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Advanced Paternal Age and Parental History of Schizophrenia

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Abstract

Introduction—Advanced paternal age (APA) is a risk factor for nonaffective psychosis (NAP) in the offspring, although the mechanism(s) of this association are not clear. The aim of this study was to examine whether later childbearing can be explained by parental schizophrenia, and in doing so, further evaluate the “de novo mutation” hypothesis for the association between APA and NAP.

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Contributors

Drs. Miller, Suvisaari, Isohanni, and Kirkpatrick designed the study. Dr. Miller managed the literature searches and the analyses. Drs. Miller, Suvisaari, Isohanni, and Kirkpatrick wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

Dr. Miller received grant support from the University of Oulu and Oy H. Lundbeck.

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Methods—Using binary logistic regression, the association between APA and parental history of schizophrenia in the offspring, considering maternal and paternal history separately, was examined in 1) all persons with NAP born in Finland between 1950 and 1969 (Finnish NAP Cohort, n=13,712), and 2) members of the Northern Finland 1966 Birth Cohort (NFBC 1966, n=10,224), a general population birth cohort.

Results—In the Finnish NAP Cohort, having a *mother* with schizophrenia was associated with APA (Odds Ratio [OR] for linear trend=1.20, 95% confidence interval 1.12–1.29, $p<0.01$). In the NFBC 1966 sample, having a *mother* with schizophrenia was associated with APA at the trend level (OR=1.14, 0.99–1.31, $p=0.07$). By contrast, there was no association between having a father with schizophrenia and APA.

Discussion—In both a general population cohort and a birth cohort of subjects with nonaffective psychosis, APA was associated with *maternal*, but not paternal, schizophrenia. These findings suggest that increased genetic risk from the mother may explain the association between APA and nonaffective psychosis, and argue against the “de novo mutation” hypothesis.

Keywords

Paternal age; schizophrenia; epidemiology; family history

Introduction

Advanced paternal age (APA) is a risk factor for nonaffective psychosis (NAP) in the offspring (Miller et al., 2010). Potentially confounding factors such as maternal age, maternal parity, socioeconomic status, ethnicity, and geography do not appear to account for the effect (Brown et al., 2002; Byrne et al., 2003; Dalman and Allebeck, 2002; Sipos et al., 2004; Zammit et al., 2003). In a meta-analysis, we did not find an obvious cut-off point beyond which paternal age should be considered “advanced” (Miller et al., 2010). Instead, we observed a significant linear increased risk of NAP in the offspring of older fathers (>30), with no gender differences, and in the sons of younger fathers (<25), compared to a reference paternal age of 25–29.

Despite the robust relationship between APA and NAP, the mechanism(s) and pathways of this association are unclear. One hypothesis is increased *de novo* mutations in the paternal germ line (Malaspina et al., 2001). APA is associated with *de novo* mutations in other conditions (Crow 1997; Dakouane et al., 2008; Kuhnert et al., 2004; Rannan-Eliya et al., 2004), but this has not been explored in NAP. The possibility of epigenetic changes, such as imprinting or DNA methylation has been proposed, but not investigated (Perrin et al., 2007). Another hypothesis is that the association between APA and NAP may be due to delayed childbearing by fathers with increased liability for schizophrenia (e.g., schizotypal or other cluster A personality traits). A recent study found that after accounting for paternal age at birth of the father’s first child, schizophrenia risk did not depend on paternal age for later-born children, which supports the “selection into late fatherhood” hypothesis (Petersen et al., 2010). APA may also be associated with an adverse psychosocial environment for offspring, thereby increasing schizophrenia risk. For example, unwantedness of pregnancy (Myhrman et al., 1996) and paternal death during childhood (Morgan et al., 2007; Watt et al., 1979) are

potential risk factors for schizophrenia that might be associated with APA, although APA did not confound the relationship with unwanted pregnancy in one study (Herman et al., 2006). However, these different mechanisms are not mutually exclusive.

The association between APA and family history of schizophrenia, which could provide insights into the mechanism of the “APA effect”, has not been adequately explored. One small study found a higher mean paternal age in sporadic versus familial cases of schizophrenia (Malaspina et al., 2002), but there is a failure to replicate (Pulver et al., 2004). One cohort study found an association between APA and risk of schizophrenia in offspring without, but not with, a family history of the disorder (Sipos et al., 2004), but another did not find evidence for an interaction between APA and family history (Zammit et al., 2003). None of these studies considered maternal and paternal history of schizophrenia separately.

