ORIGINAL ARTICLE

Autism Risk Across Generations

A Population-Based Study of Advancing Grandpaternal and Paternal Age

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Importance: Advancing paternal age has been linked to autism.

Objective: To further expand knowledge about the association between paternal age and autism by studying the effect of grandfathers' age on childhood autism.

Design: Population-based, multigenerational, case-control study.

Setting: Nationwide multigeneration and patient registers in Sweden.

Participants: We conducted a study of individuals born in Sweden since 1932. Parental age at birth was obtained for more than 90% of the cohort. Grandparental age at the time of birth of the parent was obtained for a smaller subset (5936 cases and 30 923 controls).

Main Outcome and Measure: *International Classification of Diseases* diagnosis of childhood autism in the patient registry.

Results: A statistically significant monotonic association was found between advancing grandpaternal age at the time of birth of the parent and risk of autism in grandchildren. Men who had fathered a daughter when they were 50 years or older were 1.79 times (95% CI, 1.35-2.37; $P<.001$) more likely to have a grandchild with autism, and men who had fathered a son when they were 50 years or older were 1.67 times (95% CI, 1.35-2.37; $P<.001$) more likely to have a grandchild with autism, compared with men who had fathered children when they were 20 to 24 years old, after controlling for birth year and sex of the child, age of the spouse, family history of psychiatric disorders, highest family educational level, and residential county. A statistically significant monotonic association was also found between advancing paternal age and risk of autism in the offspring. Sensitivity analyses indicated that these findings were not the result of bias due to missing data on grandparental age.

Conclusions and Relevance: Advanced grandparental age was associated with increased risk of autism, suggesting that risk of autism could develop over generations. The results are consistent with mutations and/or epigenetic alterations associated with advancing paternal age.

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AUTISM IS A NEURODEVELOPmental disorder characterized by social deficiencies, language impairments, and repetitive behavior patterns.[1] The disorder begins early in life, has a high heritability, and is associated with a marked reduction in birth rates.[2]

During the last decade, evidence suggesting that the offspring of older fathers have an increased risk of developing autism has accumulated.[3-6] A recent meta-analysis[5] found that fathers 50 years and older were 2.2 times more likely to have a child diagnosed as having autism compared with fathers younger than 30 years. Advanced paternal age has also been associated with other mental disorders, such as schizophrenia,[7-9] bipolar disorder,[10] and general neurocognitive development in children.[11] The mechanism behind the paternal age effect on adverse neuropsychiatric outcomes is unknown. It has been suggested that de novo mutations occurring in the male germ cell line underlie the relation.[12] In men, spermatogonial cells replicate every 16th day, resulting in approximately 200 divisions by the age of 20 years and 660 divisions by the age of 40 years.[13] Each time the cell divides, the replication of the genome introduces the possibility of copy error mutations. In humans, it has been confirmed that sperm from older men have significantly more mutations.[12,14,15] Levels of DNA proofreading and repair enzymes decrease as a func-

tion of advancing paternal age[16,17] and DNA fragmentation increases,[18] further compromising the integrity of gene replication. Experiments based on mouse models related to advanced paternal age have confirmed that the offspring of older sires have a significantly increased risk of de novo copy number variants, and several of these mutations involved genes previously linked to autism.[19]

Recently, several studies[20-23] have reported that de novo mutations in autism pedigrees are predominantly paternal in origin and are significantly associated with advancing paternal age. An Icelandic study[24] on individuals with sporadic schizophrenia or autism even found that the rate of new mutations in relation to paternal age is 2 new mutations per year. In addition, commentators have noted that the genetic architecture of neurodevelopmental disorders, such as autism and schizophrenia, is characterized by locus heterogeneity, variable expressivity of the same mutations, and a cumulative effect on common biological pathways.[25,26] Thus, it is feasible that some paternal age–related de novo mutations may not result in adverse health outcomes in the offspring but still contribute the overall burden of mutations inherited by subsequent generations. Thus, it would be predicted that both paternal and grandpaternal age could contribute to a cumulative threshold of mutation that emerges in an increased risk of neurodevelopmental disorders, such as schizophrenia and autism. By using the unique Swedish national registers, we can test whether the older the grandfather is when the parent is born, the greater the risk of autism in the grandchild and thus further explore the paternal age effect.

