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Grether et al (2009) “Risk of Autism and Increasing Maternal and Paternal Age in a Large North American Population,” Am J Epidemiology 170(9):1118-1134.

The parent age at which a child is born and the potential increased risk for a genetic disease has been identified as an issue for Down Syndrome (maternal age risk), achondroplasia (paternal age risk) and now autism. Several studies have attempted to answer the question, “Does increasing parental age affect and increase the risk of autism?”

BACKGROUND: There are a number of studies that have suggested that as paternal age increases the risk for having a child with autism increases. Much attention has been given to the paternal age effect. The newest study, (Hultman et al. “Advancing paternal age and risk of autism: new evidence from a population based study and a meta-analysis of epidemiological studies,” Molecular Psychiatry 2010 epub ahead of print Nov 30) has a population smaller than the Grether study and the Grether study is open access and included for you to review.

There are also a number of studies that suggest that there may also be a maternal age effect. The Grether study included all California single births born between 1989 and 2002 (n=7,550,026). From this group of single births, 23,311children with autism were identified through the California Department of Developmental Services and compared with the other children born during this period. The two groups were compared on the following variables: maternal and paternal age, year of birth, maternal and paternal education, race/ethnicity, birth weight, gestational age, parity and source of payment (insurance status as an indicator of socioeconomic status). Women were represented up to the age of 44. Men were represented up to the age of 64.

RESULTS: There were both paternal and maternal age effects. Looking at maternal age alone over a 10 year period, there was a 38% increase in the risk for autism over each 10 year increment. Another way to look at this is for women age 20-24 the odds ratio of having a child with autism was 0.75. At ages 40-44, the odds ratio was 1.84, more than double.

Looking at paternal age alone, over a 10 year period, there was a 22% increase in the risk for autism over each 10 year increment. For men age 20-24 the odds ratio of have a child with autism was 0.76. At age 40-44, the odds ratio was 1.92 and at age 50-54 the odds ratio was 2.17 (in agreement with the Hultman study). Finally at age 60-64 the odds ratio was 2.61. Similar to the effect seen in mothers, the risk of having a child with autism more than doubled by age 40-44 and more than tripled by age 60-64.

CONCLUSIONS:
There is both a maternal and a paternal age effect and it appears from the attached paper that it is greater for the first born child, but is also significant for later born children. These effects persisted within racial/ethnic and gender subgroups, as well as within the other subgroups mentioned above.

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Original Contribution

Risk of Autism and Increasing Maternal and Paternal Age in a Large North American Population

Judith K. Grether, Meredith C. Anderson, Lisa A. Croen, Daniel Smith, and Gayle C. Windham

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Previous studies are inconsistent regarding whether there are independent effects of maternal and paternal age on the risk of autism. Different biologic mechanisms are suggested by maternal and paternal age effects. The study population included all California singletons born in 1989–2002 ($n = 7{,}550{,}026$). Children with autism ($n = 23{,}311$) were identified through the California Department of Developmental Services and compared with the remainder of the study population, with parental ages and covariates obtained from birth certificates. Adjusted odds ratios and 95% confidence intervals were used to evaluate the risk of autism associated with increasing maternal and paternal age. In adjusted models that included age of the other parent and demographic covariates, a 10-year increase in maternal age was associated with a 38% increase in the odds ratio for autism (odds ratio = 1.38, 95% confidence interval: 1.32, 1.44), and a 10-year increase in paternal age was associated with a 22% increase (odds ratio = 1.22, 95% confidence interval: 1.18, 1.26). Maternal and paternal age effects were seen in subgroups defined by race/ethnicity and other covariates and were of greater magnitude among first-born compared with later-born children. Further studies are needed to help clarify the biologic mechanisms involved in the independent association of autism risk with increasing maternal and paternal age.

autistic disorder; California; maternal age; paternal age

Abbreviations: CI, confidence interval; DDS, Department of Developmental Services; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; OR, odds ratio.

Previous investigations have sought to determine whether the risk of autism in offspring increases with advancing maternal and/or paternal age and to estimate the magnitude of association (1–18). Although no studies have reported *decreased* risk with increasing parental age, early studies yielded inconsistent findings (1–11), as have more recent studies reporting maternal effects only (12), paternal effects only (13–16), or both maternal and paternal effects (17, 18). Differences across studies may, in part, be due to considerations of sample size and study design, but they may also reflect true differences across populations. Because age-related reproductive mechanisms differ between men and women, disentangling the interrelations between risk of autism and age of mothers and fathers is likely to be helpful in the search for etiologic factors.

