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Meta-analysis of Paternal Age and Schizophrenia Risk in Male Versus Female Offspring

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Introduction: Advanced paternal age (APA) is a reported risk factor for schizophrenia in the offspring. We performed a meta-analysis of this association, considering the effect of gender and study design. Methods: We identified articles by searching Pub Med, PsychInfo, ISI, and EMBASE, and the reference lists of identified studies. Previously unpublished data from the Northern Finland 1966 Birth Cohort (NFBC 1966) study were also included. Results: There were 6 cohort studies and 6 case–control studies that met the inclusion criteria. In both study designs, there was a significant increase in risk of schizophrenia in the offspring of older fathers (≥30) compared to a reference paternal age of 25–29, with no gender differences. The relative risk (RR) in the oldest fathers (≥50) was 1.66 [95% confidence interval (95% CI): 1.46–1.89, $P < 0.01$]. A significant increase in risk was also found for younger fathers (<25) in males (RR = 1.08, 95% CI: 1.02–1.14, $P = 0.01$) but not females (RR = 1.04, 95% CI: 0.97–1.14, $P = 0.28$). The population attributable risk percentage (PAR%) was 10% for paternal age ≥30 and 5% for paternal age <25. Discussion: Both APA (≥30) and younger paternal age (<25) increase the risk of schizophrenia; younger paternal age may be associated with an increased risk in males but not females. This risk factor increases the risk of schizophrenia as much as any single candidate gene of risk. The mechanism of these associations is not known and may differ for older and younger fathers.

Key words: paternal age/schizophrenia/epidemiology/meta-analysis/gender differences

Introduction

There is an extensive literature on advanced paternal age (APA) as a risk factor for a wide variety of adverse health outcomes in the offspring that occur throughout the lifespan, including cleft lip and palate, cancer, congenital heart defects, and neuropsychiatric conditions such as autism, epilepsy, and bipolar disorder.[1,2] APA has also been associated with poorer intellectual performance in the offspring.[3,4] The literature suggests that for many disorders, there is no obvious cut-off point beyond which paternal age should be considered "advanced."[5–8] Instead, there is usually a linear increase in risk of a disorder with increasing paternal age.

APA has also been reported to increase the risk of schizophrenia in the offspring. Potentially confounding factors such as maternal age, parity of the mother, socioeconomic status, family history, social support, ethnicity, marital status, and geography have all been examined and do not appear to account for the effect.[9–13] A majority of these studies, however, did not consider male and female offspring separately, although there is evidence that APA has a sexually dimorphic effect for other neuropsychiatric disorders. For instance, Reichenberg *et al.*[14] found that the adjusted odds ratio for APA-associated risk of autism was about 3 times greater in females than in males. Within schizophrenia spectrum disorders, there is also evidence for another risk factor with a sexually dimorphic effect: maternal–fetal blood incompatibility may increase risk in males but not in females.[15]

We performed a meta-analysis in order to better estimate the effect size of this association and to determine whether there was a sexually dimorphic effect. We included data from the Northern Finland 1966 Birth Cohort (NFBC 1966) study, which has not previously been published, in the meta-analysis (see Supplemental material for details).

Table 1. Characteristics of Studies of Paternal Age and Schizophrenia

Study	Location	Type	Diagnosis	Cases (*n*)	Included	Comment
Johanson, 1958	Sweden	Case–control	Schizophrenia	138	**Yes**	No comparison group
Gregory, 1959	Canada	Case series	Schizophrenia	453	No	No comparison group
Farina, 1963	US	Case series	Schizophrenia	167	No	No comparison group
Granville-Grossman, 1966	UK	Case–control	Schizophrenia	942	**Yes**	
Bojanovsky and Gerylovová, 1967		Case series	Schizophrenia	221	No	No comparison group
Costello *et al.*, 1968	UK	Case–control	Schizophrenia	29	No	Summary data not available
Hare and Moran, 1979	UK	Case–control	Schizophrenia	1032	No	Summary data not available
Gillberg, 1982	Sweden	Case–control	Psychosis[a]	30	No	Summary data not available
Kinnell, 1983	UK	Case–control	Schizophrenia	320	No	Summary data not available
Malama *et al.*, 1988	Greece	Case–control	Schizophrenia (Feighner criteria)	221	No	Summary data not available
Bertranpetit and Fananas, 1993	Spain	Case–control	Schizophrenia	120	No	Summary data not available
Raschka, 1998	Canada	Case series	Schizophrenia (DSM)	574	No	Summary data not available
Malaspina *et al.*, 2001	Israel	Birth cohort	Nonaffective psychosis (ICD-10)	630	**Yes**	
Brown *et al.*, 2002	US	Birth cohort	Schizophrenia spectrum disorders (ICD-9)	71	**Yes**	
Dalman and Allebeck, 2002	Sweden	Case–control	Schizophrenia (ICD-8,9)	420	**Yes**	
Byrne *et al.*, 2003	Denmark	Case–control	Schizophrenia (ICD-8,10)	7704	**Yes**	For case–control analyses only
Zammit *et al.*, 2003	Sweden	Conscript cohort	Schizophrenia (ICD-8,9)	337	**Yes**	
El-Saadi *et al.*, 2004	Sweden	Case–control	Psychosis (ICD-8-10)	134	No	>20% of cases with affective psychosis
	Australia	Case–control	Psychosis (DSM-III-R)	117	No	>20% of cases with affective psychosis
	Denmark	Birth cohort	Psychosis (ICD-10)	11672	No	Sample overlaps with Laursen *et al.*, 2007
Pulver *et al.*, 2004	US	Case series	Schizophrenia and schizoaffective disorder	376	No	No comparison group
Sipos *et al.*, 2004	Sweden	Birth cohort	Schizophrenia (ICD-9,10)	639	**Yes**	
Ekeus *et al.*, 2005	Sweden	Birth cohort	Schizophrenia (ICD-9,10)	366	No	Sample overlaps with Sipos *et al.*, 2004
Tsuchiya *et al.*, 2005	Japan	Case–control	Schizophrenia (DSM-IV)	99	**Yes**	
Laursen *et al.*, 2007	Denmark	Birth cohort	Schizophrenia (ICD-8,10)	13297	**Yes**	
Torrey *et al.*, 2009	US	Birth cohort	Schizophrenia (DSM-IV)	88	**Yes**	
Lopez-Castroman *et al.*, 2009	Spain	Case–control	Schizophrenia spectrum disorders (ICD-10)	356	No	Summary data not available
Miller *et al.*, 2009 (present study)	Finland	Birth cohort	Schizophrenia (DSM-III-R)	100	**Yes**	Northern Finland 1966 birth cohort

