

**Media contact**

Rhiannon Bugno

+1 214 648 0880

Biol.Psych@sobp.org

Advanced paternal age increases risk of early-onset schizophrenia in offspring

The effect of advanced paternal age on offspring risk is not explained by parental predisposition for schizophrenia, according to a study in Biological Psychiatry

Philadelphia, March 26, 2019 – Advanced paternal age increases the risk in offspring of early-onset schizophrenia, a severe form of the disorder, according to a [study](#) in *Biological Psychiatry*, published by Elsevier. The association between paternal age and risk in children remained after accounting for the contributions of the fathers' and mothers' genetic predispositions for schizophrenia, indicating that advanced paternal age itself contributes to risk.

Advanced paternal age has been associated with increased schizophrenia risk in offspring before, but it has been difficult to disentangle the effects of age versus factors related to age. "The paternal age association could be spurious if it was explained by selection into late fatherhood, which reflects fathers' own predisposition to schizophrenia," said senior author Wei J. Chen, MD, National Taiwan University in Taipei.

Maternal predisposition could also lead to late parenthood and increased risk in offspring. Recent advances in technology have allowed for schizophrenia predisposition to be estimated through genotyping—combining the individual contribution of genetic variations associated with schizophrenia across the entire genome provides a polygenic risk score, which helps predict the risk of developing the disorder.

Dr. Chen and colleagues determined the polygenic risk scores for the parents of over 1,600 people with schizophrenia to estimate the maternal and paternal predispositions to the disorder. Men who had their first child later in life tended to have increased polygenic risk for schizophrenia.

"After controlling for parental polygenic risk scores, every 10-year delay in paternal age increased the risk of early-onset schizophrenia in offspring by about 30 percent," said lead author Shi-Heng Wang, PhD, China Medical University in Taichung. Maternal age was not associated with risk of early onset in offspring. This finding supports that paternal age itself plays an independent role in the increased psychiatric risk in offspring, rather than being associated with increased risk through other factors related to late parenthood.

The authors defined early-onset schizophrenia as occurring before 18-years old, which tends to be a more severe form of the disorder and associated with more genetic abnormalities. Patients included in the study had healthy parents and no apparent family history of schizophrenia. These cases, referred to as sporadic, are thought to arise mainly from increased genetic mutations.

“Presumably, advanced paternal age increases risk for early-onset schizophrenia because advancing age is associated with an accumulation of mutations. These age-related mutations appear to be distinct from those more commonly associated with the risk for schizophrenia. It would be important to understand the distinct neural mechanisms through which advanced paternal age influenced the age of onset,” said John Krystal, MD, Editor of *Biological Psychiatry*.

Identifying these mechanisms is of particular concern with the increasing age of fathers. The findings that the association with risk of early-onset schizophrenia exists after accounting for paternal and maternal polygenic risk provides an important advance in understanding the advanced paternal age effect on schizophrenia.

Notes for editors

The article is "Advanced paternal age and early-onset of schizophrenia in sporadic cases: not confounded by parental polygenic risk to schizophrenia," by Shi-Heng Wang, Po-Chang Hsiao, Ling-Ling Yeh, Chih-Min Liu, Chen-Chung Liu, Tzung-Jeng Hwang, Ming H. Hsieh, Yi-Ling Chien, Yi-Ting Lin, Yen-Tsung Huang, Chia-Yen Chen, Sharon D. Chandler, Stephen V. Faraone, Benjamin Neale, Stephen J. Glatt, Ming T. Tsuang, Hai-Gwo Hwu, and Wei J. Chen (<https://doi.org/10.1016/j.biopsych.2019.01.023>). It appears in *Biological Psychiatry*, published by [Elsevier](#).

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at Biol.Psych@sobp.org or +1 214 648 0880. Journalists wishing to interview the authors may contact Wei J. Chen, MD, at wjchen@ntu.edu.tw or +886 0910 276 113.

The authors' affiliations and disclosures of financial and conflicts of interests are available in the article.

John H. Krystal, MD, is Chairman of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale-New Haven Hospital, and a research psychiatrist at the VA Connecticut Healthcare System. His disclosures of financial and conflicts of interests are available [here](#).

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Rhiannon Bugno, Editorial Office

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+1 214 648 0880

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