

## Original Investigation

# Paternal Age at Childbearing and Offspring Psychiatric and Academic Morbidity

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**IMPORTANCE** Advancing paternal age is associated with increased genetic mutations during spermatogenesis, which research suggests may cause psychiatric morbidity in the offspring. The effects of advancing paternal age at childbearing on offspring morbidity remain unclear, however, because of inconsistent epidemiologic findings and the inability of previous studies to rigorously rule out confounding factors.

**OBJECTIVE** To examine the associations between advancing paternal age at childbearing and numerous indexes of offspring morbidity.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a population-based cohort study of all individuals born in Sweden in 1973-2001 (N = 2 615 081), with subsets of the data used to predict childhood or adolescent morbidity. We estimated the risk of psychiatric and academic morbidity associated with advancing paternal age using several quasi-experimental designs, including the comparison of differentially exposed siblings, cousins, and first-born cousins.


**EXPOSURE** Paternal age at childbearing.

**MAIN OUTCOMES AND MEASURES** Psychiatric (autism, attention-deficit/hyperactivity disorder, psychosis, bipolar disorder, suicide attempt, and substance use problem) and academic (failing grades and low educational attainment) morbidity.

**RESULTS** In the study population, advancing paternal age was associated with increased risk of some psychiatric disorders (eg, autism, psychosis, and bipolar disorders) but decreased risk of the other indexes of morbidity. In contrast, the sibling-comparison analyses indicated that advancing paternal age had a dose-response relationship with every index of morbidity, with the magnitude of the associations being as large or larger than the estimates in the entire population. Compared with offspring born to fathers 20 to 24 years old, offspring of fathers 45 years and older were at heightened risk of autism (hazard ratio [HR] = 3.45; 95% CI, 1.62-7.33), attention-deficit/hyperactivity disorder (HR = 13.13; 95% CI, 6.85-25.16), psychosis (HR = 2.07; 95% CI, 1.35-3.20), bipolar disorder (HR = 24.70; 95% CI, 12.12-50.31), suicide attempts (HR = 2.72; 95% CI, 2.08-3.56), substance use problems (HR = 2.44; 95% CI, 1.98-2.99), failing a grade (odds ratio [OR] = 1.59; 95% CI, 1.37-1.85), and low educational attainment (OR = 1.70; 95% CI, 1.50-1.93) in within-sibling comparisons. Additional analyses using several quasi-experimental designs obtained commensurate results, further strengthening the internal and external validity of the findings.

**CONCLUSIONS AND RELEVANCE** Advancing paternal age is associated with increased risk of psychiatric and academic morbidity, with the magnitude of the risks being as large or larger than previous estimates. These findings are consistent with the hypothesis that new genetic mutations that occur during spermatogenesis are causally related to offspring morbidity.

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Epidemiologic studies have indicated that advancing paternal age (APA) at childbearing is associated with increased risk of offspring psychiatric problems, including autism spectrum disorders (ASDs),<sup>1-3</sup> schizophrenia,<sup>4,5</sup> and bipolar disorder,<sup>6,7</sup> as well as intellectual<sup>8</sup> and academic problems.<sup>9</sup> Recent genomic studies have reported that the age of the fathers at conception is an important factor in determining the number of de novo mutations in children<sup>10</sup> and also linked de novo mutations to ASDs, suggesting a mediating biological pathway leading to ASDs.<sup>11-13</sup> De novo mutations associated with APA have been linked with numerous offspring outcomes.<sup>14</sup>

