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ORIGINAL ARTICLE

Association of older paternal age with earlier onset among co-affected schizophrenia sib-pairs

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Background. Advanced paternal age is associated with increased risk of schizophrenia. This study aimed to explore whether older paternal age is associated with earlier onset among co-affected schizophrenia sib-pairs with the same familial predisposition.

Method. A total of 1297 patients with schizophrenia from 630 families, which were ascertained to have at least two siblings affected, throughout Taiwan were interviewed using the Diagnostic Interview for Genetic Studies. Both inter-family comparisons, a hierarchical regression model allowing for familial dependence and adjusting for confounders, and within-family comparisons, examining the consistency between onset order and birth order, were performed.

Results. An inverted U shape was observed between paternal age and onset of schizophrenia. Affected offspring with paternal age of 20–24 years had the oldest onset. As paternal age increased over 25 years, older paternal age exhibited a linear decrease in the onset of schizophrenia. On average, the onset was lowered by 1.5 years for paternal age of 25–29 years and by 5.5 years for paternal age $\geqslant$50 years ($p = 0.04$; trend test). The proportion of younger siblings with earlier onset (58%) was larger than that of older siblings with earlier onset (42%) ($p = 0.0002$).

Conclusions. These findings indicate that paternal age older than 25 years and younger than 20 years were both associated with earlier onset among familial schizophrenia cases. The associations of advanced paternal age with both increased susceptibility to schizophrenia and earlier onset of schizophrenia are consistent with the rate of increases in spontaneous mutations in sperm as men age.

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Key words: Age at onset, co-affected sib-pairs, familial predisposition, paternal age, schizophrenia, spontaneous mutation.

Introduction

Evidence is accumulating that advanced paternal age is a risk factor for cognitive impairment (Saha *et al.* 2009) and a variety of neuropsychiatric disorders (Malaspina *et al.* 2001; Zammit *et al.* 2003; Reichenberg *et al.* 2006; Frans *et al.* 2008; Miller *et al.* 2011*a*; Grigoroiu-Serbanescu *et al.* 2012; McGrath *et al.* 2014; Racinea *et al.* 2014). Recent detection of genome-wide *de novo* mutations provides plausible links to such associations (Kong *et al.* 2012). There are numerous divisions in spermatogonial stem cells during the life span, and delaying fatherhood may produce more mutations (Buwe *et al.* 2005) and increase the occurrence of more severe biological sequelae (Goriely *et al.* 2013). Aberrant epigenetic regulation, which affects methylation status rather than causing changes in the nucleic acids of the genome, increases with age and may also contribute to this phenomenon (Perrin *et al.* 2007; Garcia-Palomares *et al.* 2009).

A meta-analysis has shown that advancing paternal age increases the risk of schizophrenia (Miller *et al.* 2011*a*). The association between advanced paternal age and increased risk of schizophrenia has been attributed to the increased risk of *de novo* mutations in paternal germ cells (Malaspina, 2001). Compared with the general population, sporadic schizophrenia cases had older fathers (Malaspina *et al.* 2002). In addition, advanced paternal age was associated with reduced familial aggregation of schizophrenia (Svensson *et al.* 2012), and a stronger paternal age effect was observed in sporadic cases than in familial cases (Sipos *et al.* 2004), though the moderating effect of family history on paternal age was not observed in another study (Petersen *et al.* 2011). Alternatively, a predisposition to schizophrenia, which can be passed to the offspring, might lead to late fatherhood

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(Petersen *et al.* 2011). Both *de novo* mutation and selection into late fatherhood can lead to the paternal age effect. However, previous studies were based on comparing singleton patients from different families, indicating potentially confounding differential characteristics across families, such as predisposition, socio-economic characteristics and maternal age (Saha *et al.* 2009). To delineate these possibilities, it is critical to examine the effect of paternal age in siblings affected with schizophrenia in a family who have the same familial predisposition and socio-economic features. Other characteristics of the affected siblings can help to elucidate the underlying mechanism of the paternal age effect.

