The Age Gauge: Older Fathers Having Children

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Editor's Note: In recent years, scientists have debated the existence of a link between a father's age and his child's vulnerability to psychiatric problems. Our authors led a research team that produced a paper that analyzed data on all individuals born in Sweden from 1973 through 2001. Both the authors' study and another study raise as many questions as they answer, but they suggest that children born to middle-aged men are more likely than their older siblings to develop a range of mental difficulties, including bipolar disorder, autism, and schizophrenia.

"When should I have children?" "Am I too old to have a child?" "How old is too old?" "Is my daughter destined to have problems because I had her when I was older?" These are just some of the questions that many people, including colleagues, friends, and anonymous individuals (via email), posed to both of us after the news media covered the results of two large-scale studies on the association between paternal age at childbearing and mental-health problems of offspring. One study, which was conducted by John McGrath and colleagues, was based on data from Denmark.[1] The second study, based on data from Sweden, was conducted by the two of us and our colleagues.[2] How did we answer these questions from the public? What does the science say—and not say—about the topic?

At the outset, let us first acknowledge that these two studies address very sensitive issues. Decisions about whether to have children and when to have children are incredibly private. In addition, the prospect that one's children will have both mental-health and physical problems is a major concern for parents, and caring for offspring with such problems can cause considerable pain and suffering.

Overview of the Studies

The two recent studies had many similarities. First, both analyzed comparable data sets to explore the associations with parental age at childbearing via epidemiologic methods that use large, representative samples to examine the distribution and determinants of health. The data sets in both studies were based on extensive population records kept by the governments of Scandinavian countries, including Denmark and Sweden. For example, these countries have extensive records of all inpatient and outpatient visits to hospitals. Scandinavian governments also are able to use personal identification numbers to link several databases. As a result, separate databases can be combined such that they contain information across different generations and domains (e.g., psychiatric diagnoses and age at childbearing). To facilitate the analysis of these population data sets while protecting personal information, government agencies in both countries alter the personal identifiers after merging the data sets, a practice that has led to extensive psychiatric epidemiology

research.[3,4] Unfortunately for research purposes, no such data sets are available in the United States.

Second, both studies took advantage of the size and scope of the national data sets. Access to these large data sets enabled both research groups to explore a fuller range of parental age at childbearing because the data sets included high numbers of individuals at the extreme ends of childbearing (e.g., older than 45 years). The large data sets had sufficient numbers of exposed cases (e.g., offspring diagnosed with autism whose parents were older than 45 years at childbirth), enabling both groups to predict relatively rare outcomes in the offspring (e.g., schizophrenia and autism). Previous research teams, which relied on smaller data sets, could not explore advancing paternal age at childbearing with as much precision.

Third, both studies presented population and adjusted estimates of the magnitude of the association between paternal age at childbearing and disorders of offspring. Notably, the two estimates address different research questions. The population estimates respond to this question: How common is it that an offspring born to an older father has psychiatric problems? Both research teams sought to answer this question by comparing the rates of several disorders among offspring born to fathers of different ages in the entire population. The adjusted estimates, on the other hand, respond to this question: When it comes to psychiatric problems in offspring, how much risk is *specifically* due to advancing paternal age?

The studies addressed the latter question by using statistical techniques and other approaches to estimate the magnitude of the association between paternal age at childbearing and offspring disorders while trying to hold constant the highest possible number of factors that differ among fathers who have children at different ages (e.g., parents' socioeconomic status). Researchers must use various techniques to study advancing paternal age at childbearing because men who have children when they are younger differ, sometimes greatly, from men who delay childbearing. Plus, it is impossible to conduct a randomized experiment in humans—you can't randomly assign men to have children at different ages.