The aim of this study was to examine whether later childbearing can be explained by parental schizophrenia, and in doing so, further evaluate the “de novo mutation” hypothesis for the association between APA and NAP. The absence of an association between APA and both maternal and paternal schizophrenia would support the “de novo mutation” hypothesis. A positive association between APA and paternal schizophrenia would suggest that delayed childbearing by fathers with schizophrenia may explain the “APA effect.” A positive association between APA and maternal schizophrenia would suggest increased genetic risk from the mother may explain the association.

Methods

STUDY POPULATIONS AND STUDY SAMPLES

We investigated the association between paternal age and parental history of schizophrenia in two cohorts: 1) 13,712 persons with nonaffective psychosis born in Finland between 1950 and 1969 (Finnish NAP Cohort), and 2) 10,224 members of the Northern Finland 1966 Birth Cohort (NFBC 1966). The broader category of NAP appears to share family history and other characteristics of schizophrenia (Addington et al., 2005; Lichtermann et al., 2000; Niemi et al., 2004), and most previous studies of the “APA effect” used NAP as the index diagnosis (Miller et al., 2010). The Finnish NAP Cohort study was approved by the Ethics Committee of the National Public Health Institute, and the case notes were collected with permission from the Finnish Ministry of Social Affairs and Health. The NFBC 1966 study protocol has been conducted under the supervision of the Ethics Committee of the Oulu University Hospital. The study was also overseen by the Human Assurance Committee of Georgia Health Sciences University.

Finnish NAP Cohort—This cohort consists of all persons born in Finland between 1950 and 1969 who developed NAP before 1992, which has been described previously (Suvisaari et al., 1998). Individuals with NAP (International Classification of Diseases, Eighth Revision [ICD-8] and Ninth Revision [ICD-9] diagnostic code 295.x, excluding 295.5 and 295.8, and Tenth Revision [ICD-10] diagnostic codes 20.x and 25, including schizophrenia, schizophreniform disorder, and schizoaffective disorder) were ascertained from three nationwide healthcare registers: 1) the Finnish Hospital Discharge Register (FHDR), and two registers of the Social Insurance Institution, 2) the Pension Register and 3) the

Medication Reimbursement Register. Individuals with at least one diagnosis of NAP in these registers were included, which has good diagnostic stability (Pihlajamaa et al., 2008).

The FHDR was founded in 1967, and covers all mental, general and private hospitals in Finland (Miettunen et al., 2011). It contains the unique social security number for each individual and the hospital identification code, which lists data on date of birth, gender, admission and discharge dates, and primary plus up to three subsidiary diagnoses for each inpatient stay. The Pension Register includes the beginning dates and the diagnoses for all disability pensions. The Medication Reimbursement Register includes the diagnoses and type of medication of persons receiving free outpatient medication. All healthcare registers were computerized in 1968, and used the ICD-8 diagnostic criteria and codes before 1987 (WHO 1967). Between 1987 and 1995, psychiatric diagnoses were coded according to ICD-9 (WHO 1977), applying the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) diagnostic criteria (APA 1987). ICD-10 diagnostic codes and criteria have been used since 1996 (WHO 1994). The data in all registers were linked by each individual's unique social security number. Register information was available for the period January 1, 1969, through December 31, 1991.

Parental ages at birth were identified from the National Population Register Centre (NPRC), which also records information on gender and maternal parity for each Finnish citizen. Parental information was linked to the above registers to obtain data on hospital treatments, pensions and free medications for schizophrenia (or schizoaffective disorder). The search of these registers identified 16,069 individuals with a diagnosis of NAP, of whom 13,712 (85.3%) had complete data on parental age and history of schizophrenia, gender, and maternal parity.

NFBC 1966—The NFBC 1966 is a general population birth cohort of 12,068 pregnant women and their 12,231 children. Data were compiled beginning at the 24th gestational week for all pregnancies in the northern counties of Finland, and at ages 1, 14, and 31, and 34 (Alaraisanen et al., 2006, Penttila et al., 2010). The data used here were collected prospectively for 11,058 singleton-birth cohort members living in Finland at age one. There is little loss to follow-up, as emigration from Finland is rare. In a 1997 field survey, 93 individuals did not consent to the use of their data and were excluded, leaving 10,965 cohort members.

Information on parental ages at birth was collected from the NPRC. Information on paternal age was obtained from the mother by questionnaire due to missing identification codes for 30 (0.3%) subjects. Information on father's social class based on occupation in 1966 and maternal parity was collected by questionnaire. Social class was trichotomized to high (I–II), low (III–IV), and farmers (V). The vast majority of farms in Finland were small at that time. If data on father's social class were missing, it was replaced by mother's social class ($n=232$, 2.1%). Information on maternal parity was obtained from the mother by questionnaire. Complete data on parental age and history of schizophrenia, gender, paternal social class, and maternal parity were available for 10,224 (93.2%) of cohort members.

