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Advanced paternal age and parental history of schizophrenia

Brian Miller [a,b,*], Jaana Suvisaari [c], Jouko Miettunen [b], Marjo-Riitta Järvelin [d,e], Jari Haukka [c,f], Antti Tanskanen [c], Jouko Lönnqvist [c], Matti Isohanni [b], Brian Kirkpatrick [g]

[a] Department of Psychiatry and Health Behavior, Medical College of Georgia Health Sciences University, Augusta, Georgia, United States
[b] Department of Psychiatry, University of Oulu and Oulu University Hospital, Oulu, Finland
[c] Department of Mental Health and Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland
[d] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom
[e] Institute of Health Sciences, University of Oulu, Finland
[f] Hjelt Institute, Department of Public Health, University of Helsinki, Finland
[g] Department of Psychiatry and Behavioral Science, Texas A&M University and Scott & White Healthcare, Temple, Texas, United States

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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.
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.

1. Introduction

Advanced paternal age (APA) is a risk factor for nonaffective psychosis (NAP) in the offspring (Miller et al., 2011). 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; Dalman and Allebeck, 2002; Byrne et al., 2003; Zammit et al., 2003; Sipos et al., 2004). In a meta-analysis, we did not find an obvious cut-off point beyond which paternal age should be considered "advanced" (Miller et al., 2011). 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; Kühnert and Nieschlag, 2004; Rannan-Eliya et al., 2004; Dakouane Giudicelli et al., 2008), 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., 2011). 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 (Watt and Nicholi, 1979; Morgan et al., 2007) are potential risk factors for schizophrenia

* Corresponding author at: Department of Psychiatry and Health Behavior, Georgia Health Sciences University, 997 Saint Sebastian Way, Augusta, Georgia 30912, United States. Tel.: +1 706 721 4445; fax: +1 706 721 1793.
E-mail address: brmiller@georgiahealth.edu (B. Miller).

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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.

2. Methods

2.1. 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., 2011). 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.

2.1.1. 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, 1992). 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.

2.1.2. 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; Penttilä 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.

2.2. 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 of 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).

3. Results

3.1. 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 Fig. 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).

3.2. 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 Fig. 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.

Table 1
Demographic characteristics of the two cohorts.

	Cohort	
	Finnish NAP (N = 13,712)	NFBC 1966 (N = 10,518)
Mean (± 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)

3.3. 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., 2011). 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, $p<0.01$).

3.4. 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).

4. 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

Table 2
Associations between parental age and parental history group in the Finnish NAP Cohort.

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	OR	95% CI	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	12,419				1.20	1.12–1.29	<0.01	1.20	1.10–1.32	<0.01
	Maternal age, y											
	<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	12,419				0.75	0.69–0.82	<0.01			
Father only affected	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		
	Total	473	12,419				0.83	0.74–0.92	<0.01	0.94	0.83–1.07	0.35
	Maternal age, y											
	<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	12,419				0.95	0.84–1.07	0.39			
Either mother or father affected	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	12,419				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					
	Total	1248	12,419				0.81	0.76–0.88	<0.01			
Both parents affected	Paternal age, y											
	<25	4	1778	0.35	0.12–1.01	0.05	0.26	0.09–0.79	0.02			
	25–29	22	3384	1.00	Reference		1.00	Reference				
	30–34	8	2924	0.42	0.19–0.95	0.04	0.57	0.25–1.34	0.20			
	35–39	6	2084	0.44	0.18–1.09	0.08	0.85	0.30–2.42	0.76			
	40–44	3	1352	0.34	0.10–1.14	0.08	0.83	0.21–3.37	0.80			
	45–49	2	601	0.51	0.12–2.18	0.37	1.48	0.28–7.86	0.65			
	≥50	0	296	0.00			0.00					
	Total	45	12,419				1.12	0.83–1.50	0.46			
	Maternal age, y											
	<25	16	3419	0.98	0.49–1.94	0.95	0.97	0.46–2.03	0.93			
	25–29	17	3559	1.00	Reference		1.00	Reference				
	30–34	9	2695	0.70	0.31–1.57	0.39	0.71	0.30–1.69	0.44			
	35–39	2	1820	0.23	0.05–1.00	0.05	0.24	0.05–1.16	0.08			
	40–44	1	848	0.25	0.03–1.86	0.17	0.26	0.03–2.31	0.23			
	45–49	0	77	0.00			0.00					
	≥50	0	1	0.00			0.00					
	Total	45	12,419				0.73	0.49–1.08	0.11			

[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.

