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RESEARCH REPORT

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The impact of general anesthesia on child development and school performance: a population-based study

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Summary

Background: There has been considerable interest in the possible adverse neurocognitive effects of exposure to general anesthesia and surgery in early childhood.

Aims: The aim of this data linkage study was to investigate developmental and school performance outcomes of children undergoing procedures requiring general anesthesia in early childhood.

Methods: We included children born in New South Wales, Australia of 37+ weeks' gestation without major congenital anomalies or neurodevelopmental disability with either a school entry developmental assessment in 2009, 2012, or Grade-3 school test results in 2008-2014. We compared children exposed to general anesthesia aged <48 months to those without any hospitalization. Children with only 1 hospitalization with general anesthesia and no other hospitalization were assessed separately. Outcomes included being classified developmentally high risk at school entry and scoring below national minimum standard in school numeracy and reading tests.

Results: Of 211 978 children included, 82 156 had developmental assessment and 153 025 had school test results, with 12 848 (15.7%) and 25 032 (16.4%) exposed to general anesthesia, respectively. Children exposed to general anesthesia had 17%, 34%, and 23% increased odds of being developmentally high risk (adjusted odds ratio [aOR]: 1.17; 95% CI: 1.07-1.29); or scoring below the national minimum standard in numeracy (aOR: 1.34; 95% CI: 1.21-1.48) and reading (aOR: 1.23; 95% CI: 1.12-1.36), respectively. Although the risk for being developmentally high risk and poor reading attenuated for children with only 1 hospitalization and exposure to general anesthesia, the association with poor numeracy results remained.

Conclusion: Children exposed to general anesthesia before 4 years have poorer development at school entry and school performance. While the association among children with 1 hospitalization with 1 general anesthesia and no other hospitalization was attenuated, poor numeracy outcome remained. Further investigation of the specific effects of general anesthesia and the impact of the underlying health conditions that prompt the need for surgery or diagnostic procedures is required, particularly among children exposed to long duration of general anesthesia or with repeated hospitalizations.

KEYWORDS
children, cognitive outcomes, hospitalization, neurodevelopment, operative procedures, pediatric anesthetics

1 | INTRODUCTION

In recent times, advances in anesthesia medication and delivery systems, surgical techniques, and diagnostic and medical procedures have increased both the number of children exposed to general anesthesia and the frequency of exposure.[1] Despite the fact that general anesthesia for surgery or diagnostic investigation may be life-saving or unavoidable, there has been mounting concern regarding potential neurotoxicity from exposure to general anesthesia in early childhood. This is especially relevant following the December 2016 release of the United States Food and Drug Administration warning about the potential negative consequences of long and repeated general anesthesia exposure.[2] Information about the outcomes of general anesthesia exposure in early life remains important to determine the direction of future preclinical research and identify the subgroups where potentially less toxic agents could be trialed.

Evidence from animal studies has demonstrated that exposure to general anesthesia during infancy can modulate brain development with permanent consequences[3,4]; although human studies have been less conclusive. Three recent population-based cohort studies have reported a small association between any general anesthesia exposure and reduced school readiness measures and poorer school grades.[5-7] However, these population cohort studies included only children undergoing surgery with a general anesthesia and it is unclear whether children having simple invasive or diagnostic procedures with a general anesthesia were excluded, or included in the unexposed comparison group. Furthermore, findings may have been influenced by confounding by indication with the inclusion of children with unidentified conditions or brain injuries that may affect neurocognitive function.[6,7] It is important to differentiate outcomes of children with underlying delay because they may have different vulnerability for neurotoxicity or may be more likely to need surgery compared to otherwise unaffected children.[8-10]

In contrast, the United States multicenter Paediatric Anaesthesia Neuro Development Assessment (PANDA) study of single exposure to general anesthesia during inguinal hernia surgery compared to sibling controls found no difference in a range of neuropsychologic scores.[11] Likewise, interim results from the first randomized trial examining the impact of general anesthesia on early childhood outcomes at 2 years of age (General Anaesthesia compared to Spinal anaesthesia [GAS] trial) revealed evidence for no difference in neurodevelopment between children undergoing general anesthesia for hernia repair compared with awake-regional anesthesia.[12] However, both the PANDA and GAS studies were specific to a single indication and type of surgery and single exposure of a relatively short duration of general anesthesia; all of which limit their generalizability. The primary aim of our study was to evaluate the developmental and school performance outcomes of children undergoing 1 or more procedures requiring general anesthesia in early childhood in a population-based study, excluding potential neurocognitive confounding. Secondary aims were to further elucidate how different types of surgery or procedures, number, and age at exposure of general anesthesia influence the association.