STUDY DESIGN AND STATISTICAL ANALYSIS

Parental age was categorized into seven groups: <25, 25–29, 30–34, 35–39, 40–44, 45–49, and 50, with age 25–29 as the reference. Maternal parity was analyzed as a continuous variable. In the NFBC 1966, paternal social class was analyzed as a categorical variable as described above. Parental history of schizophrenia was categorized into four separate, dichotomous (yes/no) variables based on the affected status of each parent: “Mother only”, “Father only”, “Either mother or father”, and “Both parents”. For each of these groups, “no” was defined as “Neither parent affected,” in order to have a consistent reference group. In order to be able to compare our results with previous studies, we included the “Either mother or father” affected group.

The main method of analysis was binary logistic regression. The dependent variable was parental history group. The following two models were used: 1) unadjusted analyses on categorical parental age, and 2) analyses on categorical parental age adjusted for age of the other parent (continuous), gender, paternal social class, and maternal parity. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each parental history group. Tests of statistical hypotheses were based on the 2-sided, $\alpha=0.05$ level of significance. Separate logistic regression analyses were performed for each of the four parental history groups. Each cohort was analyzed separately. Data on paternal social class was not available for the Finnish NAP Cohort. All analyses were conducted using statistical software SPSS, version 17.0 (SPSS, Inc., Chicago, Illinois, 2009).

Results

NONAFFECTIVE PSYCHOSIS COHORT

Table 1 describes the demographic characteristics of both cohorts. In the Finnish NAP Cohort, having a *mother* with schizophrenia was associated with APA (OR for linear trend=1.20, 95% CI 1.12–1.29, $p<0.01$; see Table 2 and Figure 1). There was a significant linear trend for a positive association between *maternal* schizophrenia and increasing paternal age. Offspring of fathers age 50 were 1.94 (95% CI 1.16–3.24) times more likely to have a *maternal*/history of schizophrenia than offspring of fathers age 25–29, after adjusting for potential confounding factors ($p<0.01$).

In the Finnish NAP Cohort, having a *father* with schizophrenia was negatively associated with APA (OR=0.83, 95% CI 0.74–0.92, $p<0.01$). There was a significant linear trend for a negative association between paternal *schizophrenia* and increasing paternal age.

Having a *mother* with schizophrenia was negatively associated with advanced maternal age (AMA; OR=0.75, 95% CI 0.69–0.82, $p<0.01$). There was no association between having a father with schizophrenia and AMA (OR=0.95, 95% CI 0.84–1.07, $p=0.39$).

Having *either* a mother or father with schizophrenia was not associated with APA (OR=1.06, 95% CI 1.00–1.12, $p=0.07$), but was negatively associated with increasing maternal age (OR=0.81; 95% CI 0.75–0.87, $p<0.01$). There was also not an association between having *both* a mother and a father with schizophrenia and APA (OR=1.12, 95% CI 0.83–1.50, $p=0.46$) or AMA (OR=0.73, 95% CI 0.49–1.08, $p=0.11$).

However, as there may be missing registry data on parental schizophrenia if a parent had 1) a disability pension because of schizophrenia but was older than 65 years in 1968 (their pension would have changed into a normal pension because of age), and 2) no hospitalizations for schizophrenia between 1969 and 1998, and 3) never applied for free outpatient antipsychotic medication. It is possible that these conditions would be biased towards the exclusion of older parents. In order to address a potential “ascertainment bias”, we repeated the analyses restricting to probands born in or after 1955. The association between APA and having a *mother* with schizophrenia was still significant (OR=1.20, 95% CI 1.10–1.32, $p<0.01$), but the association between APA and having a *father* with schizophrenia was no longer significant (OR=0.94, 95% CI 0.83–1.07, $p=0.35$) (see Table 2).

GENERAL POPULATION COHORT

In the NFBC 1966, having a *mother* with schizophrenia was associated with APA at the trend level (OR=1.14, 95% CI 0.99–1.31, $p=0.07$) (see Table 3 and Figure 2), after adjusting for potential confounding factors. By contrast, there was not a relationship between APA and a *paternal* history of schizophrenia (OR=0.97, 95% CI 0.82–1.14, $p=0.69$), or having *either* a mother or father with schizophrenia and (OR=1.04, 95% CI 0.98–1.21, $p=0.11$). There were no associations between parental schizophrenia and AMA for any of the parental history groups.

