Estimated Autism Risk and Older Reproductive Age

Marissa D. King, PhD, Christine Fountain, PhD, Diana Dakhilallah, BA, and Peter S. Bearman, PhD

The prevalence of autism, a developmental disorder characterized by serious impairments in social interaction and language development as well as stereotyped and repetitive behaviors, has increased dramatically over the past 2 decades from approximately 4 to 40 cases per 10,000.1 The cause of the increase is unknown, as is the etiology of autism. Evidence from twin studies suggests that autism is likely a genetic disorder.2-4 However, genetic causes for the vast majority of autism cases have not yet been identified through molecular genetic research.5 In addition, dozens of previous studies have identified a wide range of perinatal and parental risk factors.6 Despite these studies, our understanding of even the most basic of these factors, parental age, is muddled.

Previous studies examining the association between parental age and autism have yielded contradictory results. With respect to mothers, 5 of the 11 studies that examined the risk associated with maternal age and autism spectrum disorders reported an increase in risk after adjustment for other confounding factors.7-11 Six studies did not identify significant elevated risk.12-17 Paternal age has also been associated with autism. Four of 7 studies found an association between paternal age and autism.7,18,33,37 However, there is wide variability in the reported risk, spanning from no association to an almost 6-fold increase when paternal age exceeds 40 years.17 (These previous studies are summarized in an appendix that is available as a supplement to the online version of this article at http://www.ajph.org.)

With the exception of a recent study that examined the birth cohort of 1994 in 10 US States,18 all previous studies have pooled observations across several birth cohorts; in fact, it is not uncommon for studies to pool data from individuals who are born 10 to 20 years apart.19-24 However, paternal age, and particularly the proportion of the paternal population over 40 years of age, increased rapidly during this period.

We provide the first investigation into changes in risk factors associated with autism across successive birth cohorts. We aimed to estimate the risk for autism associated with maternal and paternal age across successive birth cohorts to gain insight into possible sources of discrepancies in previous studies.

**Objectives.** We sought to estimate the risk for autism associated with maternal and paternal age across successive birth cohorts.

**Methods.** We linked birth records and autism diagnostic records from the California Department of Developmental Services for children born in California between 1992 and 2000 to calculate the risk associated with maternal and paternal age for each birth cohort as well as for the pooled data.

**Results.** The categorical risks associated with maternal age over 40 years ranged from a high of 1.84 (95% confidence interval [CI] = 1.37, 2.47) to a low of 1.27 (95% CI = 0.95, 1.69). The risk associated with paternal age ranged from 1.29 (95% CI = 1.03, 1.6) to 1.71 (95% CI = 1.41, 2.08).

**Conclusions.** Pooling data across multiple birth cohorts inflates the risk associated with paternal age. Analyses that do not suffer from problems produced by pooling across birth cohorts demonstrated that advanced maternal age, rather than paternal age, may pose greater risk. Future research examining parental age as a risk factor must be careful to avoid the paradoxes that can arise from pooling data, particularly during periods of social demographic change.

be linked typically belonged to children who were born outside of California and later moved to the state.

Our primary variables of interest, maternal and paternal age at birth, were extracted from birth certificates. Data on paternal age for the entire population was missing from 8% of the birth records. Persons subsequently diagnosed with autism were more likely to have missing paternal age data, ranging from 8% to 10% depending on the birth cohort. Maternal age was rarely missing (<1%). We also obtained the following control variables from the birth certificates: child's gender, race, birthweight, and duration of gestation; whether the child was a single or multiple-birth; and parity of the mother. Birthweight was examined categorically with birthweight less than 2500 grams considered low birthweight. Gestational age less than 35 weeks was considered premature. Whether the newborn was placed in a neonatal intensive care unit was extracted from the birth records as well. If a newborn had a birthweight greater than 2500 grams and a gestational age of more than 35 weeks but was admitted to the neonatal intensive care unit, this variable was set to 1. Otherwise, it was set to 0. Parity was used to generate a dummy variable for first birth. In addition to these variables, all analyses also included maternal and paternal education.

To examine the associations between maternal and paternal ages and autism, we conducted 3 sets of analyses. First, we ascertained the association between maternal and paternal age and autism for each birth cohort from 1992 to 2000. To do this, we ran logistic regressions treating parental age as a categorical variable (<30, 30–34, 35–39, and ≥40 years). All of the control variables identified previously were included in the models.

Second, to observe the effect of pooling data, we cumulatively pooled across birth cohorts. Using a moving window for the 1995 birth cohort, we pooled data from the 1992, 1993, 1994, and 1995 birth cohorts; for the 1996 birth cohort, we pooled observations from the birth cohorts of 1992 to 1996, and so on. This allowed us to mimic the method used in most of the previous studies, which pooled data across birth cohorts.