What is already known

- There is concern about the potential neurotoxicity of early childhood exposure to general anesthesia.
- Recent population-based studies have been limited by confounding by indication by including children with underlying morbidity or neurodevelopmental disorder.

What this article adds

- Exposure to general anesthesia is associated with poorer development at school entry and school test results.
- While there was no association between exposure to general anesthesia and developmental or reading outcomes among children with only 1 hospitalization requiring general anesthesia and no other hospitalization they did have poorer numeracy scores.

2 | MATERIALS AND METHODS

We conducted a population-based record-linkage cohort study including all children born in New South Wales (NSW), Australia, of 37+ weeks gestation with either a developmental assessment at school entry in 2009 or 2012, or Grade 3 school test result between 2008 and 2014. Information on births was ascertained from the Perinatal Data Collection, a state-wide surveillance database of all births in NSW. Data on procedures with a general anesthesia were obtained from the NSW Admitted Patient Data Collection, a census of all inpatient hospital admissions from NSW public and private hospitals that includes diagnosis and procedures coded according to the 10th revision of the International Classification of Diseases, Australian Modification and the Australian Classification of Health Interventions, respectively. Individual birth and hospital admission records for each child were probabilistically linked to their corresponding developmental assessment or school test results by the NSW Centre for Health Record Linkage. The validity of record linkage across datasets was high with <1% of records having an incorrect match.[13]

2.1 | Outcomes

Information on early child development was obtained from the Australian version of the Early Development Instrument (AvEDI), a nationwide triennial assessment of child development conducted in 2009 and 2012.[14] The AvEDI is an adaptation of the Canadian Early Development Index[8] and includes child demographic information and results from teachers' assessment of five developmental domains; physical health and well-being, emotional maturity, communication skills and general knowledge, language, and cognitive skills (numeracy and literacy); and social competence. Based on national percentiles, children with domain scores in the bottom 10% are classified as developmentally vulnerable in that domain. Children who are vulnerable in 2 or more domains are classified as developmentally high risk.[14] The AvEDI also identifies children with special needs, who require assistance due to chronic medical, physical, or intellectually disabling conditions.[14]

Children's Grade 3 school performance was ascertained from the NSW Department of Education National Assessment Program-Literacy and Numeracy (NAPLAN) conducted in public schools in 2009-2014.[9] NAPLAN tests cover 5 domains: reading, writing, spelling, grammar and punctuation, and numeracy. Only numeracy and reading were evaluated as these represent the domains with the most stable results over time.[10] Individual scores from 0 to 1000 for each domain are equated across calendar years and categorized into 1 of 6 skill bands for each school grade. These bands are curriculum-based and benchmarked to defined national minimum standards for each domain and school grade. NAPLAN data also include demographic information for the child and their parents. Children recorded as exempt from NAPLAN test represent those with intellectual disability or significant co-existing conditions.

The study outcomes were defined as children classified as developmentally high risk in the developmental assessment and children with scores below the national minimum standard in numeracy and reading in Grade 3. To reduce potential neurocognitive confounding, we excluded children with special needs and those exempt from school tests; and from hospital data, children diagnosed with major congenital anomalies,[15] neurodevelopmental disorder (eg, autism, mental retardation, cerebral palsy), and those undergoing major neurological, cardiovascular, endocrine, eye, or plastic surgery.