PARENTAL AGE IN FIRST-BORN CHILDREN

One study found that after accounting for paternal age at birth of the father’s first child, the risk of schizophrenia did not depend on paternal age at conception of later-born children (Petersen et al., 2010). Although data on paternal age at birth of the father’s first child were not available for the Finnish NAP Cohort, for first-born children of previously nulliparous mothers, paternal age would be expected to be highly correlated with paternal age at birth of the father’s first child. When we repeated the analysis restricting to first-born children, we found that having a *mother* with schizophrenia was still associated with APA (OR=1.27, 95% CI 1.14–1.43, $p<0.01$).

NONAFFECTIVE PSYCHOSIS IN THE NFBC 1966

Based on the above findings, an association APA and *maternal* schizophrenia may explain, to a degree, the observed association between APA and NAP. We examined the extent to which the association between APA and NAP is confounded by *maternal* schizophrenia. There are 129 cases of NAP in the NFBC 1966 validated through 1997 (described previously in Moilanen et al., 2010). We calculated relative risks (RRs) of NAP for paternal age groups (<25, 25–29 [reference], 30–34, 35–39, and 40) using binary logistic regression. We first adjusted for maternal age (continuous), gender, paternal social class, and maternal parity. We then adjusted for these variables plus maternal schizophrenia. As shown in Table 4, there was not a significant association between APA and NAP. However, after adjustment for *maternal* schizophrenia, the RRs were slightly, but non-significantly, lower in the 30–34, 35–39, and 40 paternal age groups. We were not able to explore this association in the Finnish NAP Cohort, which consists only of subjects with NAP (i.e., a comparison group was not available).

Discussion

In both the general population based NFBC 1966 and a birth cohort of subjects with NAP, APA was associated with *maternal*, but not paternal, schizophrenia. The association between APA and *maternal* schizophrenia suggests that increased genetic risk from the mother may explain the association between APA and NAP, and does not support the “de novo mutations” hypothesis. There was not a significant association between APA and NAP in the NFBC 1966, and relative risks by paternal age group were decreased after adjustment for *maternal* schizophrenia. An understanding of this risk factor has substantial public health importance, as average paternal ages are increasing (Bray et al., 2006) and APA is common, has widespread effects, and is a potentially modifiable risk factor.

An important strength of our study is that we replicated our findings on APA and *maternal* schizophrenia in the general population and within NAP. The subjects were drawn from population-based birth cohorts with register-based diagnoses, thus reducing selection bias. Another strength is that, to our knowledge, the Finnish NAP Cohort is the largest cohort in which the association between APA and parental history of schizophrenia has been explored. We believe ours is the first study to explore the association between APA and parental history of schizophrenia in the general population. We also considered the effect of “parent of origin” of schizophrenia on this association, which has not previously been examined.

We note several limitations of the present study. In the Finnish NAP Cohort, data were missing on paternal age and/or parental history of schizophrenia for 14.7% of subjects. For these subjects, it was not possible to differentiate between fathers who died before 1970 (which would be biased towards older fathers) and unknown fathers. Another limitation is that register-based diagnoses may be biased towards more severe cases of NAP (Moilanen et al., 2003). However, two Finnish studies found that 83–100% of people with schizophrenia have had at least one lifetime psychiatric hospitalization, and would appear in the FHDR (Arajärvi et al., 2005; Suvisaari et al., 2009).

In order to address a potential “ascertainment bias” for older parents in the Finnish NAP Cohort, we compared the prevalence of a parental history of schizophrenia in four subgroups based on birth year: 1950–1954 (8.7%), 1955–1959 (9.8%), 1960–1964 (9.7%), and 1965–1969 (7.6%), which were consistent. These results are comparable to those from previous studies, which have reported a 6–8% prevalence of schizophrenia in the offspring of affected parents (Gottesman, 1991). When combined with our post-hoc analysis of probands born after 1954, the association between APA and *maternal* schizophrenia does not appear to be confounded by missing data on parental psychiatric history.

We failed to find a significant association between APA and NAP in the NFBC 1966. Although most studies have found a positive association, there are two negative case-control studies (El-Saadi et al., 2004; Granville-Grossman, 1966). One possible explanation for our finding is the relatively small number of subjects with NAP (n=129), which limited statistical power. A diagnosis of NAP has been validated in NFBC 1966 members through age 31, which could also bias towards a negative finding, as cohort members have not passed through the period of greatest risk for NAP.

