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Advanced paternal and grandpaternal age and schizophrenia: A three-generation perspective

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Abstract

Background—Advanced paternal age has been linked with neurodevelopmental disorders such as schizophrenia. If age-related *de novo* mutations in the male germ line underlie this association, it would be expected that grandpaternal as well as paternal age may influence the risk of schizophrenia. The aim of the current study was to explore the links between both paternal and grandpaternal age with respect to the risk of schizophrenia in a large, national register-based sample.

Method—The study was based on Swedish Multi-Generation and Hospital Discharge Registers. Parents' ages at offspring birth were compared between 20,582 affected and 100,176 non-affected individuals. Grandparents' ages at the birth of the parent were compared between 2,511 affected and 15,619 non-affected individuals. The risk of schizophrenia was examined when the predictor variable (parent or grandparent age) was examined in age strata with logistic regression. Planned sensitivity analyses included exploring the variables of interest in males and females separately.

Results—After adjusting for maternal age, birth year and sex of the proband, we confirmed that the offspring of older fathers have an increased risk of schizophrenia (e.g. compared to paternal age 20–24 years, those with fathers > 55 years had a two-fold increased risk). With respect to grandparent age, older maternal (but not paternal) grandfather age was associated with an increased risk of schizophrenia. Compared to maternal grandfather age 20–24 years, those with maternal grandfathers >55 years had a significantly increased risk of schizohrpenia (Adjusted Odds ratio and 95% Confidence intervals; 2.79, 1.71 – 4.56). The pattern of findings were essentially unchanged when we examine male and female probands separately.

Contributors

CH, JM, EF and SS were involved in the design of the study. SS supervised the statistical analysis. All authors contribute to data interpretation and manuscript preparation. All authors have approved the final manuscript.

Conflicts of Interest

The authors have no conflicts to report.

Conclusion—This is the first the study to show an association between grandpaternal age and risk of schizophrenia. The selective effect of advanced maternal grandfather age suggests that the biological mechanisms involving the X chromosome may differentially contribute to the association between paternal age and risk of schizophrenia.

Keywords

schizophrenia; paternal age; grandparental age; mutation

1. Introduction

There is robust evidence indicating that the offspring of older fathers have an increased risk of schizophrenia (Byrne et al., 2003; El-Saadi et al., 2004; Malaspina et al., 2001; Sipos et al., 2004). Apart from schizophrenia, advanced paternal age has also been associated with an increased risk of autism spectrum disorder (Hultman et al., 2010; Reichenberg et al., 2010)and bipolar disorder(Frans et al., 2008). The offspring of older fathers also have subtle deficits in neurocognitive development and behaviour (Saha et al., 2009a; Saha et al., 2009b; Weiser et al., 2008). However, the mechanisms behind the association between advanced paternal age and increased risk of adverse neuropsychiatric outcomes remain unclear. It has been suggested that *de novo* mutations occurring in the male germ cell line are responsible for this association (Crow, 2000). In men, spermatogonia undergo cell division every sixteen day, resulting in approximately 200 divisions by the age of 20 years and 660 divisions by the age of 40 years (Drake et al., 1998). Each time the cell divides, the replication of the genome introduces the possibility of copy error mutations, that might result in point mutations, or larger copy number variants (e.g. deletions, amplifications). In humans, it has been confirmed that sperm from older men have more mutations (Bosch et al., 2003; Crow, 2000; Glaser et al., 2003).

It has been proposed that age-related mutations in the male germ line could accumulate over several generation, and influence the health of subsequent descendents after a ‘mutational threshold’ has been breached, when a phenotype could ‘break through’ (Crow, 2000; McGrath, 2006). Mendelian inheritance laws indicate that offspring who acquire a *de novo* autosomal mutations from their father’s sperm should (on average) pass this mutation to half of their offspring (who in turn should then pass the mutation to half their offspring etc). However, paternally-derived mutations that impact on the X chromosome will only be passed to daughters, as sons receive the maternal X chromosome and the paternal Y chromosome. Subsequently, on average half of the male and female offspring of these daughters can inherit this X-linked mutation.

Apart from mutations that change the DNA sequence, epigenetic mechanisms may also be involved in the links between paternal age and risk of schizophorenia (Perrin et al., 2007). For example, epigenetic changes are known to occur in the sperm at an elevated rate with increased age (Oakes et al., 2007; Oakes et al., 2003). The pattern of inheritance of epigenetic changes in human germ cells is incompletely understood (Daxinger and Whitelaw, 2010; Hochberg et al., 2010; Rakyan et al., 2002). In general, normal epigenetic marks are ‘wiped’ between fertilization and implantation, however the dynamics of this varies for maternal versus paternal chromosomes, and ‘imprinted’ regions of the genome are generally protected from this genome-wide reprogramming (Morgan et al., 2005; Weaver et al., 2009).