2.2 | Exposure variable and potential confounders

We compared outcomes of children undergoing procedures with general anesthesia before 4 years of age (48 months) to those without any hospitalization until developmental or school test assessment. Exposed children were defined as having any general anesthesia and then categorized by different types of surgical procedures (urogenital, circumcision, abdominal, inguinal hernia, myringotomy, adenotonsillectomy, other nose and throat, dental, skin, respiratory, and musculoskeletal surgery), simple invasive procedures (biopsies, endoscopy with excision of tissue, drainage of abscess, skin tag excisions, simple incisions, closed reduction of fractures, laser therapy, and excision or debridement of soft tissue), and non-surgical procedures (computed tomography scans, endoscopy, angiography, magnetic resonance imaging, ultrasound, and bone or renal studies). As children undergoing brain magnetic resonance imaging or computed tomography scans may have underlying pathology and increased risk of poor neurocognitive outcomes, these children were grouped separately. The age at first general anesthesia exposure (<12, 12 to <24, 24 to <36, and 36+ months) and the number of general anesthesia exposures (1, 2, and 3+) were also assessed. Children who had only 1 hospitalization and undergoing a procedure requiring general anesthesia and no re-presentation or any other hospitalization up to outcome assessment, were also differentiated. Potential confounders were identified from the literature and are detailed in Table 1. Missing values were uncommon for all variables (0%-0.2%) and excluded from analyses.

2.3 | Statistical analysis

Characteristics of exposed and unexposed children for each study outcome cohort (AvEDI and NAPLAN cohorts) were compared using contingency tables. We assessed the association between any general anesthesia exposure and subcategories (type of procedure, number of and age at first general anesthesia exposure) with study outcomes using multivariable binary generalized estimating equations with a logit link and exchangeable correlation, adjusting for all available confounders and clustering effect of individual schools. We also repeated analyses restricting to children with only 1 hospitalization involving a procedure with general anesthesia and no other hospitalization. To overcome any effect of multiple testing, we calculated 95% confidence intervals using corrected *P*-values with a sequential adjustment for multiplicity according to the step-down Holm-Bonferroni procedure.[16] This was also applied to the models restricted to children with only a single hospitalization with general anesthesia. All analyses were conducted using SAS, 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

Of the 407 089 children with linked developmental or school test records, 82 156 had a developmental assessment (AvEDI cohort) and 153 025 children school test results (NAPLAN cohort, Figure 1) with general anesthesia exposure in the study period. Children who did not have at least 1 hospitalization requiring a procedure with a general anesthetic were excluded (Figure 1). Table 1 reports child sociodemographic characteristics by exposure to general anesthesia

TABLE 1 Sociodemographic characteristics by exposure to general anesthesia for children with a developmental assessment (AvEDI cohort) or school test result (NAPLAN cohort) in NSW, Australia

	AvEDI cohort		NAPLAN cohort	
	Exposed N = 12 848 n (%)[a]	Unexposed N = 69 308 n (%)[a]	Exposed N = 25 032 n (%)[a]	Unexposed N = 127 993 n (%)[a]
Sex				
Male	7973 (62.1)	31 481 (45.4)	16 027 (64.0)	58 495 (45.7)
Female	4875 (37.9)	37 827 (54.6)	9005 (36.0)	69 498 (54.3)
Small for gestational age (<10th centile)				
Yes	1227 (9.6)	7028 (10.1)	2769 (11.1)	14 093 (11.0)
No	11 607 (90.3)	62 216 (89.8)	22 243 (88.9)	113 826 (88.9)
Apgar score at 5 min				
0-6	127 (1.0)	558 (0.8)	273 (1.1)	1106 (0.9)
7+	12 696 (98.8)	68 586 (99.0)	24 705 (98.7)	126 603 (98.9)
Socioeconomic disadvantage quintile				
1 (Most disadvantaged)	3652 (28.4)	16 604 (24.0)	6471 (25.9)	28 768 (22.5)
2, 3, and 4	7186 (55.9)	40 315 (58.2)	14 171 (56.6)	75 872 (59.3)
5 (Least disadvantaged)	2004 (15.6)	12 326 (17.8)	4376 (17.5)	23 278 (18.2)
Parents education				
Year 12 or equivalent or below	854 (6.6)	4268 (6.2)	5349 (21.4)	26 620 (20.8)
Certificate	1248 (9.7)	5797 (8.4)	7145 (28.5)	35 353 (27.6)
Diploma	554 (4.3)	2910 (4.2)	3535 (14.1)	17 226 (13.5)
Bachelor's degree or above	1141 (8.9)	6462 (9.3)	7021 (28.0)	39 519 (30.9)
Not-stated or missing	9051 (70.4)	49 871 (72.0)	1982 (7.9)	9275 (7.2)
Parents occupation				
Senior management and professionals	879 (6.8)	4498 (6.5)	5388 (21.5)	27 474 (21.5)
Other business managers	886 (6.9)	4577 (6.6)	5302 (21.2)	28 042 (21.9)
Trades people and skilled staff	821 (6.4)	4254 (6.1)	5076 (20.3)	25 503 (19.9)
Machine operators and laborers	565 (4.4)	3074 (4.4)	3349 (13.4)	18 547 (14.5)
Not in paid work in the last 12 mo	357 (2.8)	1696 (2.4)	2085 (8.3)	10 498 (8.2)
Not-stated or missing	9340 (72.7)	51 209 (73.9)	3832 (15.3)	17 929 (14.0)
Language background other than English				
No	11 114 (86.5)	56 078 (80.9)	19 342 (77.3)	90 935 (71.0)
Yes	1734 (13.5)	13 230 (19.1)	5663 (22.6)	36 960 (28.9)
Age at developmental assessment				
<5	867 (6.7)	5687 (8.2)	-	-
5 to <6	10 712 (83.4)	57 720 (83.3)	-	-
6+	1269 (9.9)	5901 (8.5)	-	-
Age at school test				
≤7	-	-	1324 (5.3)	8089 (6.3)
8	-	-	20 321 (81.2)	104 956 (82.0)
9+	-	-	3387 (13.5)	14 948 (11.7)