No previous studies of APA and parental history of schizophrenia considered maternal and paternal history separately (Malaspina et al., 2002; Pulver et al., 2004; Sipos et al., 2004; Zammit et al., 2003). Our findings in the Finnish NAP Cohort demonstrate how the associations of APA and *maternal* versus *paternal* history of schizophrenia effectively “cancel each other out”, such that there was no association between APA and parental history of schizophrenia when maternal and paternal history were not considered separately (see Figure 1, “Either mother or father” affected).

The association between APA and *maternal* schizophrenia also raises the possibility that older fathers may be more likely to mate with women who have increased schizophrenia liability in the form of schizotypal (or other cluster A) personality traits, which would be more common than maternal schizophrenia. In the NFBC 1966, the RRs of NAP by paternal age group decreased after adjustment for *maternal* schizophrenia. Similarly, in a Danish cohort study, adjustment for family psychiatric history also slightly weakened the association between APA and schizophrenia, although the individual effect of maternal schizophrenia is unclear (Petersen et al., 2010). Future studies should investigate the relationship between APA and personality traits associated with increased schizophrenia liability.

In addition to increased genetic risk from the mother, assortative mating may contribute to the observed association between APA and *maternal* schizophrenia. Assortative mating, the tendency for mated pairs to be more similar for a given phenotypic trait than expected if mating occurred at random, has been shown for a variety of psychiatric conditions, including schizophrenia (Parnas 1988). A study of offspring at high-risk for psychosis found an increased prevalence of Axis I and II diagnoses in the mates of mothers with schizophrenia, although the relationship to paternal age was not considered (Parnas, 1985). A Finnish study found an increased prevalence of psychiatric disorders, particularly substance use, in the offspring, and (nonsignificantly) increased mean paternal age, in the mates of women with schizophrenia-spectrum disorders (Niemi et al., 2004). Thus, older fathers—regardless of the schizophrenia liability of their mates—may have increased schizophrenia liability in the form of schizotypal (or other cluster A) personality traits, leading to both “selection into late fatherhood” and increased risk of NAP in the offspring.

We did not find an association between APA and *paternal* schizophrenia in either the NFBC 1966 or the Finnish NAP cohort (in a post-hoc analysis). These findings also argue against the “de novo mutation” hypothesis, which would predict a significant negative association between APA and *paternal* schizophrenia. Consistent with our findings, maternal (versus paternal) history of schizophrenia is a stronger predictor of schizophrenia in the offspring (Mortensen 2010).

Our findings suggest that increased genetic risk from the mother may explain the association between APA and NAP. The study by Petersen et al. (2010) suggests that factors related to greater paternal age at first conception, not paternal age at conception of later children, is responsible for the “APA effect”. Although this study used a different design and provides different information from ours, the findings are not mutually exclusive. Furthermore, both studies provide evidence against the “de novo mutation” hypothesis. Replication of our

findings in large cohorts is warranted. Future studies should also investigate the relationship between older parental age and personality traits associated with increased schizophrenia liability.

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Figure 1.
Association Between Paternal Age and Parental History Group in the Finnish NAP Cohort

Figure 2.
Association Between Paternal Age and Parental History Group in the NFBC 1966

Table 1

Demographic Characteristics of the Two Cohorts

	Cohort	
	Finnish NAP (N=13,712)	NFBC 1966 (N=10,518)
Mean ($\pm$ SD) Paternal Age	32.8 (7.5)	31.0 (7.2)
Mean Maternal Age	29.5 (6.3)	28.0 (6.6)
Gender (% Male)	57.6	51.1
Mean Maternal Parity	2.5 (1.6)	2.9 (2.2)

Table 2
Associations Between Parental Age and Parental History Group in the Finnish NAP Cohort

