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Association between exposure of young children to procedures requiring general anesthesia and learning and behavioral outcomes in a population-based birth cohort

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Abstract

Background—Exposure of young animals to general anesthesia (GA) causes neurodegeneration and lasting behavioral abnormalities; whether these findings translate to children remains unclear. This study used a population-based birth cohort to test the hypothesis that multiple, but not single, exposures to procedures requiring GA prior to age 3 years are associated with adverse neurodevelopmental outcomes.

Methods—A retrospective study cohort was assembled from children born in Olmsted County, MN from 1996 to 2000 (inclusive). Propensity matching selected children exposed and not exposed to GA prior to age 3. Outcomes ascertained via medical and school records included learning disabilities (LD), attention deficit hyperactivity disorder (ADHD), and group-administered ability and achievement tests. Analysis methods included proportional hazard regression models and mixed linear models.

Results—For the 116 multiply exposed, 457 singly exposed, and 463 unexposed children analyzed, multiple, but not single, exposures were associated with an increased frequency of both LD and ADHD (hazard ratio for LD of 2.17 [95% CI 1.32 to 3.59], unexposed as reference). Multiple exposures were associated with decreases in both cognitive ability and academic achievement. Single exposures were associated with modest decreases in reading and language achievement but not cognitive ability.

Conclusion—These findings in children anesthetized with modern techniques largely confirm those found in an older birth cohort, and provide further evidence that children with multiple exposures are more likely to develop adverse outcomes related to learning and attention. Although a robust association was observed, these data do not determine whether anesthesia *per se* is causal.

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INTRODUCTION

Substantial preclinical evidence shows that exposure to anesthetics changes the developing brain.[1–4] These changes are linked to long-term learning and behavioral deficits in various animal models including non-human primates.[1,5–7] To explore whether these findings translate to humans, several studies have investigated the association of receiving procedures requiring general anesthesia with long-term neurodevelopmental outcomes in children. Multiple exposures to procedures requiring general anesthesia affect learning and behavior in most retrospective studies.[8–14] Some, but not all, human studies also find an association between single exposures and a variety of outcomes related to learning and behavior.[8,12,13,15–24] This heterogeneity of results is perhaps not surprising given the wide range of study designs and outcomes employed among these studies. Indeed, if exposure is associated with changes in specific domains of cognition or behavior, results should depend upon the outcomes examined.[25,26]

A series of prior studies based on a birth cohort of children born in Olmsted County, MN found an association between multiple, but not single, exposures to procedures requiring general anesthesia prior to ages 2–4 and subsequent learning disabilities (LD) and attention-deficit hyperactivity disorder (ADHD), with multiple exposures associated with approximately a doubling in the incidence of both outcomes.[9–11] Multiple, but not single, exposures also impaired performance on school-administered group tests of cognitive ability and academic performance.[9] The particular impact of multiple exposures is consistent with emerging data from animal studies.[27,28]

Nonetheless, these prior birth cohort studies[9–11] had several limitations as extensively discussed the time of their publication[29] and subsequently. As with many frequently-cited studies of this issue,[18,21,22,30] children in the prior cohort (born 1976–1982) were anesthetized before the transition from halothane to sevoflurane and the routine adoption of pulse oximetry and capnography, which does not reflect contemporary anesthesia practice. In addition, the number of exposed children was relatively modest in the original studies, making it difficult to determine if exposure is associated with a particular pattern of learning disabilities, or whether even single exposures may affect some domains of cognitive function. Finally, given the considerable potential limitations of observational studies and the relatively small number of children with the outcomes of interest in the prior studies it is critically important to confirm or refute the fundamental observations of this first series of studies, which have proved to be one of the drivers of research in this field.

The aim of this study was to test the hypothesis that multiple, but not single, exposures to procedures requiring general anesthesia prior to age 3 years (i.e., prior to the child's third birthday) are associated with adverse neurodevelopmental outcomes, including LD, ADHD, need for Individualized Education Programs (IEPs) for emotional/behavioral and speech/language disorders, and impaired performance in group-administered ability and achievement tests. This hypothesis was evaluated using a new population-based birth cohort (born from 1996–2000) in which children were anesthetized with largely contemporary anesthetic techniques.

METHODS

This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. The parents of all children included in this analysis had provided consent for the use of their children's medical records in research.

Study cohort

Prior papers described the methods used to assemble the study cohort of children used for this analysis.[31,32] To summarize, a birth cohort of children born from January 1, 1994 to December 31, 2007 in Olmsted County, MN was identified. To create the study cohort, children in the birth cohort born from January 1, 1996 to December 31, 2000 were first selected. This time range was chosen to allow sufficient duration of follow up to ascertain the outcomes of interest, and to coincide with widespread clinical replacement of the volatile anesthetic halothane with sevoflurane. Next, children 1) who moved from Olmsted County prior to their third birthday, 2) who died prior to their fifth birthday, and; 3) who were not enrolled in the local school district at age 5 were excluded, as relevant outcomes were not available.

A propensity matching strategy was then used to select children who met eligibility criteria for inclusion in the study cohort, utilizing multiple variables to calculate sex-specific propensity scores for receiving single or multiple exposures to general anesthesia (GA) and procedures prior to age 3. This age was chosen as comparable to the prior work of ourselves and others, and to provide a balance between a presumed window of vulnerability and including sufficient numbers of children for statistical analysis. However, it should be acknowledged that evidence to support this particular age a representing a threshold of risk is limited. Based on quintiles of the observed distribution of propensity scores, 50 sex-specific propensity-matched strata were defined and used to select children for study. After propensity matching, the study cohort consisted of 126 children who had two or more exposures, 466 exposed only once, and 465 children unexposed (n=1,057 children). Seventy children exposed to GA were excluded from the study cohort because an appropriate propensity-matched control could not be identified. Analyses for potential biases in study cohort selection revealed; 1) the characteristics of children born during the study period who were and were not enrolled in the school district were similar, 2) characteristics of children in the study cohort were similar across exposure groups, suggesting successful propensity matching, and 3) characteristics of children exposed to procedures requiring anesthesia who were and were not included in the study cohort were similar.[32]

Outcomes

Using medical and school records, four learning/behavioral outcomes were sought: 1) LDs, including three subtypes of LDs: reading, mathematic, and written language; 2) ADHD; 3) receipt of an IEP for speech/language or emotional/behavioral disorders; and 4) performance in the group-administered tests of ability and achievement. Using record-linkage services from the Rochester Epidemiology Project,[33] we performed a manual review of medical records for each of the 1,057 children from two major medical facilities in Olmsted County, Mayo Clinic and Olmsted Medical Center. Through a contractual agreement with

Independent School District (ISD) 535 which serves Rochester, MN, the enrollment status and cumulative school records were also available for review for all children. Two of the four outcomes, receipt of an IEP and group-administered ability and achievement test scores, are indexed in school record systems for automated retrieval. LD and ADHD were ascertained through manual review of the school and medical records.

