Edlow and colleagues have published the findings of a study evaluating the association between exposure to SARS-CoV-2 in utero and neurodevelopmental disorders within the first 12 months of life. They included 7772 live births across 6 hospital sites with 222 births to mothers who tested positive for SARS-CoV-2 and found an association between SARS-CoV-2 and a diagnostic code for a neurodevelopmental disorder after adjusting for preterm birth. Although the prevalence of neurodevelopmental disorder diagnoses cannot be calculated exactly due to suppressed counts, it was estimated to be approximately 3% in the unexposed group and 6% in the exposed group within the first 12 months.

Given that we are only 2 years into the pandemic, much of the effect of in utero exposure to maternal SARS-CoV-2 infection remains poorly understood. As noted by Edlow et al, the inflammatory environment that is observed with infection is concerning for long-term adverse health consequences for the offspring and has been demonstrated with other infections. Yet we wonder whether it is the virus itself or the societal changes and stresses of the pandemic that are adversely affecting childhood outcomes.

A prior study found an association between delivery during the pandemic and delays in fine motor and communication skills at 1 year of age. Similarly, Shuffrey et al found an association between delivering during the pandemic and lower scores on the Ages and Stages Questionnaire, third edition (ASQ-3) in the subdomains of gross motor, fine motor, and personal-social. Despite these observed changes when those children born during the pandemic were compared with historical control groups, there were not similar differences observed when comparing those with and without exposure to maternal SARS-CoV-2 in utero as measured by the ASQ-3. Thus, the findings in the study by Edlow et al contrast those previously published. These differences may be a result of differences in ascertainment or a different age of interest (6 months vs 1 year). They may also be related to infection severity as the majority of the mothers in the Edlow et al study were symptomatic as universal screening was not being performed at the time of this work, whereas one-third of those in the Shuffrey et al study were asymptomatic and screened with polymerase chain reaction or antibody testing.

Edlow et al appropriately note 2 critical limitations of their work: (1) it is difficult to fully adjust for all the baseline differences between groups with and without a positive SARS-CoV-2 test in pregnancy and (2) there is potential for ascertainment bias. Although the authors performed a series of sensitivity analyses to ensure that their data are robust and performed multivariable modeling to adjust for confounding, there may still be residual confounding from differences in the home environment or other exposures during pregnancy. The earlier timing of diagnosis of neurodevelopmental disorders in the exposed group suggests that they may have been evaluated earlier or more frequently for neurodevelopmental disorders when compared with the unexposed group. Ideally, all offspring in the cohort would have been evaluated using standardized methodology, which will be important moving forward as prospective studies are designed rather than needing to rely on diagnostic codes.

These preliminary data are critically important, yet many questions remain. Essentially all of what we know now about the effects of in utero exposure to maternal SARS-CoV-2 infection is from children who were exposed to the early and Alpha variants of SARS-CoV-2 as those are the only
children now old enough to undergo rigorous neurodevelopmental assessments. Knowledge about the effects of other variants is lacking. We know that the Delta variant substantially damaged the placenta and was associated with a much higher risk of stillbirth compared with other variants. This placental damage in conjunction with inflammation and cytokine release has the potential for substantial ramifications for the offspring. Thus, outcomes may be different by variant of maternal SARS-CoV-2 infection. Importantly, we also have no data on whether prior vaccination will have a protective effect against adverse neurodevelopmental outcomes for the offspring of mothers with SARS-CoV-2 beyond the direct benefit of persistent antibodies in the cord blood and through infancy.

Ultimately, it is not surprising that the pandemic and in utero exposure to maternal SARS-CoV-2 infection may adversely affect neurodevelopmental outcomes in young children. As a retrospective cohort study, this publication by Edlow et al can only demonstrate associations, and causality cannot be determined. This type of work is intended to be hypothesis-generating, and that goal has been accomplished as these preliminary findings generate numerous additional research questions to explore. Are there genetic predispositions to adverse outcomes? Will we observe differential effects by SARS-CoV-2 variant, by severity of infection, and by trimester of infection? Is it the virus itself or all of the societal changes that occurred during this period including differences in how those changes were experienced among those with and without SARS-CoV-2?

Perhaps the most important question is how do we intervene to help mitigate the adverse effects of the pandemic on young children? Prospective studies to validate these findings, tease out some of the nuance, and identify those at highest risk will help health care practitioners appropriately dedicate resources to improve outcomes as we follow the life course of this generation of children born during the COVID-19 pandemic.

REFERENCES