Age at onset has been an important component phenotype for schizophrenia. Two recent reviews found that early onset of schizophrenia may disrupt the normal processes of brain maturation and may cause neurodevelopmental deviance (Gogtay *et al.* 2011; Vyas *et al.* 2011). Patients with schizophrenia with an earlier onset were found to have a higher incidence of structural genomic variation (Walsh *et al.* 2008; Addington & Rapoport, 2009). Patients with an early onset are more likely to have relatives affected with schizophrenia (Kendler & MacLean, 1990), and a greater correlation in age at onset was found in affected monozygotic twin pairs than in dizygotic twin pairs (Kendler *et al.* 1987). A recent linkage analysis used age onset along with neurocognitive deficits to identify a subset of families that led to a strong linkage signal (Lien *et al.* 2011). However, few investigations have examined whether older paternal age is associated with earlier onset of schizophrenia, particularly in the context of co-affected schizophrenia sib-pairs, a relationship that may be free from many potential confounders. If the earlier onset of schizophrenia could be caused by genetic factors, the increased number of *de novo* mutations along with men's age could be associated with not only the elevated risk of schizophrenia but also the earlier onset of schizophrenia.

To fill the gap in the literature, we turned to a large collection of co-affected schizophrenia sib-pairs recruited throughout the country in Taiwan. The specific aim of this study was to examine whether older paternal age is associated with earlier onset of schizophrenia in affected sib-pairs. Statistical analysis that allows for familial dependence in the data was adopted to adjust for potential confounders in the regression of sibling age at onset of schizophrenia on paternal or maternal age.

Method

Participants

Schizophrenia probands and their first-degree relatives were recruited from four research programmes in Taiwan: the Multidimensional Psychopathological Group Research Project (MPGRP) from 1993 to 1998 (Chen *et al.* 1998; Chang *et al.* 2002); the Multidimensional Psychopathological Study on Schizophrenia (MPSS) from 1998 to 2001 (Tsuang *et al.* 2006); the Taiwan Schizophrenia Linkage Study (TSLS) from 1998 to 2002 (Hwu *et al.* 2005); and the Study on Etiological Factors of Schizophrenia (SEFOS) from 2002 to 2005. The first programme, the MPGRP, recruited patients consecutively admitted to acute in-patient wards of the National Taiwan University Hospital, Taipei City Psychiatric, and Provincial Tao-Yuan Psychiatric Center who met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R criteria for schizophrenia. These MPGRP participants were then re-diagnosed with DSM-IV criteria. The second and third programmes aimed to recruit families with at least two siblings who met the DSM-IV criteria for schizophrenia. The affected sib-pair probands were identified from either in-patient wards or out-patient clinics of the National Taiwan University Hospital and Provincial Tao-Yuan Psychiatric Center for the MPSS or six data collection field research centres throughout Taiwan for the TSLS. The fourth programme, the SEFOS, aimed to recruit families of patients with schizophrenia of different familial loadings from the National Taiwan University Hospital and Ju-Shan Psychiatric Hospital. All of the participants provided written informed consent after receiving a complete description of the study. There were five, 62, 595 and 31 families with co-affected schizophrenia sib-pairs recruited, respectively, in the individual programmes. Families that had any parent affected with schizophrenia were excluded from this study. A total of 1297 patients with schizophrenia from 630 families, which were ascertained to have at least two siblings affected, were included for subsequent analysis.

Clinical evaluation

Probands and their first-degree relatives were interviewed with the Diagnostic Interview for Genetic Studies (DIGS) (NIMH Genetics Initiative, 1992*a*), which was designed specifically for family-genetic studies of schizophrenia and bipolar disorder with good inter-rater reliability (Nurnberger *et al.* 1994). The Chinese version of the DIGS and its reliability have been described previously (Chen *et al.* 1998). Interviews using the Chinese version of the DIGS were conducted by research assistants who had received standardized psychiatric interview training. In addition to the DIGS, interviewers used the Chinese version of the Family Interview for Genetic Studies (FIGS) (NIMH Genetics Initiative, 1992*b*) to

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collect relevant information on relatives who were not interviewed for the study. Two psychiatrists independently reviewed all available information, including the DIGS, the FIGS, hospital records and the interviewers' notes. The best-estimate lifetime psychiatric diagnosis according to the DSM-IV criteria was determined independently. If both psychiatrists disagreed about a diagnosis, a third psychiatrist was sought, and a consensus diagnosis was reached after discussion.