[a]Psychosis = infantile autism, other childhood psychosis, schizophrenia or schizophreniform psychosis, affective psychosis.

Methods

Study Design

Studies on paternal age and schizophrenia risk in the offspring were systematically searched using Medline (PubMed), EMBASE, PsycInfo (via Ovid), and ISI (Science and Social Science Citation Index) in May 2008 and again in December 2009. The search strategy used was "paternal age and (schizophrenia or psychotic disorders)." This search resulted in 38 citations from Medline, 55 from EMBASE, 34 from PsycInfo, and 35 from ISI. From these citations, as well as a manual review of their reference lists, we identified 27 potential studies (including previously unpublished data from the NFBC 1966) for inclusion in the meta-analysis, which are described in Table 1. We excluded 6 studies due to either (1) absence of a comparison group,[16–18] (2) >20% of cases had a diagnosis of affective psychosis[19] (2 of the 3 samples), or (3)

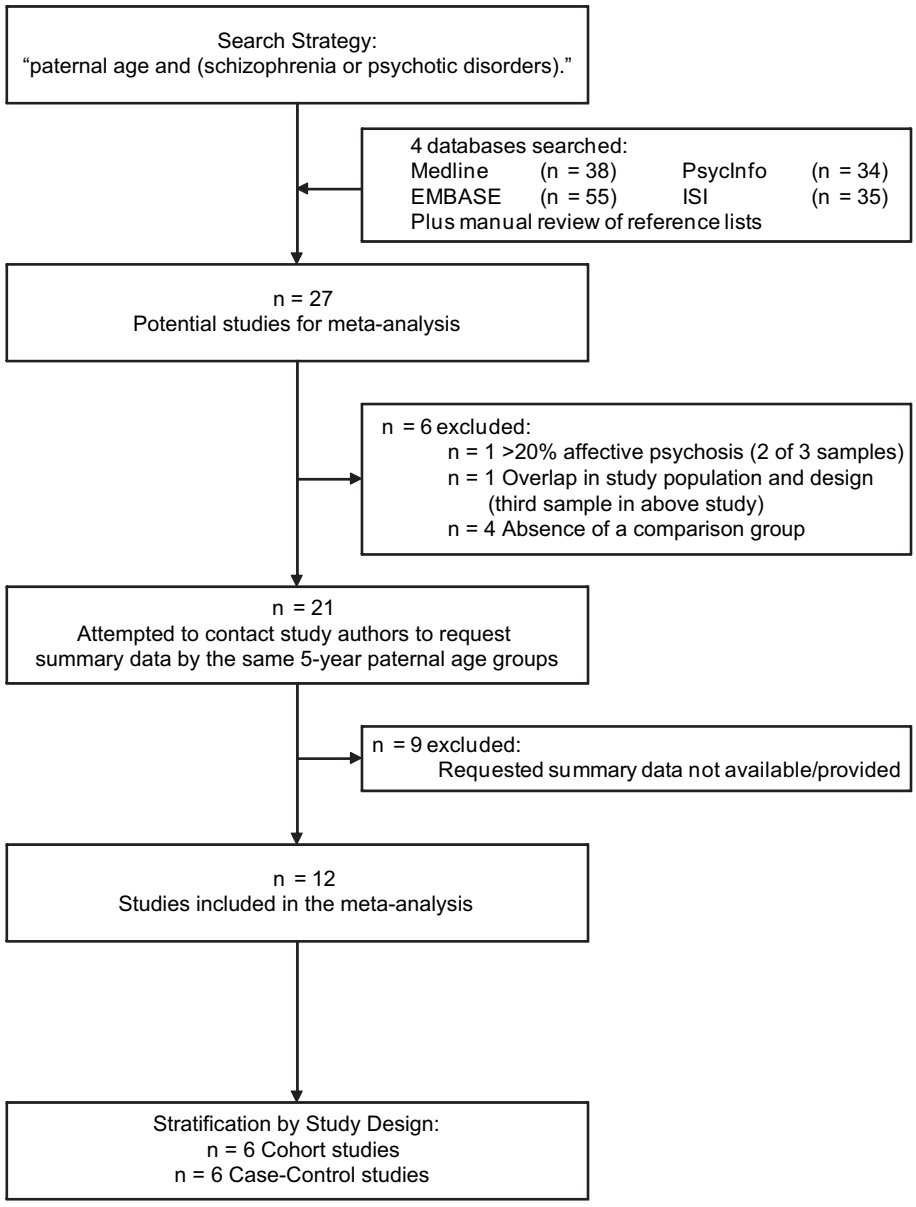

Fig. 1. Flow Chart of the Study Selection Process.

significant overlap in the study population.[20,21] In the 2 cases of overlap in the study population, we excluded the study with fewer cases of schizophrenia.