We sought to further clarify the presence and magnitude of maternal and paternal age effects associated with autism risk in a very large and diverse North American population.

MATERIALS AND METHODS

Subjects

The study population included 7,550,026 singletons born in California between January 1, 1989, and December 31, 2002, to mothers residing in the state (fetal and infant deaths excluded). Children with autism were identified through electronic files of the California Department of Developmental Services (DDS) that operates a statewide system of regional centers and developmental centers that coordinate services for persons with autism, mental retardation, and other developmental disabilities. All remaining births in the study population constituted the comparison group for analyses.

Correspondence to Dr. Judith K. Grether, Environmental Health Investigations Branch, California Department of Public Health, 850 Marina Bay Parkway, P-3, Richmond, CA 94804 (e-mail: judith.grether@cdph.ca.gov).

DDS eligibility is determined and services are provided without regard to citizenship or financial status. Although the system is widely utilized across different socioeconomic levels and racial/ethnic groups, disparities in utilization may exist. A Client Development Evaluation Report is completed when an individual has met the eligibility requirements for active status in the DDS system and is updated periodically thereafter. Individuals with more than one qualifying condition may have one or multiple conditions coded on the Client Development Evaluation Report, depending on local practices. Autism/autistic disorder (*Diagnostic and Statistical Manual of Mental Disorders* (DSM), Third Edition-Revised, prior to 1994; DSM, Fourth Edition, starting in 1994) is a DDS-qualifying condition; individuals with Asperger's or pervasive developmental disorder, not otherwise specified, may not meet eligibility requirements for ''substantial handicap.'' Following DDS eligibility practice, we considered a child to have autism if the child was reported as being eligible for services based on autism (DDS codes 1 or 2) on at least one Client Development Evaluation Report prior to April 2006, irrespective of other qualifying conditions or diagnoses.

To identify DDS clients who were California resident births, we linked DDS electronic data to livebirth certificates using a series of matching algorithms based on personal identifiers. By use of predetermined probabilistic criteria, the algorithms classified the resulting matched records as ''sure matches'' or ''possible matches.'' Children whose records were not matched to a birth certificate were assumed to be out-of-state births and excluded from further consideration. Identifying variables for ''possible matches'' were manually reviewed for reclassification of the record as a ''sure match'' or ''nonmatch'' on the basis of obvious discrepancies of name spelling, hyphenation, and so on. Only children whose records were considered ''sure matches'' in either step were included in analyses. On the basis of a field validation study of DDS clients ($n = 39{,}969$) born in 1987–2000, we estimate that less than 0.2% of all records finally classified as ''sure matches'' may be inaccurately matched using these procedures.

Maternal and paternal age

Maternal and paternal ages at the time of the child's birth were obtained from birth certificates. Reported maternal age ranged from 7 to 96 years and paternal age from 0 to 97 years. To exclude improbable ages, we limited analyses to maternal age 15–44 years and paternal age 15–64 years. This restriction resulted in exclusion of maternal records for those less than 15 years for 12 cases (0.05%) and 17,571 noncases (0.23%), maternal records for those over 44 years for 51 cases (0.22%) and 8,220 noncases (0.11%), paternal records for those less than 15 years for 3 cases (0.01%) and 1,398 noncases (0.02%), and paternal records for those over 64 years for 11 cases (0.05%) and 2,340 noncases (0.03%). In addition, maternal age was missing for 5 cases (0.02%) and 1,678 noncases (0.02%) and paternal age for 1,225 cases (5.3%) and 522,982 noncases (7.0%).

Covariates

The covariates examined in adjusted models were those available from birth certificates and classified as follows: gender (male, female); year of birth (indicator variables for each year); maternal and paternal education (less than high school, high school graduate, some college, postgraduate); maternal race/ethnicity (white non-Hispanic, white Hispanic-US born, white Hispanic-not US born, black, Asian-US born, Asian-not US born, other); paternal race/ethnicity (white non-Hispanic, white Hispanic, black, Asian, other); birth weight ($<$1,500, 1,500–2,499, $\geq$2,500 g); gestational age ($<$32, 32–36, $\geq$37 weeks); parity (0, 1, $\geq$2); and, as a rough proxy for socioeconomic status, source of payment for delivery (private insurance (higher status) vs. self-insured/government/other).