The DIGS includes a psychosis section that inquires about age at onset of the first psychotic episode that could not be attributed to medical illness, medications, or substance abuse. In an inter-rater reliability study of 31 participants (Chen *et al.* 1998), the intraclass correlation of age at onset of the first psychotic episode was 0.90. When information about onset of the first psychotic episode in the interview was unclear, research psychiatrists reviewed the medical history and determined the onset age. The intraclass correlation of age at onset of psychotic patients retrieved from medical records using a standardized clinical data schedule was found to be greater than 0.9 in another earlier study (Hwu *et al.* 1985).

Statistical analysis

The paternal age of each patient's father was calculated by the father's age minus the offspring's age at the time of recruitment. For a family without information about the father, information on the offspring's father's paternal age was treated as missing.

Paternal age was stratified into eight groups: <20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, and ⩾50 years. We drew a box plot of age at onset of schizophrenia by paternal age groups to observe whether there was a pattern. Then, a hierarchical regression model of the affected offspring's onset age on paternal age was conducted with a random intercept (i.e. each family has its own intercept), and potential confounders such as maternal age, gender, education years, and parents' education years were included as covariates. For the eight categories of paternal age groups, the group whose offspring had the oldest onset of schizophrenia was used as the reference to create seven dummy variables, $D^{(1)}$ to $D^{(7)}$, to designate the remaining paternal age groups. For the j-th affected sibling of the i-th family, his or her age at onset of schizophrenia Y_{ij} can be expressed as a function of the individual's paternal age, indicated by $D^{(1)}$ to $D^{(7)}$, as well as other covariates X as follows:

$$Y_{ij} = \alpha_i + \sum_{g=1}^{7} \beta^{(g)} \times D_{ij}^{(g)} + \theta \times X_{ij} + \varepsilon_{ij},$$

where α_i stands for the family-specific random effect (i.e. the participants in the same family share the same baseline onset age of schizophrenia), $\beta^{(g)}$ represents the effect due to paternal age $D^{(g)}$, and θ represents the effect of other explanatory variables X, and ε_{ij} for the residual.

Additionally, we compared age at onset of schizophrenia between co-affected sib-pairs within each family. The proportions of these sib-pairs in which the younger sibling was earlier or the older sibling was earlier were tested against the expected proportions of 50% under the null hypothesis of no association between age at onset of schizophrenia and birth order. The p value was derived from the generalized linear model and generalized estimating equations (Liang & Zeger, 1986) to control for the dependence of nesting data.

All statistical analyses were performed using the SAS statistical package (version 9.2 for Windows; SAS Institute Inc., USA). A p value of less than 0.05 was considered statistically significant.

Table 1. *Distribution of sociodemographic characteristics among 1297 patients with schizophrenia from 630 families, which were ascertained to have at least two siblings affected, in Taiwan*

Variables	n[a]	Mean (S.D.)
Male gender, *n* (%)	1297	820 (63.2)
Age, years	1297	35.1 (8.0)
Education, years	1281	10.4 (3.1)
Paternal age, years	804	31.4 (6.3)
Maternal age, years	1019	27.1 (5.3)
Paternal education, years	802	6.2 (4.2)
Maternal education, years	1013	3.9 (3.8)

S.D., Standard deviation.
[a] Number of available individuals.

Results

The distributions of sociodemographic characteristics among 1297 offspring with schizophrenia from 630 families are shown in Table 1. The box plot of age at onset of schizophrenia by paternal age interval is shown in Fig. 1, which appears to be an inverted U shape. Affected offspring with paternal age of 20–24 years had the oldest age of onset. As paternal age increased over 25 years, the age at onset of the affected offspring decreased. Affected offspring with paternal age <20 years had an earlier age of onset than those with paternal age of 20–24 years.

