

## Interpreting New Evidence on Prenatal Infections and Mental Disorders

Ezra Susser, Michaeline Bresnahan, and W. Ian Lipkin

The article by Lydholm *et al.* (1) in this issue of *Biological Psychiatry* examines the relationship between treated maternal infection during pregnancy and treated offspring psychiatric disorders up to 20 years of age. The study is based on linked data from Danish national registers for a cohort of more than 1.2 million children. The most salient result was that treatment for maternal infections during pregnancy did not show a stronger relationship to offspring mental disorders than treatment for maternal infections before or after pregnancy.

We comment on three aspects of this study: 1) its relatively novel design, 2) the implications of the main result, and 3) the use of linked national data sets, noting what we can learn from them as well as their limitations.

An array of complementary epidemiologic designs are widely used for the testing of associations reported between prenatal exposures and offspring outcomes in population-based observational studies (2). These designs include but are not limited to the comparison of outcomes in siblings who are discordant for the exposure, the comparison of outcomes after paternal versus maternal exposure, and the use of genetic variants that mimic the exposure in an adapted version of the method termed Mendelian randomization. Although there is the potential for bias in these designs, they reduce certain kinds of bias that compromise standard observational studies; the remaining sources of bias tend to be different in each design. Therefore, results that are concordant with standard approaches tend to support the inference that the observed association may be causal; conversely, results that are discordant with the standard approaches raise questions about the validity of causal inference.

Lydholm *et al.* (1) use a complementary design that in our view could and should be used more often, comparing results for exposure before, during, and after pregnancy (in addition to comparing results for paternal vs. maternal exposure). Although they are not the first to use this approach, it has not been widely applied. In general, if a prenatal exposure is causal, exposure during pregnancy should have more impact on the outcome than exposure either before or after pregnancy. We should note that this design would not be applicable for all prenatal exposures, one of many exceptions being chronic maternal exposures. Also, there are various kinds of imprecision in its application by Lydholm *et al.* (1)—for example, the fact that the timing of treatment may not equal the timing of infection, and the fact that they assume a 40-week gestation period for all pregnancies.

The implications of the main results are intriguing in the landscape of current research. The primary analysis comparing the relationships between “any treated maternal infection” and

“any treated mental disorder in offspring” for the periods before, during, and after pregnancy found that the relationship was not stronger for treated infections during pregnancy. Maternal infection generally showed a somewhat stronger relationship than paternal infection, but the difference was not specific to treated infections during pregnancy. These results are inconsistent with some but not all theories and are inconsistent with previous findings regarding prenatal infection and offspring mental disorders.

It is indisputable that fetal development is especially vulnerable to certain specific prenatal infections. The discovery and elucidation of congenital rubella was a landmark that drew attention to this vulnerability. Among a host of other prenatal infections that can disrupt fetal development are syphilis, human immunodeficiency virus, and Zika virus (3). The adverse effects of these exposures on offspring are often evident in a variety of domains and include brain disorders. Studies of selected maternal infections can surely still help elucidate our understanding of fetal and child brain development, the origins of mental disorders, and the interplay of genes and environment in that process. Furthermore, more effective prevention of the aforementioned prenatal infections is still relevant to public health in some regions of the globe.

Still, we know little about common prenatal infections as causes of mental disorders in children and youths in high-income countries. Some studies have suggested that common maternal prenatal infections including influenza, common latent infections that may reactivate during pregnancy, such as toxoplasmosis and herpes simplex virus type 2, and recurrent maternal prenatal fevers could contribute to the risk in offspring mental disorders, such as autism spectrum disorder and schizophrenia. For example, Stoltenberg *et al.* (4) and Mahic *et al.* (5) examined the Norwegian Autism Birth Cohort and suggested an increased risk for autism spectrum disorder when mothers had influenza symptoms associated with serological evidence of prenatal influenza infection, high plasma titers of antibodies to herpes simplex virus type 2, or three or more episodes of fever after gestational week 12. Our earlier work in the Prenatal Determinants of Schizophrenia Study [Bresnahan *et al.* (6)] suggested an increased risk of schizophrenia when there was serologic evidence of exposure to influenza in the first half of pregnancy or when there was serologic evidence of exposure to latent toxoplasmosis. As yet, none of these exposures have been definitively established as causes. Nonetheless, given the wide range of prenatal infections with suggestive findings across numerous studies, investigators have formulated hypotheses about pathogenic mechanisms that might be common across these infections. Some of the suspected

SEE CORRESPONDING ARTICLE ON PAGE 317

infections may not be transmitted to the fetus, and therefore these hypotheses generally pertain to various forms of maternal immune activation that lead to a disruption of molecular pathways that are implicated in fetal brain development.

The exposure data available to Lydholm *et al.* (1) were treated infections in parents, derived from national pharmacy and hospital registers. Maternal exposure to treatment for infection was common. Approximately half of the women were exposed before, during, or after pregnancy. The majority were treated with antibacterial agents, although some were treated with antiviral, antimycotic, or antiparasitic agents. The results provide strong evidence that, taken together, such treated infections (and their treatments) are unlikely to influence mental disorders as a result of prenatal exposure. As the authors note, there have been reports that prenatal bacterial infections (e.g., genitourinary tract, upper respiratory, and gonococcal infections) are related to offspring mental disorders. Their results pose a particular challenge to those findings and to theories that build upon them, including the broadest theory that the entire spectrum of maternal prenatal infections provoke a maternal response that disrupts fetal development. As Lydholm *et al.* (1) recognize, however, many of the suspect prenatal infections are not bacterial, are not usually treated, and are of a different type than treated infections. Measures of these other kinds of infections were imprecise or absent in their study, and these infections may involve different mechanisms—for example, bacterial and viral infections activate the innate immune system via different pattern recognition receptors. Therefore, their study underscores the need for more precise epidemiologic studies of these other infections and of the particular mechanisms by which they may disrupt fetal development.