Based on population-based Swedish registers, we had the opportunity to explore the association between schizophrenia versus (a) parental age (i.e. maternal, paternal) and (b) grandparental age (maternal grandmother, maternal grandfather, paternal grandmother,

paternal grandfather). Based on the hypothesis that paternal age-related mutations involve copy error mutations distributed across the entire genome (i.e. both autosomes and sex chromosomes), we predicted that paternal-age related mutations should follow classic Mendelian patterns of inheritance, and thus we predicted that advanced grandpaternal age on both sides of the family (i.e. maternal grandfather and paternal grandfather) would be associated with an increased risk of schizophrenia.

2. Method

2.1 Setting

We compared the ages of parents and grandparents at offspring birth among cases and controls by linking two population-based Swedish registers. The primary key for the register linkage was the unique personal identification number assigned to each Swedish citizen at birth or upon arrival to the country (immigrants). The Hospital Discharge Register includes diagnostic data for practically all psychiatric hospitalizations in Sweden since 1973 recorded according to ICD-8 (World Health Organization, 1967) ICD-9 (World Health Organization, 1977) and ICD-10 (World Health Organization, 1992). The Hospital Discharge Register is tested regularly for misclassification and the quality is high (The National Board of Health and Welfare, 2003). The Swedish Multi-Generation Register enables the identification of an "index person", his/hers biological parents and birth date (Statistics Sweden, 2005). A prerequisite for being included in the register is that the index person was born after January 1st 1932, and ever registered as living in Sweden after 1960. Ethical approval for this record linkage study was given by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

2.2 Participants

We identified all subjects diagnosed with schizophrenia during inpatient care in Sweden between 1973 and 2004. During a 10-year period, previous studies have found that 90% of all individuals with schizophrenia in Sweden were admitted for inpatient care (Hansson et al., 2001). In validation studies, Swedish register diagnoses of schizophrenia has displayed high concordance with diagnosis based on semi-structured interviews (Ekholm et al., 2005). To further improve the validity of the schizophrenia diagnoses we defined individuals with schizophrenia as individuals who had received a diagnosis of schizophrenia on at least two separate admissions (ICD-8 and ICD-9 code 295 and ICD-10 codes F20, F21, F23.1 F23.2, and F25). For each affected subject, we randomly selected five unaffected age- and sex-matched individuals from the population register. Age data for parents and grandparents were linked to the study subjects from the Multi-Generation Register. Our study population consisted of 20,582 individuals affected with schizophrenia and 100,176 non-affected individuals with available data on both paternal and maternal age. After linking ages of the grandparents, our final study sample consisted of 2,511 affected individuals and 15,619 unaffected individuals with complete data on both maternal and paternal grandparents.

2.3 Statistical methods

In order to quantify the size of the paternal age effect, we performed logistic regression after categorizing parents/grandparents ages into 5 year intervals, in keeping with several previous studies (Byrne et al., 2003; Malaspina et al., 2001; Sipos et al., 2004). These analyses were controlled for age of the partner/spouse, gender and year of birth. These analyses were repeated for males and females separately.

All analyses were performed in SAS (version 9.1.3; SAS Institute Inc, Cary, North Carolina), using proc LOGISTIC for the logistic regression analyses. Statistical testing of hypotheses was based on the 2-sided 5% level of significance.

3. Results

In keeping with previous studies, we found that the offspring of older fathers were at increased risk of schizophrenia (Table 1). For example, compared to the reference group (paternal age 20 to 24 years), the highest risk was found in offspring of men aged 55 years or older (OR: 1.95; 95 % CI: 1.58–2.40).

With respect to grandpaternal age, we found that only maternal grandfathers' age was associated with risk of schizophrenia (Table 2). Compared to the reference age category (20–24 years), those with maternal grandfathers aged greater than 55 years over a two- to three -fold increased risk of schizophrenia (Adjusted OR 2.79; 95% CI 1.71–4.56). Across the range of paternal age, there was a significant trend with older age strata being associated with increased risk (chi-square = 21.28, $p < 0.0001$). In contrast, there were no significant associations with paternal grandfathers age. With respect to grandmothers age, there was an isolated finding for paternal grandmother age (increase risk in those aged 40–44 compared to reference category), but no indication of a significant trend across the age strata (chi-square = 0.24, $p = 0.62$).

