

Association between Exposure of Young Children to Procedures Requiring General Anesthesia and Learning and Behavioral Outcomes in a Population-based Birth Cohort

Danqing Hu, M.D., Randall P. Flick, M.D., M.P.H., Michael J. Zaccariello, Ph.D., L.P., Robert C. Colligan, Ph.D., L.P.,† Slavica K. Katusic, M.D., Darrell R. Schroeder, M.S., Andrew C. Hanson, B.S., Shonie L. Buenvenida, R.N., Stephen J. Gleich, M.D., Robert T. Wilder, M.D., Juraj Sprung, M.D., Ph.D., David O. Warner, M.D.

ABSTRACT

Background: Exposure of young animals to general anesthesia 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 general anesthesia before age 3 yr are associated with adverse neurodevelopmental outcomes.

Methods: A retrospective study cohort was assembled from children born in Olmsted County, Minnesota, from 1996 to 2000 (inclusive). Propensity matching selected children exposed and not exposed to general anesthesia before age 3 yr. Outcomes ascertained *via* medical and school records included learning disabilities, attention-deficit/hyperactivity disorder, 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 learning disabilities and attention-deficit/hyperactivity disorder (hazard ratio for learning disabilities = 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.

Conclusions: These findings in children anesthetized with modern techniques largely confirm those found in an older birth cohort and provide additional 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. (**ANESTHESIOLOGY 2017; 127:227-40**)

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 nonhuman 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 used among these studies. Indeed, if exposure is associated with changes in specific domains of

What We Already Know about This Topic

- Exposure of young children to procedures requiring general anesthesia is associated with later development of learning disabilities and attention-deficit/hyperactivity disorder. However, data supporting this association were obtained in an era when older anesthetic agents were used and the current standards of monitoring were not used.

What This Article Tells Us That Is New

- In a more recent population-based birth cohort in which contemporary anesthetic techniques were used, multiple, but not single, exposures before age 3 yr are associated with increased frequency of learning disabilities and attention-deficit/hyperactivity disorder. However, single exposures are associated with deficits in some domains of academic achievement tests.
- Although these data confirm previous reports and thus demonstrate a robust association, they do not permit evaluation of whether anesthesia *per se* is causal.

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cognition or behavior, results should depend on the outcomes examined.^{25,26}

A series of previous studies based on a birth cohort of children born in Olmsted County, Minnesota, found an association between multiple, but not single, exposures to procedures requiring general anesthesia before ages 2 to 4 yr and subsequent learning disabilities (LDs) 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 previous birth cohort studies^{9–11} had several limitations, as extensively discussed at the time of their publication²⁹ and subsequently. As with many frequently cited studies of this issue,^{18,21,22,30} children in the previous cohort (born 1976 to 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 whether exposure is associated with a particular pattern of LDs 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 previous 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 before age 3 yr (*i.e.*, before 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 between 1996 and 2000) in which children were anesthetized with largely contemporary anesthetic techniques.

Materials and Methods

This study was approved by the Mayo Clinic (Rochester, Minnesota) and Olmsted Medical Center (Rochester, Minnesota) institutional review boards. The parents of all of the children included in this analysis had provided consent for the use of their child's medical records in research.

Study Cohort

Previous articles 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, Minnesota, 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 who (1) moved from Olmsted County before their third birthday; (2) died before their fifth birthday; and (3) were not enrolled in the local school district at age 5 yr were excluded, because 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, using multiple variables to calculate sex-specific propensity scores for receiving single or multiple exposures to general anesthesia (GA) and procedures before age 3 yr. This age was chosen as comparable to the previous work by us 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 as 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 the following: (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 535, which serves Rochester, Minnesota, the enrollment status and cumulative school records were also available for review for all of the 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.

LDs (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 an 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 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, 4th 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 six or more separate entries in the medical or school records that were consistent with DSM-IV criteria) were not used, because previous work in the Olmsted County population indicated that use of these criteria did not alter case ascertainment.^{11,36}

IEPs for Speech/Language and Emotional/Behavioral Disorder. As in our previous analysis, receipt of these two types of IEPs was investigated as potentially indicating a concern for language abilities and behavior.^{9,11} A different IEP for LD is available but was not analyzed because LD was separately ascertained.

Group-administered Ability and Achievement Tests. Since 2001, when the oldest members of the study cohort enrolled in independent school district 535, several group-administered tests have been implemented. Of these, the Stanford/Otis-Lennon School Ability Test (OLSAT) was administered every 2 to 3 yr 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 who were home schooled, such that 79% of study cohort members had at least one Stanford/OLSAT while enrolled in independent school district 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 additional 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 or less at or before 8 yr 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 GA, as described previously.³² Each child was at risk from birth until he/she met criteria for LD (including three subtypes of LD), ADHD, or IEPs. For these three outcomes, cumulative frequencies were calculated according to the Kaplan–Meier method, 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 so that the resulting estimates would be reflective of a 1:1 matching of exposed and unexposed individuals. For the prespecified primary analyses, separate stratified proportional hazards regression analyses were performed to assess the association of the number of anesthesia exposures (none, single, and multiple) with LDs, ADHD, or IEPs. In prespecified secondary analyses, stratified proportional hazards regression analyses were performed to assess whether the total duration of anesthesia exposures before age 3 yr (rather than number of exposures) is a risk factor for the aforementioned neurodevelopmental outcomes. For these analyses, separate models were used with cumulative duration of GA quantified as a continuous variable and as a categorical variable using 30-min 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 min).

