

DR FRANCISCO J SCHNEUER (Orcid ID : 0000-0002-6245-7159)

DR ANDREW DAVIDSON (Orcid ID : 0000-0002-7050-7419)

DR JUSTIN J SKOWNO (Orcid ID : 0000-0002-4398-2150)

Article type : Letter

Editor : Dr David Polaner

**Reply to Ritchie-McLean, Susanna; Wilmshurst, Sally, regarding their comment 'Can population cohort studies assess the long-term impact of anesthesia in children?'**

**Letter**

Francisco J Schneuer<sup>1</sup>, Jason P Bentley<sup>1</sup>, Andrew J Davidson<sup>2</sup>, Andrew JA Holland<sup>3</sup>, Nadia Badawi<sup>4</sup>, Andrew J Martin<sup>5</sup>, Justin Skowno<sup>3,6</sup>, Samantha J Lain<sup>1</sup>, and Natasha Nassar<sup>1</sup>

**Affiliations:** <sup>1</sup>Child Population and Translational Health Research, The Children's Hospital at Westmead Clinical School, The University of Sydney, Australia; <sup>2</sup>Anaesthesia and Pain Management Research Group, Murdoch Children's Research Institute, Melbourne, Australia; <sup>3</sup>Discipline of Child and Adolescent Health, The Children's Hospital at Westmead, Sydney Medical School, The University of Sydney, Australia; <sup>4</sup>Grace Centre for Newborn Care, The Children's Hospital at Westmead, Sydney, Australia; <sup>5</sup>School of Education, University of New South Wales, Sydney, Australia; <sup>6</sup>Department of Anaesthesia, The Children's Hospital at Westmead, Sydney, Australia;

**Address correspondence to:** Dr F. Schneuer, Child Population and Translational Health Research, Level 2 The Hub, Charles Perkins Centre D17, The University of Sydney, NSW 2006, Australia.

Telephone: +61 2 86274674. Email: [francisco.schneuer@sydney.edu.au](mailto:francisco.schneuer@sydney.edu.au)

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/pan.13520](https://doi.org/10.1111/pan.13520)

This article is protected by copyright. All rights reserved

Dear Editor,

We thank Drs Ritchie-McLean and Wilmshurst for their comments<sup>1</sup> regarding our study entitled 'The impact of general anesthesia on child development and school performance: a population-based study'<sup>2</sup>. The authors suggest that residual confounding has the potential to diminish the conclusions that can be drawn from our study. We agree that residual confounding is a possibility and it is important to recognize when interpreting results. In our study we acknowledge the demonstrated associations and highlight that causation must be regarded with caution. Similar studies have attempted to reduce the impact of known confounders in various ways<sup>3</sup>. Our study has strived to address confounding factors using multiple methodological and analytical approaches. This includes excluding children with underlying conditions, those undergoing major neurological or cardiovascular surgery or with neurodevelopmental disorders; stratifying analyses by type of surgery or procedure, number and age of general anesthesia exposure; conducting multivariable statistical analyses and restricting analyses to children with a single exposure to general anesthesia and hospitalization.

We would also like to respond to the three specific points highlighted by the authors. First, regarding the identification of children with autism, neurodevelopmental and behavioral conditions, we identified children diagnosed with these conditions and they were excluded from all analyses, as noted in our methods. In addition, children with physical or behavioral disabilities were excluded *a priori* if they were classified as having special needs in the developmental assessment or were exempt from school tests. While some confounding may persist from children with unidentified conditions in our data, this is likely to be those with milder forms of neurodevelopmental impairment which we have addressed in our discussion.

Second, we did not assess a comparison group of children with hospitalization/s not requiring general anesthesia. This was because such a group would be too heterogeneous and may have underlying or

experienced conditions such as traumatic brain injury, assault or trauma that may have long-term neurodevelopmental effects and confound results. We also note the authors' suggestion that the surgery and other perioperative events such as pain, anxiety and sleep disturbances may play a role in developmental outcomes of children. These perioperative factors were not measured in our study (and, to our knowledge, have not been explored by other similar studies assessing outcomes following exposure to general anesthesia), and may be worthwhile considering in future studies<sup>4</sup>. Third, Ritchie-McLean and Wilmschurst suggest that the higher proportion of boys exposed to general anesthesia and who were also classified as developmentally high-risk, may explain our finding of increased risk. We note, however, that the results presented were adjusted for gender. Indeed, additional analyses revealed no interaction by gender and similar results were found when stratified analysis for boys and girls (results not presented).

Going forward, population-based longitudinal studies using linked clinical, operative and administrative data provide a cost-effective, timely and comprehensive information on important confounders and mediators (such as child characteristics, perioperative and procedural factors and anesthetics used)<sup>4</sup> to explore. Combined, these data with appropriate research questions and patient selection, and application of causal inference frameworks and analytical techniques to control for bias and confounding, provide an opportunity to estimate associations and increase our understanding of the possible effect of early exposure to general anesthesia, including the potential impact of repeated or lengthy use on child cognitive development. As Davidson and Sun note in their recent editorial, no amount of adjustment can reduce the possible impact of unknown confounding factors<sup>3</sup>. Nevertheless, future findings may give us an insight as to the other possible causes of poor outcomes and inform clinical trials comparing different strategies to reduce any impact on neurocognitive outcome.

Ethical approval not sought

**Funding source:** Supported by a National Health and Medical Research Council Project Grant (#APP1047263); Dr Nassar National Health and Medical Research Council Career Development Fellowship (#APP1067066) and Dr Lain National Health and Medical Research Council Early Career Fellowship (#APP1054571).

**Conflict of Interest:** AJD is the editor-in-chief of Pediatric Anesthesia. All other authors have no conflicts of interest to disclose.

## References

1. Ritchie-McLean S, Wilmschurst S. Can population cohort studies assess the long-term impact of anesthesia in children? *Paediatric anaesthesia*. 2018;In press.

2. Schneuer FJ, Bentley JP, Davidson AJ, et al. The impact of general anesthesia on child development and school performance: a population-based study. *Paediatric anaesthesia*. 2018;28(6):528-536.
3. Davidson AJ, Sun LS. Clinical Evidence for Any Effect of Anesthesia on the Developing Brain. *Anesthesiology*. 2018;128(4):840-853.
4. Warner DO, Shi Y, Flick RP. Anesthesia and Neurodevelopment in Children: Perhaps the End of the Beginning. *Anesthesiology*. 2018;128(4):700-703.

Author Manuscript