Several major issues remain in the study of APA, however. First, the associations between early risks and offspring psychiatric problems have been questioned because most studies have not rigorously ruled out plausible confounding factors, which could be competing explanations for the statistical associations.<sup>15,16</sup> Epidemiologic studies may overestimate the magnitude of the effects because selection factors may account for part of the associations; personality traits associated with postponing parenthood<sup>17-19</sup> or birth order effects<sup>2</sup> could better explain the associations. In contrast, increased maturity,<sup>20</sup> conscientiousness,<sup>21</sup> and social and cultural capital<sup>22</sup> associated with delayed childbearing could suppress the statistical estimates of the specific effects of APA found in epidemiologic studies. Researchers, therefore, must use quasi-experimental designs, approaches that rely on design features rather than relying solely on statistical controls, to better address confounding factors because of the inability to conduct randomized experiments of APA in humans.<sup>15,23,24</sup> Family-based, quasi-experimental designs can help control for unmeasured confounders that family members share.<sup>25</sup> For instance, the sibling-comparison design provides an approach that rules out all genetic and environmental factors shared by siblings.<sup>24-27</sup> Sibling-comparison studies of APA have been inconsistent, however. Two sibling-comparison studies<sup>2,28</sup> indicated that APA was robustly associated with ASDs, whereas 2 sibling-comparison studies<sup>18,19</sup> found no association between APA and schizophrenia within families.

Second, the existing research has been unable to explore whether APA has general effects across numerous indexes of morbidity because most studies have explored only one outcome at the time, and several indexes of morbidity, such as suicidal behavior, substance use problems, and attention-deficit/hyperactivity disorder (ADHD), have not yet been extensively studied in relation to APA.

The current study explored the association between APA and numerous indexes of offspring psychiatric (ASDs, ADHD, psychosis, bipolar disorder, suicide attempt, and substance use problem) and academic morbidity (failing grades and low educational attainment) in a large population-based study of all offspring born in Sweden across 28 years. Rather than focus on a single indicator of functioning, the current study included several indexes of psychiatric problems and educational outcomes to explore the scope and specificity of the associations with APA. The main analyses compared differentially exposed siblings (with the exposure being paternal age at child-

bearing) to more precisely estimate the specific effects of APA. The sibling-comparison design has a number of limitations and assumptions, however, that can limit the internal and external validity of the findings.<sup>25-27,29,30</sup> We therefore estimated the effects of APA using numerous additional family-based, quasi-experimental designs,<sup>25</sup> including the comparison of differentially exposed cousins and first-born cousins, in addition to using statistical controls for measured covariates, because the designs have different strengths and limitations. As such, we sought to find converging evidence from multiple designs, each with its own assumptions and limitations, which is critical for making causal inferences.<sup>31</sup>

## Methods

All data for this population-based study were obtained by linking information available in the following population-based registries: (1) the Medical Birth Register, which includes data on more than 99% of pregnancies in Sweden since 1973; (2) the Multi-Generation Register, which contains information about biological relationships for all individuals living in Sweden since 1933; (3) the Migration Register, which supplies information on dates for migration in or out of Sweden; (4) the Cause of Death Register, which contains information on dates and causes of all deaths since 1958; (5) the Patient Register, which provides diagnoses for all inpatient psychiatric hospital admissions in Sweden since 1973 and outpatient care since 2001; (6) the National Crime Register, which includes detailed information about all criminal convictions since 1973; (7) the National School Register, which includes grades in all subjects for all students at the end of grade 9 since 1983; (8) the Education Register, which contains information on the highest level of completed formal education through 2008; (9) the Military Conscription Register, which includes cognitive assessments for all 18-year-old men in Sweden between 1970 and 2009; and (10) the Longitudinal Integration Database for Health Insurance and Social Studies, which contains yearly assessments of income, marital status, employment status, social welfare status, and education for all individuals 15 years or older since 1990. More details about these registers, the variables, and the methods are provided elsewhere.<sup>32</sup>

All individuals in the analysis cohort were born in Sweden between 1973 and 2001. Birth-related data for 2 917 399 children were obtained from the Swedish Medical Birth Register. We first excluded those from multiple births ( $n = 66\,089$ ), with missing data on gestational age ( $n = 7923$ ), with recorded gestational age younger than 23 weeks ( $n = 102$ ), and with recorded gestational age of older than 42 weeks 6 days ( $n = 38\,588$ ). We then excluded children with at least one recorded emigration from Sweden during this 28-year period ( $n = 172\,535$ ) and those with a missing identifier for the biological mother ( $n = 158$ ), missing or invalid sex ( $n = 2$ ), or an invalid birth order variable ( $n = 19$ ). After linkage with the Multi-Generation Register, we excluded an additional 16 902 individuals with insufficient data to establish a birth date for the biological father. The resulting cohort of 2 615 081 individuals represents 89.6% of the entire population and in-