Learning disabilities (LD; reading, math, and written)—LD cases were ascertained according to previously-described research criteria[10,34,35] based on one of two formulas: an intelligence quotient (IQ)-achievement discrepancy formula and a low achievement formula. Children were considered to have LD if they met research criteria for at least one of the three LD subtypes (reading, written language, and mathematics disabilities) determined by either of the formulas using contemporaneous IQ and achievement scores.

Attention-deficit hyperactivity disorder (ADHD)—ADHD cases were ascertained based on criteria previously described and validated.[11,36] The criteria rely on documentation within medical and school records of ADHD diagnoses and questionnaires. Children were identified as ADHD cases if their records included either a clinical diagnosis or positive ADHD questionnaire. ADHD questionnaire results were considered positive only when both parent and teacher questionnaires were positive. The exclusion criteria specified in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) were followed (i.e., ADHD was not present if children had a diagnosis of a psychotic disorder, schizophrenia, severe intellectual disability, or pervasive developmental disorder). DSM-IV criteria for ADHD (with 6 or more separate entries in the medical or school records that were consistent with DSM-IV criteria) were not used, as prior work in the Olmsted County population indicated that use of these criteria did not alter case ascertainment.[11,36]

Individualized Education Programs for Speech/Language (IEP-SL) and Emotional/Behavioral Disorder (IEP-EBD)—As in our prior analysis, receipt of these two types of IEPs were investigated as potentially indicating concerns for language abilities and behavior.[9,11] A different IEP for LD is available but was not analyzed as LD was separately ascertained.

Group-administered ability and achievement tests—Since 2001, when the oldest members of the study cohort enrolled in ISD 535, several group-administered tests have been implemented. Of these, the Stanford/Otis-Lennon School Ability Test (OLSAT) was administered every 2–3 years for the longest period of time (from 2003 to 2013). The Stanford measures academic performance in several domains, whereas the OLSAT measures cognitive abilities. Test results were not available for children attending private schools or were home schooled, such that 79% of study cohort members had at least one Stanford/OLSAT while enrolled in ISD 535. The last available Stanford/OLSAT scores were abstracted as a measure of academic performance and cognitive ability. Achievement scores in the subdomains of reading, mathematics, language, and spelling were analyzed and expressed as age-related national percentile ranks using z scores transformed from these ranks

Statistical analysis

Children with severe intellectual disability are not at risk for the four learning/behavioral outcomes and were not considered for further analysis. Identification of these children was based on research criteria,[37] defined as meeting at least one of the following criteria: 1) at least one full-scale IQ score of ≤50 at or before 8 years of age; 2) a diagnosis of severe intellectual disability or similar diagnoses documented in the medical or school records, or; 3) documentation in the medical or school records indicating ineligibility of a child for neurodevelopmental tests due to severe cognitive disabilities.

In this propensity-matched study cohort, children exposed to procedures requiring anesthesia were matched with unexposed children based on their propensity for receiving general anesthesia as previously described.[32] Each child was at risk from birth until they met criteria for LD (including three subtypes of LD), ADHD, or IEPs. For these three outcomes, cumulative frequencies were calculated according to the method of Kaplan and Meier with censoring at the date of emigration, death, last follow-up, or the end of the study on December 31, 2014. Although the original intent was to include an equal number of exposed and unexposed individuals within each propensity matched strata, this was not achieved for all strata. For the calculation of the Kaplan-Meier estimates, strata specific weights were used to so that the resulting estimates would be reflective of a 1:1 matching of exposed and unexposed individuals. For the pre-specified primary analyses, separate stratified proportional hazards regression analyses were performed to assess the association of the number of anesthesia exposures (none, single, multiple) with LDs, ADHD, or IEPs. In pre-specified secondary analyses, stratified proportional hazards regression analyses were performed to assess whether the total duration of anesthesia exposures before age 3 (rather than number of exposures) is a risk factor for the aforementioned neurodevelopmental outcomes. For these analyses, separate models were used to with cumulative duration of general anesthesia quantified as a continuous variable and as a categorical variable using 30-minute intervals.

Two *post hoc* exploratory analyses were also performed with LD and ADHD as outcomes. The first explored whether the total duration or the total number of exposures (or both) was associated with the outcome by including both cumulative duration of GA and the number of exposures in the model. The second examined the same question by restricting analysis to only those children who had similar moderate total durations of exposure to GA (between 61 and 120 minutes).

National percentile ranking scores in the group-administered achievement tests were transformed to z scores using a probit transformation. The resulting z scores were compared across the three exposure groups (none, single, multiple) using Generalized Estimating Equations with robust standard error estimates.

The propensity matching strategy was designed to account for factors such as possible differences in health status between the multiply-, singly-, and un-exposed children. Since all individuals within a given propensity strata were not matched exactly on all covariates, two adjusted analyses were performed. One included 4 covariates that are known to influence the incidence of LD or ADHD: sex, birth weight, gestational age, and mother’s education. These analyses were also intended to facilitate comparisons with our prior work as these 4 factors were also used in our previous analyses.[9–11] The other adjusted analysis also included socioeconomic status as a fifth covariate,[32,38] as socioeconomic status has also been reported as a risk factor for LD or ADHD. In addition, in analyses seeking potential factors moderating the effects of exposure, 4 multivariate logistic regression models were created for each outcome that included all significant variables from univariate analyses and the interaction terms between exposure (multiple, single, none) and sex, gestational age, birth weight, and socioeconomic status, respectively, allowing for assessment of the significance of the interaction terms after adjustment for potential confounders.

Statistical power for the primary analyses assessing differences in the incidence of LD and ADHD across exposure groups was determined based on the number of events observed for each of these outcomes. Based on the observed number of events for LD, the smallest hazard ratio that can be detected with statistical power (two-tailed, alpha=0.05) of 80% is 1.7 for the comparison of a single exposure versus no exposure, and 2.1 for the comparison of multiple exposures versus no exposure. For ADHD, the minimum detectable hazard ratio is 1.6 for the comparison of a single exposure versus no exposure and 2.1 for the comparison of multiple exposures vs no exposure.

The effect estimates and 95% confidence intervals (CIs) are presented for comparisons between multiply- and singly- exposed children groups and the unexposed children. In all cases, two-tailed p-values are reported with no adjustment for multiple comparisons. P values of <0.05 were considered significant. All data were analyzed using SAS 9.3 (SAS institute, INC, Cary, NC).

RESULTS

The propensity-matched study cohort consisted of 1,057 children, of which 21 (2%) were excluded from further analysis because of severe intellectual disability. These included 10 multiply exposed children, 9 singly exposed children, and 2 unexposed children. Therefore 1,036 children were analyzed, including 116 multiply exposed, 457 singly exposed, and 463 unexposed.

Anesthesia and surgery characteristics

The 573 children exposed to GA underwent 760 procedures prior to their third birthday (Table 1). The American Society of Anesthesiologists physical status was significantly higher among multiply-exposed children compared with singly-exposed children (p<0.001), although most (86%) children with multiple exposures were physical status 1–2. The age at first exposure was significantly higher in those children with single exposures (p<0.001), with 68% occurring after 1 year of age. The mean total duration of anesthetic exposure was approximately 3-fold higher in multiply-exposed children, with 52% of multiply-exposed children exposed to greater than 2 hours of anesthesia, compared with 12% of singly-exposed children.