For the remaining 21 studies, we attempted to contact the authors to request summary data stratified by the same paternal age groups and gender. We were unable to consider paternal age as a continuous measure because a majority of authors were unable to share data at the level of the individual subject. The summary data included (1) the number of cases of schizophrenia and (2) the number of non-cases, for the following paternal age groups: <20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, and ≥ 55. The requested summary data were not obtained for 9 of these studies,[22–29] as either (1) we were unable to contact the authors or (2) the authors were unable to provide the requested summary data.

The 12 studies are included in the meta-analysis,[9–13,30–34] including 6 cohort studies and 5 case–controls studies are in bold in Table 1. In one of the cohort studies,[31] data were provided in person-years for each 5-year paternal age group. We divided each of these values by 16.2—the mean duration of follow-up in this study—to estimate the number of cases of schizophrenia and the number of non-cases. With the exception of the study by Malaspina *et al.*,[33] which included subjects with nonaffective psychosis, cases were restricted to a diagnosis of schizophrenia (either DSM or ICD criteria) for all studies. A flow chart summarizing the study selection process is presented in Figure 1. A detailed description of the Northern Finland 1966 Birth Cohort is available as Supplementary material.

Statistical Analysis

Meta-analysis We initially stratified paternal age into 9 age groups: <20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, and ≥55. However, because the upper and lower ends of this distribution led to relatively smaller cells sizes, we combined the ≤19 and 20–24 groups into a <25 age group and the 50–54 and ≥55 groups into a ≥50 age group. From the summary data, we calculated relative risk (RR) and 95% confidence intervals (95% CIs) for schizophrenia by paternal age group *for each of the 12 individual studies*, with risk set equal to 1.00 for the reference group (paternal age 25–29). We then performed a meta-analysis to estimate pooled effect sizes (and 95% CIs) for the risk of schizophrenia by 5-year paternal age groups, again with risk = 1.00 for the reference group (paternal age 25–29). Separate meta-analyses were performed for (1) all studies, (2) cohort studies, and (3) case–control studies. For the analysis of all studies, the study by Byrne *et al.*[10] was excluded due to its substantial overlap with the larger sample from Laursen *et al.*[32] In secondary meta-analyses, we considered males and females separately for (1) all studies, (2) cohort studies, and (3) case–control studies. For the analyses of case–control studies by gender, the study by Byrne *et al.*[10] could not be included as gender-stratified data were unavailable. Fixed effects pooled estimates and 95% CIs were calculated using the method of Mantel and Haenszel. *P*-values were considered statistically significant at the $\alpha = 0.05$ level. Random effects estimates were also calculated. Funnel plots were generated to assess for publication bias. The statistical analyses were performed using Stata 10.0 (StataCorp LP, College Station, TX).

Results

Meta-analysis

As described in Table 2, the cohort studies included a total of 3 000 729 subjects (53% male) and 14 568 cases of schizophrenia (66% male). The case–control studies included a total of 8733 cases of schizophrenia and 1 945 092 controls.

Table 2 and Figure 2 present the estimates of effect sizes with 95% CIs from the meta-analysis, compared to a reference paternal age of 25–29, for each paternal age group, by study design. In cohort, case–control, and all studies, we found (1) an increase in risk of schizophrenia in the offspring with increasing paternal age (>30 years of age), as well as a significant increase in risk of schizophrenia in the offspring of *younger* fathers (<25 years of age). Effect sizes were similar for cohort and case–control studies. The results of all meta-analyses were similar when repeated using a random effects model (data not shown). Funnel plots showed no evidence of publication bias (see Supplemental Figure 1). In all studies, there was significant heterogeneity between the