We explored the influence of parental and grandparental age of risk of schizophrenia in males and females separately, however the general pattern of results was unchanged (see Appendix 1 Tables A1–A4).

4. Discussion

We show, for the first time, that maternal grandfather's age is associated with risk of schizophrenia. Compared to the reference category (20 to 24 years), the offspring of women with paternal age of 40 years or more, have an increased risk of schizophrenia Unexpectedly, we find that paternal grandfathers's age is not associated with risk of schizophrenia. In keeping with previous studies (Byrne et al., 2003; Malaspina et al., 2001; Sipos et al., 2004), we confirm a statistically significant association between advanced paternal age and an increased offspring risk of schizophrenia.

The selective effect for maternal but not paternal grandpaternal age may provide clues to the biological mechanisms underpinning the link between advanced paternal age and risk of schizophrenia. One key difference between maternal versus paternal grandfathers is the segregation of the X chromosome. The paternal grandfather's X chromosome is not inherited by his son, nor any of this son's children (i.e. grandsons and granddaughters). In contrast, the maternal grandfather's X chromosome is inherited by his daughter and to half of her sons, and half of her daughters. In many instances, X-linked transmission is associated with disease phenotypes emerging in males only (for X-linked recessive) or in a more prominent fashion in males compared to females (for X-linked dominant). While the incidence of schizophrenia has been reported to be higher in men compared to women (Aleman et al., 2003; McGrath et al., 2008) and there are a range of sex differences in the features of schizophrenia in women versus men (Leung and Chue, 2000), when we examined the variables of interest in men and women separately, we did not detect any appreciable difference according to the sex of the proband. A study based on Danish mental health registries identified, in fathers older than 50 years, a higher risk of schizophrenia in female compared to male offspring (Byrne et al., 2003). The authors also speculated that paternal age might specifically impact on X-chromosome linked genes. A study based on the Jerusalem birth cohort has also reported a substantially increased risk of schizophrenia in the sisters of women with schizophrenia who have older fathers – this pattern of affected female sibpairs suggests that paternal age may differentially impact on the X chromosome (Perrin et al., 2010). A recent systematic review did not detect any sex difference in risk of schizophrenia in the offspring of older fathers (Miller et al., 2010). Our findings related to

the specificity of association with maternal versus paternal grandfather adds weight to the hypothesis that the X chromosome may be differentially affected by age-related mutagenesis in the male germ line. However, on first principles, age-related *de novo* mutations should impact on autosomes as well as the sex chromosomes. Thus, the lack of association between paternal grandfathers age and risk of schizophrenia is hard to explain.

Recently, it has been demonstrated that the expression of genes on maternal versus paternal chromosomes operate in different regions of the brain during development and in adulthood. For example, genes on maternal chromosomes are preferentially transcribed in the developing brain, while genes from paternal chromosomes are preferentially transcribed in adult brain (Gregg et al., 2010a). To further complicate the complex links between genotype and phenotype, there are also differences in maternal versus paternal genome transcription in male versus female offspring (Gregg et al., 2010b). There is also evidence that candidate single nucleotide polymorphisms (SNPs) within known imprinted regions of the genome can be either protective or harmful for disease outcomes depending on the parent of origin of the variant (Kong et al., 2009) (Kong et al., 2009). This type of biological complexity cannot be unravelled with epidemiology (McGrath and Richards, 2009), but recently developed animal models related to advanced paternal age may provide clues to underlying mechanisms (Foldi et al., 2010; Smith et al., 2009)

The main strengths of the present study were the large sample size, the nation-wide coverage of psychiatric inpatient care in Sweden, the standardized routines for ICD diagnostic reporting in Sweden (which optimizes the reliability of case ascertainment) (Ekholm et al., 2005) and access to the Multigeneration Register. However, the study has several limitations. The registers are currently limited in respect to follow-up time for the three-generation study resulting in a much smaller sample with present grandparental age data compared to the sample with parental age data. Furthermore, our three-generation sample would over-represent early-onset patients and/or those with younger parents. With respect age of onset, there is some evidence to suggest that advanced paternal age is associated with an earlier age of onset of schizophrenia (Lee et al., 2011; Rosenfield et al., 2010), so this feature may lead to over-estimates of effect size in our sample. With respect to a possible over-representation of younger second-generation parents, some studies examining paternal age and risk of schizophrenia have identified a J-shaped curve, with a slight excess risk in the offspring of younger fathers as well as a larger effect for older fathers (Miller et al., 2010). It is not clear how this feature would impact on our findings – it is plausible that different biological and/or psychosocial mechanisms underlie the J shaped curve. Regardless of this speculation, it will be important to see if the pattern of associations persists as the Swedish register can access more third-generation pedigrees in the years ahead. It will also be of interest to explore if other neurodevelopmental disorders associated with paternal age also show differential maternal versus paternal grandfather effects. In particular, the association between grandpaternal age and disorders such as autism would be better suited to the register-based studies, as more three-generation pedigrees could be identified with an early onset disorder.