Table. Descriptive Statistics of the Study Population

Variable	Birth Year	Total No.	Cases, No. (%) <sup>a</sup>
Offspring	1973-2001	2 615 081	
Female			1 264 248 (48.34)
First born			1 084 993 (41.49)
Second born			963 970 (36.86)
Third born			402 855 (15.41)
Fourth born or higher			163 263 (6.24)
Paternal	1904-1987	1 408 669	
Nationality (Swedish)			2 291 415 (87.62)
Upper secondary education (minimum, 3 y)			1 122 661 (42.93)
Serious adult psychiatric problem			46 670 (1.78)
Criminality (any)			1 041 427 (39.82)
Father's age at birth, mean (SD), y			31.27 (5.96)
Father's age at birth of first child, mean (SD), y			28.92 (5.54)
Disposable income at birth, mean (SD), \$		895 833	47.22 (22.72)
Maternal	1924-1987	1 404 484	
Nationality (Swedish)			2 308 587 (88.28)
Upper secondary education (minimum, 3 y)			1 336 236 (51.10)
Serious adult psychiatric problem			48 524 (1.86)
Criminality (any)			306 779 (11.73)
Mother's age at birth, mean (SD), y			28.42 (5.09)
Psychiatric morbidity			
Autism <sup>b</sup>	1992-2001	900 337	2424 (0.27)
ADHD <sup>b</sup>	1992-2001	900 337	2861 (0.32)
Psychosis <sup>c</sup>	1973-1997	2 293 032	10 739 (0.89)
Bipolar disorder <sup>c</sup>	1973-1997	2 293 032	6819 (0.61)
Suicide attempt <sup>c</sup>	1973-1997	2 293 032	29 148 (2.24)
Substance use problem <sup>c</sup>	1973-1997	2 293 032	43 377 (3.04)
Academic achievement			
Failing grades	1973-1992	1 767 091	264 132 (14.95)
Educational attainment of <10 y	1973-1991	1 679 921	484 799 (28.86)
Higher educational attainment	1973-1983	906 458	288 374 (31.81)
Low IQ (males)	1973-1992	641 020	62 646 (9.77)

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

<sup>a</sup> Data are presented as number of identified cases (percentage of cases) unless otherwise indicated.

<sup>b</sup> Kaplan-Meier estimate by the age of 15 years.

<sup>c</sup> Kaplan-Meier estimate by the age of 30 years.

cludes offspring from 1 408 669 distinct fathers and 1 404 484 distinct mothers.

See the **Table** for descriptive statistics and the birth cohorts used for each outcome. eAppendix 1 in the Supplement includes descriptive statistics by subgroups based on APA.

An ordered categorical representation of APA at childbearing was used as the main explanatory variable in our statistical models. Consistent with previous research,<sup>18</sup> we grouped APA for each offspring into 7 categories, ranging from 20 years or younger to 45 years or older in 5-year intervals with 20 to 24 years as the reference group.

Ten offspring outcomes from 2 different outcome domains were analyzed in this study. The 6 indexes of psychiatric morbidity, which have been found to be valid in previous studies, were as follows: (1) ASDs<sup>33</sup> and (2) ADHD,<sup>34</sup> which were identified using inpatient and outpatient diagnoses according to *International Classification of Diseases, Ninth Revision (ICD-9)* and *ICD-10*; (3) psychosis, which was measured as the age of first inpatient hospitalization for schizophrenia or other nonorganic (ie, affective) psychotic disorders according to *ICD-8*, *ICD-9*, and *ICD-10* criteria<sup>35</sup>; (4) bipolar disorder, which

was measured as first hospitalization using *ICD* criteria<sup>35</sup>; (5) suicide attempt, which was identified as age of first attempt using the *ICD* codes for any primary or secondary diagnosis for individuals 12 years or older in the Patient Register<sup>36</sup>; and (6) substance use problem, which was defined as first inpatient hospitalization that involved a primary or secondary diagnosis of alcohol or any other nonnicotine substance use disorder for individuals 12 years or older.<sup>37,38</sup>