Problems may arise from pooling data across birth cohorts. Categorical specifications are particularly prone to reversal paradoxes in contexts in which there are large differences by group in the denominators of a rate. To assess the effect these problems may have had on previous studies, we first examined whether there were large by-group differences in maternal and paternal age, as well as how these differences changed over time. Last, we conducted logistic regressions by using a decomposition strategy.

In this approach, maternal and paternal ages were considered in a continuous framework: that is, we did not treat age as a categorical variable. The decomposition was necessary to avoid the multicollinearity problems that arise when simultaneously including continuous maternal and paternal age in a regression. The decomposition enabled us to disentangle whether paternal or maternal age had a stronger association with autism while avoiding some of the problems generated by multicollinearity and categorical specifications. The decomposition was as follows:

\[ \gamma_1(A_{m} + A_{f}) + \gamma_2(A_{m} - A_{f}) = 2(\beta_{m}A_{m} + \beta_{f}A_{f}) \]

\[ \gamma_1 A_{m} + \gamma_2 A_{f} = 2(\beta_{m}A_{m} + \beta_{f}A_{f}) \]

\[ A_{m}(Y_1 + Y_2) = 2(\beta_{m}A_{m}) \]

\[ A_{f}(Y_1 - Y_2) = 2(\beta_{f}A_{f}) \]

where \( A_{m} \) is maternal age and \( A_{f} \) is paternal age. For instance, assume the case of a 32-year-old mother and a 35-year-old father. The sum of their ages, \( A_{m} + A_{f} \), is 67. The difference in their ages, \( A_{m} - A_{f} \), is 3. Following the decomposition, adding the sum, \( \gamma_1(A_{m} + A_{f}) \), and the difference, \( \gamma_2(A_{m} - A_{f}) \), gives us 64. This is twice the mother's age. Similarly, the difference, \( (A_{m} + A_{f}) - (A_{m} - A_{f}) = 70 \), is twice the father's age. Using this approach, we can disentangle parental age effects without significant multicollinearity by including the sum and the difference of parental ages as separate terms and then rearranging the parameter estimates from the analysis to recover the parameters for maternal and paternal age. In the decomposition, \( \beta \) represents 2 parent years.

RESULTS

The risk of autism ranged from 29 per 10000 persons in the 1992 birth cohort to 43 per 10000 persons in the 2000 birth cohort.

Mean maternal and paternal ages at the time of the child's birth increased from 1992 to 2000. The mean maternal age was 26.9 (±6.03) years in 1992 and increased to 27.7 (±6.33) years in 2000. Similarly, paternal age increased from 29.6 (±6.84) years to 30.6 (±7.11) years over the same period. The increasing standard deviation, particularly of paternal age, is noteworthy because parents' age at birth is strongly bounded on the left tail of the distribution. Thus, there was a considerable increase in advanced paternal age, extending the length of the right tail of the distribution.

The percentage of California births to fathers and mothers over the age of 40 years for our observation period is reported in Figure 1. Note that the share of births associated with older fathers increased markedly from 7.45% (44 973 out of 603 712) in 1992 to 10.1% (53 611 out of 533 078) in 2000. In contrast, the share of births to women over the age of 40 years increased more slowly from 1.9% (11 636 out of 603 396) in 1992 to 3.1% (16 633 out of 533 078) in 2000.

Association of Parental Age and Autism Over Time

Parental age over 40 years was consistently found to be associated with an increased risk of autism. As Figure 2 shows, prevalence rates for autism when parental age exceeded 40 years were higher than the prevalence in the general population. Among all children born between 1992 and 2000, regardless of paternal age, the prevalence of autism was 34 per 10 000. In contrast, the prevalence rate for children born to parents over 40 years of age was 56 per 10 000. Prevalence rates were slightly higher when maternal age exceeded 40 years relative to when paternal age exceeded 40 years. However, there were significantly more men over 40 years of age, with and without children with autism, in our population.

Although the prevalence rates for maternal and paternal ages were roughly comparable, the raw proportions by gender differed dramatically. Out of 123 896 children born to a
FIGURE 1—Percentage of the population over 40 years of age at child's birth by gender, California, 1992-2000.

FIGURE 2—The observed prevalence of autism in the total population and in populations born to a mother or father over 40 years of age, California, 1992-2000.
mother over the age of 40 years, 764 were later diagnosed with autism (764 out of 123,896). In contrast, there were 426,744 children born to men over the age of 40 years. Of these, 2357 were later diagnosed with autism (2357 out of 426,744). These strikingly different raw proportions may create a reversal paradox and lead to a consistent inflation of the risk associated with paternal age when examined in a pooled regression framework.