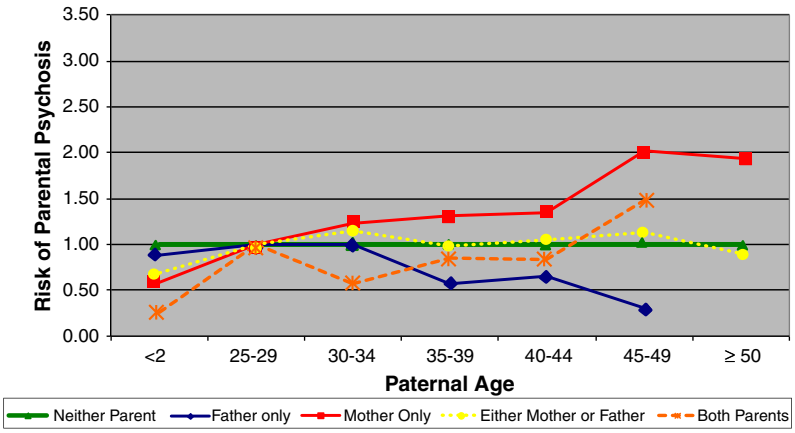

Fig. 1. Association between paternal age and parental history group in the Finnish NAP Cohort.

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 (Arajarvi 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 (Granville-Grossman, 1966; El-Saadi et al., 2004). 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; Zammit et al., 2003; Pulver et al., 2004; Sipos et al., 2004). 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 Fig. 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., 2011). 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 et al., 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. (2011) 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

Table 3
Associations between parental age and parental history group in the NFBC 1966.

Parental history group	Variable	Yes (n)	No (n)	Model 1[a]			Model 2[b]		
				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
	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			0.00		
	Total	217	9692				0.97	0.80–1.18	0.79
Either mother or father affected	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		
	Total	502	9692				0.99	0.87–1.12	0.82
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.

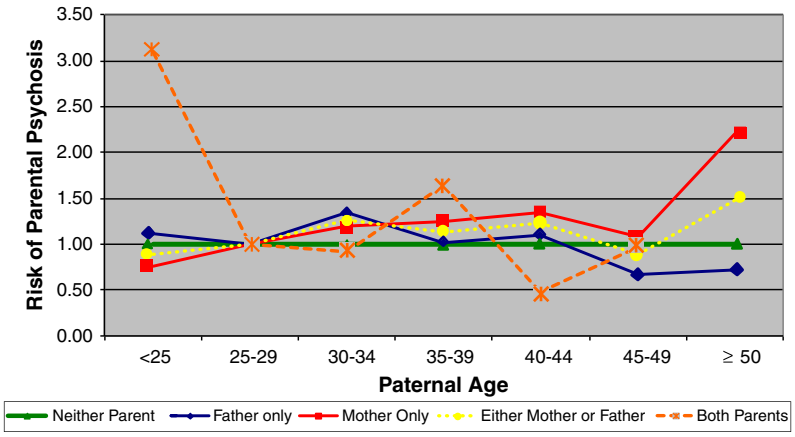

Fig. 2. Association between paternal age and parental history group in the NFBC 1966.

studies should also investigate the relationship between older parental age and personality traits associated with increased schizophrenia liability.

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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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Table 4
Effect of paternal age on NAP Risk in the NFBC 1966.

Paternal age group	Cases (n)	Model 1[a]			Model 2[b]		
		Risk	95% C	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						

[a] Adjusted for maternal age (continuous), gender, paternal social class, and maternal parity.

[b] Adjusted for maternal age (continuous), gender, paternal social class, maternal parity, and maternal schizophrenia.

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References

Addington, J., Saeedi, H., Addington, D., 2005. The course of cognitive functioning in first episode psychosis: changes over time and impact on outcome. Schizophr. Res. 78, 35–43.

Alaraisanen, A., Miettunen, J., Lauronen, E., Rasanen, P., Isohanni, M., 2006. Good school performance is a risk factor of suicide in psychoses: a 35-year follow up of the Northern Finland 1966 Birth Cohort. Acta Psychiatr. Scand. 114, 357–362.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual for Mental disorders. 3rd ed. revised, DSM-3-R. American Psychiatric Association, Washington DC.