METHODS

DATA SOURCE

By linking population-based Swedish longitudinal registers, we compared the ages of parents and grandparents at offspring birth among individuals with or without childhood autism diagnosis. The unique personal identification number assigned to each Swedish citizen at birth or on arrival to the country (immigrants) enables linkage of national registers. The Swedish Patient Register includes practically all psychiatric inpatient discharge diagnoses in Sweden since 1973 recorded according to the *International Classification of Diseases* (*ICD*).[27-29] The Swedish Patient Register also includes outpatient care in Sweden since 2001. The Swedish Multi-Generation Register contains information about biological parents of an index person and their birth dates.[30] A prerequisite for being included in the register is that the index person was born after January 1, 1932, and ever registered as living in Sweden after 1960. Ethical approval was given by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

ANALYTIC COHORT

We identified individuals diagnosed as having childhood autism in the patient register (*ICD-9* code 299.0 and *ICD-10* code F84.0). We included diagnoses given at discharge from inpatient care since 1987 when the specific diagnostic code for childhood autism was first introduced and diagnoses given during outpatient care since 2001. Medical records are computerized and contain notations from psychiatrists, psychologists, neurologists, social workers, and nurses for inpatient and outpatient treatment. High validity of *ICD* diagnoses recorded in the Swedish Patient Register has been found by comparing diagnostic register code with medical records. The positive predictive value for most somatic and psychiatric diagnoses is approximately 85% to 95%,[31] and a medical record review substantiated the presence of *DSM-IV* autism in 83 of 88 cases (94.3%). The Swedish Patient Register was followed up until December 31, 2009. Individuals who did not meet our criteria for autism were considered unaffected. Five unaffected individuals for each affected child were frequency matched for sex and exact year of birth. Age data for parents and grandparents were linked to the study participants. Ages of parents were defined as the parent's age at the time of the index person's birth. Ages of grandparents were defined as the grandparent's age at the time of the parent's birth. Birth dates were obtained from the Swedish Multi-Generation Register. We identified 9868 individuals affected with childhood autism and 49 340 unaffected individuals. After linking ages of parents and grandparents, the final study sample consisted of 5936 (60.2% of the initial sample) affected individuals and 30 923 (62.7% of the initial sample) unaffected individuals with complete data on both maternal and paternal grandparents. A description of the study sample is outlined in the **Figure**.

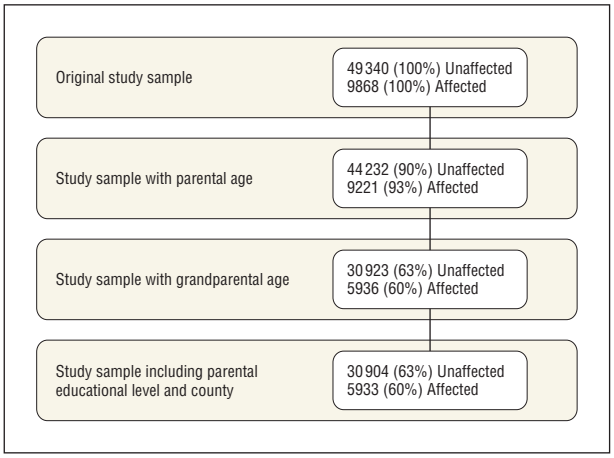

Figure. Study sample.

COVARIATES

A family history of psychiatric diagnosis was defined as having a parent or a grandparent with a diagnosis of schizophrenia, bipolar disorder, or autism in the patient register, defined by *ICD-8* and *ICD-9* codes 295-299 (except 296.2 and 296B) and *ICD-10* codes F21-29, F30-31, and F84. The selected diagnoses are possible confounders because they have been associated with paternal age in earlier studies. For the analyses without grandparental information, only information of parental history of psychiatric diagnosis was used. As a proxy measure of the socioeconomic home environment of the grandchild, we examined parental education defined as the highest achieved educational level within each parental pair. Information about educational level was retrieved from the longitudinal integration database for health insurance and labor market studies. Because coverage of outpatient care might vary across counties and place of residence might be a potential confounder, we also collected information about the probands' residential county from the Total Population Register. A table listing the distribution of covariates in the final data set and the distribution of the child's birth year divided into 10-year categories and the child's sex distribution, with boys representing 71.7% of our sample and girls representing 28.3% is avail-

Table 1. Results From Logistic Regression Analyses on Grandpaternal Ages and Autism Risk[a]