**Autism and Advanced Parental Age in a Logistic Regression Framework**

Here we considered the risk of advanced maternal and paternal age in a logistic regression framework, in which we controlled for all of the variables previously identified and treated age as a categorical variable. In this framework, as can be observed in Figure 3, advanced maternal age was a significant risk factor for autism in most of the birth cohorts.

The risk associated with maternal age exceeding 40 years varied from a high of 1.84 (95% confidence interval [CI] = 1.37, 2.47) in 1993 to a low of 1.27 in 1995 (95% CI = 0.95, 1.69), roughly a 3-fold difference in risk. Thus, there was considerable variability in risk associated with maternal age across birth cohorts.

Paternal age was also associated with an increased risk of autism across all birth cohorts, though the risk estimates were wide-ranging. The relative risk for fathers over 40 years of age by birth cohort is also reported in Figure 3. The risk ranged from a low of 1.29 (95% CI = 1.03, 1.60) in 1992 to a high of 1.71 (95% CI = 1.41, 2.08) in 1995, more than a 2-fold difference in risk.

**Moving Windows by Successive Pooling Over Time**

Although no clear pattern was observed associated with parental age across the birth cohorts, a very clear pattern emerged when we successively pooled the data. The pattern produced by pooling risk across successive birth cohorts was seen most clearly when looking at the pooled risk associated with maternal and paternal ages simultaneously. In this framework, the large variability in risk across successive birth cohorts hid a much clearer and consistent trend that arose from pooling the data where there were large by-group differences in age denominators. As can be seen in Figure 4, pooling the data led to an increase in measured paternal age risk. This held even in years in which the risk was lower than the pooled risk for all previous years. For instance, from 1997 until 2000, the paternal risk observed by birth cohort declined from roughly 1.65 to 1.44. However, as we pooled across these cohorts, no comparable decrease in risk was observable.

For maternal age, which did not experience as large an increase in either mean maternal age or the proportion of births to women over 40 years of age, pooling across birth cohorts helped to smooth some of the cohort variability and produced reasonable estimates of risk that were in line with the findings based on cohorts. However, this strategy underestimated the risk of maternal age relative to paternal age.

Pooling data across birth cohorts consistently inflated the risk associated with paternal age and obscured real and considerable variability in the association between parental age and risk for autism. In the case of paternal age, pooling led to a serious overstatement of risk.

**Linear Decomposition**

The results of the linear decomposition indicated that the risk associated with maternal age was significantly larger than the risk associated with paternal age. As shown in Figure 5, the risk associated with an additional maternal year exceeded the risk of an additional paternal year. Remembering that the relative risk was the risk for 2 additional parental years, the maternal risk obtained from the decomposition closely approximated the risk obtained from the cohort analysis. The risk of autism for a child born to a 40-year-old mother peaked among the 1992 birth cohort with an 80% increase in risk and then settled to between 40% and 50% after 1994. In contrast,
FIGURE 4—The effect of cumulatively pooling data across additional birth cohorts on the measured risk associated with maternal or paternal age, California, 1992–2000.

Note. The coefficient represents the increased odds of autism resulting from the unique contribution of maternal and paternal age.

FIGURE 5—Effects of maternal and paternal age obtained from the decomposition equation, California, 1992–2000.
the paternal risk estimates from the decomposition did not accord with those obtained from the cohort analysis. The decomposition suggested that the effect of parental age operated solely through maternal age. With the exception of the 1992 birth cohort, the risk associated with paternal age was not statistically significant.

**DISCUSSION**

To our knowledge, ours is the first study that has looked at changes in risk factors associated with autism across successive birth cohorts. The categorical risks associated with maternal age over 40 years ranged from a high of 1.84 (95% CI=1.37, 2.47) in 1993 to a low of 1.27 in 1995 (95% CI =0.95, 1.69). The risk associated with advanced paternal age ranged from a low of 1.29 (95% CI=1.03, 1.6) in 1992 to a high of 1.71 (95% CI =1.41, 2.08) in 1995. The risks associated with paternal age for the 1994 birth cohort were identical to those reported for the same birth cohort in a recent study examining autism spectrum disorders.7 The maternal age estimates presented in the present study were higher, however, which may reflect different maternal age categorizations.

Our study produced 3 new findings. First, variability exists in risk associated with both maternal and paternal age across birth cohorts. This substantial variability is masked in data that combine multiple birth cohorts. Second, pooling across multiple birth cohorts artifically inflates the risk associated with paternal age. Finally, analyses that do not suffer from the statistical fallacies produced by pooling demonstrate that advanced maternal age, rather than paternal age, may pose a greater risk.