To control for potential confounders, we conducted a hierarchical regression of the affected offspring's onset age on paternal age using a random-intercept model to adjust for maternal age, gender, education years and parents' education years. Treating the group of paternal age of 20–24 years as the reference group, the estimates of the regression coefficients for individual paternal age

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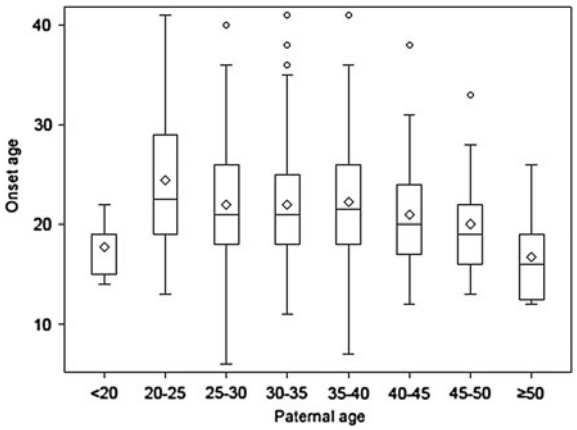

Fig. 1. Box plot of patients' age at onset of schizophrenia by paternal age among 1297 affected offspring from 630 families with co-affected sib-pairs in Taiwan. The bottom and top of the box represent the first and third quartiles; the band inside the box is the second quartile; the diamond is the mean; the ends of the whiskers are the lowest (highest) datum still within 1.5 interquartile ranges of the lower (upper) quartile; circles are outliers.

interval are displayed in the upper part of Table 2. Compared with the affected offspring with paternal age of 20–24 years, increasing paternal age greater than 25 years was associated with a decrease in the age of onset of the affected offspring (i.e. negative β coefficients), with the trend test reaching statistical significance. Decreasing paternal age less than 20 years was also associated with a decrease in the age of onset of the affected offspring, with borderline significance. In contrast, in the lower half of Table 2, the hierarchical regression of the affected offspring's onset age on maternal age failed to show association of maternal age with the affected offspring's onset age. Additionally, we repeated the hierarchical regression analysis treating the paternal age and maternal age as continuous variables, and the coefficient was −0.14 [95% confidence interval (CI) −0.25 to −0.03, $p = 0.02$] for paternal age (⩾20 years) and −0.04 (95% CI −0.18 to 0.09, $p = 0.56$) for maternal age.

We compared the age at onset in each co-affected sib-pair in a family by limiting the analysis to those pairs with paternal age ⩾20 years (Table 3). The proportion of sib-pairs in which the younger sibling had earlier onset *versus* the sib-pairs in which the older sibling had earlier onset was tested against the expected proportions of 50% under the null hypothesis of no association between age at onset of schizophrenia and birth order, which reflects both paternal age and maternal age. The results revealed that the proportion of younger siblings with earlier onset (58%) was significantly larger than the proportion of older siblings with earlier onset (42%). Because the onset of male patients with schizophrenia was earlier than that of female patients with schizophrenia (Faraone *et al.* 1994; Eranti *et al.* 2013), the proportions were compared with stratification by gender. For both male sib-pairs and female sib-pairs, more pairs reported that the younger sibling had earlier onset than the older sibling.

We then repeated the analysis among the 130 co-affected siblings from 63 families with parental schizophrenia, and the results (online Supplementary Tables S1–S3) were similar to those reported above. Treating the variables of paternal age and maternal age as continuous, the coefficient derived from the hierarchical regression was −0.30 (95% CI −0.55 to −0.05, $p = 0.02$) for paternal age (⩾20 years) and −0.24 (95% CI −0.62 to 0.13, $p = 0.20$) for maternal age.

