



## Reply to the letter by Obara S

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Received: 2 October 2024 / Accepted: 3 October 2024 / Published online: 13 October 2024  
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**Keywords** Cohort study · General anesthesia · Neurodevelopment · Questionnaires

To the Editor,

We thank Dr. Soichiro Obara for his interest in our article [1]. The association between early childhood exposure to general anesthesia and long-term neurodevelopmental outcomes remains uncertain. Although many epidemiological studies have been conducted worldwide, there were few findings in Japan.

We investigated the effects of general anesthesia in early childhood on neurodevelopment, using the data from the Japan Environment and Children's Study (JECS) [2]. The JECS is an ongoing prospective nationwide birth cohort study, which registered over 100,000 pregnant women throughout Japan. We previously reported neurodevelopmental delays at age 1 year [3], evaluated by the Japanese translation of the Ages and Stages Questionnaires, Third Edition (J-ASQ-3) [4]. In the present study [1], we investigated neurodevelopmental delay during 1–4 years of age, and reported that general anesthesia administration before age 1 was associated with neurodevelopmental delay during 1–4 years of age.

Dr. Obara pointed out the possibility of recall bias and inaccuracies on the information from self-administered

questionnaires. The JECS has been designed to investigate the effects of various environmental factors on the health of the children [2], and it was not designed for the specific purpose to investigate the effects of general anesthesia. The information relating to the surgical procedure for general anesthesia was obtained from the responses to “surgery under general anesthesia” item of a parent/guardian-administered questionnaire. It may lead to a misclassification that some children might have taken any anesthetics to undergo some procedures or examinations. Also, some procedures might underwent with sedation rather than general anesthesia, which is hard to distinguish from non-healthcare workers. These potential recall bias and misclassification are due to the nature of an observational study. The information from questionnaire may differ from medical records, and should be used with caution.

Additionally, there are insufficient details on the type, duration, or context of surgery and anesthesia. The diagnosis of causative diseases that required general anesthesia could not be also clarified in this study. We understand that these are important confounding factors in the association between anesthesia exposure and neurodevelopmental outcomes. It is desirable to review the medical records of the children who were reported to receive general anesthesia from parents. In this study, we could not review the medical records about the general anesthesia, because it was not included in the protocol of the JECS. For the confounding, we excluded the children with congenital anomalies, such as anorectal malformation and intestinal atresia from our analysis. Therefore, the total number of children who received general anesthesia under 1 year was 1419 among overall participants in the JECS, but the number of the children included in this analysis was limited to 668, who were considered to have relatively mild diseases. We also evaluated the risk of new onset neurodevelopmental delay every 12 months after 1 year of age, to exclude the children with preexisting neurodevelopmental diagnosis before undergoing surgery.

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This reply refers to the comment available online at <https://doi.org/10.1007/s00540-024-03401-w>.

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Furthermore, we conducted the analysis stratified by age to assess the relationship between age at first general anesthesia administration and neurodevelopment. The results showed that children who received general anesthesia for the first time at the ages of 1–2 or 2–3 years had a small risk of developmental delay compared with those received general anesthesia before 1 year. Children exposed to anesthesia under 2 years showed more behavioral disturbances than children in whom surgery was performed after age 2 year, although the difference was not significant [5]. On the other hand, Graham et al. [6] showed that negative neurodevelopmental findings were accounted in children exposed to general anesthesia between 2 and 4 years than those exposed under 2 years. In the Pediatric Anesthesia Neurodevelopment Assessment (PANDA) study [7], no significant differences at the age ranges before age 36 months were observed in neurocognitive outcomes. Thus, the effects of the time of first exposure to general anesthesia remain inconclusive. Therefore, it is important to accumulate the findings from many studies. We believe that the JECS could provide the important findings, although it has many limitations.

Finally, the association between early childhood anesthesia and neurodevelopment in children has been investigated in many clinical and epidemiological studies [8]. The findings from a recent systematic review and meta-analysis support the hypothesis that the association between early life anesthesia exposure and subsequent neurodevelopmental deficits differ by neurocognitive domain [9]. However, the long-term neurodevelopmental effects of early exposure to anesthesia still remain uncertain [10]. Further researches which follow up the subjects exposed to anesthesia in early childhood for a long term with growth are required.

Again, we thank Dr. Obara for important and critical comments on this topic.

## Declarations

**Conflict of interest** The authors declare that they have no competing interest.

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