Records with missing data or ''improbable'' maternal or paternal age were excluded from both unadjusted and adjusted statistical models (11.2% of cases and 13.6% of noncases).

Statistical analysis

We used logistic regression to investigate the association between autism and increasing maternal age and paternal age in cases compared with the remainder of the study population. First, we calculated the unadjusted odds ratios and 95% confidence intervals separately for maternal and paternal age, using 5-year age categories (25–29 years as the reference group). We then recalculated the odds ratios and confidence intervals in models adjusted only for the age of the other parent and in separate models adjusted for all covariates (in this large population, all covariates were significantly associated with autism, and all but child's sex were associated with both maternal and paternal age).

To determine if maternal or paternal age were linearly associated with the log(odds ratio) of autism, and, if so, over what age ranges, we performed assessments of age as a continuous versus a categorized variable, using likelihood ratio tests. We also assessed whether the association between autism and 10-year increments in maternal or paternal age persisted among subgroups defined by the covariates; we ran logistic models for the association between the risk of autism and parental age separately for each stratum of each covariate (adjusted for all other covariates). We then evaluated whether the magnitude of a maternal or paternal age effect was similar across the strata of each covariate by testing the equality of the log(odds ratio) with a chi-square test of homogeneity (19).

This study was conducted with approval from the California Committee for the Protection of Human Subjects.

RESULTS

From this study population of over 7.5 million singletons, we identified 23,311 children with DDS-reported autism, yielding a prevalence of autism of 3.1/1,000 for the total time period. Children with autism were more likely to be male than female (odds ratio (OR) = 4.6, 95% confidence interval (CI): 4.4, 4.8). After exclusion of observations with missing data and improbable parental ages, the analytical file included 20,701 singletons with DDS-reported autism and 6,506,555 singletons without autism. The median age at delivery for mothers at the beginning of the study period in 1989 was

Table 1. Risk of Department of Developmental Services-reported Autism and Maternal and Paternal Age (Categorical), California Resident Births, 1989–2002

	Singletons Without Autism[a] (n = 6,506,555)		Singletons With Autism[a] (n = 20,701)		Crude Odds Ratio[a]	95% Confidence Interval	Adjusted Odds Ratio[a,b]	95% Confidence Interval	Adjusted Odds Ratio[a,c]	95% Confidence Interval
	No.	%	No.	%						
Maternal age, years										
15–19	651,054	10.0	960	4.6	0.49	0.46, 0.52	0.62	0.57, 0.67	0.65	0.59, 0.70
20–24	1,556,113	23.9	3,531	17.1	0.75	0.72, 0.79	0.84	0.81, 0.88	0.86	0.82, 0.90
25–29	1,852,900	28.5	5,581	27.0	1.00	Referent	1.00	Referent	1.00	Referent
30–34	1,558,709	24.0	6,144	29.7	1.31	1.26, 1.36	1.18	1.14, 1.23	1.14	1.10, 1.19
35–39	738,308	11.3	3,659	17.7	1.64	1.58, 1.72	1.37	1.31, 1.44	1.33	1.27, 1.40
40–44	149,471	2.3	826	4.0	1.84	1.70, 1.97	1.44	1.33, 1.56	1.43	1.32, 1.55
Paternal age, years										
15–19	280,837	4.3	385	1.9	0.52	0.47, 0.58	0.74	0.66, 0.83	0.76	0.67, 0.85
20–24	1,208,883	18.6	2,416	11.7	0.76	0.72, 0.80	0.89	0.84, 0.94	0.89	0.84, 0.94
25–29	1,717,336	26.4	4,534	21.9	1.00	Referent	1.00	Referent	1.00	Referent
30–34	1,690,238	26.0	5,944	28.7	1.33	1.28, 1.38	1.17	1.12, 1.22	1.12	1.07, 1.17
35–39	1,028,251	15.8	4,432	21.4	1.63	1.57, 1.70	1.31	1.25, 1.37	1.23	1.17, 1.30
40–44	408,114	6.3	2,063	10.0	1.92	1.82, 2.02	1.46	1.38, 1.55	1.39	1.30, 1.47
45–49	123,373	1.9	649	3.1	1.99	1.84, 2.16	1.50	1.38, 1.64	1.41	1.29, 1.54
50–54	35,083	0.5	201	1.0	2.17	1.88, 2.50	1.64	1.42, 1.90	1.53	1.32, 1.77
55–59	10,799	0.2	52	0.3	1.82	1.39, 2.40	1.39	1.06, 1.83	1.35	1.02, 1.77
60–64	3,641	0.1	25	0.1	2.61	1.76, 3.86	2.00	1.35, 2.97	2.05	1.38, 3.05

