represent a genuine effect. As such, we recommend further investigation and a reopening of the discussion around early gluten intake and prevention of CD and hypothesize that high-dose gluten introduction could be the missing link not previously investigated by other prevention randomized clinical trials.

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1. Logan K, Perkin MR, Marrs T, et al. Early gluten introduction and celiac disease in the EAT study: a prespecified analysis of the EAT Randomized Clinical Trial. *JAMA Pediatr*. 2020;174(11):1041-1047. doi:10.1001/jamapediatrics.2020.2893

Methodologic Concerns With Concluding a Link Between Epidural and Autism Spectrum Disorder

To the Editor We have strenuous concerns about the conclusions of Qiu et al,[1] implying a causal link between maternal labor epidural analgesia (LEA) and an increased risk of autism spectrum disorder (ASD) in children, based on their analysis of a retrospective cohort of women who underwent vaginal delivery between 2008 and 2015 in Kaiser Permanente Southern California hospitals. Autism spectrum disorder is a major public health concern attributed primarily to genetic and environmental risk factors[2] but, as the authors mention, has a purported association with general anesthesia for cesarean delivery (CD) and CD itself.[3] The ASD incidence was lower than prior reports, possibly suggesting missing cases based on very early screening and loss to follow-up. Information regarding LEA management was omitted; however, the authors speculated that transplacental transfer of epidurally administered local anesthetics may be causal factors. Contemporary practice consists of minimal local anesthetics doses at levels insufficient to cause fetal neurotoxicity.[4] Longer labors may reflect inherently more complicated pregnancies, and the incidence of ASD according to duration of labor among the no-LEA group is glaringly absent.

Despite the proposed association between epidural analgesia and maternal fever,[5] and of fever with adverse neonatal outcomes, fever is dismissed as a mediator based on an adjusted model which ignored preexisting fever and numerous possible confounders, including Apgar scores and neonatal resuscitation.

Numerous statistically significant findings may be attributable to the large data set and the difference in ASD incidence between the exposed and unexposed cohorts (0.6%) is likely not clinically meaningful. Furthermore, the findings from a single hospital system localized to 1 region may not be generalizable, given the strong contribution of genetic and environmental factors to ASD.

Our serious contention with this study is the danger of misinterpretation by women making decisions about their choices for labor pain relief. Millions of women around the world benefit from LEA every year and give birth without any complications to mother or infants. Similar to persistent skepticism related to the safety of vaccines, we are concerned that it may be difficult to reverse false notions, even with contradictory scientific evidence. It is critical to reassure lay persons that no evidence was found that LEA causes ASD: the study's findings were that the risk of ASD per 1000 deliveries is 13 among women who do not receive LEA vs 19 among those who do receive LEA, and pregnant women should feel safe receiving the most effective labor analgesic technique available.

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1. Qiu C, Lin JC, Shi JM, et al. Association between epidural analgesia during labor and risk of autism spectrum disorders in offspring. *JAMA Pediatr*. 2020; 174(12):1168-1175. doi:10.1001/jamapediatrics.2020.3231

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To the Editor We read with interest the work by Qiu et al[1] investigating a potential association between intrapartum epidural analgesia and autism spectrum disorder (ASD) in offspring. We understand the urgency of uncovering the etiology of ASD given the rising rates in recent years, and we acknowledge the challenges of conducting clinical trials in this field. However, methodologic concerns and lack of biologic plausibility preclude conclusions of a causal relationship between epidural anesthesia and ASD.

The first concern is residual confounding. The investigators used inverse probability of treatment weighting to balance potential confounders, but this does not address the many

unmeasured confounders that remain. They used an E-value to demonstrate that only unmeasured variables strongly associated with both epidural and ASD would nullify the study's findings. However, numerous unmeasured covariates could achieve this and substantially alter the results. Examples include antepartum and intrapartum characteristics, such as medical comorbidities, length of labor, and labor complications, which have all been associated with epidural use. Additionally, maternal and paternal history of psychiatric disorders, including anxiety and depression, were not included but have been linked to both epidurals as well as ASD.[2,3] Furthermore, there are social and cultural differences between women who do and do not receive an epidural.[4] Many of these differences also result in disparities with respect to timely evaluation and diagnosis of ASD, leading to ascertainment bias in the ASD outcome.

Furthermore, the biologic plausibility for a mechanistic link between epidural and ASD is weak. The cited animal trial included only 19 monkeys with the findings at high risk for type 1 error given the numerous tests and multiple comparisons. Additionally, the doses of local anesthetics in labor epidurals have minimal systemic absorption and low levels in the neonatal bloodstream.[5] The authors posit immune dysregulation and cytokines as a potential mechanism, but the lack of an association between epidural-related fever and ASD in this large cohort suggests that this is not the biologic link.

In summary, residual confounding, ascertainment bias, and lack of a clear biologic mechanism prohibit concluding a causal link between epidurals and ASD. The implications of this report are profound and will lead to unnecessary angst among pregnant patients, increased intrapartum pain, and potential use of alternative pain management strategies that may be less safe. The study may also precipitate unwarranted guilt among parents seeking explanations for their child's ASD diagnosis.

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Conflict of Interest Disclosures: None reported.

