



Challenges in database research for anesthetic neurotoxicity

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To the Editor:

I recently read with great interest the article “Neurodevelopmental Outcomes Following General Anesthesia in Infants: A Longitudinal Analysis” [1].

The debate over whether early childhood exposure to anesthesia causes long-term neurodevelopmental harm continues to engage medical professionals in pediatrics and anesthesiology [2, 3]. Existing evidence generally suggests that early anesthesia exposure does not correlate with global neurodevelopmental deficits [2, 3]. However, there is ongoing investigation into whether specific neurodevelopmental domains may be impacted, seeking to identify the so-called “phenome” of potential injury [4, 5]. For instance, an analysis of the Western Australian Pregnancy Cohort (Raine) Study found some associations between early anesthesia and poorer performance in language and cognitive domains [6]. In contrast, the ALSPAC study did not find significant deficits in general cognitive abilities but noted associations with dynamic balance, manual dexterity, and social communication [7]. The discordance between findings from different studies highlights the complexity of this issue. Variability in results across studies may be due to differences in study design, outcome measures, and statistical thresholds. The risk of type I error increases with multiple outcomes, and statistical adjustments for multiple testing do not completely address this risk. Despite these methodological challenges, the question of whether early childhood anesthesia leads to long-term neurodevelopmental harm remains a critical topic of discussion [8].

In addressing such unresolved issues, the authors of the article “Neurodevelopmental Outcomes Following General

Anesthesia in Infants: A Longitudinal Analysis” [1] are commendable for utilizing a large dataset to explore the association between early anesthesia exposure and subsequent neurodevelopmental delays. Such extensive database research is invaluable for investigating complex, multifactorial issues. Additionally, their longitudinal study design, which assesses neurodevelopment repeatedly over time, allows children to serve as their own controls, potentially mitigating confounding by static factors such as genetics, perinatal and socioeconomic status. However, certain aspects of the study’s methodology and data interpretation warrant further scrutiny.

Firstly, self-reported data in epidemiological studies can be subject to recall bias and inaccuracies, potentially affecting study validity. Research indicates that patients often struggle with medical terminology related to anesthesia. A study found that approximately 45% of patients did not fully understand terms used during pre-anesthesia consultations, with common misunderstandings including “reflux,” “aspiration,” and “sedation” [9]. Although this study may not be broadly generalizable, it highlights the potential for miscommunication in anesthesia-related terminology. From this perspective, parent-completed questionnaires used in the study might not accurately capture “sedation,” even if children were exposed to anesthetics or sedatives, leading to possible misclassification. Therefore, relying on questionnaire data from mothers to determine anesthesia exposure, rather than using medical records, raises questions about the accuracy and reliability of anesthesia exposure assessment. In general, researchers should account for potential recall bias and misclassification when designing studies and interpreting results based on self-reported data. Validating self-reported data against more objective sources, such as medical records, should be considered where possible.

Secondly, the questionnaires used in the study do not capture details on the type, duration, or context of surgery and anesthesia. These are important factors that could confound the relationship between anesthesia and neurodevelopment. Therefore, the lack of detailed information on critical confounding variables—such as patient comorbidities, type and duration of surgery and anesthesia, and specifics

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about anesthetic or sedative agents—is a notable concern. In general, confounding is a significant limitation in observational studies. Numerous known/measured and potentially unknown/unmeasured confounding variables affect the association between anesthesia exposure and neurodevelopmental outcomes [2], including baseline comorbidities, indications for procedures, and perioperative factors that might influence neurodevelopment. Increasing sample size does not eliminate the risk of confounding. Statistical adjustments and careful matching can reduce confounding impacts but cannot completely eliminate them. Observational studies of anesthetic-induced neurotoxicity must control (via restriction, stratification, or regression adjustment) for differences in known/measured confounding variables between groups to avoid extensive bias. The study in the subject [1] has data on pregnancy and peripartum variables but lacks information on important perioperative variables such as temperature, hypoxia or hyperoxia, hemodynamics, and adverse events. Without accounting for these variables, the study's findings might be affected by not only unknown/unmeasured, even known/measured confounding variables.

Lastly, despite the limitations and potential issues with self-reported data and lack of detailed contextual information on surgery and anesthesia, the study's conclusion suggests that general anesthesia administered after the age of one year may be associated with more favorable neurodevelopmental outcomes. This might oversimplify the complexities involved in clinical decision-making. The public has a great appetite for health-related information; indeed, one of the most frequent uses of the Internet is to obtain information about medical conditions and health care [10]. This demand provides a fertile ground for high impact medical news stories, often based on the publication of new study results. Not surprisingly, media reporting of medical studies has been shown to influence not only popular opinion, but also the opinion of healthcare providers and regulatory authorities [11]. Distorted reporting of medical risks can promote false concepts that persist for years, impacting medical care and public health negatively [12]. The widely debunked study linking the MMR vaccine to autism is a prime example of how such misinformation can have lasting effects [13].

In light of these considerations, it is crucial and expected that ongoing research comprehensively address anesthetic neurotoxicity in the developing brain. Clinicians should interpret the data with a nuanced understanding of the potential risks and benefits.

Thank you for considering these points. Addressing these concerns will contribute to a deeper understanding of the association between anesthesia exposure and neurodevelopmental outcomes and support better-informed clinical and public health decisions.

Declarations

Conflict of interest The authors declare that they have no competing interest related to this publication.

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