[a] Excluded are observations with missing values for child's sex and birth weight, maternal age, maternal race/ethnicity, paternal race/ethnicity, maternal education, paternal education, parity, gestational age, delivery method of payment, and birth year.
[b] Adjusted for age of other parent only.
[c] Adjusted for child's sex and birth weight, maternal age, paternal age, maternal race/ethnicity, paternal race/ethnicity, maternal education, paternal education, parity, gestational age, delivery method of payment, and birth year.

27 years and increased to 28 years by 2002. For fathers, the median age at delivery was 29 years in 1989 and 31 years in 2002.

Maternal and paternal age as categorical variables

When parental ages were treated as 5-year categorical variables in unadjusted models, the odds ratio for autism increased with each increasing maternal age category over the age span 15–44 years and with each increasing paternal age category over the age span 15–64 years, except for the 55–59 age group (Table 1). When considered in multivariate models adjusted for only the other parent's age, the magnitude of the associations with increasing maternal age, and, independently, increasing paternal age, was considerably attenuated but remained statistically significant (Table 1). Adjustment for additional covariates resulted in minimal further attenuation of the estimates of association; for both maternal and paternal age, the odds ratios continued to be significantly different from the reference group (Table 1), with reduced risk for young parents and increased risk for older parents.

Maternal and paternal age as continuous variables

Figures 1 and 2 present the log(odds ratio) for autism plotted against maternal and paternal ages based on fully adjusted multivariate models. In the figures, the line represents the log(odds ratio) when parental age was modeled as a continuous variable, and the dots represent the log(odds ratio) at each year of age when parental age was represented as indicator variables. For maternal age, a linear trend was observed within maternal ages 20–39 years (86.4% of children) but not ages 15–19 years (11.4% of children) or ages 40–44 years (2.3% of children) (Figure 1). Paternal age demonstrated a similar pattern, exhibiting a linear trend for ages 20–59 years (95.4% of children) but not for ages 15–19 years (4.5% of children) or for ages 60–64 years (0.1% of children) (Figure 2).

In adjusted models with maternal age restricted to 20–39 years (and paternal age restricted to 20–59 years), the odds ratio for autism associated with each 1-year increase in maternal age was 1.03; for each 10-year increment in maternal age, the risk increased by 38% ($OR_{adjusted} = 1.38$, 95% CI: 1.32, 1.44). For paternal age 20–59 years (with maternal age 20–39 years), the odds ratio for autism associated with each 1-year increase in age was 1.02, and for each 10-year increment in paternal age, the odds ratio for autism increased by 22% ($OR_{adjusted} = 1.22$, 95% CI: 1.18, 1.26). The results were similar when the age ranges were expanded to include maternal ages 15–44 years ($OR_{adjusted} = 1.39$, 95% CI: 1.34, 1.44) and paternal ages 15–64 years

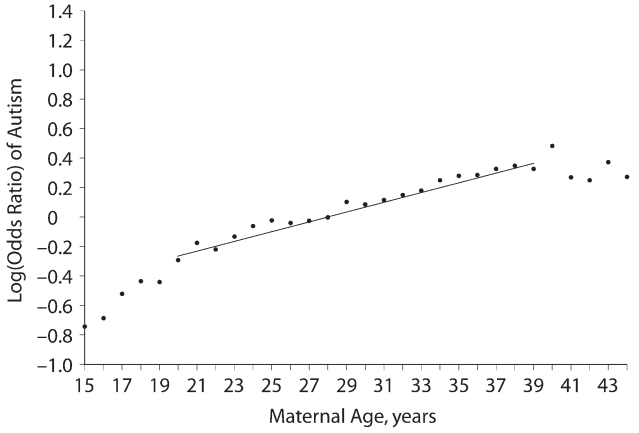

Figure 1. Maternal age and risk of autism, California resident births, 1989–2002. Children with autism are clients of the California Department of Developmental Services; the denominator population is all remaining resident livebirths alive at 1 year of age. The line (—) represents the log(odds ratio) when parental age was modeled as a continuous variable; the dots (•) represent the log(odds ratio) at each year of age when parental age was represented as indicator variables.