Additional caveats should be noted about the main result. The study may have obscured effects by lumping all treated infections and all treated mental disorders together in the main analysis, creating exposure and outcome groups that were too heterogeneous for the detection of more specific relationships within the available data sets. The treated mental disorders in offspring were derived from the Danish Central Psychiatric Research Register. If underlying population dimensions of mental health rather than diagnoses were their outcome of interest, they would not be represented well by transdiagnostic analysis of registry data. Further analyses did examine broad groups of infections (e.g., bacterial vs. other) and of diagnoses but may still not have been sufficiently specific. The authors themselves draw attention to other caveats. For example, there was some evidence of a relation of maternal infection in any period to offspring mental disorder, usually (though not always) greater than for paternal infection, a result that is difficult to explain but that might be related to a shared vulnerability to infection among parents of offspring who develop mental disorders.

Studies based on the linkage of national or regional records have become increasingly common and have greatly enhanced our power to examine causal relationships in populations (7). Less widely recognized are the limitations and the pitfalls of these data. It is tempting to assume that bias will be minimized and that results will be valid in a vast study of a whole population, but that is not always the case. Indeed, the results sometimes differ across similar countries, using similar registries, for reasons that are not always easy to discern. Although countries developing and maintaining these registries typically invest significant

resources and expertise in maintaining and updating data, harmonizing data over time, and ensuring data quality, registries remain especially vulnerable to certain vicissitudes of data collection, such as imprecise or missing data, misclassification/miscoding, blind spots in the system (e.g., over-the-counter medications in this instance), and ascertainment bias (8). The degree of impact likely varies across analyses (9,10). The magnitude of the data will not swallow all of these problems whole and deliver valid results. Above all these considerations, the data available in linked registries may not enable investigators to directly or precisely address the central research questions in a field. That may have occurred in the present study, although the study remains a valuable contribution.

### Acknowledgments and Disclosures

This work was supported by National Institute of Child Health and Human Development Grant No. R01 HD090051 and Simons Foundation Grant No. 336384 (to MB, WIL).

The authors report no biomedical financial interests or potential conflicts of interest.

### Article Information

From the Department of Epidemiology (ES, MB, WIL) and the Center for Infection and Immunity (WIL), Mailman School of Public Health, Columbia University, and the New York State Psychiatric Institute (ES, MB), New York, New York.

Address correspondence to Ezra Susser, M.D., Dr.P.H., Mailman School of Public Health, Columbia University, 722 W 168th St, Office 1030, New York, NY 10032; E-mail: [ess8@cumc.columbia.edu](mailto:ess8@cumc.columbia.edu).

Received Dec 5, 2018; accepted Dec 7, 2018.

### References

1. Lydholm CN, Köhler-Forsberg O, Nordentoft M, Yolken RH, Mortensen PB, Petersen L, Benros ME (2019): Parental infections before, during, and after pregnancy as risk factors for mental disorders in childhood and adolescence: A nationwide Danish study. *Biol Psychiatry* 85:317–325.
2. Keyes KM, Smith GD, Susser E (2014): Commentary: Smoking in pregnancy and offspring health: Early insights into family-based and 'negative control' studies? *Int J Epidemiol* 43:1381–1388.
3. Arora N, Sadovsky Y, Dermody TS, Coyne CB (2017): Microbial vertical transmission during human pregnancy. *Cell Host Microbe* 21:561–567.
4. Stoltenberg C, Schjølberg S, Bresnahan M, Hornig M, Hirtz D, Dahl C, *et al.* (2010): The Autism Birth Cohort: A paradigm for gene-environment-timing research. *Mol Psychiatry* 15:676–680.
5. Mahic M, Che X, Susser E, Levin B, Reichborn-Kjennerud T, Magnus P, *et al.* (2017): Epidemiological and serological investigation into the role of gestational maternal influenza virus infection and autism spectrum disorders. *mSphere* 2:e00159-17.
6. Bresnahan M, Schaefer CA, Brown AS, Susser ES (2005): Prenatal determinants of schizophrenia: What we have learned thus far? *Epidemiol Psychiatr Soc* 14:194–197.
7. Pedersen CB, Bybjerg-Grauholm J, Pedersen MG, Grove J, Agerbo E, Bækvad-Hansen M, *et al.* (2018): The iPSYCH2012 case-cohort sample: New directions for unravelling genetic and environmental architectures of severe mental disorders. *Mol Psychiatry* 23:6–14.
8. Ehrenstein V, Nielsen H, Pedersen AB, Johnsen SP, Pedersen L (2017): Clinical epidemiology in the era of big data: New opportunities, familiar challenges. *Clin Epidemiol* 9:245–250.
9. Jørgensen LK, Dalgaard LS, Østergaard LJ, Andersen NS, Nørgaard M, Mogensen TH (2016): Validity of the coding for herpes simplex encephalitis in the Danish National Patient Registry. *Clin Epidemiol* 8:133–140.
10. Gradel KO, Nielsen SL, Pedersen C, Knudsen JD, Østergaard C, Arpi M, *et al.* (2015): Low completeness of bacteraemia registration in the Danish National Patient Registry. *PLoS One* 10:e0131682.