AvEDI, Australian version of the Early Development Instrument; NAPLAN, National Assessment Program-Literacy and Numeracy.
[a]Percentages may not add to 100 due to missing values.

for both study cohorts. A total of 12 848 (15.7%) and 25 032 (16.4%) children were exposed to general anesthesia in the AvEDI cohort and NAPLAN cohort, respectively. Children exposed to general anesthesia were more likely to be male and from an English-speaking background. The mean age (standard deviation, SD) at developmental assessment was 5.5 (SD: 0.4) years and for Grade 3 school test was 8.1 (SD: 0.4) years. There were 6875 (8.4%) children assessed as developmentally high risk in the AvEDI cohort, while

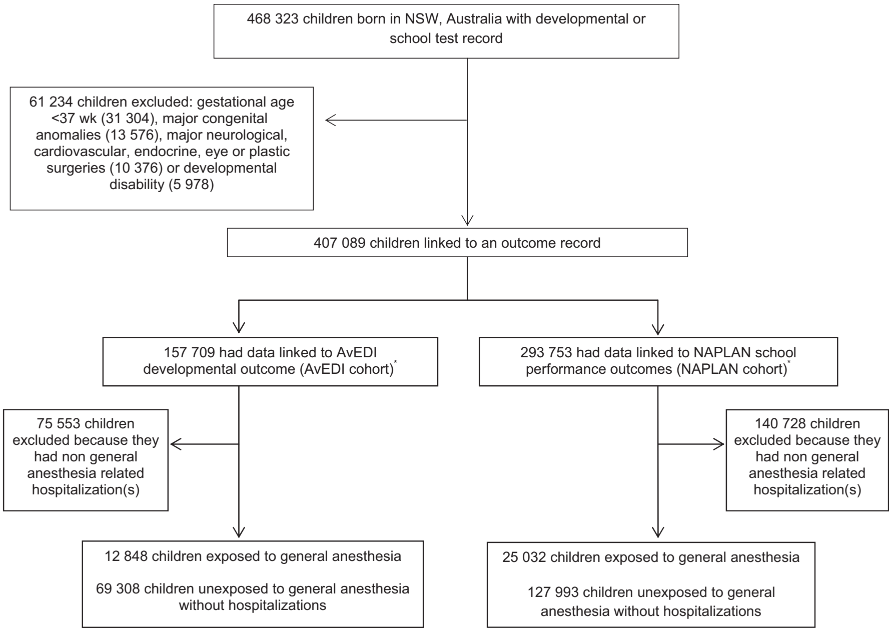

FIGURE 1 Flowchart of study population. AvEDI, Australian version of the Early Development Instrument; NAPLAN, National Assessment Program-Literacy and Numeracy; NSW, New South Wales; *Numbers do not add to 407 089 because there were 44 373 children included in both cohorts