The 4 dichotomous outcomes that indexed academic achievement (ie, cognitive ability) were as follows: (1) failing grades, measured as poor school performance as assessed in grade 9 using standardized numeric scales, which is commensurate with receiving an overall failing grade across 16 academic subjects<sup>39,40</sup>; (2) educational attainment of less than 10 years, which compared offspring with a low level of academic achievement (ie, ≤9 years of primary and secondary education) with those with higher levels of achievement (ie, completed ≥10 years of education); (3) higher educational attainment, which indexed individuals who completed at least 3 years or more of postsecondary education; and (4) low IQ (male conscripts only), which indexed general intellectual per-

formance, including logical-inductive reasoning, verbal ability, visual-spatial perception, and theoretical-technical skills. Offspring in the low IQ group were assessed with stanine scores within the lowest 10th percentile.

Measured offspring covariates were sex, birth parity (categorized into second, third, or fourth born or higher with first born as the reference group), and year of birth. Measured maternal and paternal covariates included indexes of Swedish nationality, highest level of completed education (categorized into 5 levels), lifetime history of psychiatric hospitalization, and lifetime history of any criminal conviction. Additional covariates included maternal age at childbearing (ordinal and grouped into the same 7 bins as APA) and paternal disposable household-level income in the proband birth year (categorized into quintiles to control for inflation and other time-varying socioeconomic events with the lowest, ie, 0-20th percentile, serving as the reference class). Correlations between APA and the covariates can be found in eAppendix 2 in the Supplement.

We used Cox proportional hazards regressions to estimate hazard ratios (HRs) associated with APA for the right-censored psychiatric outcomes; we used information on the date of death or the end of the assessment period (2009) to calculate age at censoring. We used logistic regression to estimate odds ratios (ORs) for the dichotomous academic achievement outcomes. All of the analyses controlled for offspring sex and birth order while using robust ("sandwich") SEs to account for the clustered nature of the data. We fitted 3 main models. First, we used a baseline model to estimate the crude associations in the population. The logistic models additionally controlled for proband birth year. Second, the adjusted model included all of the covariates. Note that only ASDs and ADHD were adjusted by paternal income because valid information regarding disposable income was not available for birth years earlier than 1992. Third, the sibling fixed-effects model (a stratified Cox or conditional logistic regression model)<sup>41</sup> accounted for all genetic and environmental factors shared among paternal siblings by controlling for unmeasured cluster-level covariates. The model also included offspring-specific and maternal measured covariates. The fixed-effects model extends the Cox and logistic models by stratifying (conditioning) on the set of siblings, adjusting for all factors that are shared within each sibling set. We also ran several sensitivity analyses using various designs, including cousin and first-born cousin comparisons, to test the robustness of the results.

## Results

The **Figure** presents the results by outcome. In line with previous studies, APA was associated with greater risk of ASDs (baseline model), with the association being relatively unaffected by adjustment for measured covariates (adjusted model). For example, after adjustment for the covariates, offspring born to fathers older than 45 years had an increased risk of having a diagnosis of an ASD of approximately 75% (HR = 1.76; 95% CI, 1.36-2.28) compared with

fathers 20 to 24 years old (Figure, A). In contrast, the fixed-effects sibling model suggests that APA was even more strongly associated with ASDs in the offspring; when accounting for all factors shared by siblings and several measured covariates, parental age of 45 years and older was associated with a 3.5 times increased risk of an offspring ASD (HR = 3.45; 95% CI, 1.62-7.33).