It is important to stress that both research questions (based on population and adjusted estimates) are valid and might be of interest for public-health policy. Both questions can also have important implications for subsequent basic research because the analysis of large population data sets can provide critical information about mechanisms at multiple levels of analysis that researchers should explore in the future.[5–9]

Previous epidemiological research on advancing paternal age had suggested that advancing paternal age is associated with increased risk for psychiatric problems in the offspring, but the findings were inconsistent.[10–16] Furthermore, many researchers suggested that any association between advancing paternal age and offspring psychiatric problems was not due to the specific consequences of delaying childbearing; rather, differences associated with advancing paternal age, such as personality and psychiatric problems in the fathers[17–19] and birth-order effects in the offspring,[11] could better explain any associations. Given these concerns, the two recent studies based on the large, population-based registries were intended to provide more understanding of the associations between paternal age at childbearing and offspring psychiatric problems.

The Danish Study

The study by McGrath and colleagues included all individuals born in Denmark from 1955 through 2006, a sample of almost 3 million people. The study indexed psychiatric problems based on inpatient hospitalizations and outpatient visits to psychiatric departments. The study presented population estimates for several psychiatric disorders. For instance, researchers found that compared to offspring born to fathers 25 to 29 years old (the reference group in the study), offspring born to fathers over the age of 45 were 1.4 times more likely to have schizophrenia and 1.7 times more likely to have autism. However, the offspring of older fathers were less likely to have hyperkinetic disorders, which is similar to the diagnosis of attention-deficit/hyperactivity disorder (ADHD): Offspring born to men 30 to 34 years old (21 percent less likely), 35 to 39 years old (26 percent less likely), 40 to 44 years old (21 percent less likely), and older than 45 years old (5 percent less likely) had lower rates of these disorders than offspring in the reference group.

In order to provide adjusted estimates that assessed the magnitude of the association between paternal age at childbearing and the offspring disorders that was independent of other factors, the researchers ran a series of analyses that statistically controlled for multiple factors that are correlated with advancing paternal age. For example, the researchers statistically controlled for maternal age at childbearing because men who have children when they are older are more likely to have children with women who are older. In those models, advancing paternal age was still associated with the disorders of offspring, and the magnitudes of the associations were as large or larger than the population estimates. The researchers also accounted for urbanization at place of birth and family history of mental illness. The same pattern or results emerged. For example, offspring born to men over the age of 45 were 1.4 times more likely to have schizophrenia and 1.7 times more likely to have autism. Notably, offspring born to fathers older than 45 were 1.2 times more likely to have a hyperkinetic disorder when statistically controlling for the other factors, despite the fact that in the population, offspring born to men above age 45 were less likely to have the disorder.

The results from the Danish study indicate that in the population offspring of older fathers, some psychiatric problems, such as schizophrenia and autism, are more likely, and that hyperkinetic disorders are less likely. In trying to examine the pattern of associations when accounting for correlated factors, such as maternal age at childbearing and family history of psychiatric problems (the adjusted estimates), the researchers found that advancing paternal age at childbearing was still associated with psychiatric problems. In other words, these measured factors do not explain the associations between advancing paternal age and offspring psychiatric problems. The differences between the population and the adjusted estimates also indicated that researchers must take into account other differences among men who have children at different ages.

The Swedish Study

Our study—conducted separately from the Danish study—included all individuals born in Sweden from 1973 through 2001, a sample of just over 2.6 million people. We similarly

explored psychiatric problems, indexed by inpatient hospitalizations and outpatient visits, but our study also included information regarding criminal convictions, low academic achievement based on school grades at age 15, and dropping out of school early. The first analysis provided population estimates. We found that the population of offspring born to older fathers (above 45) had higher rates of schizophrenia (1.6 times more likely) and autism (1.4 times more likely) compared to offspring born to men 20 to 24 years old (the reference group in the study). For many of the other outcomes, however, offspring born to older fathers had fewer problems than offspring in our reference group. For instance, offspring born to men over the age of 45 were 43 percent less likely to have a diagnosis of ADHD.

Our team also used statistical techniques to obtain adjusted estimates that were independent of factors that could correlate with advancing paternal age, but we controlled for a more extensive list of measured variables than the Danish study. We accounted for maternal age at childbearing, as well as paternal and maternal nationality, highest level of education, lifetime history of serious psychiatric conditions, and lifetime history of criminality. Similar to the results in the Danish study, the associations between advancing paternal age and the outcomes in the adjusted group were as large or larger than the overall population estimates. The results indicated that the associations could not be explained by these factors; rather, when accounting for these measured variables, the associations were in some cases larger than the population estimates.

