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Psychological Medicine

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Dear Editor,

Many more studies are directed toward disproving the association between advancing paternal age and increasing offspring risk for schizophrenia, first proposed in 2001 (Malaspina et al., 2001), than were brought to bear against the 'schizophrenogenic mother' hypothesis (Fromm-Reichmann, 1948) that predominated for over 30 years! Weiser and colleagues have published the latest of these studies, concluding that older paternal age did not predict an increased risk for schizophrenia or bipolar disorder after controlling for father's age at the birth of his first child (Weiser et al., 2019). Missing from this consideration are the results of two recent and highly salient studies. First of all, Wang and colleagues demonstrated a robust association between advancing paternal age and offspring risk for early onset schizophrenia that was unexplained by parental polygenic risk scores for schizophrenia, supporting a *de novo* origin for paternal age-related schizophrenia (Wang et al., 2019), despite an independent association between later fatherhood and genetic susceptibility. In addition, another recent study found that fathers who married later sired their offspring after significantly shorter periods of pre-pregnancy sexual contact with the mother, a newly described independent risk factor for schizophrenia across all paternal ages (Malaspina et al., 2019). A short duration of parental sexual cohabitation is also a risk factor for preeclampsia. As placental genes activated by pregnancy complications are included in the genome wide association signal for schizophrenia (Ursini et al., 2018), older fathers may contribute to schizophrenia risk by siring their first offspring after a relatively short sexual relationship. The Weiser study also erred in dichotomizing paternal age at 45 years with respect to offspring risks. There is consistent evidence of a linearly increasing offspring risk for schizophrenia as paternal age advances, even for men across their 30s, so their analysis did not place most of the population level burden for the paternal age-related risk pathway in their older father category. Crucially, although the increased risk for schizophrenia is small for men aged 30–39 years, most offspring are sired by men of these ages, so this risk substantially contributes to the population-attributable risk. Further studies can illuminate the pathobiology of risk factors that may bear on person specific treatments, including paternal aging and short durations of sexual contact by specific parents before conception.

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