($OR_{adjusted} = 1.22$, 95% CI: 1.18, 1.25), despite deviations from linearity.

Subgroup analyses

In subgroup analyses in which maternal age was restricted to 20–39 years and paternal age to 20–59 years, the odds ratios for autism associated with a 10-year increase in both maternal age and paternal age remained statistically significant within all subgroups defined by the covariates (Table 2). The magnitude of autism risk associated with 10-year increments in parental age was statistically similar ($P > 0.05$) for boys compared with girls and for subgroups of gestational age, birth weight, maternal race, maternal education, and paternal race. The risk of autism associated with paternal age showed some variation across subgroups of paternal education ($P = 0.009$), without a clear pattern. The risk of autism associated with maternal age was of somewhat greater magnitude for children whose delivery was not paid for through private insurance compared with those with private insurance ($P = 0.016$) and across birth year categories ($P = 0.032$).

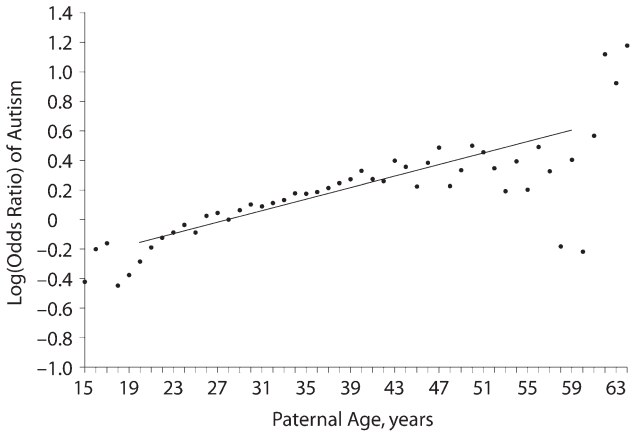

Figure 2. Paternal age and risk of autism, California resident births, 1989–2002. Children with autism are clients of the California Department of Developmental Services; the denominator population is all remaining resident livebirths alive at 1 year of age. The line (—) represents the log(odds ratio) when parental age was modeled as a continuous variable; the dots (•) represent the log(odds ratio) at each year of age when parental age was represented as indicator variables.

The increased risk of autism associated with older maternal and paternal age was of greater magnitude for first-born children compared with second or later-born children (maternal age, $P = 0.003$; paternal age, $P = 0.017$) (Table 2). Among first-born children, the increase in adjusted risk of autism associated with a 10-year increment in maternal age was approximately 49%, decreasing to 32% among second-born, and 26% among later-born children. The risks associated with paternal age followed a similar pattern, although the odds ratios were smaller.

All covariate subgroup results were similar when the maternal age range was extended to 15–44 years and the paternal age range was extended to 15–64 years (data not shown).

DISCUSSION

In this very large and diverse contemporary North American population, both increasing maternal age and increasing paternal age were independently associated with increased risk of autism. These associations were statistically linear with the log(odds) over a typical reproductive age range. For each 10-year increment in age, the odds ratio for autism associated with maternal age increased by 38% and that with paternal age by 22%. These maternal and paternal age effects persisted within racial/ethnic and gender subgroups, as well as within subgroups defined by other demographic and pregnancy-related covariates. Maternal age effects were of somewhat greater magnitude among children presumed to be at the lower end of the socioeconomic spectrum and among children born in the earlier study years. Both maternal and paternal age effects were greater for first-born compared with later-born children.