Otorhinolaryngological procedures accounted for the greatest number of procedures, including the majority of those performed in children greater than one year of age (Table 2), with cardiovascular and neurologic procedures accounting for 3%. Most children received sevoflurane and nitrous oxide, with a small minority receiving midazolam premedication or intravenous hypnotics (Table 3). During this transitional time in practice, ~1 in 6 children received a halothane induction, with most of these then receiving isoflurane after induction.

Outcomes

Learning disabilities (LD)—A total of 142 children (13.7%) developed any LD, including 55 (11.9%), 57 (12.5%), and 30 (25.9%) children who were un-, singly-, and multiply-exposed, respectively. The estimated cumulative frequency of any type of LD at 18 years of age by Kaplan-Meier analysis was 14.1% (95% CI: 10.8% – 18.2%) for unexposed children, 13.5% (95% CI: 10.5% – 17.1%) for singly exposed children, and 29.9% (95% CI: 21.6% – 40.5%) for multiply exposed children (Figure 1A). In both adjusted and unadjusted analyses, multiple, but not single, exposures were significantly associated with an increased frequency of LD, including the analysis that adjusted for socioeconomic status (Table 4). In secondary analyses, the frequency of LD was also increased with longer cumulative duration of anesthetic exposures expressed as a continuous variable. When exposure duration was analyzed as a categorical variable, durations of 90–120 min were significantly associated with LD in fully adjusted analysis (HR=1.82, p=0.039), with a similar magnitude of effect estimated for durations of >121 min HR=1.62, p=0.080). Multiple exposures were also associated with increased frequencies of the each of the three subtypes of LDs (reading, mathematics, and written language) when analyzed separately (Table 5).

In exploratory analyses, when both number and duration of exposures (as a continuous variable) were included in the models, the number of exposures was still a significant factor, but not duration (Table 4). When analysis was restricted to children with a similar moderate total duration of exposure and controls (61–120 min), multiply-exposed children had an increased frequency of LD compared with singly-exposed children (Table 4).

Attention deficit hyperactivity disorder (ADHD)—A total of 165 children (15.9%) developed ADHD, including 54 (11.7%), 75 (16.4%), and 36 (31.0%) children who were un-, singly-, and multiply-exposed, respectively. The estimated cumulative frequency of ADHD at 18 years of age by Kaplan-Meier analysis was 11.7% (95% CI: 9.3% – 14.8%) for unexposed children, 17.7% (95% CI: 14.3% – 21.9%) for singly exposed children, and 33.6% (95% CI: 25.1% – 44.0%) for multiply exposed children (Figure 1B). In both adjusted and unadjusted analyses, multiple, but not single, exposures were significantly associated with an increased frequency of ADHD, including the analysis that adjusted for socioeconomic status (Table 6). The frequency of ADHD was also increased with longer cumulative duration of anesthetic exposures expressed as a continuous variable. When exposure duration was analyzed as a categorical variable, durations of 90–120 min were significantly associated with ADHD in fully adjusted analysis, and durations of >121 min significantly so only in unadjusted analysis.

In exploratory analyses, when both number and duration of exposure were included in the models, the number of exposures was still a significant factor, but not duration (Table 6). When analysis was restricted to children with a similar moderate total duration of exposure

(61–120 min), multiply-exposed children had an increased frequency of ADHD compared with singly-exposed children (Table 6).

Consistent with other literature,[39] LD and ADHD frequently co-occurred. Children with both conditions often have more severe symptoms than children with only either condition alone.[40,41] Of the 142 children with LD, 72 (51%) met criteria for both LD and ADHD, while 70 met criteria for LD only. Of the 165 children with ADHD, 72 (44%) met criteria for both LD and ADHD, while 93 met criteria for ADHD only. The co-occurrence of LD and ADHD was more common among those children who were multiply exposed (among children with either LD or ADHD, 57% of multiply-exposed children, 27% of singly-exposed children, and 23% of unexposed children had both, $p<0.001$, chi square). This raises the possibility that LD and ADHD associated with multiple anesthesia exposures may be more severe, or that these children are at particular risk for the combination of ADHD and LD.

Individualized Education Programs for Emotional/Behavioral Disorders (IEP-EBD) and Speech/Language (IEP-SL)—Ninety-three (9%) children had an IEP-SL and 32 (3%) had an IEP-EBD. Exposures were not associated with need for an IEP-SL or IEP-EBD (Table 7) in either unadjusted or adjusted analyses.

Group-administered ability and achievement tests—The median (min, max) age at the time of the last available Stanford/OLSAT test was 14 (7, 15) years and did not differ significantly across exposure groups. The total cognitive ability score (OLSAT) differed according to exposure status (Table 8), with multiple, but not single, exposures associated with a significant decrease (approximately −0.26 SD in the fully-adjusted model). Scores in all subdomains differed significantly according to exposure status (Table 8), with the exception of spelling in the fully-adjusted model ($p=0.087$). The associations with multiple exposures were significant for all subdomains, with effect sizes ranging from −0.23 to −0.36 SD in the fully-adjusted model. Associations with single exposures were significant in the subdomain of reading for all models (approximately −0.17 SD), and for language (approximately −0.15 SD) for all but the fully-adjusted model ($p=0.054$). Single exposures were not significantly associated with the differences in the subdomains of mathematics or spelling.

Moderating factors—Sex, gestational age, birth weight, and socioeconomic status did not moderate the association between exposures and LD or ADHD, as when interaction terms were included in the fully-adjusted model, they were not significant (Table 9). For example, the risk of LD and ADHD associated with exposure did not differ between boys and girls. There were also no significant interaction terms in the analysis of OLSAT scores. For the subdomains of the Stanford Achievement Test, significant interaction terms were obtained for sex and single exposures in mathematics, and for multiple exposures according to gestational age for language. However, given the multiple interaction terms sought across multiple outcomes, the significance of these isolated interaction terms is unclear.

Physical status and indication for procedures—A complete listing of chronic conditions and surgical procedures received by children multiple exposures to anesthesia is provided as Supplemental Digital Content 1. If physical status is used as a crude measure of burden of illness, for children exposed to multiple anesthetics, 66 of the 100 children (66%) classified as physical status 1 or 2 did not develop LD or ADHD, and 8 of the 16 children (50%) classified as physical status 3 or 4 did not develop LD or ADHD (p=0.26, Fisher's exact test; Supplemental Digital Content 2, which is a table listing the maximum ASA physical status among exposed children who had LD and/or ADHD). Of the 42 multiply-exposed children who developed LD or ADHD, 23 (55%) were assessed as healthy (physical status 1), 11 (26%) were classified as physical status 2, and 8 (19%) were classified as physical status 3 or 4, respectively.