In analyses using decomposition, we found very little evidence for an independent paternal age effect. This stands in contrast with the findings of 2 previous studies that found maternal and paternal age to be independently associated with autism spectrum disorders.2,10 One of the aforementioned studies, however, only found a paternal age effect when examining autistic disorder.9,19 Comparing the decomposition results with the categorical results suggests that certain specifications of age data may produce a reversal paradox. Reversal paradoxes are well-known phenomena that occur in the analysis of categorical variables when the combining of nonhomogeneous groups results in the reversal of an association.21,22 Reversal paradoxes are most likely to occur when there are large differences by group in the denominators of a rate, such as in this context when we observe a substantially larger number of fathers over the age of 40 years. The resulting paradox can cause the total rate for the combined groups to be higher than the rate for any of the component groups.

Substantial compositional changes within the population of persons with autism have also occurred over the previous decade as a consequence of changes in diagnostic criteria and enhanced ascertainment.23 For instance, over the course of our study, the level of autism—mental retardation comorbidity declined from 40.3% among the 1992 birth cohort to 22.7% among the 2000 birth cohort. Changes in the composition of the autism population may account for some of the variability in risk observed across birth cohorts, as well as across various studies. One possibility is that there is a relation between compositional changes and etiologic heterogeneity.

Understanding the biological factors underlying the association between maternal age and increased risk for autism will require further research. The maternal effect could be explained by chromosomal changes, changes in reproductive technologies, pregnancy complications, or environmental exposures, to name a few possibilities.7,24 Our study suggests that whatever may be undergirding the association has not had a constant effect over time. The temporality of the variations in risk may provide important clues about possible causal mechanisms. For instance, variations in risk may be correlated with variations in toxic exposure. However, this temporal change must be considered simultaneously with the compositional heterogeneity that has arisen over the last decade.

Our study had several limitations. First, our analyses were limited to persons enrolled with the DDS in the state of California, as well as persons born in California. Because our analyses examined the population of Californians, the population dynamics we describe are limited to that context. Future research is needed to uncover whether these dynamics are occurring elsewhere. Second, because we utilized birth records, our analyses are subject to the coding errors and missing data that accompany any analysis using birth records, which have been widely described elsewhere. However, relative to other birth record data, our data set was relatively complete. Furthermore, with the exception of gestational age, the data we used are typically reported accurately.25 Finally, case ascertainment potentially posed problems for the most recent birth cohorts. Our analyses ended with the 2000 birth cohort to mitigate this problem. To assess whether our results were capturing age at diagnosis, rather than general risk for autism, we conducted ancillary analyses examining factors associated with age at diagnosis. The only individual-level variables consistently associated with age at diagnosis were maternal and paternal education. Parental age was not associated with age at diagnosis. In addition, we reanalyzed the 1999 birth cohort without allowing for diagnoses after June 2005, thus mimicking the time allowed for diagnostic capture for the 2000 birth cohort. Our results remained stable. This assuages our concern that we might be capturing ascertainment rather than risk.

The risk for autism associated with advanced maternal age is considerable. However, the risk associated with paternal age is likely considerably less than reported in previous studies. Future research examining paternal age as a risk factor must be careful to avoid the paradoxes that can arise from pooling data across successive birth cohorts. As noted above, these paradoxes are exacerbated in this context because of rapid social demographic change, specifically, the marked increase in older parents. The findings in this article thus point to the importance of simultaneously considering social, demographic, and biological factors, as well as how they may interact, when examining hypothesized risk factors for autism.

**About the Authors**

At the time of the study, the authors were with the Institute for Social and Economic Research and Policy, Columbia University. Mrs Luzamfeld Center for the Social Sciences, Columbia University, New York; Mrs Fountain was also with the Department of Sociology at the University of South Carolina, Columbia. Peter S. Bearman was also with the Department of Sociology, Columbia University, New York.

Correspondence should be sent to Peter S. Bearman, PhD, Paul Lazarsfeld Center for the Social Sciences, Columbia University, 420 West 118th Street, L2B Building Room 7903, MC: 7355, New York, NY, 10027 (e-mail: psh17@columbia.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints/Errants" link.

This article was accepted December 14, 2008.
References


Confronting Violence

Answers to Questions about the Epidemic Destroying America's Homes and Communities, 2nd Edition
George A. Gellert, MD

"... A great addition to the resources necessary to understand, diagnose, treat, and more important, prevent violence in America."
Robert E. McAlee, Past President, American Medical Association

ORDER TODAY!
384 pages, softcover, 2002
$21.00 APHA Members (plus s&h)
$30.00 Nonmembers (plus s&h)

American Public Health Association
PUBLICATION SALES
WEB: www.aphabookstore.org
E-MAIL: APHA@pbcs.com
TEL: 888-320-APHA FAX: 888-361-APHA