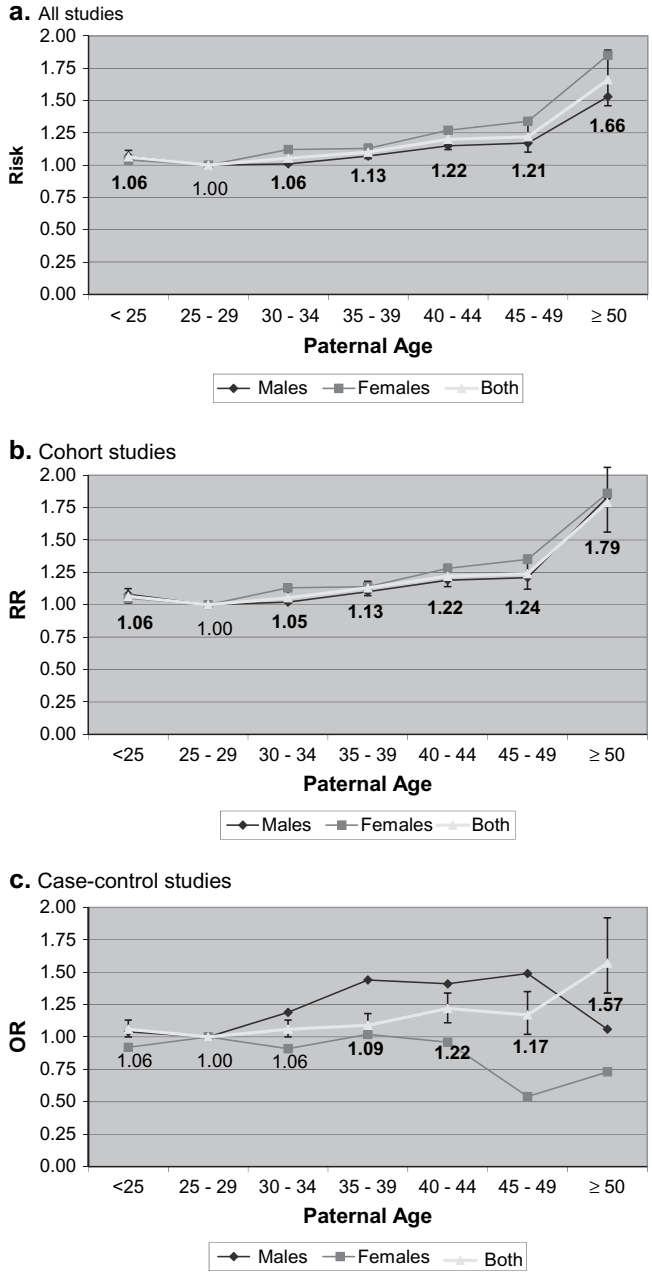

Fig. 2. Effect of Paternal Age on Schizophrenia Risk in 5-Year Groups. Error bars represent confidence interval boundaries for the estimates for males and females combined ("Both"). (a) All studies; (b) Cohort studies; (c) Case–control studies. Note that the study by Byrne *et al.*[10] could not be included in the curves for males and females as gender-stratified data were unavailable.

studies in 3 paternal age classes: (1) 35–39, heterogeneity $\chi^2 = 29.95$, $P < 0.01$, I^2 (variation in effect size attributable to heterogeneity) = 70.0%, (2) 45–49, heterogeneity $\chi^2 = 27.02$, $P < 0.01$, $I^2 = 70.4\%$, and (3) ≥50, heterogeneity $\chi^2 = 31.56$, $P < 0.01$, $I^2 = 77.8\%$. In a sensitivity analysis, the heterogeneity in the paternal age 35–39 class was no longer significant after removing the study by Laursen *et al.*,[32] the heterogeneity in the paternal age