One potential selection bias in this study was that the families with a younger sibling having late onset may not yet have co-affected siblings at recruitment and therefore not be sampled in this study. To assess the possible impact of this ascertainment bias, a series of sensitivity analyses was conducted. First, we repeated the within-family comparison by limiting patients to those with a current age greater than 32 years (the 90th percentile of the age at onset of schizophrenia in our data). The results were similar to those reported above: the proportion of younger siblings with earlier onset (56%, $n = 185$) was larger than that of older siblings with earlier onset (44%, $n = 148$) ($p = 0.04$). Second, we repeated the inter-family comparison by choosing only the oldest patient from each family. The coefficient of the continuous paternal age was −0.11 (95% CI −0.26 to 0.05, $p = 0.19$), which was close the −0.14 reported above. Third, when the inter-family comparison was limited to the youngest patient from each family, the coefficient of the continuous paternal age remained similar (−0.11, 95% CI −0.24 to 0.02, $p = 0.09$).

Discussion

This study examined the association between paternal age and age at onset of schizophrenia among co-affected schizophrenia sib-pairs. An inverted U-shaped relationship was observed between paternal age and age at onset of schizophrenia, whereas no association was found for maternal age. Paternal age older than 25 years and paternal age younger than 20 years were both associated with earlier onset among familial schizophrenia cases, as revealed in a hierarchical regression model with adjustment for potential confounders. These findings shed light on the possible nature of the bi-modal influence of paternal age on the age at onset of schizophrenia.

There are several strengths of this study that support the robustness of the findings. The sample of co-affected schizophrenia sib-pairs frees this study from confounding by family characteristics, such as predisposition, socio-economic features and maternal

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Table 2. *Hierarchical regression of the age at onset of schizophrenia in affected offspring on paternal age among co-affected schizophrenic sib-pairs from 630 families in Taiwan*

Variable	n[a]	Mean (S.D.)	β (95% CI)[b]	p
Paternal age, years[c]				
<20	5	17.8 (3.3)	−5.3 (−11.2 to 0.6)	0.08
20–24	72	24.4 (7.4)	Reference	Reference
25–29	252	22.0 (6.1)	−1.5 (−3.3 to 0.3)	0.11
30–34	250	21.9 (5.4)	−2.1 (−4.2 to −0.1)	0.04
35–39	122	22.2 (5.8)	−1.6 (−4.0 to 0.8)	0.20
40–44	46	20.9 (5.2)	−2.0 (−4.9 to 1.0)	0.19
45–49	17	20.0 (5.0)	−4.4 (−8.6 to −0.3)	0.04
⩾50	12	16.8 (4.6)	−5.5 (−10.7 to −0.4)	0.04
				p of the trend test[d] = 0.04
Maternal age, years[e]				
<20	54	22.2 (6.6)	1.2 (−0.8 to 3.3)	0.24
20–24	270	23.0 (6.9)	Reference	Reference
25–29	361	22.2 (6.1)	0.0 (−1.2 to 1.2)	0.95
30–34	213	22.8 (6.1)	0.5 (−1.2 to 2.1)	0.57
35–39	69	22.6 (6.3)	−2.1 (−4.9 to 0.8)	0.15
⩾40	32	19.7 (4.3)	−3.4 (−8.4 to 1.5)	0.18
				p of the trend test[f] = 0.83

S.D., Standard deviation; CI, confidence interval.

[a] Limited to patients with schizophrenia having information on parental age and the covariates.

[b] Estimated from a random-intercept model with adjustment for the age of the other parent (i.e. maternal age when regressing on paternal age and paternal age when regressing on maternal age), gender, education years and parents' education years.

[c] Total $n = 776$.

[d] Testing for the trend of decreasing age at onset of the affected offspring with increasing paternal age from the interval of 20–24 years to the interval ⩾50 years.

[e] Total $n = 999$.