In conclusion, as well as replicating earlier findings of a positive association between advanced paternal age and schizophrenia, we have found that the advanced age of the maternal but not paternal grandfather is associated with an increased risk of schizophrenia in the grandchild.

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Appendix 1

Table A1

The association between paternal and maternal age and risk of schizophrenia: Male offspring

Paternal age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
<20	197	1.60	963	1.63	1.00	0.85	1.19
20–24	1888	15.35	9647	16.29	Reference		
25–29	3261	26.51	17151	28.97	1.00	0.93	1.06
30–34	2983	24.25	14923	25.20	1.04	0.96	1.12
35–39	2081	16.92	9302	15.71	**1.13**	**1.04**	**1.23**
40–44	1137	9.24	4714	7.96	**1.20**	**1.08**	**1.33**
45–49	509	4.14	1778	3.00	**1.42**	**1.25**	**1.62**
50–54	160	1.30	529	0.89	**1.51**	**1.24**	**1.84**
≥ 55	86	0.70	202	0.34	**2.14**	**1.64**	**2.80**
Maternal age							
<20	883	7.18	4256	7.19	1.07	0.98	1.17
20–24	3197	25.99	16522	27.90	Reference		
25–29	3503	28.48	18093	30.56	0.98	0.93	1.04
30–34	2602	21.15	11868	20.04	1.05	0.98	1.13
35–39	1565	12.72	6333	10.70	**1.10**	**1.01**	**1.20**
40–44	508	4.13	2000	3.38	1.04	0.92	1.18
≥ 45	44	0.36	137	0.23	1.15	0.81	1.65

*Adjusted for age of spouse, birth year and sex of proband

Significant results shown in bold

Table A2

The association between grand-paternal and grand- maternal age and risk of schizophrenia: Male grandchild

Grandparent age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
Maternal GF age							
<20	23	1.48	121	1.23	1.20	0.74	1.94
20–24	205	13.23	1300	13.19	Reference		
25–29	393	25.35	2727	27.66	0.92	0.76	1.12
30–34	370	23.87	2556	25.93	0.93	0.75	1.15
35–39	278	17.94	1753	17.78	1.00	0.79	1.28
40–44	163	10.52	881	8.94	1.19	0.90	1.58
45–49	72	4.65	355	3.60	1.39	0.98	1.98
50–54	27	1.74	130	1.32	1.43	0.88	2.32
≥ 55	19	1.23	35	0.36	**3.64**	**1.97**	**6.74**
Maternal GM age							
<20	98	6.32	618	6.27	0.99	0.77	1.27
20–24	398	25.68	2588	26.25	Reference		
25–29	410	26.45	2873	29.14	0.93	0.80	1.10
30–34	357	23.03	2162	21.93	1.01	0.84	1.22
35–39	211	13.61	1152	11.69	1.01	0.80	1.28
40–44	69	4.45	437	4.43	0.76	0.55	1.07
≥ 45	7	0.45	28	0.28	1.07	0.44	2.56
Paternal GF age							
<20	20	1.29	85	0.86	1.46	0.87	2.44
20–24	202	13.03	1263	12.81	Reference		
25–29	409	26.39	2657	26.95	0.95	0.78	1.15
30–34	420	27.10	2588	26.25	0.97	0.78	1.20
35–39	263	16.97	1763	17.88	0.88	0.69	1.13
40–44	151	9.74	969	9.83	0.92	0.69	1.22
45–49	49	3.16	370	3.75	0.77	0.52	1.13
50–54	23	1.48	118	1.20	1.11	0.66	1.87
≥ 55	13	0.84	45	0.46	1.72	0.88	3.38
Paternal GM age							
<20	91	5.87	512	5.19	1.15	0.89	1.49
20–24	375	24.19	2552	25.89	Reference		
25–29	463	29.87	2858	28.99	1.13	0.97	1.33
30–34	355	22.90	2211	22.43	1.14	0.95	1.38
35–39	188	12.13	1270	12.88	1.08	0.85	1.37
40–44	74	4.77	429	4.35	1.24	0.89	1.73
≥ 45	4	0.26	26	0.26	1.02	0.34	3.06