5605 (3.7%) and 5786 (3.8%) in the NAPLAN cohort scored below the national minimum standard in numeracy and reading, respectively. Table 2 presents the characteristics and types of procedures of children exposed to general anesthesia in each cohort. The mean age at first general anesthesia exposure was 27.2 (SD: 13.2) months, and the majority (86%) had 1 exposure, with 14% two or more. Among those exposed to general anesthesia, 1254 (9.8%) and 4287 (17.1%) were identified as having only 1 hospitalization involving a procedure with general anesthesia and no other hospitalization in the AvEDI and NAPLAN cohorts, respectively.

Among the AvEDI cohort, after adjusting for confounders, children exposed to general anesthesia had 17% increased odds of being developmentally high risk (adjusted odds ratio [aOR] 1.17; 95% CI: 1.10-1.25), and particularly for those having dental (aOR: 1.37; 95% CI: 1.13-1.67) or skin surgeries (aOR: 1.53; 95% CI: 1.23-1.89) or simple invasive procedures (aOR: 1.24; 95% CI: 1.09-1.41). Similar results were also observed for each of the 5 developmental domains (data not shown). However, after restricting to children with only 1 hospitalization involving general anesthesia and no other hospitalization, the estimates were attenuated and no longer statistically significant (Figure 2, Table S1).

Among the NAPLAN cohort, exposure to any general anesthesia was associated with a 34% and 24% increased odds of scoring below the national minimum standard in numeracy (aOR: 1.34; 95% CI: 1.25-1.43) and reading (aOR: 1.24; 95% CI: 1.16-1.32), respectively, including higher odds following certain procedures (Figure 2, Table S1). After restricting to children with only 1 hospitalization involving general anesthesia and no other hospitalization, the odds of scoring below the national minimum standard in numeracy remained significant for any exposure to general anesthesia and children undergoing specific procedures. There was no association, however, for children having poor reading outcome (Figure 2, Table S1).

There was an association between the number of exposures to general anesthesia and children classified as developmentally high risk or scoring below the national minimum standard in numeracy and reading at school, regardless of the number of exposures (Figure 3, Table S2). Results were imprecise for 3 or more exposures, due to small numbers. Age at first general anesthesia exposure had mixed results, with an increased odds ranging between 1.14 and 1.42. The odds were increased and highest in children exposed to general anesthesia after 36 months. After restricting to children with only 1 hospitalization involving general anesthesia and no other hospitalization, the association persisted for children scoring below the national minimum standard in numeracy (aOR: 1.40; 95% CI: 1.18-1.66) and reading (aOR: 1.24; 95% CI: 1.05-1.48; Figure 3, Table S2).

4 | DISCUSSION

In this population-based study, we found that among children without known, preexisting neurodevelopmental disorders, those exposed to general anesthesia before 4 years of age had an increased risk of poor development at school entry and reduced scores in reading and numeracy in Grade 3. However, after restricting to children with only 1 hospitalization involving general anesthesia and no other hospitalization, exposure to general anesthesia remained associated only with poorer numeracy outcome.

To date, the only interventional study, the GAS trial reported no difference in neurodevelopment at 2 years of age (N = 363) using the Bailey Scales of Infant and Toddler Development III with the main outcome of the trial,[16] intelligence quotient (IQ) scores at 5 years of age, yet to be published. In the PANDA study (N = 105 pairs), the authors reported no difference in IQ scores, verbal fluency, and behavior at 10 years of age between exposed and unexposed siblings.[11] This study included a potentially biased sample

TABLE 2 Characteristics and type of procedures for children exposed to general anesthesia and with developmental assessment (AvEDI cohort) or school test results (NAPLAN cohort) in NSW, Australia