Variable	No. (%) of Participants in Models 1-3		OR (95% CI) by Model			
	Controls	Cases	1	2	3	4
Maternal grandfather age, y						
<20	675 (2.2)	122 (2.1)	0.96 (0.79-1.18)	0.91 (0.74-1.12)	0.91 (0.73-1.12)	0.90 (0.73-1.11)
20-24	6721 (21.7)	1253 (21.1)	1.00	1.00	1.00	
25-29	9801 (31.7)	1787 (30.1)	0.98 (0.91-1.06)	1.07 (0.98-1.17)	1.07 (0.98-1.17)	1.08 (0.99-1.18)
30-34	7082 (22.9)	1334 (22.5)	1.01 (0.93-1.10)	1.18 (1.06-1.31)	1.18 (1.06-1.31)	1.19 (1.07-1.32)
35-39	3868 (12.5)	808 (13.6)	1.10 (1.00-1.22)	1.33 (1.17-1.50)	1.32 (1.16-1.50)	1.31 (1.15-1.49)
40-44	1843 (6.0)	393 (6.6)	1.12 (0.99-1.27)	1.32 (1.13-1.55)	1.31 (1.11-1.53)	1.32 (1.12-1.54)
45-49	666 (2.2)	154 (2.6)	1.22 (1.01-1.46)	1.39 (1.12-1.73)	1.37 (1.10-1.71)	1.34 (1.07-1.67)
≥50	267 (0.9)	85 (1.4)	1.67 (1.30-2.15)	1.90 (1.44-2.51)	1.87 (1.42-2.48)	1.79 (1.35-2.37)
Paternal grandfather age, y						
<20	702 (2.3)	123 (2.1)	0.96 (0.79-1.18)	0.88 (0.72-1.09)	0.88 (0.72-1.09)	0.91 (0.73-1.12)
20-24	6293 (20.4)	1139 (19.2)	1.00	1.00	1.00	
25-29	9694 (31.4)	1793 (30.2)	1.02 (0.94-1.11)	1.09 (1.00-1.19)	1.09 (0.99-1.19)	1.10 (1.00-1.20)
30-34	7046 (22.8)	1387 (23.4)	1.08 (0.99-1.17)	1.18 (1.06-1.31)	1.17 (1.05-1.30)	1.17 (1.05-1.30)
35-39	4277 (13.8)	831 (14.0)	1.05 (0.95-1.16)	1.17 (1.04-1.33)	1.17 (1.03-1.32)	1.15 (1.02-1.31)
40-44	1971 (6.4)	405 (6.8)	1.11 (0.98-1.26)	1.26 (1.08-1.47)	1.24 (1.06-1.46)	1.23 (1.05-1.44)
45-49	672 (2.2)	180 (3.0)	1.45 (1.22-1.74)	1.64 (1.34-2.02)	1.62 (1.32-1.99)	1.60 (1.30-1.97)
≥50	268 (0.9)	78 (1.3)	1.56 (1.20-2.02)	1.76 (1.32-2.35)	1.72 (1.29-2.30)	1.67 (1.25-2.24)

Abbreviation: OR, odds ratio.

[a]Model 1 was adjusted for birth year and sex. Model 2 was adjusted for birth year, sex, and age of spouse. Model 3 was adjusted for birth year, sex, age of spouse, and family history. Model 4 was adjusted for birth year, sex, age of spouse, family history, highest educational level, and county. In models 1 through 3, there were 30 923 controls and 5936 cases. In model 4, there were 30 904 controls and 5933 cases.

able on the authors' website (http://ki.se/ki/jsp/polopoly/jsp?d=39803&l-sv).

STATISTICAL ANALYSIS

We estimated the relative risk (RR) of autism in offspring comparing different categories of parental and grandparental age by calculating the odds ratio (OR) and associated 2-sided 95% CIs using logistic regression. Ages were categorized into 5-year intervals, with 20 to 24 years as the reference category. The analyses were performed in 4 steps. First, we adjusted only for birth year and sex (model 1), followed by an analysis also adjusted for the age of each parent's or grandparent's partner/spouse (model 2). We did not control for age of the maternal grandparents when analyzing paternal grandparents and vice versa because we do not consider these ages to be directly correlated in the same manner as age of spouses. In model 3, we added family history of psychiatric disorders. Finally, we included parental educational level and residential county (model 4). Logistic regression analyses were performed in SAS statistical software, version 9.2 (SAS Institute, Inc), using PROC LOGISTIC. Statistical hypothesis testing was based on the 2-sided .05 level of significance. The models were evaluated for goodness-of-fit by visual inspections of the model residuals. We calculated variance inflation factors to check for colinearity between parental and grandparental age covariates and found no signs of such problems. Using a paternal age cutoff of 40 years, we calculated the attributable risk by (RR − 1)/RR. In other words, we obtain estimates on the proportion of autistic children who could be avoided if fathers and grandfathers had had their child before age 40 years, assuming a causal effect.