* Adjusted for age of spouse, birth year and sex of proband

GM -= grandmother; GF = grandfather. Significant results shown in bold

Table A3

The association between paternal and maternal age and risk of schizophrenia: Female offspring

Paternal age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
<20	100	1.21	598	1.46	0.93	0.74	1.16
20–24	1117	13.49	6380	15.57	Reference		
25–29	2175	26.27	11726	28.62	1.08	0.99	1.18
30–34	2092	25.27	10233	24.98	**1.19**	**1.08**	**1.30**
35–39	1436	17.34	6790	16.57	**1.20**	**1.08**	**1.34**
40–44	823	9.94	3431	8.38	**1.35**	**1.19**	**1.52**
45–49	365	4.41	1254	3.06	**1.62**	**1.38**	**1.90**
50–54	121	1.46	389	0.95	**1.72**	**1.36**	**2.17**
≥ 55	51	0.62	166	0.41	**1.71**	**1.23**	**2.39**
Maternal age							
<20	497	6.00	2696	6.58	1.04	0.93	1.17
20–24	2074	25.05	11267	27.50	Reference		
25–29	2393	28.90	12427	30.33	0.99	0.93	1.06
30–34	1828	22.08	8476	20.69	1.05	0.97	1.15
35–39	1082	13.07	4584	11.19	1.08	0.98	1.20
40–44	371	4.48	1411	3.44	1.10	0.95	1.28
≥ 45	35	0.42	106	0.26	1.28	0.86	1.92

*Adjusted for age of spouse, birth year and sex of proband

Significant results shown in bold

Table A4

The association between grand-paternal and grand- maternal age and risk of schizophrenia: Female grandchild

Grandparent age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
Maternal GF age							
<20	8	0.83	67	1.16	0.79	0.36	1.70
20–24	122	12.70	824	14.30	Reference		
25–29	235	24.45	1550	26.91	1.03	0.80	1.32
30–34	248	25.81	1532	26.59	1.13	0.86	1.48
35–39	176	18.31	1033	17.93	1.25	0.92	1.71
40–44	102	10.61	472	8.19	**1.59**	**1.10**	**2.28**
45–49	43	4.47	195	3.38	**1.63**	**1.04**	**2.56**
50–54	19	1.98	56	0.97	**2.58**	**1.38**	**4.85**
≥ 55	8	0.83	32	0.56	1.80	0.77	4.18
Maternal GM age							
<20	0.83	5.93	352	6.11	1.16	0.84	1.61
20–24	12.70	23.93	1578	27.39	Reference		
25–29	24.45	30.18	1626	28.22	1.13	0.92	1.39
30–34	25.81	20.19	1246	21.63	0.90	0.70	1.15

Grandparent age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
35–39	18.31	14.05	707	12.27	0.98	0.73	1.33
40–44	10.61	5.10	233	4.04	0.93	0.61	1.41
≥ 45	4.47	0.62	19	0.33	1.21	0.45	3.30
Paternal GF age							
<20	7	0.73	47	0.82	0.80	0.35	1.85
20–24	132	13.74	701	12.17	Reference		
25–29	246	25.60	1562	27.11	0.83	0.65	1.06
30–34	279	29.03	1581	27.44	0.96	0.74	1.25
35–39	149	15.50	1024	17.77	0.81	0.60	1.11
40–44	96	9.99	552	9.58	0.90	0.63	1.29
45–49	35	3.64	196	3.40	0.83	0.51	1.36
50–54	12	1.25	71	1.23	0.84	0.42	1.67
≥ 55	5	0.52	27	0.47	0.97	0.35	2.67
Paternal GM age							
<20	51	5.31	302	5.24	0.93	0.66	1.31
20–24	249	25.91	1435	24.91	Reference		
25–29	297	30.91	1738	30.17	0.99	0.81	1.21
30–34	197	20.50	1296	22.50	0.89	0.70	1.13
35–39	107	11.13	750	13.02	0.85	0.63	1.16
40–44	58	6.04	226	3.92	**1.53**	**1.02**	**2.29**
≥ 45	2	0.21	14	0.24	0.81	0.18	3.76