In addition to using statistical techniques to account for differences among fathers who had children at different ages, we also used several advanced research designs to help account for factors that could bias our estimates. In particular, we conducted a sibling-comparison analysis, which estimated the association between paternal age at childbearing and the outcomes while comparing offspring born to the same father. We explored the rates of problems in offspring born when the father was younger compared to their siblings born when the father was older. This design accounted for (or held constant) all traits that made siblings similar, including unmeasured environmental and genetic factors, thus arguably

providing a more precise estimate of the specific association with advancing paternal age.[9,20,21]

When we compared siblings, the magnitude of the associations with each outcome was as large as, and sometimes quite larger than, the estimates in the other analyses. For instance, offspring born to fathers over the age of 45 were 2.1 times more likely to have schizophrenia and 3.4 times more likely to have autism than their siblings who were born when their father was younger. Furthermore, whereas the population estimates found advancing paternal age to be correlated with lower incidence of ADHD, the sibling comparisons indicated that advancing paternal age was more strongly associated with the disorder (for example, offspring of fathers over the age of 45 were 13 times more likely to have the disorder than their siblings born when the father was 20 to 24 years old). The sibling-comparison approach has many advantages, but the design also has several limitations (for example, do the results apply or generalize to other populations?).[9] To help address several concerns, we conducted numerous additional analyses, including the comparison of cousins and firstborn cousins, and found comparable results: advancing paternal age was associated with more psychiatric problems, and the magnitude was stronger than the population estimates.

The population estimates from our Swedish study were generally consistent with the findings from the Danish study: Advancing paternal age was associated with greater risk for some disorders, such as schizophrenia and autism, but less risk for others, including ADHD. The adjusted estimates (when controlling for measured traits of both parents and when comparing siblings and cousins born at different ages) suggested that advancing paternal age was even more strongly associated with psychiatric problems than previous estimates indicated.

Understanding the Underlying Processes

What could explain the finding that advancing paternal age at childbearing is associated with more offspring psychiatric problems? The working hypothesis that guided both studies was that genetic mutations during the production of sperm, referred to as de novo

mutations, increase as men get older and have a causal influence on offspring psychiatric problems. Unlike in women, who are born with all of their eggs, in men sperm continue to replicate throughout their lifetime. In fact, sperm cells undergo 20 to 30 divisions per year—approximately 600 divisions by the age of 40.[22] Each cell division brings the possibility of new mutations. Recent studies suggest that there are approximately two new mutations each year, and there is an exponential increase where mutations double every 16.5 years.[23] A growing number of molecular genetic studies have found that these de novo mutations play a large role in human diseases, including psychiatric problems.[24] For instance, several studies have indicated that de novo mutations are associated with autism, suggesting a mediating biological pathway that could explain the association between advancing paternal age and the disorder.[25–27] The two recent epidemiological studies we reviewed above, which found independent associations between advancing paternal age and offspring psychiatric problems, are consistent with the role of de novo mutations.

But why would the adjusted estimates in the studies be larger—sometimes quite larger—than the population estimates? To understand the differences in magnitude of these two types of estimates, it may be important to understand the genetic, psychological, educational, social, and financial context associated with advancing paternal age because many of these factors predict fewer psychiatric problems in the offspring. Twin, adoption, and family-based studies have clearly shown that genetic factors influence age at first childbearing. There are no genes "for" early or late childbearing; rather, genetic factors influence personality traits, psychiatric problems, and other characteristics that in turn influence age at childbearing.[28] For instance, a recent family study found that women who have ADHD, their siblings who did not have the disorder, and men who have children with women who have ADHD are all more likely to have children as teenagers.[29] Offspring born to older parents, therefore, have lower genetic risk for ADHD on average than offspring born to parents who were teenagers at childbearing. Furthermore (as we also showed in our study), advancing paternal age at childbearing is also correlated with higher levels of parental education and higher family income, both of which lead to increased social and cultural capital.[30] In sum, delaying childbearing is correlated with a host of factors that also predict fewer psychiatric problems in offspring.