Table 2. Effect of Paternal Age on Schizophrenia Risk by Gender

Study design	Gender	Paternal age group	Cases (*n*)	Total (*N*)	Risk	95% CI	*P*-value	Heterogeneity χ^2	Heterogeneity *P*-value	I^2
All	Male	<25	2223	322 272	**1.08**	**1.02–1.14**	**0.01**	3.31	0.97	0.0
		25–29	3242	541 871	1.00	Reference				
		30–34	2463	403 014	1.03	0.97–1.08	0.35	11.75	0.30	14.9
		35–39	1444	197 934	**1.12**	**1.06–1.19**	**<0.01**	**29.04**	**<0.01**	**65.6**
		40–44	705	84 639	**1.21**	**1.11–1.32**	**<0.01**	14.28	0.16	30.0
		45–49	268	30 372	**1.24**	**1.09–1.41**	**<0.01**	**18.51**	**0.03**	**51.4**
		≥50	160	13 318	**1.73**	**1.47–2.04**	**<0.01**	**42.59**	**<0.01**	**83.6**
		Total	10505	1 593 420						
	Female	<25	1131	292 431	1.04	0.97–1.12	0.28	3.55	0.90	0.0
		25–29	1747	490 458	1.00	Reference				
		30–34	1438	358 326	**1.10**	**1.03–1.19**	**<0.01**	7.55	0.48	0.0
		35–39	796	173 377	**1.12**	**1.03–1.23**	**0.01**	5.42	0.71	0.0
		40–44	412	72 362	**1.24**	**1.10–1.38**	**<0.01**	4.37	0.74	0.0
		45–49	156	26 471	**1.22**	**1.03–1.44**	**0.02**	**15.27**	**<0.01**	**73.8**
		≥50	96	11 304	**1.61**	**1.30–1.99**	**<0.01**	**9.84**	**0.02**	**69.5**
		Total	5776	142 4729						
	Both	<25	3359	614 202	**1.06**	**1.01–1.11**	**0.02**	5.24	0.87	0.0
		25–29	4975	1 030 437	1.00	Reference				
		30–34	3876	759 384	**1.06**	**1.01–1.10**	**0.02**	9.52	0.48	0.0
		35–39	2219	369 965	**1.13**	**1.08–1.19**	**<0.01**	**30.01**	**<0.01**	**66.7**
		40–44	1106	156 254	**1.22**	**1.14–1.30**	**<0.01**	10.34	0.41	3.3
		45–49	417	56 543	**1.21**	**1.09–1.34**	**<0.01**	**28.03**	**<0.01**	**67.9**
		≥50	252	24 481	**1.66**	**1.46–1.89**	**<0.01**	**31.56**	**<0.01**	**77.8**
		Total	16 204	3 011 266						
Cohort	Male	<25	2122	321 496	**1.08**	**1.02–1.14**	**0.01**	1.96	0.86	0.0
		25–29	3025	539 437	1.00	Reference				
		30–34	2207	400 513	1.02	0.96–1.07	0.58	8.00	0.16	37.5
		35–39	1261	196 274	**1.10**	**1.03–1.18**	**<0.01**	**22.63**	**<0.01**	**77.9**
		40–44	613	83 734	**1.19**	**1.09–1.31**	**<0.01**	9.97	0.08	49.7
		45–49	226	29 994	**1.21**	**1.06–1.39**	**<0.01**	7.00	0.22	28.6
		≥50	138	13 126	**1.83**	**1.54–2.18**	**<0.01**	**28.36**	**<0.01**	**85.9**
		Total	9592	1 584 574						
	Female	<25	1057	291 749	1.05	0.97–1.14	0.21	2.68	0.31	0.0
		25–29	1541	488 133	1.00	Reference				
		30–34	1219	355 888	**1.13**	**1.04–1.21**	**<0.01**	2.05	0.73	0.0
		35–39	643	171 757	**1.14**	**1.03–1.25**	**<0.01**	2.54	0.64	0.0
		40–44	321	71 447	**1.28**	**1.13–1.44**	**<0.01**	1.36	0.85	0.0
		45–49	124	26 075	**1.35**	**1.13–1.62**	**<0.01**	0.51	0.78	0.0
		≥50	71	11 107	**1.86**	**1.48–2.35**	**<0.01**	0.10	0.75	0.0
		Total	4976	1 416 156						
	Both	<25	3179	613 245	**1.06**	**1.01–1.12**	**0.01**	4.00	0.54	0.0
		25–29	4566	1 027 570	1.00	Reference				
		30–34	3426	756 401	**1.05**	**1.01–1.10**	**0.03**	5.01	0.42	0.0
		35–39	1904	368 031	**1.13**	**1.07–1.18**	**<0.01**	**24.51**	**<0.01**	**79.6**
		40–44	934	155 181	**1.22**	**1.14–1.31**	**<0.01**	7.72	0.17	35.3
		45–49	350	56 069	**1.24**	**1.12–1.38**	**<0.01**	6.67	0.25	25.1
		≥50	209	24 232	**1.79**	**1.56–2.06**	**<0.01**	**14.75**	**<0.01**	**72.9**
		Total	14 568	3 000 729						
Case–control	Male	<25	101	776	1.04	0.78–1.37	0.80	1.30	0.86	0.0
		25–29	217	2434	1.00	Reference				
		30–34	256	2501	1.19	0.96–1.47	0.11	1.72	0.79	0.0
		35–39	183	1660	**1.44**	**1.14–1.83**	**<0.01**	1.84	0.77	0.0
		40–44	92	905	**1.41**	**1.04–1.90**	**0.03**	3.26	0.52	0.0
		45–49	42	378	1.49	0.99–2.24	0.06	**10.64**	**0.01**	**71.8**
		≥50	22	192	1.06	0.63–1.78	0.83	**10.57**	**<0.01**	**81.1**
		Total	913	8846						
	Female	<25	74	682	0.92	0.67–1.27	0.62	0.27	0.97	0.0
		25–29	206	2325	1.00	Reference				
		30–34	219	2438	0.91	0.72–1.15	0.43	2.71	0.44	0.0

Table 2. Continued

Study design	Gender	Paternal age group	Cases (*n*)	Total (*N*)	Risk	95% CI	*P*-value	Heterogeneity χ^2	Heterogeneity *P*-value	I^2
		35–39	153	1620	1.02	0.78–1.34	0.88	2.33	0.51	0.0
		40–44	91	915	0.96	0.69–1.34	0.82	0.53	0.77	0.0
		45–49	32	396	**0.54**	**0.33–0.89**	**0.02**	2.95	0.09	66.0
		≥50	25	197	0.73	0.42–1.25	0.25	0.00	0.99	0.0
		Total	800	8573						
	Both	<25	1781	42 218	1.06	1.00–1.13	0.06	1.29	0.94	0.0
		25–29	2666	65 172	1.00	Reference				
		30–34	2104	46 108	1.06	1.00–1.13	0.07	4.62	0.46	0.0
		35–39	1185	24 480	**1.09**	**1.02–1.18**	**0.02**	6.82	0.24	26.6
		40–44	621	11 125	**1.22**	**1.10–1.34**	**<0.01**	2.66	0.75	0.0
		45–49	236	4268	**1.17**	**1.02–1.35**	**0.03**	**20.69**	**<0.01**	**80.7**
		≥50	140	1721	**1.57**	**1.31–1.89**	**<0.01**	**15.88**	**<0.01**	**81.1**
		Total	8733	195 092						

Values in bold were statistically significant at the $P < 0.05$ level.

45–49 class was no longer significant after removing the study by Granville-Grossman,[29] and the heterogeneity in the paternal age ≥50 was no longer significant after removing 2 studies (Granville-Grossman[30] and Laursen *et al.*[32]; data not shown). For each of these 3 paternal age classes, the effect size estimates remained significant.