*Adjusted for age of spouse, birth year and sex of proband

GM -= grandmother; GF = grandfather. Significant results shown in bold

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Table 1

The association between paternal and maternal age and risk of schizophrenia

Paternal age (years)	Count of cases	%	Count of controls	%t	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
<20	297	1.44	1561	1.56	0.98	0.85	1.12
20–24	3005	14.60	16027	16.00	Reference		
25–29	5436	26.41	28877	28.83	1.03	0.97	1.08
30–34	5075	24.66	25156	25.11	1.09	1.03	1.16
35–39	3517	17.09	16092	16.06	**1.16**	**1.08**	**1.24**
40–44	1960	9.52	8145	8.13	**1.25**	**1.16**	**1.36**
45–49	874	4.25	3032	3.03	**1.50**	**1.35**	**1.66**
50–54	281	1.37	918	0.92	**1.59**	**1.37**	**1.85**
≥ 55	137	0.67	368	0.37	**1.95**	**1.58**	**2.40**
Maternal age							
<20	1380	6.70	6952	6.94	1.06	0.99	1.14
20–24	5271	25.61	27789	27.74	Reference		
25–29	5896	28.65	30520	30.47	0.98	0.94	1.03
30–34	4430	21.52	20344	20.31	1.05	1.00	1.11
35–39	2647	12.86	10917	10.90	**1.10**	**1.03**	**1.17**
40–44	879	4.27	3411	3.41	1.07	0.97	1.17
≥ 45	79	0.38	243	0.24	1.21	0.93	1.58

*Adjusted for age of spouse, birth year and sex of proband

Significant results shown in bold

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Table 2

The association between grand-paternal and grand- maternal age and risk of schizophrenia

Grandparent age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
Maternal GF age							
<20	31	1.23	188	1.20	1.06	0.71	1.59
20–24	327	13.02	2124	13.60	Reference		
25–29	628	25.01	4277	27.38	0.96	0.83	1.12
30–34	618	24.61	4088	26.17	1.00	0.85	1.19
35–39	454	18.08	2786	17.84	1.09	0.90	1.32
40–44	265	10.55	1353	8.66	**1.33**	**1.07**	**1.66**
45–49	115	4.58	550	3.52	**1.47**	**1.12**	**1.94**
50–54	46	1.83	186	1.19	**1.76**	**1.21**	**2.58**
≥ 55	27	1.08	67	0.43	**2.79**	**1.71**	**4.56**
Maternal GM age							
<20	155	6.17	970	6.21	1.06	0.86	1.29
20–24	628	25.01	4166	26.67	Reference		
25–29	700	27.88	4499	28.80	1.01	0.89	1.15
30–34	551	21.94	3408	21.82	0.97	0.84	1.13
35–39	346	13.78	1859	11.90	1.00	0.83	1.20
40–44	118	4.70	670	4.29	0.83	0.64	1.08
≥ 45	13	0.52	47	0.30	1.12	0.58	2.15
Paternal GF age							
<20	27	1.08	132	0.85	1.19	0.77	1.84
20–24	334	13.30	1964	12.57	Reference		
25–29	655	26.09	4219	27.01	0.90	0.78	1.05
30–34	699	27.84	4169	26.69	0.96	0.82	1.14
35–39	412	16.41	2787	17.84	0.86	0.71	1.04
40–44	247	9.84	1521	9.74	0.91	0.73	1.14
45–49	84	3.35	566	3.62	0.80	0.59	1.08
50–54	35	1.39	189	1.21	0.99	0.65	1.49
≥ 55	18	0.72	72	0.46	1.40	0.80	2.44
Paternal GM age							

Grandparent age (years)	Count of cases	%	Count of controls	%	Adjusted Odds Ratio	Lower 95% CI	Upper 95% CI
<20	142	5.66	814	5.21	1.06	0.86	1.30
20–24	624	24.85	3987	25.53	Reference		
25–29	760	30.27	4596	29.43	1.07	0.95	1.22
30–34	552	21.98	3507	22.45	1.04	0.90	1.21
35–39	295	11.75	2020	12.93	0.99	0.82	1.19
40–44	132	5.26	655	4.19	**1.36**	**1.06**	**1.76**
≥ 45	6	0.24	40	0.26	0.94	0.39	2.30

*Adjusted for age of spouse, birth year and sex of proband

GM -= grandmother; GF = grandfather. Significant results shown in bold