Results of early studies focusing only on the age of mothers, without consideration of the age of fathers, were inconsistent with regard to whether children born to older mothers were more likely to have autism (1–9, 11). More recent population-based studies have evaluated the risk of autism in models that considered both maternal and paternal age, adjusting for the age of the other parent and additional covariates. In Western Australia, children of mothers aged 30–34 years or 35 years or more were found to have an elevated risk for autism compared with children of mothers aged 25–29 years, with the magnitude of risk similar to our current findings; older paternal age was not a significant risk factor in this population (12). In contrast, 2 studies from Denmark, with overlapping populations born in 1973–1994 (13) and 1984–1998 (14), reported an association of autism with increasing paternal, but not maternal, age.

Table 2. Risk of Department of Developmental Services-reported Autism Associated With 10-Year Increase in Maternal and Paternal Ages for Demographically Defined Subgroups, California Resident Births, 1989–2002[a]

Subgroups	No. of Cases	No. of Noncases	Maternal Age, 20–39 Years		*P* Value[b]	Paternal Age, 20–59 Years		*P* Value[b]
			Odds Ratio	95% Confidence Interval		Odds Ratio	95% Confidence Interval	
Child's sex					0.298			0.421
Male	15,573	2,882,025	1.37	1.31, 1.43		1.21	1.17, 1.25	
Female	3,210	2,761,075	1.45	1.31, 1.59		1.25	1.17, 1.35	
Parity					0.003			0.017
0	7,879	1,977,055	1.49	1.40, 1.59		1.27	1.22, 1.33	
1	7,123	1,921,604	1.32	1.24, 1.41		1.21	1.15, 1.27	
≥2	3,781	1,744,441	1.26	1.15, 1.37		1.13	1.06, 1.20	
Gestational age, weeks					0.931			0.246
<32	289	58,800	1.46	1.08, 1.97		1.01	0.80, 1.28	
32–36	1,494	408,070	1.37	1.19, 1.57		1.20	1.08, 1.33	
≥37	17,000	5,176,230	1.38	1.32, 1.44		1.23	1.19, 1.27	
Birth weight, g					0.561			0.112
<1,500	192	31,690	1.69	1.17, 2.46		0.92	0.69, 1.24	
1,500–2,499	768	201,223	1.36	1.13, 1.65		1.30	1.12, 1.49	
≥2,500	17,823	5,410,187	1.38	1.32, 1.44		1.22	1.18, 1.26	
Maternal race					0.562			
White non-Hispanic	7,987	2,219,660	1.40	1.31, 1.49				
White Hispanic, US born	2,211	678,211	1.43	1.26, 1.62				
White Hispanic, not US born	4,000	1,700,688	1.38	1.27, 1.50				
Black	1,441	342,563	1.45	1.26, 1.67				
Asian, US born	329	72,785	1.68	1.19, 2.37				
Asian, not US born	2,418	494,898	1.31	1.17, 1.47				
Other	397	134,295	1.31	0.98, 1.74				
Paternal race								0.079
White non-Hispanic	8,446	2,218,193				1.19	1.13, 1.24	
White Hispanic	5,983	2,367,264				1.19	1.13, 1.26	
Black	1,527	412,178				1.35	1.24, 1.48	
Asian	2,397	505,120				1.28	1.17, 1.39	
Other	430	140,345				1.12	0.91, 1.38	

Table continues

When the models were further adjusted for parental psychiatric history, the increase in risk seen for older fathers remained but was statistically significant only in the later cohort. In these 2 Danish studies, the prevalence of autism was low, 0.52/1,000 for the earlier cohort and 0.86/1,000 for the later one. Reichenberg et al. (15) evaluated maternal and paternal age in an historical population-based cohort of Israeli draft board registrants with an autism prevalence of 0.84/1,000. When evaluated as a continuous variable, the odds ratio associated with each 10-year increase in paternal age was 2.14 (95% CI: 1.44, 3.16); no association was found with maternal age.

In a birth cohort study of autism in singleton children enrolled with Kaiser Permanente of Northern California (~1.6% overlap with the current study population) (17), autism was significantly and independently associated with both maternal age and paternal age, with the magnitude of risk similar to that found in the present report. The prevalence of autism in this population was 4.46/1,000. Analyzing data from 10 US study sites participating in the Autism and Developmental Disabilities Monitoring Network, Durkin et al. found that maternal age and paternal age were independently associated with autism in adjusted models (18). Site-specific prevalence ranged from 3.3 to 10.6/1,000 (20); the parental age effects were similar in magnitude to our findings and were also greater for first-born than for later-born children.

