

LETTERS

ADVANCING PATERNAL AND MATERNAL AGE ARE BOTH IMPORTANT FOR AUTISM RISK

King et al.¹ addressed 2 questions using data from the California Department of Developmental Services. The first concerned possible bias in estimating the association between parental age and autism as a result of pooling data across birth years. In their analysis, pooling caused a “reversal paradox” for paternal age—that is, the association between paternal age and autism was substantially inflated in pooled data. On this basis, they argued that the relation between paternal age and autism has been overestimated in previous research.

We, however, do not agree with this conclusion. Previous studies have considered birth years and the effects of pooling data. Birth year is often included as a confounder in the statistical models, and data by birth year are often inspected by researchers to check for such possible pooling artifacts.^{2–6} In fact, a recent study by Grether et al.⁵ used the same California data source as King et al. and found no evidence for an inflated paternal-age effect when pooling data. For every 10-year increase in paternal age the pooled odds ratio (OR) for autism was 1.22 (95% confidence



The Maneki Neko (literally “Beckoning Cat”) is a common Asian sculpture, often made of ceramic, which is believed to bring good luck to the owner. The sculpture depicts a cat (traditionally a Japanese Bobtail) beckoning with an upright paw, and is usually displayed—many times at the entrance—in shops, restaurants, pachinko parlors, and other businesses. In the design of the sculptures, a raised right paw supposedly attracts money, while a raised left paw attracts customers. Image from Punchstock.com. Printed with permission.

interval [CI]=1.18, 1.26). The equivalent OR for individual years was lower than was the pooled OR in 7 of the 14 individual years and higher in 6 (Table 2 in Grether et al.⁵). These results suggested that bias, if it exists, is only minimal. Furthermore, the research clearly indicated that an association between paternal age and autism in offspring can be detected in most populations and is not an artifact of confounding by maternal age or of pooling across birth cohorts.

The second question that King et al. addressed is the relative importance of paternal or maternal age. The authors used a statistical method of decomposition—about which we have some qualms—to examine this. However, is it really important whether the association with autism is stronger for paternal or for maternal age? Is there a “competition” between the two? At this point, an abundance of large and well-designed studies have demonstrated

that advancing maternal and paternal age are associated with autism. One can draw different conclusions about their relative importance depending upon the perspective adopted. For example, men can and often do conceive at much later ages than can women, broadening the paternal age range. So, even if 10 years of maternal age confers greater risk than does 10 years of paternal age, the oldest men carry greater risk than do the oldest women (Table 1 in Grether et al.⁵).

Regardless of the relative importance of paternal and maternal age, it is noteworthy that so many credible epidemiologic studies (including that conducted by King et al.) have now confirmed that paternal and maternal age at birth are related to autism risk. The evidence is substantial enough to justify a search for the underlying mechanisms. Genomic alterations could be involved in either the case of men or of women,⁷ as could other factors. All possible

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mechanisms can and should be studied in both human and animal models.⁸ ■

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References

1. King MD, Fountain C, Dakhllallah D, Bearman PS. Estimated autism risk and older reproductive age. *Am J Public Health*. 2009;99(9):1673–1679.
2. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. *J Child Psychol Psychiatry*. 2005;46(9):963–971.
3. Larsson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status. *Am J Epidemiol*. 2005;161(10):916–925; discussion 926–928.
4. Croen LA, Najjar DV, Fireman B, Grether JK. Maternal and paternal age and risk of autism spectrum disorders. *Arch Pediatr Adolesc Med*. 2007;161(4):334–340.
5. Grether JK, Anderson MC, Croen LA, Smith D, Windham GC. Risk of autism and increasing maternal and paternal age in a large north American population. *Am J Epidemiol*. 2009;170(9):1118–1126.
6. Reichenberg A, Gross R, Weiser M, et al. Advancing paternal age and autism. *Arch Gen Psychiatry*. 2006;63(9):1026–1032.
7. Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. *Arch Pediatr Adolesc Med*. 2007;161(4):326–333.
8. Smith RG, Kember RL, Mill J, et al. Advancing paternal age is associated with deficits in social and exploratory behaviors in the offspring: a mouse model. *PLoS One*. 2009;4(12):e8456.

KING AND BEARMAN RESPOND

We appreciate the interest that Reichenberg et al. have shown in our work. In our article, we showed that examining parental age effects by birth cohort can yield important insight into variability in risk across time and ameliorate risk inflation arising from pooling data across birth cohorts.¹ A recent study published by Grether et al.² further affirmed the value of careful attention to temporality in risk, rather than diminishing the importance of cohort analyses as Reichenberg et al. suggested. Using the same dataset employed in our analyses but extending it to several additional birth cohorts, Grether et al.'s analysis revealed a striking temporal pattern of maternal risk. Among early birth cohorts born between 1989 and 1994 the autism risk associated with maternal age was consistently and substantially greater than was the risk among later born cohorts. The risk associated with maternal age for cohorts born after 1994 never approached the levels of risk observed among earlier cohorts. This not only has implications for pooling data but, more importantly, may offer etiological clues. Simply controlling for birth cohort as Reichenberg et al. suggested is insufficient. Rather, it is necessary to allow the effect of age to vary across years either by including a parental age-cohort interaction³ or by stratifying by birth cohort as we did.¹

We absolutely agree with Reichenberg et al. that the importance of parental age as a risk factor for autism has been well established and can be detected in most populations. However, we believe that it is time to move beyond this fact to understand how and why parental age is associated with autism risk. One important step toward understanding how parental age may be causally related to autism is to begin to disentangle the differential importance of maternal and paternal age. There are several possible age-related biologic pathways through which parental age could influence risk for autism. These are different for men and women. Untangling the relative importance of maternal and paternal age may yield important insight into which biologic mechanisms may

be causally related to autism. We obviously agree that parental age matters for autism, but we think that considering the temporal patterning and parental distribution of risk may allow us to move from just asserting that parental age matters to understanding why it matters—a goal we know that Reichenberg et al. share with us. ■

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References

1. King M, Fountain C, Dakhllallah D, Bearman PS. Estimated autism risk and older reproductive age. *Am J Public Health*. 2009;99(9):1673–1679.
2. Grether JK, Croen LA, Smith D, Windham GC. Risk of autism and increasing maternal and paternal age in a large North American population. *Am J Epidemiol*. 2009;170(9):1118–1126.
3. Lauritsen MB, Pederson CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. *J Child Psychol Psychiatry*. 2005;46(9):963–971.

CAPACITY-BUILDING ASSISTANCE AND STRUCTURAL CHALLENGES IN HIV PREVENTION SERVICES

Friedman et al. produced a thoughtful essay that presented theoretical and practical considerations of underlying reasons for social and behavioral actions of African Americans. Their work revealed a higher order of social structures that can impact HIV transmission. These higher-order structures included themes of survival, struggle, and propriety found in African American communities.¹ While we applaud them in their analyses of myriad higher-order