[f] Testing for the trend of decreasing age at onset of the affected offspring with increasing maternal age from the interval of 20–24 years to the interval ⩾40 years.

age (Saha *et al.* 2009). Furthermore, the association of older paternal age with younger age at onset of schizophrenia was demonstrated in both inter-family and within-family comparisons. For the inter-family comparison, our use of a random-intercept hierarchical regression model helps us to adjust for several potential confounders and to allow for within-family resemblance. For the within-family comparison, we examined the consistency between onset order and birth order in each affected sib-pair. Although the within-family comparison cannot explicitly differentiate the paternal age effect from the maternal age effect because paternal age and maternal age have the same change from one sibling to the next within a family, the results of the inter-family comparison indicate that this effect was mainly due to paternal age on the earlier onset of the affected siblings.

Our findings derived from both inter-family and within-family comparisons may help clarify an ongoing debate about the nature of the association between advanced paternal age and increased risk for schizophrenia. Although a recent whole-genome sequencing study using trios of patients with schizophrenia or autism revealed an association between older paternal age at time of childbearing and higher mutation rate of single nucleotides (Kong *et al.* 2012), whether such finding is representative of the general population has been questioned (Ek *et al.* 2014; Pedersen *et al.* 2014). One Finnish population study found that advanced paternal age was associated with maternal, but not paternal, schizophrenia (Miller *et al.* 2011*b*). It raised the possibility that the increased genetic risk from the mother may explain the paternal age effect. In addition, among second or later-born children, the association between older paternal age and increased risk of schizophrenia disappeared after accounting for paternal age at the time of the first child's birth (Petersen *et al.* 2011; Ek *et al.* 2014; Pedersen *et al.* 2014), and these findings imply that there may be unknown factors related to delayed

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Table 3. *Comparison of age at onset of schizophrenia between co-affected sib-pairs (limited to both affected siblings with paternal ages ⩾20 years within a family)*

Within-pair comparison in onset age	All sib-pairs[a] ($n = 584$) n (%)	Male sib-pairs[b] ($n = 238$) n (%)	Female sib-pairs[c] ($n = 83$) n (%)
Younger sibling is earlier	338 (57.9)	139 (58.4)	50 (60.2)
Older sibling is earlier	246 (42.1)	99 (41.6)	33 (39.8)
Two-sided p[d]	0.0002	0.0102	0.0457

[a] 45 pairs with same age at onset were excluded from the analysis.
[b] 14 pairs with same age at onset were excluded from the analysis.
[c] Eight pairs with same age at onset were excluded from the analysis.
[d] The proportions of sib-pairs in which the younger sibling is earlier or the older sibling is earlier were tested against the expected proportions of 50% under the null hypothesis of no association between age at onset of schizophrenia and birth order. The p value was derived from the generalized linear model and generalized estimating equations.

fatherhood of the first child that are responsible for the paternal age effect. Under these circumstances, population-based family studies such as a large population Swedish cohort (D'Onofrio *et al.* 2014) and the present study are useful to rigorously rule out unknown confounders by means of within-family comparisons. The findings of both studies are consistent with the hypothesis that an increased number of *de novo* mutations along with men's age are causally related to offspring neuropsychiatric disorders.

Given the nature of family data and the statistical model used in this study, our results clearly indicate that older paternal, but not maternal, age was associated with younger age at onset for schizophrenia among co-affected sib-pairs. Our findings extend beyond the link between advanced paternal age and elevated risk of schizophrenia (Miller *et al.* 2011*a*). It is noteworthy that previous studies have shown that the association of paternal age was stronger in schizophrenia or bipolar disorder patients without a family history (Sipos *et al.* 2004; Grigoroiu-Serbanescu *et al.* 2012). Taken together, the increase in susceptibility to sporadic schizophrenia and earlier age at onset of familial schizophrenia may share a common underlying mechanism.

The relationship between older paternal age and earlier onset of familial schizophrenia was seen in both male and female affected siblings in this study. This finding is compatible with a meta-analysis showing no evidence of gender effects on the correlation between advanced paternal age and elevated risk of schizophrenia (Miller *et al.* 2011*a*) and the findings from a large three-generation study of no gender difference for the paternal and grandpaternal age effect between male and female offspring (Frans *et al.* 2011). In addition, patients with parental schizophrenia did not show a differential pattern of paternal effect compared with patients without parental schizophrenia. These negative findings indicate that neither the gender of patients nor the presence of parental schizophrenia was a modifier of paternal effect on the onset of schizophrenia.