The extent to which these reported inconsistencies in maternal and paternal age effects may reflect a true difference across populations is difficult to evaluate in light of

Table 2. Continued

Subgroups	No. of Cases	No. of Noncases	Maternal Age, 20–39 Years		*P* Value[b]	Paternal Age, 20–59 Years		*P* Value[b]
			Odds Ratio	95% Confidence Interval		Odds Ratio	95% Confidence Interval	
Maternal education					0.762			
Less than high school	2,647	1,482,071	1.34	1.22, 1.48				
High school graduate	5,076	1,688,114	1.39	1.29, 1.50				
College	8,350	1,947,044	1.40	1.32, 1.49				
Postgraduate	2,710	525,871	1.46	1.29, 1.66				
Paternal education								0.009
Less than high school	2,644	1,459,374				1.18	1.10, 1.28	
High school graduate	5,060	1,743,094				1.25	1.18, 1.33	
College	7,729	1,785,742				1.15	1.10, 1.21	
Postgraduate	3,330	654,890				1.32	1.23, 1.42	
Delivery payment					0.016			0.428
Insurance	11,402	2,871,823	1.32	1.25, 1.39		1.23	1.18, 1.28	
Self, government, other	7,381	2,771,277	1.46	1.38, 1.56		1.20	1.15, 1.26	
Birth year					0.032			0.071
1989	649	419,447	1.55	1.24, 1.94		1.25	1.07, 1.47	
1990	772	451,666	1.62	1.32, 1.98		1.14	0.98, 1.33	
1991	988	447,614	1.58	1.32, 1.89		1.14	0.99, 1.30	
1992	1,183	439,926	1.63	1.38, 1.92		1.08	0.96, 1.23	
1993	1,190	425,181	1.48	1.26, 1.74		1.25	1.11, 1.41	
1994	1,352	413,745	1.28	1.10, 1.50		1.15	1.03, 1.30	
1995	1,361	398,649	1.21	1.04, 1.41		1.34	1.20, 1.49	
1996	1,452	387,804	1.30	1.12, 1.50		1.24	1.11, 1.38	
1997	1,517	374,334	1.33	1.16, 1.53		1.33	1.20, 1.47	
1998	1,646	372,815	1.37	1.20, 1.57		1.27	1.15, 1.41	
1999	1,720	370,804	1.29	1.13, 1.48		1.22	1.11, 1.35	
2000	1,775	382,640	1.41	1.24, 1.60		1.21	1.09, 1.33	
2001	1,703	379,904	1.31	1.14, 1.50		1.18	1.07, 1.31	
2002	1,475	378,571	1.41	1.22, 1.63		1.19	1.07, 1.33	

[a] Excluded are observations with missing values for any covariates. Subgroup-specific models were adjusted for all the other covariates listed in Table 2.
[b] Chi-square test of homogeneity.

unexplained but substantial differences in the observed prevalence of autism in the different study populations.

There are several possible age-related biologic mechanisms through which increasing maternal and paternal age could affect fetal brain development leading to autism. For women, these include hormonal factors that alter the in utero environment (21), greater risk of infertility and exposure to assisted reproductive technologies (22–24), nucleotide repeat instability (25), and an increase in body burdens from cumulative toxic exposures (26, 27). These factors are not mutually exclusive and could work synergistically to increase the risk of atypical fetal brain development, but they have been little studied with regard to autism.

For men, the most likely age-related biologic explanation is increased de novo mutations in sperm, occurring more commonly in older fathers and perhaps affected by cumulative toxic exposures. Of possible relevance to autism, studies have shown an independent association of bipolar disorder (28) and schizophrenia (29–33) in offspring with advancing paternal, but not maternal, age. The association for schizophrenia is limited to sporadic cases that lack a family history of the disorder, consistent with the hypothesis of accumulating de novo mutations in the germ cells of older fathers (33). It has been hypothesized that de novo mutations are associated with nonfamilial or sporadic autism (34), and limited evidence indicates that de novo copy number variations may be associated with autism in some children (35).