Parental History Group	Variable	Yes (n)	No (n)	OR	95% CI	Model 1 ^a p-value	OR	95% CI	Model 2 ^b p-value	OR	95% CI	Model 3 ^c p-value
Mother only affected	Paternal age, y											
	<25	85	1778	0.70	0.54–0.90	0.01	0.59	0.45–0.76	<0.01	0.61	0.44–0.84	<0.01
	25–29	232	3384	1.00	Reference		1.00	Reference		1.00	Reference	
	30–34	203	2924	1.01	0.83–1.23	0.90	1.23	1.00–1.51	0.05	1.30	1.00–1.69	0.05
	35–39	123	2084	0.86	0.69–1.08	0.19	1.31	1.01–1.69	0.05	1.41	1.00–1.97	0.05
	40–44	70	1352	0.76	0.57–0.99	0.05	1.34	0.97–1.86	0.08	1.21	0.77–1.90	0.40
	45–49	42	601	1.02	0.73–1.43	0.91	2.02	1.35–3.02	<0.01	2.48	1.51–4.07	<0.01
	50	20	296	0.99	0.62–1.58	0.95	1.94	1.16–3.25	0.01	1.85	0.95–3.59	0.07
	Total	775	12419				1.20	1.12–1.29	<0.01	1.20	1.10–1.32	<0.01
	Maternal age, y											
Father only affected	<25	243	3419	1.09	0.90–1.31	0.39	1.26	1.03–1.53	0.02			
	25–29	233	3559	1.00	Reference		1.00	Reference				
	30–34	173	2695	0.98	0.80–1.20	0.85	0.83	0.67–1.03	0.09			
	35–39	95	1820	0.80	0.62–1.02	0.07	0.57	0.43–0.76	<0.01			
	40–44	27	848	0.49	0.32–0.73	<0.01	0.30	0.19–0.47	<0.01			
	45–49	4	77	0.79	0.29–2.19	0.66	0.44	0.15–1.24	0.12			
	50	0	1	0.00			0.00					
	Total	775	12419				0.75	0.69–0.82	<0.01			
	Paternal age, y											
	<25	70	1778	0.86	0.64–1.15	0.30	0.88	0.66–1.19	0.42	0.69	0.47–1.02	0.06
	25–29	155	3384	1.00	Reference		1.00	Reference		1.00	Reference	
	30–34	139	2924	1.04	0.82–1.31	0.76	1.01	0.78–1.30	0.95	1.15	0.85–1.56	0.36
	35–39	57	2084	0.60	0.44–0.81	<0.01	0.57	0.40–0.82	<0.01	0.72	0.46–1.12	0.14
	40–44	43	1352	0.69	0.49–0.98	0.04	0.66	0.43–1.01	0.06	1.02	0.61–1.70	0.94
	45–49	9	601	0.33	0.17–0.64	<0.01	0.31	0.15–0.64	<0.01	0.64	0.30–1.41	0.27
	50	0	296	0.00			0.00			0.00		

Parental History Group	Variable	Yes (n)	No (n)	Model 1 ^a		Model 2 ^b		Model 3 ^c	
				OR	95% CI	p-value	OR	95% CI	p-value
Maternal age, y									
	Total	473	12419			0.83	0.74–0.92	<0.01	0.83–1.07
	<25	140	3419	0.91	0.72–1.15	0.43	0.85	0.66–1.09	0.19
	25–29	160	3559	1.00	Reference		1.00	Reference	
	30–34	106	2695	0.88	0.68–1.12	0.30	0.97	0.74–1.27	0.83
	35–39	53	1820	0.65	0.47–0.89	0.01	0.81	0.56–1.17	0.25
	40–44	14	848	0.37	0.21–0.64	<0.01	0.51	0.28–0.95	0.03
	45–49	0	77	0.00			0.00		
	50	0	1	0.00			0.00		
	Total	473	12419			0.95	0.84–1.07	0.39	

Parental History		Variable		Yes	No	Model 1 ^a		Model 2 ^b			
Group		(n)	(n)	(n)	(n)	OR	95% CI	p-value	OR	95% CI	p-value
Paternal age, y											
	<25	155	1778			0.76	0.63–0.93	0.01	0.69	0.56–0.84	<0.01
	25–29	387	3384			1.00	Reference		1.00	Reference	
	30–34	342	2924			1.02	0.88–1.19	0.77	1.15	0.98–1.35	0.09
	35–39	180	2084			0.76	0.63–0.91	<0.01	0.98	0.79–1.21	0.82
	40–44	113	1352			0.73	0.59–0.91	0.01	1.05	0.80–1.36	0.74
	45–49	51	601			0.74	0.55–1.01	0.06	1.14	0.80–1.62	0.47
	50	20	296			0.59	0.37–0.94	0.03	0.90	0.55–1.48	0.69
	Total	1248	12419						1.05	0.99–1.12	0.08

Maternal age, y

<25	383	3419	1.01	0.88–1.18	0.85	1.09	0.93–1.28	0.28
25–29	393	3559	1.00	Reference		1.00	Reference	
30–34	279	2695	0.94	0.80–1.10	0.43	0.87	0.73–1.03	0.11
35–39	148	1820	0.74	0.61–0.90	<0.01	0.64	0.51–0.80	<0.01
40–44	41	848	0.44	0.32–0.61	<0.01	0.36	0.25–0.52	<0.01
45–49	4	77	0.47	0.17–1.29	0.14	0.38	0.13–1.05	0.06
50	0	1	0.00			0.00		