Arajarvi, R., Suvisaari, J., Suokas, J., Schreck, M., Haukka, J., Hintikka, J., et al., 2005. Prevalence and diagnosis of schizophrenia based on register, case record and interview data in an solated Finnish cohort born 1940–1969. Soc. Psychiatry Psychiatr. Epidemiol. 40 (10), 808–816.

Bray, I., Gunnell, D., Davey Smith, G., 2006. Advanced paternal age: how old is too old? J. Epidemiol. Community Health 60, 851–853.

Brown, A.S., Schaefer, C.A., Wyatt, R.J., Begg, M.D., Goetz, R., Bresnahan, M.A., et al., 2002. Paternal age and risk of schizophrenia in adult offspring. Am. J. Psychiatry 2002 (159), 1528–1533.

Byrne, M., Agerbo, E., Ewald, H., Eaton, W.W., Mortensen, P.B., 2003. Parental age and risk of schizophrenia: a case–control study. Arch. Gen. Psychiatry 60, 673–678.

Crow, J.F., 1997. The high spontaneous mutation rate: is it a health risk? Proc. Natl. Acad. Sci. U. S. A. 94, 8380–8386.

Dakouane Giudicelli, M., Serazin, V., Le Sciellour, C.R., Albert, M., Selva, J., Giudicelli, Y., 2008. Increased achondroplasia mutation frequency with advanced age and evidence for G1138A mosaicism in human testis biopsies. Fertil. Steril. 89 (6), 1651–1656.

Dalman, C., Allebeck, P., 2002. Paternal age and schizophrenia: further support for an association. Am. J. Psychiatry 159, 1591–1592 67 227–236.

El-Saadi, O., Pedersen, C.B., McNeil, T.F., Saha, S., Welham, J., O'Callaghan, E., et al., 2004. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. Schizophr. Res.

Gottesman, I.I., 1991. Schizophrenia Genesis: The Origins of Madness. W.H. Freeman, New York, p. 96.

Granville-Grossman, K.L., 1966. Parental age and schizophrenia. Br. J. Psychiatry 112, 899–905.

Herman, D.B., Brown, A.S., Opler, M.G., Desai, M., Malaspina, D., Bresnahan, M., et al., 2006. Does unwantedness of pregnancy predict schizophrenia in the offspring? Findings from a prospective birth cohort study. Soc. Psychiatry Psychiatr. Epidemiol. 41, 605–610.

Kühnert, B., Nieschlag, E., 2004. Reproductive functions of the ageing male. Hum. Reprod. Update 10 (4), 327–339.

Lichtermann, D., Karbe, E., Maier, W., 2000. The genetic epidemiology of schizophrenia and of schizophrenia spectrum disorders. Eur. Arch. Psychiatry Clin. Neurosci. 250, 304–310.

Malaspina, D., Harlap, S., Fennig, S., Heiman, D., Nahon, D., Feldman, D., et al., 2001. Advancing paternal age and the risk of schizophrenia. Arch. Gen. Psychiatry 58, 361–367.

Malaspina, D., Brown, A., Goetz, D., Alia-Klein, N., Harkavy-Friedman, J., Harlap, S., et al., 2002. Schizophrenia risk and paternal age: a potential role for de novo mutations in schizophrenia vulnerability genes. CNS Spectr. 7, 26–29.

Miettunen, J., Suvisaari, J., Haukka, J., Isohanni, M., 2011. Use of register data for psychiatric epidemiology in the Nordic countries, In: Tsuang, M., Tohen, M., Jones, P.