	AvEDI cohort N = 12 848 n (%)	NAPLAN cohort N = 25 032 n (%)
Number of general anesthesia		
1	11 006 (85.7)	21 562 (86.1)
2	1515 (11.8)	2865 (11.4)
3+	327 (2.5)	605 (2.4)
Age at first general anesthesia		
<12 mo	1904 (14.8)	3840 (15.3)
12-24 mo	3361 (26.2)	6610 (26.4)
24-36 mo	3333 (25.9)	6518 (26.0)
36+ mo	4250 (33.1)	8064 (32.2)
Type of procedure[a]		
Surgical		
Uro Genital	286 (2.2)	552 (2.2)
Circumcision	1130 (8.8)	3250 (13.0)
Digestive system	591 (4.6)	1167 (4.7)
Inguinal hernia	842 (6.6)	1760 (7.0)
Nose and throat	198 (1.5)	284 (1.1)
Myringotomy	3253 (25.3)	5587 (22.3)
Adenotonsillectomy	3687 (28.7)	5769 (23.0)
Dental	1139 (8.9)	2505 (10.0)
Skin	645 (5.0)	1187 (4.7)
Musculoskeletal	633 (4.9)	1161 (4.6)
Other surgeries	82 (0.6)	150 (0.6)
Simple invasive procedures[b]	2853 (22.2)	5769 (23.0)
Diagnostic procedures[c]	1149 (8.9)	2312 (9.2)
Brain magnetic resonance imaging	264 (2.1)	583 (2.3)

AvEDI, Australian version of the Early Development Instrument; NAPLAN, National Assessment Program-Literacy and Numeracy.
[a]Percentages do not add to 100 due to children having more than 1 type.
[b]Biopsies, endoscopy with excision of tissue, drainage of abscess, skin tag excisions, simple incisions, closed reduction of fractures, laser therapy, and excision or debridement of soft tissue.
[c]Computed tomography scans, endoscopy, angiography, nonbrain magnetic resonance imaging, ultrasound, and bone or renal studies.

with sibling-matched, exposed children mostly white males (90%), with highly educated parents and from higher socioeconomic backgrounds. Not surprisingly, the study population had higher total IQ compared to the total population and results may not be generalizable to more vulnerable populations. Furthermore, the latter 2 studies only included a single indication with a relatively short duration of general anesthesia.

In the present study, we found a 17% increased risk of being developmentally high risk in exposed children, which is consistent with 2 previous Canadian population-based studies reporting developmental outcomes of children using the analogous Canadian Early Development Index. While O'Leary et al[7] (N = 84 276) reported a 5% increased odds of developmental vulnerability (1 or more developmental domain below the 10th centile) in children exposed to general anesthesia, Graham et al[6] (N = 18 056) found a significant 0.9-1.2 point decrease in the Canadian Early Development Index scores in children exposed to 1 or more episodes of general anesthesia. However, these studies did not assess the type of procedure requiring general anesthesia, nor was it clear whether children with major congenital anomalies or those undergoing general anesthesia for nonsurgical purposes were included or not. We found children exposed to general anesthesia during specific procedures, including myringotomy, dental and skin surgeries, simple invasive procedures, and brain magnetic resonance imaging, were more likely to have poor outcomes which may be attributable to their underlying conditions such as burns, lumber puncture, hearing loss and head injuries, requiring the procedure and more intensive health care.

Interestingly, when we restricted the analyses to children who had only 1 hospitalization involving a procedure requiring general anesthesia and no other hospitalization, we found that the increased risk of poor developmental outcome and reduced reading scores was attenuated. This effect was also shown in other population-based studies assessing developmental outcomes after restricting to those children with single surgeries[5,7] and cumulative length of hospital stay <2 days.[7] These were also consistent with findings from the GAS trial and PANDA project. These studies did not explore specific cognitive outcomes. Specifically, we found that despite limited exposure to general anesthesia and no other hospitalization in early childhood, the association with poor numeracy scores remained, overall and for a number of different procedures. The consistency in the numeracy results across different procedures may reflect the sensitivity of the numeracy test, or that there may be a deficit in a particular aspect of cognitive processing required for numerical tasks.[17] We found similar results on further analysis, restricting only to children with poor numeracy and no reading deficit. Research has demonstrated that children with math deficits show a different pattern of cognitive deficits than do children with both math and reading deficits.[18] A study by Bull et al[19] found that after controlling for word reading ability, arithmetic ability was best predicted by processing speed, with short-term memory, sequencing ability, and retrieval of information from long-term memory also important. If exposure to general anesthesia affects processing speed, this may play a role in the acquisition and execution of basic numeracy skills and further studies to replicate and elucidate the underlying mechanism are required.