Parental History Group	Variable	Yes (n)	No (n)	OR	95% CI	p-value	Model 1 ^a	OR	95% CI	p-value	Model 2 ^b
	Total	1248	12419								
Both parents affected	Paternal age, y										
	<25	4	1778	0.35	0.12–1.01	0.05					
	25–29	22	3384	1.00	Reference						
	30–34	8	2924	0.42	0.19–0.95	0.04					
	35–39	6	2084	0.44	0.18–1.09	0.08					
	40–44	3	1352	0.34	0.10–1.14	0.08					
	45–49	2	601	0.51	0.12–2.18	0.37					
	50	0	296	0.00							
	Total	45	12419								
	Maternal age, y										
	<25	16	3419	0.98	0.49–1.94	0.95					
	25–29	17	3559	1.00	Reference						
	30–34	9	2695	0.70	0.31–1.57	0.39					
	35–39	2	1820	0.23	0.05–1.00	0.05					
	40–44	1	848	0.25	0.03–1.86	0.17					
	45–49	0	77	0.00							
	50	0	1	0.00							
	Total	45	12419								
^a Unadjusted											
^b Adjusted for age of the other parent, gender, and maternal parity											
^c Restricted to probands born in or after 1955; Adjusted for age of the other parent, gender, and maternal parity											

^aUnadjusted^bAdjusted for age of the other parent, gender, and maternal parity^cRestricted to probands born in or after 1955; Adjusted for age of the other parent, gender, and maternal parity

Table 3

Associations Between Parental Age and Parental History Group in the NFBC 1966

Parental History		Variable	Yes	No	Model 1 ^a			Model 2 ^b		
Group			(n)	(n)	OR	95% CI	p-value	OR	95% CI	p-value
Mother only affected										
	Paternal age, y									
	<25		50	2146	0.82	0.58–1.17	0.27	0.76	0.53–1.11	0.15
	25–29		83	2927	1.00	Reference		1.00	Reference	
	30–34		65	2025	1.13	0.82–1.58	0.46	1.19	0.84–1.70	0.33
	35–39		47	1431	1.16	0.81–1.66	0.43	1.25	0.80–1.97	0.32
	40–44		26	769	1.24	0.80–1.92	0.35	1.34	0.74–2.43	0.33
	45–49		8	299	1.18	0.60–2.29	0.63	1.09	0.45–2.59	0.86
	50		6	11	1.90	0.81–4.44	0.14	2.21	0.83–5.89	0.11
	Total		285	9709				1.14	0.99–1.31	0.07
Maternal age, y										
	<25		108	3723	1.08	0.80–1.47	0.60	1.15	0.82–1.60	0.43
	25–29		71	2661	1.00	Reference		1.00	Reference	
	30–34		48	1670	1.08	0.74–1.56	0.70	0.99	0.67–1.48	0.97
	35–39		35	1104	1.26	0.84–1.88	0.27	1.00	0.61–1.64	1.00
	40–44		19	479	1.56	0.94–2.58	0.09	1.17	0.61–2.24	0.64
	45–49		4	55	2.73	0.96–7.75	0.06	2.05	0.62–6.72	0.24
	50		0	0	0.00			0.00		
	Total		285	9692				0.99	0.84–1.17	0.94
Father only affected										
	Paternal age, y									
	<25		45	2146	1.08	0.72–1.60	0.72	1.11	0.73–1.67	0.65
	25–29		57	2927	1.00	Reference		1.00	Reference	
	30–34		56	2025	1.42	0.98–2.06	0.07	1.34	0.90–2.01	0.15
	35–39		32	1431	1.15	0.74–1.78	0.54	1.01	0.59–1.73	0.98
	40–44		20	769	1.33	0.80–2.23	0.28	1.10	0.55–2.20	0.79
	45–49		5	299	0.86	0.34–2.15	0.86	0.67	0.23–1.98	0.48
	50		2	11	0.92	0.22–3.82	0.91	0.72	0.15–3.36	0.68