(Eds.), Textbook in Psychiatric Epidemiology, third ed. Wiley-Blackwell, New York, pp. 117–131.
Miller, B., Messias, E., Miettunen, J., Alaräisänen, A., Järvelin, M.R., Koponen, H., et al., 2011. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. Schizophr. Bull. 37 (5), 1039–1047.
Moilanen, K., Veijola, J., Läksy, K., Mäkikyrö, T., Miettunen, J., Kantojärvi, L., et al., 2003. Reasons for the diagnostic discordance between clinicians and researchers in the schizophrenia in the Northern Finland 1966 Birth Cohort. Soc. Psychiatry Psychiatr. Epidemiol. 38 (6), 305–310.
Moilanen, K., Jokelainen, J., Jones, P.B., Hartikainen, A.L., Järvelin, M.R., Isohanni, M., 2010. Deviant intrauterine growth and risk of schizophrenia: a 34-year follow-up of the Northern Finland 1966 Birth Cohort. Schizophr. Res. 124 (1–3), 223–230.
Morgan, C., Kirkbride, J., Leff, J., Craig, T., Hutchinson, G., McKenzie, K., et al., 2007. Parental separation, loss and psychosis in different ethnic groups: a case–control study. Psychol. Med. 37, 495–503.
Mortensen, P.B., Pedersen, M.G., Pedersen, C.B., 2010. Psychiatric family history of schizophrenia risk in Denmark: which mental disorders are relevant? Psychol. Med. 40 (2), 201–210.
Myhrman, A., Rantakallio, P., Isohanni, M., Jones, P., Partanen, U., 1996. Unwantedness of a pregnancy and schizophrenia in the child. Br. J. Psychiatry. 169, 637–640.
Niemi, L.T., Suvisaari, J.M., Haukka, J.K., Wrede, G., Lönnqvist, J.K., 2004. Cumulative incidence of mental disorders among offspring of mothers with psychotic disorder: results from the Helsinki High-Risk Study. Br. J. Psychiatry 185, 11–17.
Parnas, J., 1985. Mates of schizophrenic mothers. A study of assortative mating from the American–Danish high risk project. Br. J. Psychiatry 146, 490–497.
Parnas, J., 1988. Assortative mating in schizophrenia: results from the Copenhagen High-Risk Study. Psychiatry 51, 58–64.
Penttilä, M., Jääskeläinen, E., Haapea, M., Tanskanen, P., Veijola, J., Ridler, K., et al., 2010. Association between duration of untreated psychosis and brain morphology in schizophrenia within the Northern Finland 1966 Birth Cohort. Schizophr. Res. 123 (2–3), 145–152.
Perrin, M.C., Brown, A.S., Malaspina, D., 2007. Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. Schizophr. Bull. 33, 1270–1273.
Petersen, L., Mortensen, P.B., Pedersen, C.B., 2011. Paternal age at birth of first child and risk of schizophrenia. Am. J. Psychiatry 168 (1), 82–88.
Pihlajamaa, J., Suvisaari, J., Henriksson, M., Heilä, H., Karjalainen, E., Koskela, J., et al., 2008. The validity of schizophrenia diagnosis in the Finnish Hospital Discharge Register: findings from a 10-year birth cohort sample. Nord. J. Psychiatry 62 (3), 198–203.
Pulver, A.E., McGrath, J.A., Liang, K.Y., Lasseter, V.K., Nestadt, G., Wolyniec, P.S., 2004. An indirect test of the new mutation hypothesis associating advanced paternal age with the etiology of schizophrenia. Am. J. Med. Genet. B. Neuropsychiatr. Genet. 124B (1), 6–9.
Rannan-Eliya, S.V., Taylor, I.B., De Heer, I.M., Van Den Ouweland, A.M., Wall, S.A., Wilkie, A.O., 2004. Paternal origin of FGFR3 mutations in Muenke-type craniosynostosis. Hum. Genet. 115 (3), 200–207.
Sipos, A., Rasmussen, F., Harrison, G., Tynelius, P., Lewis, G., Leon, D.A., et al., 2004. Paternal age and schizophrenia: a population based cohort study. BMJ 329, 1070.
Suvisaari, J.M., Haukka, J., Tanskanen, A., Lönnqvist, J.K., 1998. Age at onset and outcome in schizophrenia are related to the degree of familial loading. Br. J. Psychiatry 173, 494–500.
Suvisaari, J., Perala, J., Saarni, S., Juvonen, H., Tuulio-Henriksson, A., Lonnqvist, J., 2009. The epidemiology and descriptive and predictive validity of DSM-IV delusional disorder and subtypes of schizophrenia. Clin. Schizophr. Relat. Psychoses. 2 (4), 289–297.
Watt, N.F., Nicholi, A., 1979. Early death of a parent as an etiological factor in schizophrenia. Am J. Orthopsychiatry 49, 465–473.
World Health Organization, 1967. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on Recommendations of the Eighth Revision Conference. World Health Organization, Geneva, Switzerland.
World Health Organization, 1977. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Based on the Recommendations of the Ninth Revision Conference. World Health Organization, Geneva, Switzerland.
World Health Organization, 1992. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Based on Recommendations of the Tenth Revision Conference. World Health Organization, Geneva, Switzerland.
Zammit, S., Allebeck, P., Dalman, C., Lundberg, I., Hemmingson, T., Owen, M.J., et al., 2003. Paternal age and risk for schizophrenia. Br. J. Psychiatry 183, 405–408.