SENSITIVITY ANALYSES

Diagnoses given during outpatient care have not been included in the Swedish Patient Register until 2001. We therefore performed sensitivity analyses that included only inpatient data to examine potential differences between patients treated in inpatient care and those treated in outpatient care. These analyses included 1845 cases (models 1-3) and 1843 cases (model 4), respectively, with autism diagnoses assigned only during inpatient care.

We performed additional analyses on grandparental ages, adjusting for ages of the parents, to explore whether this affected the results. We also wanted to investigate effects of potential truncation of parental ages after linkage of grandparental age data and achieved this by analyzing parental ages before the linkage and comparing the results with data from the main analysis (sample described in the Figure). We identified 9221 affected and 44 232 unaffected individuals with parental age data, corresponding to 93.4% and 89.6% of the original samples. To address the issue of potential bias due to the different probabilities of being selected for the different sets of analysis, with and without requirements of valid grandparental data, we applied inverse probability weighting to the regression models with robust SEs.

RESULTS

GRANDPARENTAL AGE AND AUTISM

The logistic regression analyses on grandpaternal ages are presented in **Table 1**. Analyses adjusted for the child's birth year and sex revealed a statistically significant association between older grandfathers and autism on both the maternal and the paternal sides. The risk of autism increased monotonically with advancing grandpaternal age. When age of the spouse was adjusted for, the effect was statistically significant across all age categories, including maternal grandfathers 30 years or older and paternal grandfathers 25 years or older. The results remained after controlling for family history of psychiatric disorders and parental educational level. The highest risk was found in the oldest age categories in all 4 models. In

Table 2. Results From Logistic Regression Analyses on Parental Ages and Autism Risk (Sample With Grandparental Ages)[a]

Variable	No. (%) of Participants in Models 1-3		OR (95% CI) by Model			
	Controls	Cases	1	2	3	4
Paternal age, y						
<20	244 (0.79)	49 (0.83)	1.11 (0.81-1.53)	0.98 (0.70-1.37)	0.97 (0.69-1.36)	1.00 (0.71-1.40)
20-24	3452 (11.16)	650 (10.95)	1.00	1.00	1.00	
25-29	9685 (31.32)	1716 (28.91)	0.96 (0.87-1.06)	1.04 (0.94-1.16)	1.05 (0.94-1.17)	1.06 (0.95-1.19)
30-34	9989 (32.30)	1836 (30.93)	1.02 (0.92-1.12)	1.14 (1.02-1.29)	1.15 (1.02-1.30)	1.18 (1.04-1.33)
35-39	5236 (16.93)	1051 (17.71)	1.13 (1.01-1.26)	1.22 (1.07-1.40)	1.23 (1.08-1.41)	1.24 (1.08-1.42)
40-44	1711 (5.53)	429 (7.23)	1.41 (1.23-1.62)	1.47 (1.24-1.73)	1.47 (1.24-1.73)	1.45 (1.23-1.71)
45-49	460 (1.49)	149 (2.51)	1.82 (1.49-2.24)	1.87 (1.49-2.34)	1.85 (1.47-2.31)	1.83 (1.46-2.30)
≥50	146 (0.47)	56 (0.94)	2.23 (1.61-3.07)	2.25 (1.61-3.15)	2.23 (1.59-3.12)	2.26 (1.61-3.18)
Maternal age, y						
<20	826 (2.67)	191 (3.22)	1.19 (1.01-1.42)	1.23 (1.02-1.48)	1.22 (1.02-1.47)	1.15 (0.96-1.39)
20-24	6255 (20.23)	1216 (20.49)	1.00	1.00	1.00	
25-29	11256 (36.40)	2009 (33.84)	0.93 (0.86-1.01)	0.89 (0.81-0.97)	0.89 (0.82-0.97)	0.93 (0.85-1.01)
30-34	8726 (28.22)	1586 (26.72)	0.98 (0.90-1.06)	0.86 (0.78-0.95)	0.87 (0.78-0.96)	0.92 (0.83-1.02)
35-39	3305 (10.69)	772 (13.01)	1.27 (1.15-1.41)	1.02 (0.90-1.16)	1.02 (0.90-1.16)	1.11 (0.97-1.26)
≥40	555 (1.79)	162 (2.73)	1.59 (1.32-1.92)	1.13 (0.92-1.40)	1.13 (0.92-1.40)	1.26 (1.02-1.56)

Abbreviation: OR, odds ratio.

