Hessami and colleagues\(^1\) evaluated the risk of neurodevelopmental impairments in 6-month to 12-month-old infants exposed in utero to maternal SARS-CoV-2 infection or screened during the pandemic regardless of their exposure status. The meta-analysis included 5 studies of generally good quality, reporting on the Ages and Stages Questionnaire, 3rd Edition (ASQ-3), a screener of neurodevelopmental outcomes, with samples from the US, Canada, China, and Kuwait. When comparing infants with and without in utero SARS-CoV-2 exposure, and infants screened during and before the pandemic, no significant difference regarding the overall neurodevelopmental impairment risk was found. However, when analyzing the ASQ-3 subdomains, infants screened during the pandemic or exposed in utero to SARS-CoV-2 scored lower on communication and fine motor skills, respectively.

Since the beginning of the COVID-19 pandemic, experts have been concerned that infants born during this unprecedented time might be at greater risk for behavioral or neurodevelopmental problems. Rapid mobilization of research efforts across the world quelled initial fears of negative outcomes through vertical transmission.\(^2\) However, potential negative outcomes could still occur through 2 hypothesized pathways.\(^3,4\) First, in utero exposure to maternal SARS-CoV-2 infection leads to maternal immune activation, which has been associated with adverse child neurodevelopmental outcomes, including attention-deficit/hyperactivity disorders and autism spectrum disorder (ASD).\(^4\) Second, there is strong evidence that the pandemic environment has led to increased maternal stress, and both prenatal and postnatal exposure to poor maternal mental health has been associated with neurodevelopmental risk, potentially increasing risk for psychopathology and behavioral problems. Situated within this context, the conclusions from Hessami and colleagues\(^1\) are reassuring.

The results from Hessami et al\(^1\) should be interpreted with caution. The systematic review included 11,438 infants screened during and 9,981 infants screened before the COVID-19 pandemic. Of the pandemic cohort, 700 infants had a confirmed exposure to in utero SARS-CoV-2 infection, and 7,778 had no documented exposure. However, data using the ASQ-3 were not available for all infants. According to the information presented in Table 1 in the original article,\(^1\) the main comparison between infants with and without in utero SARS-CoV-2 exposure relies on a mere 171 exposed and 219 unexposed infants. Similarly, the comparison between pandemic and prepandemic cohorts is based on 3,215 and 9,981 infants, respectively. The specific sample size for each comparison is not clearly presented in the text or in the figures, potentially leading a rushed reader to the conclusion that the increased risk of communication impairment in infants screened during the pandemic and increased risk of fine motor impairment in infants with in utero exposure to maternal SARS-CoV-2 infection are based on larger sample sizes than the cumulative data available to date in the literature.

Another important consideration is the interpretation of the analysis of “infants screened during the pandemic” in the study by Hessami et al,\(^1\) which does not allow for the differentiation of the independent and/or interactive associations between neurodevelopment and in utero exposure to the pandemic (with its presumed associated increase in maternal stress) vs the infant growing up in a changed environment. This is particularly true for those screened at 12 months. In Imboden et al,\(^5\) data for the pandemic cohort were collected from electronic health records from October 2020 to January 2021. Considering that the COVID-19 pandemic started in early 2020 in the US, the 12-month-old infants who attended their well-child checkup during that period were born at least 3 months before the COVID-19 pandemic began.
months before the onset of the pandemic. In Huang et al, data for the pandemic cohort included infants who had a neurodevelopmental assessment at their 6-month and 12-month visits from March 1 to May 15, 2020. Given that the onset of the pandemic in China was in December 2019, the 12-month-olds in this study were born at least 7 months before the pandemic. By our calculations, the combined prepandemic-born 12-month-olds in these 2 studies account for approximately 25% of the weight in the pooled odds ratios presented in Figure 3, panels B through D, showing no differences between infants screened during or before the pandemic in gross motor, fine motor, or personal-social skills. However, according to eFigure 1B in the original article’s Supplement, along with our calculations, the main result of lower communication scores for infants screened during the pandemic compared with those screened before the pandemic is based on 69% weight in the pooled odds ratio associated with these prepandemic-born infants. This raises the question of potential unequal contribution of in utero exposure to the pandemic vs being raised in the pandemic, as well as bias introduced by unequal weights of these factors in the meta-analysis of various subdomains. Further complicating the interpretation, all analyses of ASQ-3 scores combine 6- and 12-month-old infants.

The results of Hessami et al are important and contribute to our understanding of the outcomes of the COVID-19 pandemic on risk of neurodevelopmental impairments in infants born and raised in a rapidly changing world. Although the authors show selective associations between neurodevelopment and both in utero exposure to maternal SARS-CoV-2 infection and being screened during the pandemic, the main takeaway of this systematic review is a positive message: severe long-term neurodevelopmental impairments for the COVID-19 generation are unlikely. However, the precise impact of the COVID-19 pandemic and exposure to this novel virus on infants remains nonetheless unclear, and it should be noted that this systematic review did not consider timing of exposure during pregnancy, maternal infection severity, or exposure to various SARS-CoV-2 variants—all factors that could eventually be proven to contribute to subtle adverse neurodevelopmental outcomes. As the pandemic progresses and the knowledge base continues to evolve rapidly, regular updates of this systematic review should become a priority. If identified early, neurodevelopmental impairments have the potential to be ameliorated or reversed using proactive public health strategies, such as interventions targeting mother-infant dyadic relational health, which is known to improve infant outcomes. Thus, this topic should be considered for a living systematic review, ie, a review that is continually updated as new evidence becomes available.

The life-course of the findings presented by Hessami et al is particularly poignant when considering the main, albeit unavoidable, limitation of this systematic review: the restriction to neurodevelopmental outcomes measured at 6 to 12 months of age. Data from cohorts born during previous pandemics, such as the 1918 Spanish flu, 1964 rubella, and 2009 H1N1, have taught us to be vigilant about increases in diagnoses such as ASD and schizophrenia. ASD is generally diagnosed at age 3 to 5 years (and often not until early teens), while schizophrenia is generally diagnosed in mid-to-late 20s. The ASQ-3 administered in infancy is not predictive of either of these disorders, nor is it predictive of long-term outcomes more generally. The scientific and medical community must therefore not become complacent in the face of good news and must continue to assiduously investigate potential adverse health consequences for this vulnerable population as these infants age into various risk windows.

ARTICLE INFORMATION
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