Parental History Group	Variable	Yes (n)	No (n)	OR	95% CI	p-value	OR	95% CI	p-value
	Total	217	9709				1.01	0.97–1.05	0.67
Maternal age, y									
	<25	80	3723	0.97	0.69–1.36	0.84	1.02	0.70–1.49	0.92
	25–29	59	2661	1.00	Reference		1.00	Reference	
	30–34	42	1670	1.13	0.76–1.69	0.54	1.06	0.69–1.64	0.80
	35–39	19	1104	0.78	0.46–1.31	0.34	0.67	0.36–1.25	0.21
	40–44	16	479	1.50	0.86–2.63	0.16	1.22	0.58–2.53	0.60
	45–49	1	55	0.82	0.11–6.04	0.85	0.60	0.07–4.93	0.63
	50	0	0	0.00					
	Total	217	9692				0.97	0.80–1.18	0.79

Parental History Group	Variable	Yes (n)	No (n)	OR	95% CI	p-value	OR	95% CI	p-value
Paternal age, y									
	<25	95	2146	0.92	0.71–1.21	0.56	0.89	0.68–1.18	0.41
	25–29	140	2927	1.00	Reference		1.00	Reference	
	30–34	121	2025	1.25	0.97–1.61	0.08	1.26	0.96–1.65	0.10
	35–39	79	1431	1.15	0.87–1.53	0.32	1.14	0.81–1.62	0.45
	40–44	46	769	1.28	0.91–1.79	0.16	1.23	0.78–1.95	0.37
	45–49	13	299	1.05	0.61–1.81	0.88	0.89	0.45–1.77	0.74
	50	8	11	1.50	0.72–3.13	0.03	1.48	0.65–3.40	0.36
	Total	502	9709				1.06	0.95–1.19	0.28

Maternal age, y									
	<25	188	3723	1.03	0.82–1.30	0.80	1.09	0.85–1.40	0.51
	25–29	130	2661	1.00	Reference		1.00	Reference	
	30–34	90	1670	1.10	0.84–1.45	0.49	1.02	0.76–1.38	1.02
	35–39	54	1104	1.04	0.75–1.43	0.82	0.85	0.58–1.26	0.43
	40–44	35	479	1.53	1.04–2.24	0.03	1.19	0.73–1.95	0.49
	45–49	5	55	1.87	0.73–4.74	0.19	1.38	0.49–3.88	0.54
	50	0	0	0.00			0.00		

Parental History Group	Variable	Yes (n)	No (n)	OR	95% CI	p-value	OR	95% CI	p-value
Model 1^a									
Model 2^b									
Both parents affected									
Paternal age, y									
	<25	3	2146	2.04	0.34–12.23	0.43	3.10	0.47–20.51	0.24
	25–29	2	2927	1.00	Reference		1.00	Reference	
	30–34	2	2025	1.45	0.20–10.28	0.71	0.92	0.12–7.32	0.93
	35–39	4	1431	4.09	0.75–22.34	0.10	1.64	0.18–14.55	0.66
	40–44	1	769	1.90	0.17–20.99	0.60	0.48	0.02–10.88	0.64
	45–49	1	299	4.88	0.44–53.98	0.20	0.96	0.03–28.34	0.98
	50	0	11	0.00			0.00		
	Total	13	9709				0.76	0.37–1.53	0.44
Maternal age, y									
	<25	5	3723	3.56	0.42–30.52	0.25	4.06	0.43–38.54	0.22
	25–29	1	2661	1.00	Reference		1.00	Reference	
	30–34	3	1670	4.78	0.50–45.98	0.18	4.40	0.41–46.86	0.22
	35–39	2	1104	4.82	0.44–53.17	0.20	4.00	0.25–63.54	0.33
	40–44	2	479	11.05	1.00–122.07	0.05	8.09	0.37–176.99	0.18
	45–49	0	55	0.00			0.00		
	50	0	0	0.00			0.00		
	Total	13	9692				1.17	0.54–2.52	0.69
^a Unadjusted									
^b Adjusted for age of the other parent, gender, paternal social class, and maternal parity									

Table 4

Effect of Paternal Age on NAP Risk in the NFBC 1966

Paternal Age Group	Cases (n)	Model 1 *			Model 2 **		
		Risk	95% CI	p-value	Risk	95% CI	p-value
<25	25	0.97	0.57–1.67	0.92	1.02	0.59–1.76	0.94
25–29	37	1.00	Reference		1.00	Reference	
30–34	28	1.07	0.62–1.82	0.82	1.04	0.60–1.78	0.90
35–39	25	1.28	0.67–2.47	0.46	1.23	0.64–2.37	0.54
40	14	0.84	0.34–2.04	0.70	0.79	0.32–1.91	0.58
Total	129						

* Adjusted for maternal age (continuous), gender, paternal social class, and maternal parity

** Adjusted for maternal age (continuous), gender, paternal social class, maternal parity, and maternal schizophrenia