Table 2 and Figure 2 also present the estimates of effect sizes with 95% CIs from the meta-analyses with males and females considered separately. In all studies and in cohort studies, the association between younger fathers (<25) and schizophrenia risk was significant in males (RR = 1.08, 95% CI: 1.02–1.14, $P = 0.01$) but not females (RR = 1.04, 95% CI: 0.97–1.12, $P = 0.28$), although the point estimates were similar. In case–control studies, the estimate for male offspring of younger fathers was similar to cohort studies but was not statistically significant (OR = 1.04, 95% CI: 0.78–1.37, $P = 0.80$). In all studies, estimates for males and females were similar for all paternal age classes ≥30. The results of all-secondary meta-analyses were similar when repeated using a random effects model (data not shown).

Using the summary data provided by each of the authors, we also estimated the population attributable risk percentage (PAR%) for paternal age. The PAR% is the incidence of outcome (schizophrenia) in the total population (defined here as paternal age either <30 or ≥25), minus the incidence of outcome among the unexposed (defined here as the reference paternal age group of 25–29), divided by the incidence of outcome in the total population, and multiplied by 100%. For paternal age <25, the PAR% was 6%, 1%, and 5% in cohort, case–control, and all studies, respectively. For paternal age ≥30, the PAR% was 7%, 10%, and 10% in cohort, case–control, and all studies, respectively. These estimates did not differ significantly for males and females. For paternal age <25, the PAR% was 5% for males and 3% for females in all studies. For paternal age ≥30, the PAR% was 8% for males and 13% for females in all studies.

Discussion

We found a significant increase in risk of schizophrenia in the offspring increasing paternal age (≥30 years of age). We also found a significant increase in risk of schizophrenia in the offspring of *younger* fathers (<25), which may also be associated with an increased risk in males but not females. We did not find evidence for gender effects on the relationship between older paternal age (≥30) and schizophrenia risk in the offspring. The PAR% was 10% for paternal age ≥30 and 5% for paternal age <25 in all studies.

Strengths and Limitations

An important strength of our study is that we included data from all published (and one unpublished) cohort studies of this association. Two previous meta-analyses[35,36] found that APA was associated with an increased risk of schizophrenia. Our analysis differed from these analyses in several ways. First, we considered the effect of gender on the association, which was not previously examined. By requesting summary data from the authors, we were able to use the same age classes across all studies, which enabled us (1) to use a consistent reference group, (2) to estimate risks by 5-year age groups, as opposed to looking for a threshold age of increased risk, 3) to incorporate data from several studies not included in the previous meta-analyses (Laursen *et al.*,[32] Tsuchiya *et al.*[34] and previously unpublished data from the NFBC 1966), 4) to calculate the PAR% for paternal age, and 5) to test for an association in *younger* fathers, which was not previously examined. Last, for every study in our primary meta-analysis except Malaspina *et al.*,[33] which included subjects with nonaffective psychosis, cases were restricted to a diagnosis of schizophrenia (by *DSM* and *ICD* criteria).

An important limitation of the present study was that effect sizes were calculated as crude risks by paternal age

groups. We were not able to control for potential confounding factors such as maternal age and socioeconomic status in the analysis. However, it is reassuring that within most individual studies included in the meta-analysis, the effect of increasing paternal age remained significant and was often greater,[9,13,33] after adjusting for maternal age.

Study Heterogeneity

A vast majority of studies in the meta-analysis used national birth registries to determine paternal age, although no studies confirmed biological paternity, which could contribute to the heterogeneity of the results. Two studies, Granville-Grossman[30] and Laursen *et al.*,[32] made the largest contribution to the heterogeneity in the results of the sensitivity analysis for all studies. The controls in the study by Granville-Grossman[30] were siblings of the schizophrenia probands. The author also standardized parental ages to a reference population in order to exclude the effect of sibship size, meaning that actual parental ages were not used. Thus, selection bias may have contributed to the heterogeneity of the results. The study by Laursen *et al.* [32] was the largest single study in the meta-analysis, comprising 82% (n = 13 297) of all subjects with schizophrenia in the meta-analysis. The estimates for paternal age groups $\geq$30 were generally among the lowest for this study compared with others (see Supplemental Figure 2), which may have contributed to the observed heterogeneity.

Younger Fathers

An important finding from our analysis was a significant association between younger fathers (<25) and risk of schizophrenia, and this risk may be greater in male than in female offspring. Several previous studies,[10–12,20] as well as our data from the NFBC 1966, found a nonsignificant increased risk in the offspring of younger fathers, after adjustment for potential confounders. In one of these studies,[10] the effect was greater in males than in females. One possibility is that the association with younger fathers is due to confounding factors such as maternal age, for which we were not able to statistically control, or selection bias.

Younger paternal age is also associated with preterm birth,[37] congenital abnormalities,[38–41] and Type 1 diabetes[42] after adjustment for potential confounders, which indirectly supports the plausibility of this association. Although the effect size was small, our findings raise the interesting possibility of different causal mechanisms for schizophrenia between the offspring of younger and older fathers.

Population Attributable Risk

We found a PAR% in all studies of 10% for paternal age $\geq$30, compared to a reference paternal age of 25–29. Because the PAR% varies with both the risk (RR or OR) associated with an exposure (eg, paternal age $\geq$30) and its prevalence, caution must be exercised in the interpretation of this result. The PAR% refers to a family of concepts. Greenland and Robins[43] distinguished between the etiologic and excess fraction. The etiologic fraction is the proportion of cases that the exposure had played a *causal* role in its development. The excess fraction is the proportion of cases among the exposed population that is in excess in comparison with the unexposed. Our results describe the excess fraction for paternal age because it is not possible to establish the causality of this association.