Without further research, the extent to which these age-related biologic factors may contribute to increased risk of

autism among children born to older mothers and fathers remains speculative, as is the possibility that variation in the frequency of these factors may explain differences in parental age effects from one population to another. However, our observation of substantially greater maternal and paternal age effects among first-born children would appear to be inconsistent with a strong role for age-related biologic factors unless there is a relation between these biologic factors and parity or birth order of the child. De novo mutations in sperm are unlikely to be related to parity, but maternal age effects could potentially be related to whether or not a woman has experienced prior pregnancies.

An alternative, but not mutually exclusive, explanation is that increased parental age may be a marker of preexisting genetic risk, as suggested by the earlier Danish study in which parental psychiatric history was associated with older age at parenthood (13). Men and women with a genetic predisposition for having a child with autism may simply be more likely to delay childbearing until they are older. Parents who delay childbearing may be more likely to have fewer children, but this could not explain the greater parental age effect among low-parity children unless delayed childbearing is related to risk of autism. Parents who have an autism spectrum disorder-affected child may decide to forgo further childbearing (i.e., ''stoppage''), but stoppage could not explain the greater parental age effect among low-parity children unless stoppage is related to the age of parents. Finally, an independent age effect for both mothers and fathers may be consistent with a preexisting risk explanation, as genetic risk to the offspring could be transmitted through either or both parents.

Early studies that demonstrated preexisting risk in parents of children with autism, as defined by a history of psychiatric disorders (36–38) or characteristics of the broader autism phenotype (39–42), did not consider parental ages or parity as covariates. A recently reported study of preexisting risk and parental age did not observe an association between father's age at first paternity and characteristics of the broader autism phenotype in fathers or mothers of children with autism from multiplex families (34). Further studies are clearly needed.

We found a stronger maternal (but not paternal) age effect for children born during the early study years (1989–1993), compared with children born in more recent years. Although it is possible that this difference is related to differential age-related opportunities for obtaining an autism diagnosis, this seems unlikely because there is little difference in maternal age effects for children born in the years after 1993. The oldest children born during these years were well beyond the typical age at diagnosis in the DDS system. Alternatively, if maternal age is differentially associated with phenotypic subgroups within the autism spectrum, the difference between the early and later birth years may represent a change in the phenotypic profile for children receiving DDS services for autism after implementation of DSM, Fourth Edition, criteria in 1994 and other changes. Another possible explanation is that older mothers may have been more assertive in seeking services for their affected children during the earlier period when there was less public awareness and support. Our finding of a stronger maternal age effect among children of presumed lower socioeconomic status may indicate that, among families relatively disadvantaged by socioeconomic factors, older parents were more likely than younger ones to obtain services for their affected children.

Limitations in the data available through DDS records prevented us from further evaluating these and other possible explanations for the association between older parents and autism risk in children. Our study is also limited by reliance on a single source to ascertain autism cases, leading to underascertainment of affected children, particularly those who do not meet DDS eligibility criteria for ''substantial handicap.'' Despite this limitation, the DDS-based autism prevalence of 3.1/1,000 children is considerably higher than that reported in the Danish (13, 14) and Israeli (15) studies discussed above, although still lower than estimates obtained by several other recent studies (20, 43–49).

Strengths of our study include a very large cohort population, with comparable proportions of cases and noncases excluded for unlikely parental ages and missing data. By limiting analyses to singletons, we eliminated possible confounding by factors associated with multiple gestations. The very substantial size of this population permitted multivariate modeling and subgroup analyses with a high level of statistical precision. Diagnostic validation has been obtained for some DDS subjects through research evaluations using the Autism Diagnostic Observation Schedule (50) and the Autism Diagnostic Interview-Revised (51); less than 2% of over 300 children served by DDS for autism did not meet DSM, Fourth Edition, criteria for an autism spectrum disorder using these instruments (52).

Further understanding of the pathways that link childhood autism to older age of parents may require studies among subgroups of affected children defined by phenotypic and demographic characteristics, as well as studies focused on preexisting parental risk and age-related biologic factors.

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Author affiliations: Environmental Health Investigations Branch, California Department of Public Health, Richmond, California (Judith K. Grether, Meredith C. Anderson, Daniel Smith, Gayle C. Windham); and Division of Research, Kaiser Permanente Northern California, Oakland, California (Lisa A. Croen).

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