[a]Model 1 was adjusted for birth year and sex. Model 2 was adjusted for birth year, sex, and age of spouse. Model 3 was adjusted for birth year, sex, age of spouse, and family history. Model 4 was adjusted for birth year, sex, age of spouse, family history, highest educational level, and county. In models 1 through 3, there were 30 923 controls and 5936 cases. In model 4, there were 30 904 controls and 5933 cases.

the fully adjusted model, maternal grandfathers 50 years or older had an OR of 1.79 (95% CI, 1.35-2.37) compared with grandfathers aged 20 to 24 years, and paternal grandfathers 50 years or older had an OR of 1.67 (95% CI, 1.25-2.24).

PARENTAL AGE AND AUTISM

Logistic regression analyses on parental ages (**Table 2**) suggested a statistically significantly increased risk of childhood autism in all paternal age categories 35 years or older in model 1, again with a monotonic increase in risk with increasing age. After adjustments for age of the mother, the paternal age effect was found for fathers 30 years or older. Further adjustments did not have any evident effect on the point estimates or the CIs. In the fully adjusted model (model 4), the highest risk was found in men 50 years or older (OR, 2.26; 95% CI, 1.61-3.18). We found no evident trend of an increased risk of autism in offspring of older mothers after adjusting for father's age and the other covariates, with the exception of an excess of mothers 40 years and older in cases. The attributable risk for grandfathers older than 40 years was estimated to 3% for both maternal and paternal grandfathers. For fathers, the corresponding proportion was 6%.

SENSITIVITY ANALYSES

The analyses conducted separately on inpatients revealed similar age effects as in the main analysis (eTable; http://www.jamapsych.com). Although the CIs were expectedly broader than in the main analyses, we identified a trend of increasing autism risk in grandchildren of older maternal and paternal grandfathers. Again, no such effects of advanced age were found for grandmothers. Similarly, the association between paternal age and autism was also evident in these analyses. We could still detect an association between mothers 40 years or older, but we could not detect any overall trend between maternal age and autism. Adjustments for parental ages did not have any major effect on the risk estimates compared with the main analyses; the statistically significantly increased risk of autism in the grandchildren of older grandfathers remained.

The analyses on all individuals with parental age data revealed similar associations between parental ages and autism compared with the sample that required present grandparental age (Table 2). In addition, estimated ORs, associated CIs, and *P* values were close to identical to our main results when using the inverse probability weighting procedure.

COMMENT

We can, for the first time to our knowledge, report that grandfather's age is associated with risk of childhood autism, independent of paternal or maternal age. We also confirm a statistically significant association between advanced paternal age and an increased offspring risk of autism. Associations between paternal age and autism have been reported in previous studies,[3-6] including one using a 10-year Swedish birth cohort.[5] We could also see some evidence of an association between maternal age and autism, in congruence with a novel meta-analysis.[32]

A previous study[33] reported an association between grandpaternal age and schizophrenia. This association was exclusive for maternal grandfathers. There are, however, no reports of an association between paternal age and autism being transmitted to further generations. The only study[34] that has, to our knowledge, looked at grandparents' ages in association with autism found no evidence of an effect of grandfathers' age but instead an association between age of maternal grandmothers and

autism-spectrum disorder. This study, however, included 86 individuals with autism-spectrum disorder compared with the 5936 individuals with the specific diagnosis of childhood autism included in the present study.