At the request of the peer reviewers for this manuscript, additional *post hoc* sensitivity analyses were conducted excluding some children from analysis whose underlying conditions could be associated with specific outcomes. Excluding children who received myringotomies had almost no effect on the relationship between exposure and LD (Supplemental Digital Content 3, which is a table providing the results of this sensitivity analysis). In other models, children receiving neurological or cardiovascular surgery (a total of 16 children) were excluded from the analyses of group-administered ability and achievement tests (Supplemental Digital Content 4, which is a table providing the results of this sensitivity analysis). As a result, the associations between multiple exposures and the OLSAT Total Battery and the spelling subtest of the Stanford now did not reach statistical significance in the fully adjusted analyses, whereas the association between single exposures and the language subtest of the Stanford in the fully adjusted model was now statistically significant. Excluding children receiving neurological or cardiovascular surgery had little effect on the relationship between exposure and LD or ADHD (Supplemental Digital Content 5, which is a table providing the results of this sensitivity analysis).

Outcomes in children who were and were not included in the study cohort

Seventy children who were enrolled in ISD 535 and were exposed to general anesthesia (50 singly exposed and 20 multiply exposed) were not included into the SC after propensity matching due to the lack of representation of all exposure groups in their sex-specific propensity strata, a potential source of bias. After excluding children who developed severe intellectual disability, 67 children were exposed to (GA) but were not selected into the propensity-matched study cohort. Comparing those who were and were not included in the SC, no differences were observed in the frequencies of LD, ADHD, need for an IEP, or scores in the Stanford/OLSAT test (Supplemental Digital Content 6, which is a table showing this comparison).

DISCUSSION

Multiple, but not single, exposures before age 3 are associated with increased frequencies of LD and ADHD. Even single exposures were associated with decrements in other domains, including academic achievement. The results from this study cohort (born 1996–2000) are largely consistent with and extend the main results from a prior cohort (born 1976–82).[9–11]

Comparison with the prior cohort (PC)

Although the designs of the current and prior studies are similar, two major differences are notable. First, the current study utilized a propensity-matched design to select a comparator group of unexposed children. The sampling strata were defined for each sex based on the combination of two propensity scores (single exposure and multiple exposures to anesthesia). In two prior papers,[9,11] a single propensity score was calculated for anesthesia exposure and used as a stratification variable or to generate matched unexposed controls using a somewhat different method.[9] Thus, the characteristics of the unexposed comparator group differ among studies. The second difference relates to advances in anesthesia practice after 1985, including the 1) availability of sevoflurane and isoflurane, which largely replaced halothane, 2) adoption of pulse oximetry and capnography as standard monitors, and; 3) increased use of subspecialty-trained pediatric anesthesiologists at Mayo Clinic.

LD and ADHD—Despite these differences, the hazard ratios of LD/ADHD for single and multiple exposures were similar between the prior and current cohorts[9,11] (Supplemental Digital Content 7, which is a table showing this comparison[9,11]). This finding suggests the robustness of this fundamental observation despite interval changes in anesthetic practice, and is consistent with emerging evidence in animal models that for a given duration of anesthesia, multiple exposures may be associated with greater injury.[27,28] As in the prior cohort, the association between single exposures and ADHD approached but did not reach statistical significance,[11] which may reflect either a true lack of association or insufficient statistical power to detect this effect size.

The overall frequency of LD was decreased and the frequency of ADHD was increased in the study cohort compared to the prior cohort (from 20% to 14% for LD and from 8% to 16% for ADHD).[10,11] Both the absolute frequencies and the trends over time are consistent with national data showing recent declines in LD rates.[42] This may in part reflect a 2004 change in federal law regarding the definition of LD, which represents a potential limitation of using LD as an outcome.[25] However, the definitions of LD used by the state of MN (and in this study) remained generally consistent over the time of both studies. In contrast, the proportion of children diagnosed with ADHD continues to increase in the US.[43] The fact that these trends are reflected in the results of these two cohorts argues for the consistency and validity of LD and ADHD ascertainment.

IEP—Exposure was not associated with the need for either IEP-SL or IEP-EBD, suggesting that the more pronounced deficits necessary to generate IEPs in these areas do not contribute to observed increases in LD or ADHD risk. These findings contrast with those in the prior cohort, which revealed an association of multiple exposures with IEP-SL (but not IEP-EBD).[9] It is possible that the criteria used by the schools to generate IEPs may have changed.

Group-administered tests—The current analysis replicated the prior finding that multiple, but not single, exposures were associated with decreased total cognitive scores (mean decrease of 0.38 SD for the adjusted model in the prior cohort[9]). Regarding achievement tests, multiple exposures were associated with significant decreases in only mathematics scores in the prior cohort, which may reflect a limited number of available scores. Unlike the prior cohort, the current analysis found significant decreases in reading and language subdomains even among singly-exposed children. This may reflect differences in the group-administered tests (measuring similar domains) used in the assessment of the two cohorts (Stanford/OLSAT in the current and California Achievement Test in the prior cohorts), or the greater numbers of available test scores in the current cohort, enhancing power to detect differences. Any potential effects of single exposure on these domains were not sufficient to cause formally-diagnosed LD, perhaps because they are not sufficiently severe to affect the proportion of children falling within the lower tail of the achievement distribution.

Comparison with other studies

Many learning and behavioral outcomes have been utilized in other studies.[25,26] This multiplicity of outcomes, and other differences in experimental design, makes direct comparisons among studies problematic, as the interpretation of studies may depend critically on the particular outcome measure analyzed.[26] Nonetheless, most observational studies that specifically analyze multiple exposures find associations with adverse developmental outcomes,[8–13] although these effects may be modest. In the most recent, two studies from Canada employed the Early Developmental Index (EDI), a questionnaire completed by kindergarten teachers, as the outcome.[12,13] Both found that exposure was associated with a small but significant reduction in EDI scores. When issues of statistical power are taken into account, both also found that the effects of single and multiple exposures were similar. Neither study found evidence of increased risk with exposure at younger ages. Of interest, the predominant EDI domains (broadly divided into categories of general/language/cognitive development and wellbeing/social competence/maturity) affected by exposure differed between the two studies. Although the EDI is correlated with overall academic success in the general population,[44] its potential relationship to the specific outcomes examined in our study is not known, such that it is difficult to directly compare results.

The literature is less consistent regarding associations with single exposures. While some studies found impaired performance in a variety of domains,[12,13,15–20] others do not,[8,21,22] including preliminary results from the only available randomized trial[23] and a sibling-matched study using detailed neuropsychological assessments.[24] This heterogeneity may result in part from the wide variety of outcomes studied. In the current analysis, single exposures were associated with reduced scores in assessments of reading and written language, consistent with prior studies utilizing more sensitive measurements of related domains.[16,18] On the other hand, three studies of Scandinavian populations investigating national group-administered achievement tests (which may not be comparable to the achievement test subdomains reported in the current study) found either no or very small differences in average achievement scores between exposed and unexposed groups.[14,21,22] All found a higher proportion of exposed children who had either failed to attain a test score or performed below a certain percentile of national norms. Because we observed relatively selective impairment of some but not other subdomains, in addition to finding no significant association of single exposures with a measure of ability (the OLSAT), these results may well be consistent, as anesthetic effects on selective subdomains may not be reflected in overall average performance assessed in these other studies.