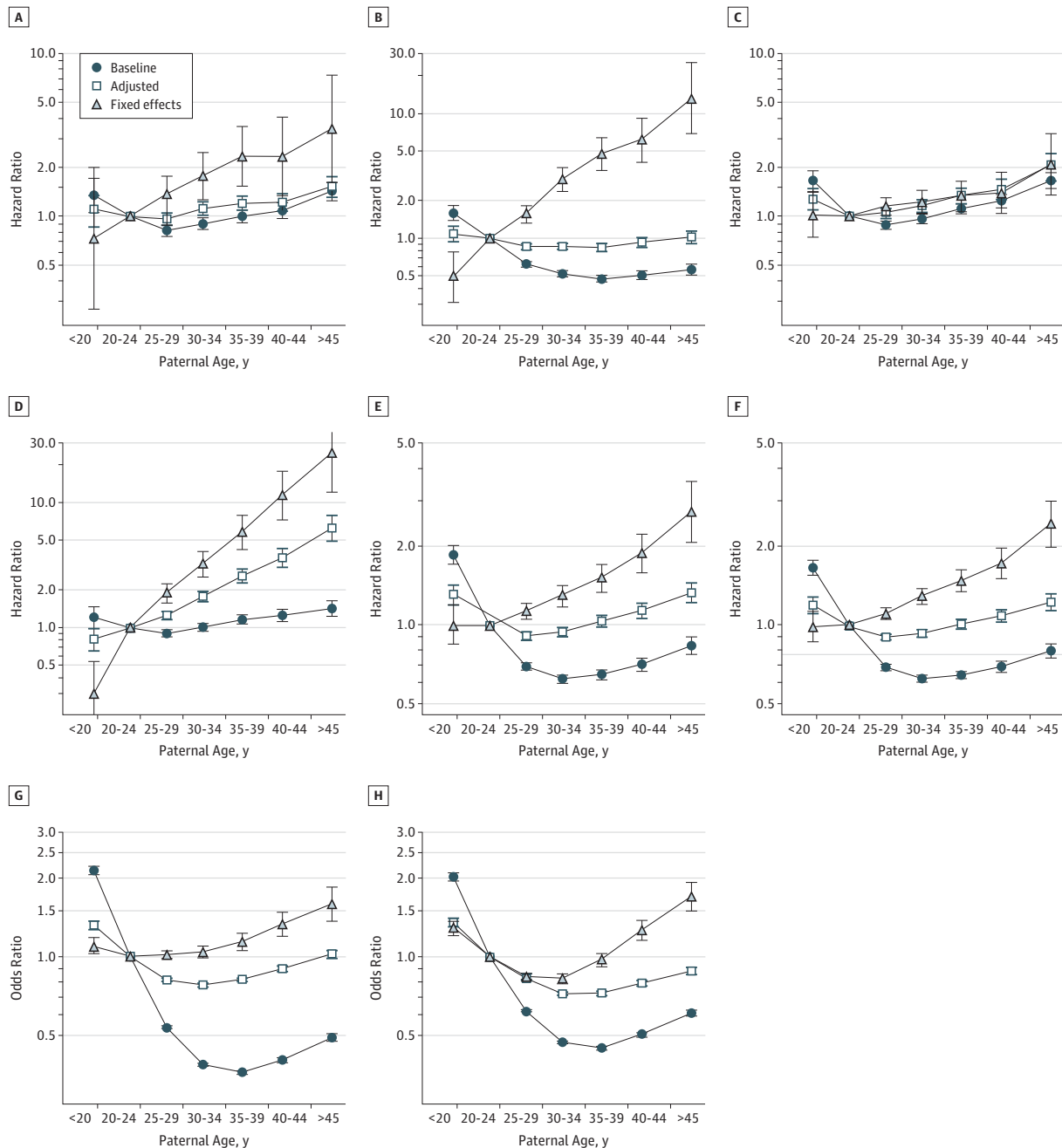
Similar patterns of associations were observed for the other indexes of psychiatric and academic morbidity (Figure, B-G), with stronger effects of APA when accounting for all factors shared by siblings. For example, in the fixed-effects sibling models, APA (age of 45 years or older) was associated with increased risk of ADHD (HR = 13.13; 95% CI, 6.85-25.16), psychosis (HR = 2.07; 95% CI, 1.35-3.20), bipolar disorder (HR = 24.70; 95% CI, 12.12-50.31), suicide attempts (HR = 2.72; 95% CI, 2.08-3.56), substance use problems (HR = 2.44; 95% CI, 1.98-2.99), failing grades (OR, 1.59; 95% CI, 1.37-1.85), and low educational attainment (OR = 1.70; 95% CI, 1.50-1.93) compared with offspring born to fathers 20 to 24 years old.