Our estimate of PAR is lower than the attributable risk for APA of 26.6% reported by Malaspina *et al.*,[33] the only other study to report this measure. Effect size estimates for each paternal age group in the study by Malaspina *et al.*[33] were consistently higher than those for all studies in this meta-analysis (see Supplemental Figure 2), which is reflected in a higher PAR% than what we found. This difference also raises the question of possible ethnic differences because the study of Malaspina *et al.*[33] was conducted in a sample that was overwhelmingly Ashkenazi Jewish, while many of the other studies may have been less ethnically homogenous. The effect of paternal age may depend on the genetic background in which it exerts its influence. Another potential factor contributing to the higher PAR% in the study by Malaspina *et al.*[33] is that this study included subjects with nonaffective psychosis. It is possible that the paternal age effect may be greater when extended beyond schizophrenia to include all nonaffective psychosis.

Conclusions

The increased risk associated with paternal age <25 raises the possibility that the mechanisms of abnormal development associated with this very young group may differ from those associated with paternal age $\geq$30. The risk factor of paternal age increases the risk for schizophrenia as much as any single candidate gene.[44]

Whether either of the associations that emerged from this analysis is due to biological or psychosocial factors, or both, remains unclear. There is some evidence for an increased rate of *de novo* mutations with APA.[45] Immature spermatids and/or low activity of DNA repair or antioxidant enzymes have also been proposed as mechanisms for increased *de novo* genetic disorders in the offspring of younger fathers.[46] It is possible that the association with APA is due to delayed childbearing by fathers with schizophrenia and related disorders. However, one study[47] found an association between APA and sporadic (versus familial) schizophrenia, but there is a failure to replicate.[19] Although the possibility of epigenetic changes, such as imprinting, DNA methylation, or histone acetylation, has also been proposed, this mechanism has not been thoroughly investigated,[48] and both mutations and epigenetic changes may contribute.

Paternal age may also be associated with an adverse psychosocial environment for offspring, thereby increasing risk of schizophrenia. Both younger and older fathers may be associated with increased unwantedness of pregnancy, which is a potential risk factor for schizophrenia.[49]

An understanding of this risk factor has substantial public health potential, as average paternal ages are increasing[1] and APA is common, has widespread effects, and is a potentially modifiable risk factor. Public awareness of the potential health hazards associated with older fatherhood may decrease the delay in having children. Accounting for the APA effect as a potential confounding factor may also increase the signal-to-noise ratio in other epidemiological and genetic analyses in schizophrenia. Subsequent studies will be important to clarifying the pathophysiology of a determinant of schizophrenia.

Supplementary Material

Supplementary material and Figures 1 and 2 are available at http://schizophreniabulletin.oxfordjournals.org.

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References

1. Bray I, Gunnell D, Davey Smith G. Advanced paternal age: how old is too old? *J Epidemiol Community Health*. 2006;60:851–853.
2. Cannon M. Contrasting effects of maternal and paternal age on offspring intelligence: the clock ticks for men too. *PLoS Med*. 2009;6:e42.
3. Malaspina D, Reichenberg A, Weiser M, et al. Paternal age and intelligence: implications for age-related genomic changes in male germ cells. *Psychiatr Genet*. 2005;15:117–125.
4. Saha S, Barnett AG, Foldi C, et al. Advanced paternal age is associated with impaired neurocognitive outcomes during infancy and childhood. *PLoS Med*. 2009;6:e40.
5. Bingley PJ, Douek IF, Rogers CA, Gale EA. Influence of maternal age at delivery and birth order on risk of type 1 diabetes in childhood: prospective population based family study. Bart's-Oxford Family Study Group. *BMJ*. 2000;321:420–4.
6. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol*. 2001;30:1428–1437.
7. Frans EM, Sandin S, Reichenberg A, Lichtenstein P, Långström N, Hultman CM. Advancing paternal age and bipolar disorder. *Arch Gen Psychiatry*. 2008;65:1034–1040.
8. Zhang Y, Cupples LA, Rosenberg L, Colton T, Kreger BE. Parental ages at birth in relation to a daughter's risk of breast cancer among female participants in the Framingham Study (United States). *Cancer Causes Control*. 1995;6:23–29.
9. Brown AS, Schaefer CA, Wyatt RJ, et al. Paternal age and risk of schizophrenia in adult offspring. *Am J Psychiatry*. 2002;159:1528–1533.
10. Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB. Parental age and risk of schizophrenia: a case-control study. *Arch Gen Psychiatry*. 2003;60:673–678.
11. Dalman C, Allebeck P. Paternal age and schizophrenia: further support for an association. *Am J Psychiatry*. 2002;159:1591–1592.
12. Sipos A, Rasmussen F, Harrison G, et al. Paternal age and schizophrenia: a population based cohort study. *BMJ*. 2004;329:1070.
13. Zammit S, Allebeck P, Dalman C, et al. Paternal age and risk for schizophrenia. *Br J Psychiatry*. 2003;183:405–408.
14. Reichenberg A, Gross R, Weiser M, et al. Advancing paternal age and autism. *Arch Gen Psychiatry*. 2006;63:1026–1032.
15. Insel BJ, Brown AS, Bresnahan MA, Schaefer CA, Susser ES. Maternal-fetal blood incompatibility and the risk of schizophrenia in offspring. *Schizophr Res*. 2005;80:331–342.
16. Gregory I. An analysis of familial data on psychiatric patients: parental age, family size, birth order, and ordinal position. *Br J Prev Soc Med*. 1959;12:42–59.
17. Farina A, Storrs C, Barry H, Garmezy N. Birth order of recovered and nonrecovered schizophrenics. *Arch Gen Psychiatry*. 1963;9:224–228.
18. Bojanovsky J, Gerylovova A. Schizophrenia and the parental age of patients. Preliminary report. *Cesk Psychiatr*. 1967;63:85–87.
19. Pulver AE, McGrath JA, Liang KY, Lasseter VK, Nestadt G, Wolyniec PS. An indirect test of the new mutation hypothesis