Limitations

This study has several limitations common to all observational studies in this area.[10,45,46] The most important is that unidentified confounders may affect outcomes. A propensity-matched design was used in an attempt to account for potential confounding resulting from differing health status among children across exposure groups, and children in the three exposure groups were similar in terms of their comorbidity clusters.[32] However, this approach may still fail to fully capture relevant confounders. For example, cardiac and neurological surgery (3% of procedures in this study) can be associated with abnormalities in neurodevelopment.[47,48] Sensitivity analyses eliminating this children affected the statistical significance of some domains of ability and achievement testing (in both directions), so that we still cannot exclude confounding effects on these domains; analyses of LD and ADHD were not affected. Myringotomy was frequent, and it possible that hearing deficits could contribute to LD. However, there is little evidence that conditions such as otitis media are associated with later abnormalities in speech and language,[49] exposure was not associated with speech and language difficulties requiring an IEP, and sensitivity analysis revealed that these children were not responsible for the observed associations. Even for children with some severe chronic diseases, the burden of illness itself may not have a major impact on cognitive development.[50] Other potential limitations include that 1) elements of the surgical experience other than anesthesia exposure, such as the surgical stress response, may be responsible for the associations, 2) although most characteristics of Olmsted County residents are similar to the rest of Minnesota, some differ from the US population as a whole,[33] and 3) lack of group test data in 21% of cohort members.

Conclusions

Multiple, but not single, exposures to procedures requiring general anesthesia prior to the age of 3 are associated with an increased frequency of LD and ADHD, and decreased scores in group-administered tests. Single exposures are associated with impaired performance in some domains measured by the group-administered tests, but not others. There was little evidence that any factors moderated observed associations between anesthetic exposure status and outcomes. These findings in children receiving contemporary anesthesia care confirm and extend prior observations in children anesthetized prior to 1985, and provide further evidence that children receiving multiple exposures are at increased risk for adverse outcomes related to learning and attention. Although there is a robust association, these data do not demonstrate whether anesthesia *per se* is causal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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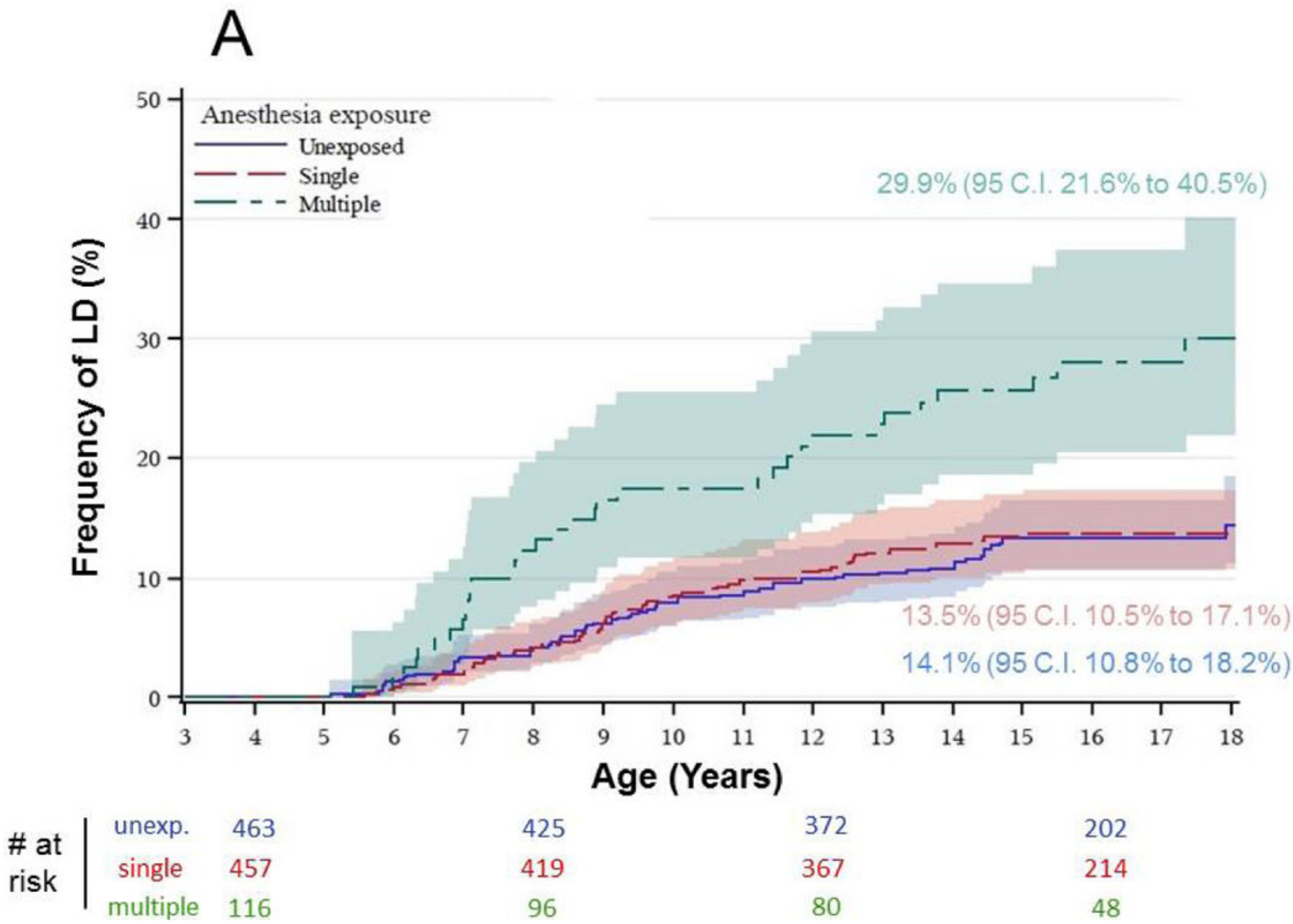
Summary statement

Multiple exposures to procedures requiring general anesthesia prior to age 3 are associated with an increased frequency of learning disabilities and attention deficit hyperactivity disorder, and decreased performance on group-administered ability and achievement tests.