In our assessment of timing and number of general anesthesia exposures, we found weak evidence for increased risk of poor school performance for children exposed to general anesthesia after 36 months and closer to the outcome measure. Others studies have also found that later timing of general anesthesia exposure (>24 months), compared to earlier exposure, negatively impacts developmental[6,7] and cognitive outcomes.[5,11] Although this may

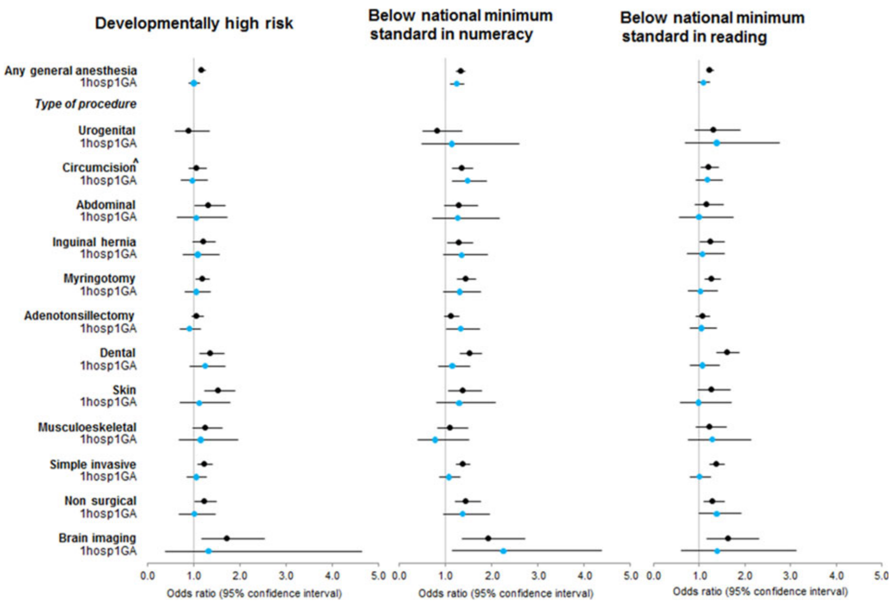

FIGURE 2 Association between general anesthesia exposure and child developmental and school performance outcomes in New South Wales, Australia. 1Hosp1GA: children with only 1 hospitalization with general anesthesia and no other hospitalization; Odds ratio adjusted for maternal age at birth, previous birth (proxy for family size), gestational age, 5-min Apgar score, small for gestational age, sex, language background, socioeconomic disadvantage, parental education and occupation (not for developmentally high-risk outcome), child age at assessment or test, and calendar year of assessment or test. ^models included boys only [Colour figure can be viewed at wileyonlinelibrary.com]

