effect is exposure to potentially neurotoxic, fat-soluble chemicals accumulated in maternal tissue that have been passed to offspring transplacentally or through breast milk (30). Because of accumulation over a lifetime, the load of such neurotoxins transmitted might be expected to be highest for firstborn children, particularly when combined with advanced maternal age. Another possible explanation for the observed birth order effect is "stoppage" or a tendency for parents of 1 child with ASD not to have subsequent children because of the demands of parenting a child with a disability or concerns about genetic susceptibility (31), thus increasing the likelihood in the cohort as a whole that a child with ASD will have a low birth order. Information available for the present study did not allow examination of these hypotheses.

Another important limitation of this study is that the cohort available for analysis excludes births with missing paternal age information. Because this exclusion applied to both the ASD cases and the comparison group (Table 1), we would not expect it to have resulted in biased estimates of the association between ASD and parental age. In a separate analysis, we examined the association between maternal age and ASD without adjusting for paternal age and including the full birth cohort, and we found the association between maternal age and ASD to be the same as that observed in the subcohort with paternal age.

Another limitation is that the birth cohort comparison group includes about 1% of births of children who died postnatally in addition to an undetermined number who moved out of the study area between birth and the age of 8 years, whereas children who died postnatally and those moving out of the study area after birth are excluded from the case group. Because of this limitation, we could not estimate cumulative incidence of ASD. Nonetheless, this limitation is unlikely to have biased the estimated odds ratios reported in this study, particularly those adjusted for factors such as gestational age and birth weight for gestational age, which are strongly associated with postnatal mortality. Another possible explanation for the increase in ASD among offspring of older parents, but one we cannot evaluate with the data available, is that, compared with younger parents, older parents may be more aware of developmental abnormalities and better able to access diagnostic and special educational services. Other limitations are that parity pertains to only mothers and does not take into account the number of previous births fathered by the fathers represented in the cohort, potential for residual confounding by factors not measured in the present study, possible misclassification of ASD case status, and missing information on paternal education.

Conclusion

The results of this study provide the most compelling evidence to date that ASD risk increases with both maternal and paternal age and decreases with birth order. Further

research involving large, well-characterized birth cohorts followed longitudinally will be required to confirm these findings and adequately evaluate the range of alternative genetic and environmental hypotheses that this and other studies raise regarding parental age and birth-order effects on ASD risk. Smaller, focused studies may also be useful, such as Crow's idea to look for mutations responsible for complex disorders of unknown etiology and with parental age effects by studying affected families with older parents (20).

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