A
Anesthesia exposure
Unexposed
Single
Multiple
29.9% (95 C.I. 21.6% to 40.5%)
13.5% (95 C.I. 10.5% to 17.1%)
14.1% (95 C.I. 10.8% to 18.2%)
Frequency of LD (%)
Age (Years)
0
10
20
30
40
50
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
at risk
unexp. 463 425 372 202
single 457 419 367 214
multiple 116 96 80 48

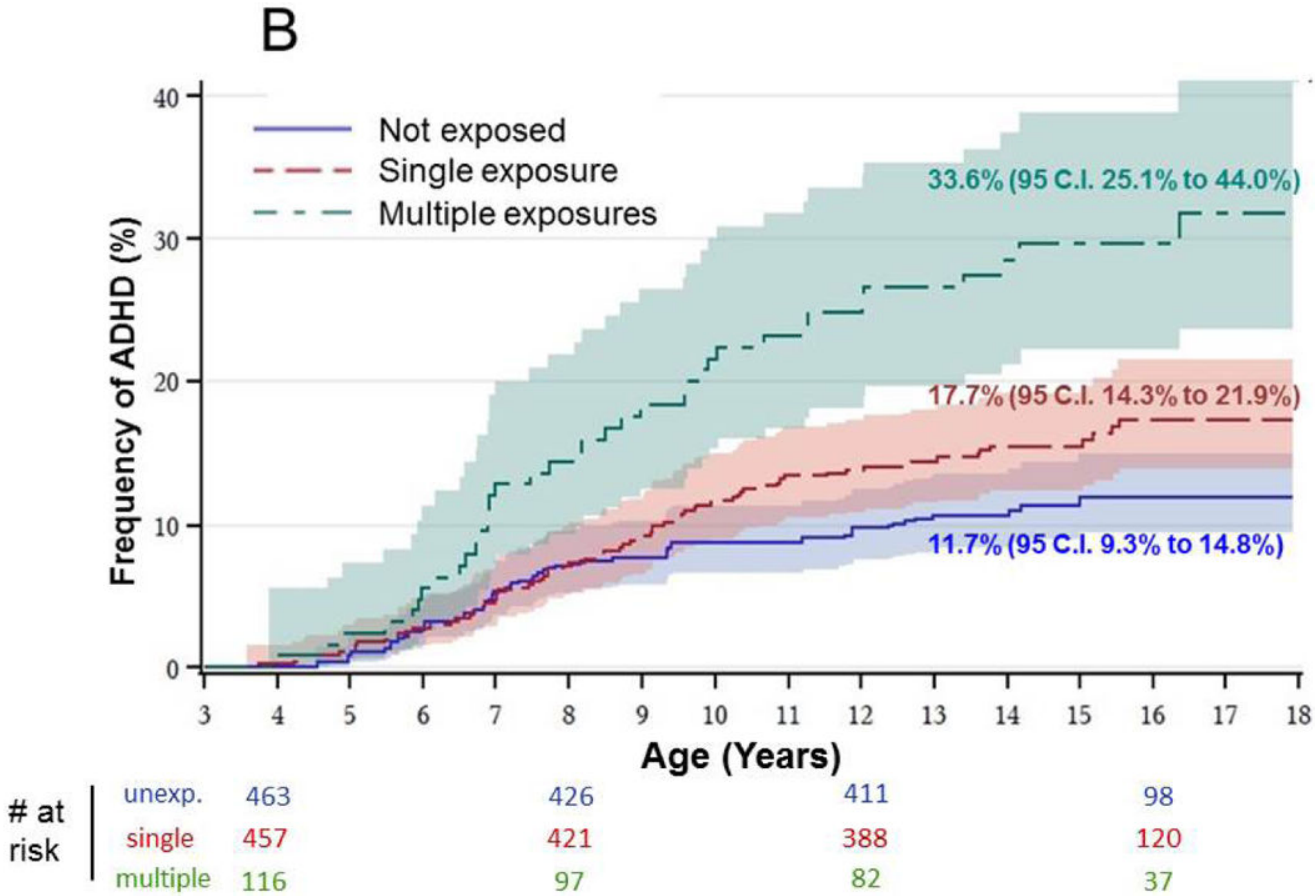


Figure 1.

Age of LD (Panel A) or ADHD (Panel B) diagnosis for children not exposed, singly exposed, or multiply exposed. Bands indicate 95% confidence intervals (CI). Cumulative incidence at age 18 estimated by Kaplan Meier analysis with 95% CI are also indicated for each exposure category. Also shown on the x-axis are the numbers of children at risk (i.e., not censored) at ages 4, 8, 12 and 16 years for each analysis, given emigration, death, last available follow-up in medical and/or school records, and end of study (at which time the youngest children were 14 years of age).

Table 1

Characteristics of patients exposed to anesthesia prior to age 3

	Single exposure (N=457)	Multiple exposures (N=116)
ASA physical status		
1	356 (78%)	67 (58%)
2	90 (20%)	33 (28%)
3	11 (2%)	13 (11%)
4	0 (0%)	3 (3%)
Age at first exposure (years)		
0–0.9	147 (32%)	65 (56%)
1–1.9	184 (40%)	43 (37%)
2–2.9	126 (28%)	8 (7%)
Duration of anesthesia (min)†		
mean (SD)	66.7 (53.7)	209.2 (200.8)
median (Q1, Q3)	52 (26, 90)	125 (87, 234)
1–30	151 (33%)	1 (1%)
31–60	102 (22%)	5 (4%)
61–90	92 (20%)	27 (23%)
91–120	59 (13%)	23 (20%)
121+	53 (12%)	60 (52%)

Q1, first quartile; Q3, third quartile.

573 children underwent 760 anesthetics. For the 116 children who underwent multiple (range, 2–11) anesthetics, the highest ASA physical status and the total cumulative duration of anesthesia are presented. The median (Q1, Q3) duration per anesthetic for all anesthetics was 53 (27, 92) minutes.

Table 2

Categories of surgery

	Overall (N=760)	0–0.9 yrs. (N=264)	1–1.9 yrs. (N=292)	2–2.9 yrs. (N=204)
Procedure type				
General	123 (16%)	76 (29%)	24 (8%)	23 (11%)
Otorhinolaryngogic	335 (44%)	63 (24%)	161 (55%)	111 (54%)
Neurologic	6 (1%)	4 (2%)	0 (0%)	2 (1%)
Urologic	66 (9%)	31 (12%)	24 (8%)	11 (5%)
Orthopedic	36 (5%)	8 (3%)	14 (5%)	14 (7%)
Plastics	21 (3%)	9 (3%)	12 (4%)	0 (0%)
Cardiovascular	17 (2%)	15 (6%)	1 (0%)	1 (0%)
Other *	156 (21%)	58 (22%)	56 (19%)	42 (21%)

* Oral surgeries, ophthalmology surgeries, diagnostic procedures, catheterization, angiography, and examination during anesthesia.

Table 3

Drugs utilized prior to or during anesthesia

	N=758*
Inhalational agents	
Sevoflurane	542 (72%)
Isoflurane	275 (36%)
Desflurane	30 (4%)
Enflurane	1 (0%)
Halothane	118 (16%)
Intravenous agents	
Propofol	27 (4%)
Ketamine	1 (0%)
Thiopental	45 (6%)
Etomidate	0 (0%)
Other	
Nitrous oxide	647 (85%)
Midazolam	62 (8%)
Lorazepam	0 (0%)
Diazepam	0 (0%)
Opioids	331 (44%)

*Data were missing from 2 anesthetics

Table 4

Association of anesthetic exposure before the age of 3 years with any learning disability (LD) (reading, mathematics, or written language)

