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Paternal and maternal ages have contrasting associations with self-reported schizophrenia liability

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ABSTRACT

Background: Older paternal age predicts schizophrenia diagnosis in offspring. If this relationship reflects a pathogenic process, paternal age should predict the expression of subclinical schizophrenia liability (schizotypy). We hypothesized that paternal and maternal ages predict positive, negative, and disorganized features of schizotypy, that family history of psychosis moderates the relationship of paternal age with schizotypy, and that stress sensitivity mediates the relationship of maternal age with schizotypy.
Method: Two studies are reported, each of undergraduates ($n = 500$ and $n = 211$) who completed the Schizotypal Personality Questionnaire. The second was designed to replicate and extend the first and included assessment of stress sensitivity.
Results: In Study 1, older paternal age and younger maternal age predicted greater positive schizotypy ($\beta = .13$ and $\beta = -.19$, respectively). Parental ages did not predict negative or disorganized features and family history did not moderate the paternal age association. In Study 2, the same pattern of associations between parental ages and schizotypy components was observed. Additionally, stress sensitivity partially mediated the association of maternal age with positive schizotypy whereas it did not contribute to the paternal age association.
Conclusion: The association between older paternal age and schizophrenia extends to self-reported positive features of schizophrenia liability, consistent with the notion that this relationship arises from a pathogenic process, such as de novo mutations. Importantly, younger maternal age was an equally potent predictor of positive schizotypy, with its association partially mediated by stress sensitivity.

1. Introduction

Case–control and epidemiological studies show that older paternal age predicts schizophrenia diagnosis (Brown et al., 2002; Hare and Moran, 1979; Johanson, 1958; Kinnell, 1983; Malaspina et al., 2002; Malaspina et al., 2001; Raschka, 2000; Zammit et al., 2003). Circumstantial evidence points to the involvement of de novo genetic mutations in this association: the relationship may be specific to sporadic rather than familial cases of schizophrenia (Malaspina et al., 2002; Sipos et al., 2004; Zammit et al., 2003); the rate of genetic mutation is higher in the male germ line than the female (Conrad et al., 2011; Ellegren, 2007; Malaspina et al., 2001); the rate of de novo mutations in the male germ line is substantial and increasing with age (Kong et al., 2012); social or environmental factors (e.g., delayed procreation and childbearing) appear not to account for the association (Malaspina et al., 2002); and a de novo mutagenic process provides a plausible account for a relatively stable rate of schizophrenia in the population (Böök, 1953). Alternative accounts have been identified. Recent evidence suggests that the paternal age relationship may reflect the influence of delayed fatherhood rather than paternal age per se, although the mechanism giving rise to this is not clear (Ek et al., 2014). Also, the paternal age association may not be specific to schizophrenia (El-Saadi et al., 2004; Hare and Moran, 1979; Torrey et al., 2009; Zammit et al., 2003). Regardless, the relative risk of schizophrenia appears greatest among offspring of fathers who are 45 years or older at conception.

If the paternal age association reflects a pathogenic process, paternal age should predict the expression of subclinical liability or psychometric risk for schizophrenia. Here the evidence is more ambiguous: paternal age is not consistently or clearly associated with mixed psychosis experiences (Vreeker et al., 2013; Zammit et al., 2008) or delusions (Varghese et al., 2008). Also, there appears to have been no examination of the relationship of paternal age with negative features of schizophrenia liability states.

Maternal age has received comparatively little attention. Often, the paternal age effect on schizophrenia is suppressed unless maternal age effects are controlled (Brown et al., 2002; El-Saadi et al., 2004; Sipos

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et al., 2004). There is some evidence that older maternal age is protective (El-Saadi et al., 2004; Zammit et al., 2008) and that the rate of schizophrenia and non-affective psychoses is elevated in association with both older and younger maternal age (Ek et al., 2014). However, these findings fall in a larger body of work suggesting no evidence of an association (Brown et al., 2002; Malaspina et al., 2001; Sipos et al., 2004; Torrey et al., 2009; Zammit et al., 2003).

2. Study 1 overview

We examined whether parental ages predict self-reported positive, negative, and disorganized features of schizotypy. In addition to expecting paternal age to be positively correlated with schizotypy, we expected maternal age also to relate to schizotypy. We expected that regression modeling incorporating an exponential relationship of paternal age with schizotypy would have better fit than linear modeling, consistent with evidence on rates of de novo mutations (Kong et al., 2012). Finally, we predicted that family history of psychosis would moderate the relationship of paternal age with schizotypy (Malaspina et al., 2002). In testing these hypotheses, we controlled for variance associated with sex, country of birth, cannabis use, socioeconomic status, and psychological distress.