Because of the need to examine the robustness of the findings and test the limitations and assumptions inherent in sibling comparisons,<sup>25</sup> we ran a series of sensitivity analyses. First, we fitted models predicting completion of higher educational attainment (in the full sample) and IQ (in males) to examine whether the results would be commensurate with the main analyses predicting academic morbidity in the main text (eAppendix 3 in the Supplement). Second, we fitted fixed-effect cousin models (ie, comparing differentially exposed cousins) to examine the generalizability of the sibling-comparison results (eAppendix 4 in the Supplement). Third, we compared differentially exposed first-born cousins to account for birth order effects (in addition to statistically controlling for birth order in all of the main analyses) and the possibility that stoppage<sup>2</sup> would explain the sibling-comparison results (eAppendix 4 in the Supplement). Fourth, we fitted models predicting ASDs and ADHD by the age of 8 years to ensure that all siblings in a family lived through the same risk period (Author Appendix 1; [www.iub.edu/~devpsych/publications.html](http://www.iub.edu/~devpsych/publications.html)). The models also controlled for year of birth to account for changing diagnostic practices and prevalence, which could confound the results.<sup>42</sup> Fifth, we fitted models that controlled for paternal age at first childbearing while estimating the association between focal age of childbearing and the outcomes for all second- and later-born offspring (Author Appendix 2; [www.iub.edu/~devpsych/publications.html](http://www.iub.edu/~devpsych/publications.html)). This explored the possibility that carryover effects could confound the sibling-comparison estimates and provided the opportunity to directly compare the results with previous studies of APA that used this analytical approach.<sup>18</sup> Sixth, we fitted models predicting continuous indexes of grades and IQ (in males) to examine the results, which were comparable to the dichotomous indexes used in the main analyses (Author Appendix 3; [www.iub.edu/~devpsych/publications.html](http://www.iub.edu/~devpsych/publications.html)). Seventh, we examined whether the results from the baseline models were comparable in offspring with and without siblings to further test the generalizability of the sibling-comparison results (Author Appendix 4; [www.iub.edu/~devpsych](http://www.iub.edu/~devpsych)

/publications.html).<sup>25,32</sup> The sensitivity analyses as a whole provide commensurate results to the main analyses and provide support for stronger causal inferences. Finally, the

parameter estimates associated with maternal age at childbearing in the adjusted models are presented in Author Appendix 5 ([www.iub.edu/~devpsych/publications.html](http://www.iub.edu/~devpsych/publications.html)).

**Figure. Baseline, Adjusted, and Fixed-Effects Associations Between Paternal Age at Childbearing and Offspring Psychiatric and Academic Morbidity**



The point estimates (with 95% CIs presented as error bars) of the association between the paternal age at childbearing and each index of offspring morbidity using paternal age of 20 to 24 years as the reference category: autism (A), attention-deficit/hyperactivity disorder (B), psychosis (C), bipolar disorder (D), suicide attempt (E), substance use problem (F), failing grades (G), and educational attainment of less than 10 years (H). The x-axis presents the ordinal bins of paternal age at childbearing. The y-axis presents effect sizes, either hazard ratios or odds ratios, which quantify the magnitude of the associations.

The effect size estimates are depicted at the median age within each bin of advancing paternal age (APA). The circle estimates provide the baseline relations, the associations in the population. The square estimates provide the adjusted relations, the associations when statistically controlling for statistical covariates, which is what is standard in ordinary epidemiologic studies of APA. The triangle estimates present the fixed-effects relations, the association when accounting for all factors shared by siblings and measured covariates.



## Discussion

The current study found clear associations between APA and indexes of psychiatric morbidity (eg, ASDs and psychosis), in line with most previous studies<sup>1-7</sup> that have used ordinary comparisons of unrelated individuals. Yet, we have extended the previous literature in several critical ways.

First, we analyzed the largest study of APA to date, with coverage across an entire country and valid indexes of offspring morbidity. This enabled us to more precisely estimate the risks of rare indexes of psychiatric and academic morbidity.