	Unadjusted		Covariate Adjusted 1*		Covariate Adjusted 2**	
	Hazard Ratio (95% CI)	**p value**	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
***A priori* analyses**						
No. of anesthesia exposures		0.004		0.005		0.006
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	1.03 (0.70 to 1.50)	0.896	1.02 (0.70 to 1.49)	0.913	1.06 (0.72 to 1.57)	0.767
≥2 (n=116)	2.13 (1.32 to 3.43)	0.002	2.10 (1.30 to 3.40)	0.003	2.17 (1.32 to 3.59)	0.002
Total duration of exposure						
Continuous (per 30min)	1.06 (1.02 to 1.10)	0.003	1.05 (1.01 to 1.10)	0.007	1.06 (1.02 to 1.10)	0.005
Categorical (30-min intervals)		0.179		0.325		0.162
0 (n=463)	Reference		Reference		Reference	
1–30 (n=152)	1.04 (0.61 to 1.77)	0.891	1.10 (0.64 to 1.89)	0.726	0.97 (0.55 to 1.73)	0.930
31–60 (n=107)	0.79 (0.41 to 1.52)	0.483	0.81 (0.42 to 1.57)	0.527	0.85 (0.44 to 1.66)	0.631
61–90 (n=119)	1.23 (0.70 to 2.14)	0.470	1.17 (0.67 to 2.06)	0.573	1.31 (0.75 to 2.31)	0.345
91–120 (n=82)	1.77 (1.01 to 3.09)	0.045	1.70 (0.97 to 2.97)	0.063	1.82 (1.03 to 3.21)	0.039
≥121 (n=113)	1.55 (0.93 to 2.59)	0.093	1.45 (0.86 to 2.43)	0.164	1.62 (0.94 to 2.77)	0.080
***Post hoc* exploratory analyses**						
No. of anesthesia exposures* **		.063		.048		.074
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	1.00 (0.66 to 1.50)	0.980	1.01 (0.67 to 1.53)	0.954	1.04 (0.68 to 1.58)	0.864
≥2 (n=116)	1.95 (1.01 to 3.79)	0.048	2.05 (1.05 to 4.00)	0.034	2.04 (1.02 to 4.06)	0.043
No. of anesthesia exposures†						
1 (n=151)			Reference		Reference	
≥2 (n=50)			2.65 (1.32 to 5.34)	0.006	2.78 (1.37 to 5.64)	0.005

*Adjusting for sex, birth weight, gestational age, and mother’s education.

**Adjusting for sex, birth weight, gestational age, mother’s education, and socioeconomic status.

***Adjusting for total duration of anesthesia exposure. In all these models, the duration of exposure was not statistically significant.

†This analysis was limited to the 201patients with total duration of exposure of 61 to 120 minutes. Due to the restricted subset of patients analyzed, models were not stratified and only covariate adjusted models were reported.

Table 5

Association of anesthetic exposure before the age of 3 years with three subtypes of learning disabilities (LD)

	Unadjusted		Covariate Adjusted 1*		Covariate Adjusted 2**	
	Hazard Ratio (95% CI)	**p value**	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
Reading LD		<.001		<.001		0.002
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	0.97 (0.60 to 1.56)	0.894	0.94 (0.58 to 1.52)	0.800	0.95 (0.57 to 1.57)	0.841
≥2 (n=116)	2.78 (1.56 to 4.93)	<.001	2.64 (1.48 to 4.71)	0.001	2.69 (1.46 to 4.95)	0.001
Mathematics LD		0.003		0.004		0.005
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	0.84 (0.53 to 1.33)	0.454	0.84 (0.53 to 1.33)	0.458	0.83 (0.52 to 1.32)	0.426
≥2 (n=116)	2.13 (1.25 to 3.63)	0.005	2.11 (1.23 to 3.61)	0.007	2.13 (1.21 to 3.73)	0.008
Written language LD		0.006		0.008		0.006
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	1.45 (0.89 to 2.37)	0.139	1.41 (0.86 to 2.32)	0.169	1.53 (0.92 to 2.55)	0.104
≥2 (n=116)	2.72 (1.47 to 5.04)	0.001	2.67 (1.43 to 4.98)	0.002	2.85 (1.50 to 5.40)	0.001

*Adjusting for sex, birth weight, gestational age, and mother's education.

**Adjusting for sex, birth weight, gestational age, mother's education, and socioeconomic status.

Table 6

Association of anesthetic exposure before the age of 3 years with ADHD

	Unadjusted		Covariate Adjusted 1*		Covariate Adjusted 2**	
	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value	Hazard Ratio (95% CI)	p value
***A priori* analyses**						
No. of anesthesia exposures		<.001		<.001		<.001
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	1.38 (0.97 to 1.97)	0.075	1.36 (0.95 to 1.95)	0.091	1.33 (0.92 to 1.94)	0.134
≥2 (n=116)	2.69 (1.70 to 4.27)	<.001	2.68 (1.68 to 4.26)	<.001	2.59 (1.59 to 4.21)	<.001
Total duration of anesthesia exposure						
Continuous (per 30min)	1.05 (1.02 to 1.09)	0.004	1.05 (1.01 to 1.09)	0.007	1.05 (1.01 to 1.09)	0.022
Categorical (30-min intervals)		0.023		0.038		0.027
0 (n=463)	Reference		Reference		Reference	
1–30 (n=152)	1.37 (0.84 to 2.24)	0.203	1.43 (0.87 to 2.34)	0.161	1.30 (0.77 to 2.20)	0.325
31–60 (n=107)	1.35 (0.77 to 2.35)	0.295	1.34 (0.76 to 2.36)	0.307	1.34 (0.75 to 2.39)	0.331
61–90 (n=119)	1.47 (0.88 to 2.47)	0.14	1.41 (0.84 to 2.37)	0.196	1.57 (0.93 to 2.65)	0.091
91–120 (n=82)	2.39 (1.44 to 3.98)	<.001	2.33 (1.40 to 3.88)	0.001	2.57 (1.51 to 4.36)	<.001
≥121 (n=113)	1.73 (1.05 to 2.84)	0.031	1.64 (0.99 to 2.71)	0.056	1.41 (0.81 to 2.45)	0.23
***Post hoc* exploratory analyses**						
No. of anesthesia exposures* **		0.003		0.002		0.003
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	1.43 (0.97 to 2.10)	0.070	1.43 (0.97 to 2.12)	0.071	1.42 (0.95 to 2.13)	0.091
≥2 (n=116)	2.98 (1.59 to 5.56)	<0.001	3.09 (1.64 to 5.82)	<0.001	3.11 (1.62 to 5.99)	<0.001
No. of anesthesia exposures†						
1 (n=151)			Reference		Reference	
≥2 (n=50)			3.22 (1.70 to 6.13)	<.001	3.27 (1.70 to 6.30)	<.001

* Adjusting for sex, birth weight, gestational age, and mother's education.

** Adjusting for sex, birth weight, gestational age, mother's education, and socioeconomic status.

*** Adjusting for total duration of anesthesia exposure. In all these models, the duration of exposure was not statistically significant.

[†]This analysis was limited to subjects with total duration of exposure of 61 to 120 minutes. Due to the restricted subset of patients analyzed, models were not stratified and only covariate adjusted models were reported.