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In Reply We appreciate the valuable perspectives and the thoughtful scrutiny that has been stimulated by our study,[1] including those brought forward by Kern-Goldberger et al and Lee et al. Our study was not an experimental or mechanistic study and as such, we explicitly stated that our findings "cannot be interpreted as a demonstration of a causal link between LEA [labor epidural analgesia] exposure and subsequent development of ASD."[1] We are concerned about the assertions about biologic plausibility because that depends on the current state of knowledge. The lack of plausibility today does not preclude biological plausibility tomorrow; rather, this newly discovered association provides impetus for more biologic research. Thus, we called for further research to both "confirm our study findings and to investigate the probable mechanistic association."[1]

The potential effect of anesthesia on neurobehavior and neurocognition has been established and continues to rapidly evolve.[2] Granted, the perinatal safety of LEA and its transformative benefits have been irrefutably proven. What constitutes a low dose and the long-term effects on neurodevelopment in offspring are unknown. Furthermore, there is concerning evidence that local anesthetics can cause acute transplacental neural toxicity and levels can persist in newborns.[3]

We agree that there may be a residual bias that could be owing to unmeasured confounders and asserted directly that "potential uncontrolled confounders may explain the association that we observed, these confounders may include factors both antecedent and subsequent to the peripartum period"[1] but we did not make a causal conclusion. However, we must highlight that for a confounder to impart a bias, it must be associated with both the exposure and outcome without an intermediate role in the causal pathway, to which many are yet to be confirmed or discovered.

Regarding the questions about our analytic approach, we used well-established statistical methods and cross-checked the results with different methods. We used inverse probability of treatment weighting to control for potential confounding owing to measured confounders and the E-value approach to illustrate how likely unmeasured confounders might explain away the association.[4] These 2 methods, in addition to standard covariate adjustment, enhanced the rigor of our study. Additionally, the overall ASD rate in our study cohort (1.7%, including children age 4 years) was both representative of our service area[5] and comparable with that of the US Centers for Disease Control and Prevention report (1.9%, age 8 years).[6] We agree that the low baseline rate of ASD should be considered when interpreting the 37% relative risk increase because the absolute risk increase is small. While there are many unanswered questions regarding our findings, for the purpose of advancing our common goal of patient safety, we feel that future efforts should be directed

toward a multidisciplinary and collaborative approach to better understand the neurodevelopmental safety of LEA to our children.

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CORRECTION

Errors in Byline and Author Contributions: In the Original Investigation titled "Effect of Family Navigation on Diagnostic Ascertainment Among Children at Risk for Autism: A Randomized Clinical Trial From DBPNet,"[1] published online January 11, 2021, there was an error in the author byline and in the Author Contributions. An author was omitted in error by the corresponding author. There should be a total of 20 authors, and the 15th should be Ivys Fernandez-Pastrana, JD. She is affiliated with the Department of Pediatrics, Boston Medical Center, Boston, Massachusetts, and has no Conflict of Interest Disclosures. Her name has also been added to the Author Contributions. This article was corrected online.

1. Feinberg E, Augustyn M, Broder-Fingert S, et al. Effect of family navigation on diagnostic ascertainment among children at risk for autism: a randomized clinical trial from DBPNet. *JAMA Pediatr*. Published online January 11, 2021. doi:10.1001/jamapediatrics.2020.5218

Error in Figure: In the Research Letter entitled "Prevalence of Spanking in US National Samples of 35-Year-Old Parents From 1993 to 2017,"[1] a percentage symbol was erroneously included in the y-axis label of the Figure. This symbol was removed and the y-axis label now reads "Weighted prevalence, SE." This article was corrected online.

1. Mehus CJ, Patrick ME. Prevalence of spanking in US national samples of 35-year-old parents from 1993 to 2017. *JAMA Pediatr*. 2021;175(1):92-94. doi:10.1001/jamapediatrics.2020.2197

Error in Methods Section and Figure: In the Original Investigation titled "Assessment of Exposure to High-Performing Schools and Risk of Adolescent Substance Use: A Natural Experiment,"[1] there were errors in the Methods section and Figure 1. In the Methods section, the number of potential participants identified should be 1995 instead of 1996, and the number of ineligible participants should be 486 instead of 487. Likewise, in Figure 1, the total number of potential participants should be 1995, and the number of ineligible patients should be 486. In addition, the number of individuals unable to be contacted or had moved should be 319 rather than 320. Under intervention baseline, the number of individuals who were unable to be reached and individuals who refused were switched. This article was corrected online.

1. Dudovitz RN, Chung PJ, Reber S, et al. Assessment of exposure to high-performing schools and risk of adolescent substance use: a natural experiment. *JAMA Pediatr*. 2018;172(12):1135-1144. doi:10.1001/jamapediatrics.2018.3074

Clarifications of Terms and for Interpreting Incidence Rate Ratios: In the Original Investigation, "Association of the Timing of School Closings and Behavioral Changes With the Evolution of the Coronavirus Disease 2019 Pandemic in the US,"[1] published online first on February 22, 2021, in *JAMA Pediatrics*, there were errors in the text for description of the incidence rate ratios (IRRs). In the Abstract and main text, "delay of 1 day" and "day of delay" have been corrected to "advance of 1 day" and "each day earlier." The term "days since" has been corrected to "each day earlier" in the text and defined in the legend of the Table as "how much earlier in the pandemic either school closures, gathering bans, or work reductions happened. Each 1-unit increase in a 'days since' variable represents 1 day earlier that the change happened." These corrections do not affect any of the IRRs or other data. The article has been corrected online.

1. Zimmerman FJ, Anderson NW. Association of the timing of school closings and behavioral changes with the evolution of the coronavirus disease 2019 pandemic in the US. *JAMA Pediatr*. Published online February 22, 2021. doi:10.1001/jamapediatrics.2020.6371