A Finnish study provides the most definitive evidence to date linking prenatal nicotine exposure to increased risk for schizophrenia in offspring, researchers say.

Investigators found a 38% increased likelihood of schizophrenia in young adults whose mothers smoked heavily while pregnant, as evidenced by higher maternal serum cotinine level.

"To our knowledge, this is the first biomarker-based study to show a relationship between fetal nicotine exposure and schizophrenia," Solja Niemelä, MD, PhD, from University of Oulu, Finland, and colleagues write.

"Given the high frequency of smoking during pregnancy, these results, if replicated, may ultimately have important public health implications for decreasing the incidence of schizophrenia," they conclude.

The study was published online May 24 in the *American Journal of Psychiatry*.

The researchers conducted a population-based, nested, case-control study of all live births in Finland from 1983 through 1998. Maternal serum cotinine levels were prospectively measured from early to mid gestation using serum samples archived in a national biobank.

They identified 977 cases of schizophrenia through 2009 and matched each case patient to a control person. The mean age of schizophrenia patients and control persons was 22.3 years.

A higher maternal cotinine level was associated with an increase in the odds of developing schizophrenia (odds ratio [OR] 3.41; 95% confidence interval [CI], 1.86 - 6.24), the researchers report.

In unadjusted analysis, categorically defined heavy maternal nicotine exposure (cotinine level > 50 ng/mL) was associated with 51% greater odds of schizophrenia (OR, 1.51; 95% CI, 1.18 - 1.93; *P* < .001). The association persisted after adjusting for key covariates, including maternal age and parental psychiatric disorders (OR, 1.38; 95% CI, 1.05 - 1.82; *P* = .02).

Impressive Research

Reached for comment, Stephen V. Faraone, PhD, distinguished professor of psychiatry, neuroscience, and physiology at the State University of New York Upstate Medical University, in Syracuse, called the study "impressive," noting that the researchers used "a large sample and very good measures of maternal smoking.

"The finding is noteworthy," he added, "because it adds another piece to the puzzle of schizophrenia's etiology. The finding makes biologic sense, because we know that nicotine affects the fetal brain and impacts brain functioning. It is likely that some of these brain changes lead to schizophrenia."

However, Dr Faraone said, "It's important for readers to understand that, like all other risk factors for schizophrenia, the increased risk due to smoking is low. That means it is unlikely that maternal smoking can account for all schizophrenia cases. Future research will need to determine if the effects of maternal smoking interact with other genetic and environmental risks to cause schizophrenia."

Sameer Jauhar, MD, an honorary consultant psychiatrist at the Maudsley Hospital, King's College London, United Kingdom, who has studied smoking as a cause of psychosis, called the study "very interesting and timely." Dr Jauhar was not involved in the new study.

"The design is very clear, and by using objective measures of smoking status, a prospective design, and controlling for various other risk factors, they have been as stringent as one could be in a case-control study," said Dr Jauhar.
Echoing Dr Faraone, Dr Jauhar said, "It is entirely biologically plausible that smoking could be a prenatal risk factor for schizophrenia, based on the effects of nicotine on neurodevelopment — smoking during pregnancy has been associated with changes in neonatal behavior. This study will require replication — though, given that this is a modifiable risk factor, the importance of this finding cannot be underestimated."

The study was supported by the National Institute of Mental Health. Dr Niemelä has received speakers' bureau honoraria from Janssen, Lilly, and Lundbeck; travel funds from Janssen and Lundbeck; and has served on advisory panels for Janssen and Lundbeck. Dr Faraone and Dr Jauhar report no relevant financial relationships.

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