Table 7

Association of anesthetic exposure before the age of 3 years with need for an Individual Educational Plan (IEP) for emotional and behavioral disorder (EBD) or speech-language disorder (SL)

	Unadjusted		Covariate Adjusted 1*		Covariate Adjusted 2**	
	Hazard Ratio (95% CI)	**p value**	**Hazard Ratio (95% CI)**	**p value**	**Hazard Ratio (95% CI)**	**p value**
IEP-EBD		0.403		0.448		0.526
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	0.60 (0.28 to 1.30)	0.194	0.60 (0.27 to 1.34)	0.213	0.60 (0.25 to 1.45)	0.258
≥2 (n=116)	0.99 (0.32 to 3.09)	0.991	0.93 (0.29 to 3.01)	0.906	0.83 (0.23 to 3.04)	0.784
IEP-SL		0.194		0.184		0.220
0 (n=463)	Reference		Reference		Reference	
1 (n=457)	0.77 (0.49 to 1.20)	0.250	0.76 (0.49 to 1.18)	0.222	0.81 (0.50 to 1.29)	0.366
≥2 (n=116)	1.40 (0.72 to 2.75)	0.324	1.38 (0.71 to 2.71)	0.342	1.52 (0.75 to 3.10)	0.248

*Adjusting for sex, birth weight, gestational age, and mother's education.

**Adjusting for sex, birth weight, gestational age, mother's education, and socioeconomic status

Table 8

Association of anesthetic exposure before the age of 3 years with group-administered ability (OLSAT) and achievement (Stanford) test scores.

	Unadjusted		Covariate Adjusted 1*		Covariate Adjusted 2**	
	Effect estimate (95% CI)	p value	Effect estimate (95% CI)	p value	Effect estimate (95% CI)	p value
OLSAT Total Battery		0.028		0.049		0.073
0 (n=351)	Reference		Reference		Reference	
1 (n=345)	−0.059 (−0.207 to 0.089)	0.433	−0.046 (−0.183 to 0.090)	0.506	−0.019 (−0.160 to 0.121)	0.786
≥2 (n=92)	**−0.312 (−0.534 to −0.089)**	**0.006**	**−0.264 (−0.470 to −0.058)**	**0.012**	**−0.255 (−0.472 to −0.038)**	**0.021**
Reading		0.003		0.003		0.002
0 (n=370)	Reference		Reference		Reference	
1 (n=358)	**−0.191 (−0.334 to −0.047)**	**0.009**	**−0.170 (−0.298 to −0.042)**	**0.009**	**−0.168 (−0.300 to −0.036)**	**0.012**
≥2 (n=97)	**−0.354 (−0.583 to −0.125)**	**0.002**	**−0.309 (−0.519 to −0.098)**	**0.004**	**−0.363 (−0.584 to −0.141)**	**0.001**
Mathematics		0.021		0.026		0.016
0 (n=370)	Reference		Reference		Reference	
1 (n=358)	−0.080 (−0.218 to 0.059)	0.259	−0.062 (−0.187 to 0.063)	0.328	−0.059 (−0.186 to 0.068)	0.361
≥2 (n=97)	**−0.327 (−0.555 to −0.099)**	**0.005**	**−0.293 (−0.505 to −0.082)**	**0.006**	**−0.318 (−0.532 to −0.104)**	**0.004**
Language		0.008		0.010		0.010
0 (n=370)	Reference		Reference		Reference	
1 (n=358)	**−0.162 (−0.313 to −0.011)**	**0.035**	**−0.147 (−0.283 to −0.011)**	**0.034**	−0.137 (−0.277 to 0.003)	0.054
≥2 (n=97)	**−0.349 (−0.585 to −0.113)**	**0.004**	**−0.304 (−0.521 to −0.087)**	**0.006**	**−0.330 (−0.555 to −0.104)**	**0.004**
Spelling		0.034		0.048		0.087
0 (n=370)	Reference		Reference		Reference	
1 (n=358)	−0.134 (−0.275 to 0.006)	0.061	−0.121 (−0.251 to 0.010)	0.069	−0.098 (−0.232 to 0.036)	0.152
≥2 (n=97)	**−0.269 (−0.494 to −0.043)**	**0.020**	**−0.229 (−0.438 to −0.021)**	**0.031**	**−0.225 (−0.443 to −0.008)**	**0.042**

Statistically significant ($p<0.05$) differences in effect estimates for z scores are indicated in **bold**

*Adjusting for sex, birth weight, gestational age, and mother's education.

**Adjusting for sex, birth weight, gestational age, mother's education, and socioeconomic status.

Table 9

Analysis of variables that potentially moderate association of anesthesia exposures with learning disabilities (LD), attention deficit hyperactivity disorder (ADHD) and Stanford/OLSAT test scores*

	Moderator variable			
	Sex	Gestational Age	Birth Weight	HOUSES index
LD				
1 exposure × moderator	0.818	0.867	0.442	0.658
≥2 exposure × moderator	0.199	0.675	0.513	0.555
ADHD				
1 exposure × moderator	0.066	0.809	0.645	0.653
≥2 exposure × moderator	0.107	0.915	0.986	0.597
OLSAT Total Battery				
1 exposure × moderator	0.123	0.127	0.129	0.290
≥2 exposure × moderator	0.817	0.344	0.080	0.989
Stanford Reading				
1 exposure × moderator	0.091	0.583	0.853	0.446
≥2 exposure × moderator	0.935	0.367	0.145	0.907
Stanford Mathematics				
1 exposure × moderator	**0.013**†	0.639	0.929	0.696
≥2 exposure × moderator	0.554†	0.711	0.232	0.343
Stanford Language				
1 exposure × moderator	0.307	0.397	0.255‡	0.620
≥2 exposure × moderator	0.763	0.075	**0.013**‡	0.654
Stanford Spelling				
1 exposure × moderator	0.381	0.510	0.437	0.499
≥2 exposure × moderator	0.714	0.662	0.413	0.934

The HOUSES index is a measure of socioeconomic status.

*Analyses were performed using stratified proportional hazards regression (LD, ADHD) or GEE (Stanford/OLSAT test scores). Separate analyses were performed for each potential moderator variable. Gestational age, birth weight, and HOUSES were analyzed as continuous variables and sex was analyzed as a categorical variable. The values presented in the table correspond to the p-value for the given moderator-by-anesthesia exposure interaction term.

†From sex-specific subgroup analyses, the effect estimate (95% CI) for those with single and multiple exposures vs no exposure was −0.22 (−0.41, −0.04) and −0.38 (−0.70, −0.07) for males, and +0.12 (−0.08, +0.33) and −0.25 (−0.57, +0.08) for females.

‡From subgroup analyses, the effect estimate (95% CI) for those with single and multiple exposures versus no exposures was −0.29 (−0.61, +0.03) and −0.39 (−0.86, +0.08) for those with BW≤2880 grams, -−0.34 (−0.69, +0.00) and −0.71 (−1.14, -−0.27) for 2881≤BW≤3270, −0.25 (−0.60, +0.09) and −0.69 (−1.32, -−0.07) for 3271≤BW≤3544, and +0.05 (−0.31, +0.41) and −0.26 (−0.76, ++0.025) for 3545≤BW≤3870, and −0.03 (−0.38, +0.33) and 0.46 (−0.10, +1.01) for BW>3870.