associating advanced paternal age with the etiology of schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2004;124:6–9.
20. El-Saadi O, Pedersen CB, McNeil TF, et al. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. *Schizophr Res*. 2004;67:227–236.
21. Ekéus C, Olausson PO, Hjern A. Psychiatric morbidity is related to parental age: a national cohort study. *Psychol Med*. 2006;36:269–276.
22. Costello AJ, Gunn JC, Dominian J. Aetiological factors in young schizophrenic men. *Br J Psychiatry*. 1968;114:433–441.
23. Hare EH, Moran PA. Raised parental age in psychiatric patients: evidence for the constitutional hypothesis. *Br J Psychiatry*. 1979;134:169–177.
24. Gillberg C. Parental age in child psychiatric clinic attenders. *Acta Psychiatr Scand*. 1982;66:471–478.
25. Kinnell H. Parental age in schizophrenia. *Br J Psychiatry*. 1983;142:204.
26. Malama IM, Papaioannou DJ, Kaklamani EP, Katsouyanni KM, Koumantaki IG, Trichopoulos DV. Birth order sibship size and socio-economic factors in risk of schizophrenia in Greece. *Br J Psychiatry*. 1988;152:482–486.
27. Bertranpetit J, Fananas L. Parental age in schizophrenia in a case-controlled study. *Br J Psychiatry*. 1993;162:574.
28. Raschka LB. Parental age and schizophrenia. *Magyar Andrologica*. 1998;2:47–50.
29. Lopez-Castroman J, Gomez DD, Bellosos JJC, et al. Differences in maternal and paternal age between schizophrenia and other psychiatric disorders. *Schizophr Res*. 2010;116:184–190.
30. Granville-Grossman KL. Parental age and schizophrenia. *Br J Psychiatry*. 1966;112:899–905.
31. Johanson E. A study of schizophrenia in the male. *Acta Psychiatr Scand*. 1958;33(suppl 125):7–107.
32. Laursen TM, Munk-Olsen T, Nordentoft M, Bo Mortensen P. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a danish population-based cohort. *J Clin Psychiatry*. 2007;68:1673–1681.
33. Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry*. 2001;58:361–367.
34. Tsuchiya KJ, Takagai S, Kawai M, et al. Advanced paternal age associated with an elevated risk for schizophrenia in offspring in a Japanese population. *Schizophr Res*. 2005;76:337–342.
35. Torrey EF, Buka S, Cannon TD, et al. Paternal age as a risk factor for schizophrenia: how important is it? *Schizophr Res*. 2009;114:1–5.
36. Wohl M, Gorwood P. Paternal ages below or above 35 years old are associated with a different risk of schizophrenia in the offspring. *Eur Psychiatry*. 2007;22:22–26.
37. Abel EL, Kruger M, Burd L. Effects of maternal and paternal age on Caucasian and Native American preterm births and birth weights. *Am J Perinatol*. 2002;19:49–54.
38. Archer NP, Langlois PH, Suarez L, Brender J, Shanmugam R. Association of paternal age with prevalence of selected birth defects. *Birth Defects Res A Clin Mol Teratol*. 2007;79:27–34.
39. Kazaura M, Lie RT, Skjaerven R. Paternal age and the risk of birth defects in Norway. *Ann Epidemiol*. 2004;14:566–570.
40. Mclntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. *Epidemiology*. 1995;6:282–288.
41. Olshan AF, Teschke K, Baird PA. Paternal occupation and congenital anomalies in offspring. *Am J Ind Med*. 1991;20:447–475.
42. Tai TY, Wang CY, Lin LL, Lee LT, Tsai ST, Chen CJ. A case-control study on risk factors for type 1 diabetes in Taipei City. *Diabetes Res Clin Pract*. 1998;42:197–203.
43. Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fraction. *Am J Epidemiol*. 1988;128:1185–1197.
44. Allen NC, Bagade S, McQueen MB, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet*. 2008;40:827–834.
45. Crow JF. The high spontaneous mutation rate: is it a health risk? *Proc Natl Acad Sci USA*. 1997;94:8380–8386.
46. Malaspina D. Paternal factors and schizophrenia risk: de novo mutations and imprinting. *Schizophr Bull*. 2001;27:379–393.
47. Malaspina D, Brown A, Goetz D, et al. Schizophrenia risk and paternal age: a potential role for de novo mutations in schizophrenia vulnerability genes. *CNS Spectr*. 2002;7:26–29.
48. Perrin MC, Brown AS, Malaspina D. Aberrant epigenetic regulation could explain the relationship of paternal age to schizophrenia. *Schizophr Bull*. 2007;33:1270–1273.
49. Herman DB, Brown AS, Opler MG, et al. Does unwantedness of pregnancy predict schizophrenia in the offspring? Findings from a prospective birth cohort study. *Soc Psychiatry Psychiatr Epidemiol*. 2006;41:605–610.