One possible explanation for the finding that paternal age older than 25 years exhibited a linear decrease in onset age among familial schizophrenia cases is that the number of spontaneous mutations in the sperm may increase as men get older. That is, for individuals who have already inherited certain predispositions to the occurrence of schizophrenia, an increased number of germ-line mutations associated with older paternal age would contribute to younger age at onset of the disease for such an individual. On the basis of the number of germ-cell divisions and some rare Mendelian genetic diseases, it has been predicted that the germ-line mutation rate in human males, especially older males, is much higher than in females (Crow, 2000). A recent genome-wide search for mutations has provided empirical evidence that the number of mutations in offspring is much larger from fathers than from mothers, with a ratio for the mutation origin of fathers to mothers of approximately 4:1 (Kong *et al.* 2012). Interestingly, the study also confirmed the existence of the same *de novo* mutation in a sib-pair that was paternal in origin.

An interesting issue arising from our findings is whether the accumulated *de novo* mutations in the offspring of an older father lead to not only increased risk of sporadic schizophrenia but also younger age at onset of familial schizophrenia. Previous research on the molecular genetic basis of the earlier onset of

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diseases was mainly derived from neurodegenerative diseases due to longer tandem repeats. For example, the size of trinucleotide repeats and the risk as well as the onset of Huntington's disease showed an inverse relationship (Ross & Tabrizi, 2011). It remains to be investigated whether the earlier onset age of schizophrenia associated with older paternal age is partly due to the instability of repeats generated in spermatogenesis.

Another important finding from the family data was a borderline significant association between paternal age younger than 20 years and early onset of schizophrenia. Although the sample size of paternal age <20 years was small, we observed that the onset for this sample was approximately 5 years earlier than the onset of affected offspring with paternal age of 20–25 years. An inverted U-shaped relationship with paternal age and risk of schizophrenia was also observed in a previous meta-analysis (Miller *et al.* 2011*a*). The evidence of the association between younger fathers and increased risk or younger onset of the disease supports the possibility of different causal mechanisms between the influence of early fatherhood and the influence of late fatherhood. Research in animal models has shown that mice born from young post-pubescent fathers exhibit poorer behavioural performances than those born from mature fathers (Auroux *et al.* 1998). The decrease in progeny quality among very young fathers may be due to the immaturity of spermatids. This inference is supported by a cross-sectional study indicating an inverted U-shaped relationship between male age and semen quality (Eskenazi *et al.* 2003). Another possible explanation of the association between younger fathers and younger onset of the disease might be that being impulsive in character was associated with early fatherhood as well as the disease.

This study has limitations. First, a common issue in family studies is ascertainment bias. If an at-risk child with an older father were censored for age (i.e. having an onset age older than the current age), this would result in a false-positive result. Based on our sensitivity analyses, the impact of this type of ascertainment bias on our results might be limited. Second, the family already having a diagnosed child, the older one, might be faster in reacting to psychiatric symptoms in the younger sibling. This could result in a pseudo-earlier onset of the younger sibling and therefore cause the false association. Nevertheless, the age at onset was based on the first psychotic episode in this study rather than hospitalization. The impact of this treatment-seeking bias might be minimal. Third, this study did not examine the genotype directly and hence cannot clarify the nature of the genetic constitution in each affected sib-pair.

Our findings have implications for both basic research and public health. The role of paternal age-related germ-line mutations in the increased risk of occurrence and younger age at onset of schizophrenia may shed light on the underpinning mechanism of the pathophysiology of the disease. In terms of population health, there appears to be an optimal period for childbearing that is neither too young nor too old. As paternal ages are increasing in the developed world (Bray *et al.* 2006), advanced paternal age, which is probably due to a delay in starting a family for the pursuit of a career or financial reasons, is becoming an important public health issue. It would be beneficial to raise public awareness about the possible health hazards for offspring related to fatherhood that occurs too early or too late.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715000203

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Declaration of Interest

None.

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