Second, the results suggest that unmeasured genetic and environmental selection factors shared by siblings, as well as the influence of several measured covariates, do not account for the associations between APA and offspring morbidity, which is consistent with a causal hypothesis. Researchers have suggested that the association between APA and offspring morbidity is not causal and that the associations could be better explained by selection factors<sup>2,17-19</sup>; the findings of the extant sibling-comparison studies were, in fact, inconsistent.<sup>2,18,19,28</sup> The current study, however, found robust within-sibling associations. The inconsistent findings from sibling-comparison studies of schizophrenia may be due to the differences in ages of the samples (eg, a previous study<sup>18</sup> was based on offspring born in 1955-1992) and different diagnostic criteria (ie, we used a broad definition of psychosis).

Third, although APA has been associated with severe psychiatric morbidity, relatively few studies have explored other indexes of morbidity. The current study also explored offspring ADHD, bipolar disorder, suicidal behavior, substance use problems, and academic problems.<sup>8,9</sup> As such, the findings suggest APA is also associated with morbidity across several psychiatric disorders and developmental domains.

Fourth, and perhaps most importantly, the current study suggests that the specific risks associated with APA follow a dose-response relationship (ie, the increased risk was not solely present in extremely advanced paternal age) and that the magnitudes of most of the associations were stronger than previous estimates. In fact, the magnitudes of the associations with ADHD and bipolar disorder, in particular, were large in the sibling comparisons. Furthermore, the direction of the associations with many outcomes (eg, suicide, substance use, and academic problems) went in the opposite direction after controlling for familial confounding. These findings indicate that the factors shared by siblings that are correlated with APA capture beneficial factors (eg, increased maturity,<sup>20</sup> conscientiousness,<sup>21</sup> and social and cultural capital<sup>22</sup>) that suppress the specific negative effects of APA on psychiatric and academic morbidity. Future research will need to specify these

familial factors. The findings, however, suggest that APA is a greater risk factor for psychiatric morbidity than has been previously reported. Notably, we replicated the findings using several advanced family-based, quasi-experimental designs, each with its own strengths, limitations, and assumptions,<sup>25</sup> which further strengthens both the internal and external validity of the findings.<sup>23,31</sup>

The sibling-comparison results are consistent with the hypothesis that genetic mutations during spermatogenesis associated with APA influence offspring morbidity across numerous indexes of morbidity.<sup>14</sup> If de novo point mutations are important genetic risk factors then molecular genetic studies should involve exome sequencing from both affected individuals and parents; reliance on genome-wide association studies would not identify such genetic factors. Environmental factors specifically associated with APA also could account for the findings. Early paternal age also was associated with increased risk of some offspring problems, notably the educational outcomes, but not others.

The findings must be considered in light of several limitations and assumptions. Sibling-comparison studies include several assumptions. Sibling comparisons are sensitive to (1) unreliable measurement of the risk factor, (2) carryover effects from one sibling to another, (3) sibling-contagion effects, (4) concerns about the nongeneralizability of differentially exposed siblings, and (5) birth order effects.<sup>25-27,29,30</sup> We believe that unreliability is a minor issue, given that APA is based on official records, and we addressed many of the other assumptions in the extensive sensitivity analyses (eg, comparison of first-born cousins). Nevertheless, observational studies can never prove causality; the sibling comparisons could not rule out within-family confounders associated with APA and the outcomes. Randomized controlled trials are necessary for causal conclusions. Because of the inability to conduct such studies of APA, causal inferences must be made from commensurate results using different designs and samples.<sup>31</sup> Together with studies exploring grandparental age<sup>43</sup> and the association between APA and criminality,<sup>44</sup> the current results, which are based on several family-based, quasi-experimental designs, provide strong evidence that APA has a specific influence on offspring morbidity.

## Conclusions

The findings suggest that APA represents a risk of numerous public health and societal problems. Regardless of whether these results should lead to policy changes, clarification of the associations with APA would inform future basic neuroscience research, medical practice, and personal decision-making about childbearing.<sup>45,46</sup>

### ARTICLE INFORMATION

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