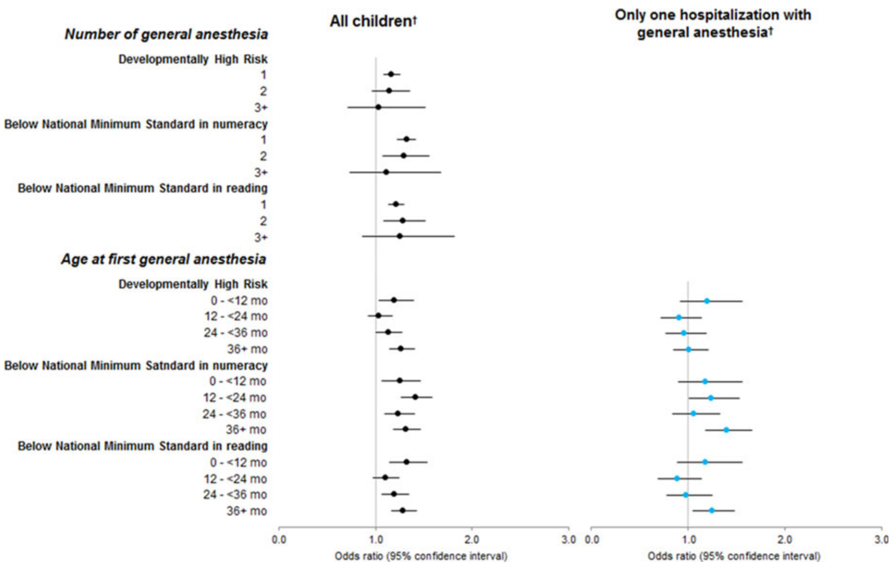

FIGURE 3 Association between number and age at general anesthesia exposure and child development and school performance in New South Wales, Australia. †Excluding children undergoing brain magnetic resonance imaging; Odds ratio estimates adjusted for maternal age at birth, previous birth (proxy for family size), gestational age, 5-min Apgar score, small for gestational age, sex, language background, socioeconomic disadvantage, parental education and occupation (not for developmentally high-risk outcome), child age at assessment or test and calendar year of assessment or test [Colour figure can be viewed at wileyonlinelibrary.com]

reflect a confounding effect, these results do not support the hypothesis that early stages of brain development are more vulnerable to the potential neurotoxicity effects of general anesthesia. The association between the number of general anesthesia exposures and poor developmental outcomes was also increased for 1 or more exposures to general anesthesia. Similar findings of an increased risk were found by a number of studies,[5,20] but not by others.[7] However, they did not exclude children with underlying conditions at risk of learning disability that may also require multiple surgeries, such as congenital heart conditions. These findings need to be explored further and the complex relationship between the underlying condition, procedure, and the potential developmental benefit of treatment needs to be teased out further.

One important factor that we could not assess was the impact of long duration of general anesthesia exposure. Studies in nonhuman primates found that general anesthesia exposure of >5 hours resulted in negative functional and behavioral outcomes.[21,22] Additionally, a recent review reported that more than 80% of animal studies investigating neurotoxicity of general anesthesia found a negative effect after exposure of 3 hours or longer.[23] However, there remains limited information from human studies on the effect of long general anesthesia duration and results have been inconsistent. One study found a 56% increased odds of disability for children exposed longer than 120 minutes compared to unexposed,[20] whereas the PANDA project found no difference in IQ scores in children exposed for more than 120 minutes.[11] It should be noted that the average exposure in the PANDA project and GAS trial was <2 hours and large population-based studies using administrative data, often lack such detailed information. Overall, evidence from human studies regarding the neurocognitive effect in children following long general anesthesia exposure (>3 hours) remains unknown and future studies are required.

A major strength of our study was the use of large population-based administrative data ensuring the power, coverage, and generalizability of findings. We also used information on developmental and educational outcomes that have been validated internationally (AvEDI)[24] and locally by the Australian Curriculum, Assessment and Reporting Authority (NAPLAN).[9] Although some effects may have been masked by these global assessments, it is unlikely given the consistent results across 2 different age points and across individual developmental domains and cognitive outcomes, which ensures the robustness and reliability of findings. However, our study also had some limitations. Firstly, we lacked information on conditions diagnosed outside the hospital setting that may affect the child's neurocognitive development. Although we attempted to minimize this by excluding children with disability and major congenital conditions and by assessing a group of children who had only 1 hospitalization involving a procedure with general anesthesia and no other hospitalization, some unmeasured confounding may still exist. On the other hand, by excluding vulnerable children we cannot elucidate whether in these children, anesthesia toxicity could plausibly have an impact. Secondly, although we conducted analyses by type of procedure, the majority involved only short-duration general anesthesia and we cannot conclude that those children exposed to longer duration have the same outcome.

In conclusion, our study reveals that children exposed to general anesthesia before 4 years of age have poorer development at school entry and school test performance in Grade 3. Although the associations for poor developmental outcome and reading scores were attenuated in children who had only 1 hospitalization with general anesthesia and no other hospitalization, the increased risk of poor numeracy skills remained for these children. Further studies should explore specific effects of general anesthesia on numeracy skills, the role of underlying health conditions that prompt the need for surgery or diagnostic procedures, and outcomes following varying duration of exposure to general anesthesia.

ETHICAL APPROVAL

Ethics approval for access and release of data and conduct of the study was obtained from the NSW Population and Health Services Research Ethics Committee.

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CONFLICT OF INTEREST

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

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information section at the end of the article.

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