3. Study 1 methods

3.1. Participants

Undergraduates ($n = 500$) aged from 17 to 55 years ($M = 20.3$, $SD = 3.3$; 126 males) provided written informed consent to participate. The majority identified as New Zealand European (77.5%) whereas there were smaller representations of Maori (7.6%), Chinese (5.2%), Indian (2.6%), Pacific Island (0.9%), and others (31.0%). Those who participated also learnt about the purpose and design of the study and could earn a small amount of extra credit toward their courses based on assessment of this learning. This project was part of a larger investigation into schizotypy for which an inclusion criterion was normal or corrected-to-normal vision in the left eye. There were no other inclusion or exclusion criteria. The study was reviewed and approved by the University of Otago Human Ethics Committee and undertaken in accordance with the Code of Ethics of the New Zealand Psychological Society.

3.2. Measures

The Likert version of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991; Wuthrich and Bates, 2005) was used to measure positive, negative, and disorganized features of schizotypy. The SPQ contains 74 items that are rated on 5-point agreement scales (*strongly disagree* to *strongly agree*). Three dependent measures were obtained: A cognitive–perceptual score by summing the ideas of reference, odd beliefs, and unusual perceptual experience subscales; an interpersonal score by summing the no close friends and constricted affect subscales; and a disorganization score by summing the odd behavior and odd speech subscales. The 14-item depression subscale of the Depression Anxiety Stress Scales (DASS; Lovibond and Lovibond, 1995) was used to measure depressed affect in the past week. DASS items are rated on a 4-point severity scale (0 = *did not apply to me at all*, 3 = *applied to me very much, or most of the time*). A 12-item validity scale was constructed to detect disingenuous responding by participants. These items were randomly interspersed among the SPQ and DASS items as well as two other self-report measures (three items within each measure). Each item instructed participants to provide a designated response.

Cannabis use was quantified using a single item from a larger self-report measure, namely the lifetime frequency of cannabis use (0 = *five or fewer occasions*, 1 = *more than five occasions*). Socioeconomic status was estimated from parental income and coded as 0 = less or 1 = more than the median household income (Statistics New Zealand, 2012). History of mental disorder (diagnosis, treatment, or both) among first- and second-degree biological relatives was obtained with a brief questionnaire. Two dependent binary measures were coded from the questionnaire: any family history of affective or non-affective psychosis and family history of non-psychotic mental disorder only.

3.3. Procedure

Having provided written informed consent, participants completed the SPQ, DASS, questions on demographics and drug use, and the family history questionnaire. Where participants were less than 80% confident of their responses on the family history questionnaire, consent was obtained to contact caregivers who were requested to provide written responses to the same questionnaire.

3.3.1. Data cleaning and statistical analyses.

Participants who made two or more errors on the validity scale were removed before analyses. Hypotheses were tested using bootstrapped Pearson's and point-biserial correlation coefficients and bootstrapped multiple linear regression coefficients obtained using the boot package in R (R Core Team, 2014) and bootstrap analysis function in Mplus (Muthén and Muthén, 2014). SPQ scores were regressed onto paternal age, maternal age, and family history of psychosis at Steps 1 to 3, respectively, while controlling for sex, migrant status, cannabis use, socioeconomic status, and depression. Modeling was undertaken using both linear and exponential paternal age and reversal of Steps 2 and 3. Moderation of the paternal age–schizotypy relationship by family history was tested using an interaction term (Baron and Kenny, 1986). Linear regression assumptions on residuals, collinearity, and homoscedasticity were tested, as was the presence of influential outliers using dfbetas in R.

4. Study 1 results

Invalid responses were given by 38 participants, 26 participants were not able to provide one or both parents' ages, and there were no influential outliers. Therefore, analyses are based on $n = 436$. Table 1 provides descriptive statistics for the sample. There was no evidence that SPQ scores were associated with missing parental age data (all $|r| < .03$) or of violation of analysis assumptions. Although paternal and maternal ages were highly correlated, variance inflation factors for these remained low (VIF ≤ 2.06) indicating no cause for concern about collinearity.

The bootstrapped correlation between paternal and maternal ages was $r = .71$ (95% CI .64, .77). Paternal age and its exponent were not significantly related to SPQ indices in bivariate analyses (Table 2). There was weak evidence that younger maternal age was associated with higher cognitive–perceptual scores ($r = -.088$, 95% CI −.180, .005,

Table 1
Attributes of Study 1 and Study 2 samples.

Variable	Study 1 ($n = 436$)			Study 2 ($n = 201$)		
	M	%	SD	M	%	SD
Paternal age (years)	32.41		5.36	33.32		6.00
Maternal age (years)	30.21		5.02	30.66		5.42
Family history, psychosis		8.7%			–	
Family history, any mental disorder		43.6%			–	
Low socioeconomic status		24.3%			30.8%	
New Zealand born		74.1%			68.2%	
Cannabis use (≥5×)		39.0%			–	
DASS depression	6.32		7.26	9.05		8.91
SPQ cognitive–perceptual	30.2		14.4	28.5		15.7
Interpersonal	19.1		9.7	19.6		11.4
Disorganized	24.6		10.5	24.2		12.4

Note. DASS = Depression, Anxiety, and Stress Scale; SPQ = Schizotypal Personality Questionnaire.

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