Because autism is characterized by lower birth rates and high heritability,[2] it is puzzling that the disorder still exists and may even be increasing in prevalence.[35,36] The strong negative selection pressure should remove genes associated with this disorder from the gene pool promptly. One possible explanation for this paradox is that genetic variants increasing the risk of autism constantly arise as de novo mutations.[37] This hypothesis is supported by recent findings of de novo mutations in autism pedigrees being predominantly paternal in origin and significantly associated with advancing paternal age.[20-24] Mendelian inheritance laws indicate that offspring who acquire a de novo autosomal mutation from their father's sperm should pass (on average) this mutation to half of their offspring. Age-related mutations in the male germ line could accumulate over several generations and only influence the offspring's health after a certain mutational threshold has been breached.[12,38] Thus, paternal and grandpaternal (both maternal and paternal grandfathers) age may contribute to an offspring's mutational load, resulting in an increased risk of disorders in the offspring. If this is true, autism should be associated not only with paternal age but also with grandpaternal age. In this study, we report, for the first time to our knowledge, that paternal age not only has an effect on autism risk in offspring but also affects subsequent generations.

The most favored hypothesis behind the paternal age effect suggests that the association is caused by an increased rate of mutations in the sperm of older men. However, it has also been suggested that the paternal age effect is explained by men with mental or personality disorders being more likely to become fathers at older ages.[39,40] Although the coverage of family history of mental disorders might be incomplete and questionable in quality, the paternal age effect has been consistent in studies controlling for mental disorders in the parents. In addition, within-family analysis of discordant siblings revealed that the siblings affected with autism had older paternal age,[5] supporting the notion of a causal association between paternal age and autism in the offspring. Petersen et al[40] reported that the paternal age effect on schizophrenia was not present in later born children when the father's age at the birth of his first child was accounted for, opposing the hypothesis of de novo mutations. By contrast, a Swedish study[5] that tested whether the paternal age effect in autism only pertains to first-born children found that the risk of autism increased in later born children irrespective of the father's age when his first child was born.

Autism risk increased with advancing paternal and grandpaternal age. The risk estimates were similar for maternal and paternal grandfathers. Although the CIs overlapped, the grandpaternal age risk estimates were lower than the risk estimates for paternal age, which is consistent with the hypothesis of genetically mediated causes because the strength of a genetically mediated effect should reflect the genetic relatedness. On average, you inherit 50% of your genes from your parent and only 25% from your grandparent, so the overall mutational load would thus be higher if your father is old compared with if your grandfather is old. Similarly, if the de novo mutation hypothesis is true, the risk of autism would be greater in offspring of old fathers than in grandchildren of older men.

The coverage of data on parental age for cases and controls was very high (approximately 90%). After grandparental ages were linked, approximately 60% of the initial sample remained. To collate a sample consisting of 3 generations, parents had to be born after 1932. Older parents are, therefore, more likely to be excluded than younger parents. Grandparental ages are not truncated, but because parental and grandparental ages are correlated, this should only result in an underestimation of the grandpaternal age effect as a result of parental age truncation. However, the analyses conducted on the sample without requiring grandparental age data linkage suggested a similar paternal age effect compared with the sample used for the main analyses. We therefore conclude that there was no major truncation of parental ages, which adds to the validity of our findings.

Although the proportion of girls with autism is relatively high in Sweden, an extensive review of 29 studies revealed the male-female ratio varied from 1.33 to 16.0.[41] Because the male-female ratio in the present study is well within this interval, we do not consider the ratio to be atypical.

The main strength of this study is the inclusion of a large number of individuals diagnosed as having childhood autism and available birth date information across 3 generations. The consistency in results between the main analyses and the analyses restricted to inpatients further strengthens our findings and the generalizability of the results.

Our findings have added salience in light of the recent evidence that autism is associated with de novo and inherited mutations.[20-24,42-44] Considering the association between advanced paternal age and de novo copy number variants in an animal model,[19] we speculate that paternal age–related mutagenesis is associated with an increased risk of autism via 2 mechanisms. The offspring of older fathers may be at increased risk of acquiring de novo mutations, as previously speculated.[45] Considering our finding linking grandpaternal age and risk of schizophrenia, we propose that a proportion of age-related de novo mutations are phenotypically silent in the offspring but can still influence risk of autism in subsequent generations, perhaps via the interaction with other susceptibility factors. This indirect mechanism is consistent with the evidence that some mutations associated with neurodevelopmental disorders can occur in apparently healthy individuals.[46,47]

Age of parenthood is increasing in many societies, and thus it is feasible that the incidence of paternal age–related disorders will increase over time. Our findings provide new information about the paternal age effect and its effect on future generations. Older men should not be discouraged to have children based on these findings, but the results may be important in understanding the mechanism behind childhood autism and other psychiatric and neurodevelopmental disorders.

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