Thus, one conceivable explanation for the discrepancies between the population and adjusted estimates stems from the possibility that the population estimates could be an amalgam of the deleterious effects associated with de novo mutations and the protective factors (e.g., genetic inheritance, personality traits, and social/cultural capital) associated with delaying childbearing. The models that adjusted for measured traits and compared siblings and cousins, therefore, may have held constant many of these protective factors. As a result, the analyses may have provided a clearer estimate of the specific influence of delaying childbearing.

Implications of the Research

The Danish and Swedish studies are examples of translational epidemiology, which can help guide subsequent basic research.[5–9] The provocative findings regarding advancing paternal age at childbearing suggest that more research needs to be conducted on de novo mutations, especially given recent technological advances that enable researchers to better measure and characterize genetic mutations.[24] It is important to note, however, that there could be other mechanisms through which advancing paternal age at childbearing comes to be associated with offspring psychiatric problems. Therefore, research into other biological and social factors is needed to better clarify the processes that account for the findings in these studies. Furthermore, the two studies also highlight the need to understand the complex and multifaceted factors that are associated with delaying childbearing.[31]

So, finally, what do these studies mean for people who are making decisions about childbearing? How did we answer the questions we received? As you might imagine, we were reluctant to provide concrete advice. We were not evading the questions. Rather, we do not think science can provide a definitive answer to these questions. (Plus, it is unethical to give medical advice to strangers via email.) But here is how we responded to the questions:

First, these are only two studies. Our study in particular, which was one of the first studies to use sibling and cousin comparisons to study advancing paternal age, needs to be

replicated. We think it was a good study (we know we are biased), but there is never one definitive study, especially in this area of research, because each and every study has limitations. Again, we cannot conduct randomized controlled studies of paternal age at childbearing. As a result, researchers must obtain consistent findings using many different designs and samples before they can make strong causal inferences (e.g., advancing paternal age causes offspring psychiatric problems), especially regarding implications for family policy.[32]

Second, researchers need to conduct more studies on the topic before any professional group can make explicit recommendations. In particular, researchers must expressly examine if (and then how) physicians and couples could incorporate information on paternal age at childbearing into their decision-making process. This examination requires studies using predictive models.

Third, both studies provide evidence that the overwhelming majority of offspring born to older dads will not have a major psychiatric or related problem. Both studies found that the risk that a child will have psychiatric problems was correlated with advancing father's age, but most of the outcomes were quite rare. For instance, in our study less than 3 percent of the offspring had psychiatric problems. Therefore, advancing paternal age does not mean that any particular child will definitely develop problems, nor does it mean that a psychiatric problem in an offspring born to an older father was actually caused by the father's age at childbearing.

Fourth, our study and others also have indicated that there can be advantages to delaying childbearing. Some factors that are correlated with delaying childbearing (e.g., attaining a higher level of education or gaining financial security) predict better outcomes in children. These two studies, therefore, add to a growing body of research suggesting that families, doctors, and society as a whole must consider both the potential advantages and the potential disadvantages of delaying childbearing.

Fifth, when trying to weigh the possible risks and benefits of delaying childbearing, there is no set age at which advancing paternal age suddenly becomes problematic. Our study's reports of increased risk for offspring born to men over the age of 45, for example, were just one illustration. Both studies found increasing risk for many of the disorders as paternal age increased, referred to as a dose-response relationship (i.e., offspring born to men 40 to 44 years old also had higher rates of the disorders compared to the reference groups). In fact, each research paper provides graphical representations of magnitude of the associations between paternal age at childbearing and the outcomes across the entire range of parental age.

Sixth, individuals and couples concerned about the consequences of delaying childbearing should consult with their physician or a specialist in their area. For instance, concerned individuals and couples can meet with genetic counselors, who can provide more detailed and personal information regarding the risks associated with delaying childbearing.

Finally, and most important, there are many personal circumstances and values that go into making the decision of when to have a child or children. Yes, we think that research can help inform personal decision-making. But no study, set of studies, or science in general should unduly influence the decision of when someone should have children.

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