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, and 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 exposed, singly exposed, and unexposed children. Since all of the individuals within a given propensity strata were not matched exactly on all covariates, two adjusted analyses were performed. One included four covariates that are known to influence the incidence of LDs or ADHD: sex, birth weight, gestational age, and mother's education. These analyses were also intended to facilitate comparisons with our previous work, because these four factors were also used in our previous analyses.^{9–11} The other adjusted analysis also included socioeconomic status as a fifth covariate,^{32,38} because socioeconomic status has also been reported as a risk factor for LDs or ADHD. In addition, in analyses seeking potential factors moderating the effects of exposure, four multivariate logistic regression models were created for each outcome that included all of the significant variables from univariate analyses and the interaction terms between exposure (multiple, single, and 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 LDs 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 LDs, the smallest hazard ratio (HR) 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 HR is 1.6 for the comparison of a single exposure *versus* no exposure and 2.1 for the comparison of multiple exposures *versus* no exposure.

The effect estimates and 95% 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 less than 0.05 were considered significant. All of the data were analyzed using SAS 9.3 (SAS Institute, Inc., USA).

Results

The propensity-matched study cohort consisted of 1,057 children, of which 21 (2%) were excluded from additional 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 children.

Anesthesia and Surgery Characteristics

The 573 children exposed to GA underwent 760 procedures before their third birthday (table 1). The American Society of Anesthesiologists physical status was significantly higher

Table 1. Characteristics of Patients Exposed to Anesthesia before Age 3 yr

	Single Exposure (N = 457)	Multiple Exposures (N = 116)
ASA physical status, n (%)		
I	356 (78)	67 (58)
II	90 (20)	33 (28)
III	11 (2)	13 (11)
IV	0 (0)	3 (3)
Age at first exposure, n (%)		
0–0.9 yr	147 (32)	65 (56)
1.0–1.9 yr	184 (40)	43 (37)
2.0–2.9 yr	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, n (%)	151 (33)	1 (1)
31–60, n (%)	102 (22)	5 (4)
61–90, n (%)	92 (20)	27 (23)
91–120, n (%)	59 (13)	23 (20)
121+, n (%)	53 (12)	60 (52)

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

Q1 = first quartile; Q3 = third quartile.

among multiply exposed children compared with singly exposed children ($P < 0.001$), although most (86%) children with multiple exposures were physical status I to II. The age at first exposure was significantly higher in those children with single exposures ($P < 0.001$), with 68% occurring after 1 yr of age. The mean total duration of anesthetic exposure was approximately threefold higher in multiply exposed children, with 52% of multiply exposed children exposed to greater than 2 h of anesthesia compared with 12% of singly exposed children.

Otorhinolaryngologic procedures accounted for the greatest number of procedures, including the majority of those performed in children greater than 1 yr 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, approximately one in six children received a halothane induction, with most of these then receiving isoflurane after induction.

Outcomes

Learning Disabilities. A total of 142 children (13.7%) developed any LD, including 55 (11.9%), 57 (12.5%), and 30 children (25.9%) who were unexposed, singly exposed, and multiply exposed, respectively. The estimated cumulative frequency of any type of LD at 18 yr of age by Kaplan–Meier analysis was 14.1% (95% CI, 10.8 to 18.2%) for unexposed children, 13.5% (95% CI, 10.5 to 17.1%) for singly exposed children, and 29.9% (95% CI, 21.6 to 40.5%) for multiply

Table 2. Categories of Surgery

Procedure Type	Overall (N = 760)		0–0.9 yr (N = 264)		1.0–1.9 yr (N = 292)		2.0–2.9 yr (N = 204)	
	n	%	n	%	n	%	n	%
General	123	16%	76	29%	24	8%	23	11%
Otorhinolaryngologic	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%

*Data include oral surgeries, ophthalmology surgeries, diagnostic procedures, catheterization, angiography, and examination during anesthesia.

Table 3. Drugs Used before or during Anesthesia

Drug	n (%)*
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)

*N = 758. Data were missing from two anesthetics.

exposed children (fig. 1A). In both adjusted and unadjusted analyses, multiple, but not single, exposures were significantly associated with an increased frequency of LDs, including the analysis that adjusted for socioeconomic status (table 4). In secondary analyses, the frequency of an 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 to 120 min were significantly associated with LDs in fully adjusted analysis (HR = 1.82; *P* = 0.039), with a similar magnitude of effect estimated for durations of more than 121 min (HR = 1.62; *P* = 0.080). Multiple exposures were also associated with increased frequencies of 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 to 120 min), multiply exposed children had an increased frequency of LD compared with singly exposed children (table 4).

Attention-deficit/Hyperactivity Disorder. A total of 165 children (15.9%) developed ADHD, including 54 (11.7%), 75 (16.4%), and 36 children (31.0%) who were unexposed, singly exposed, and multiply exposed, respectively. The estimated cumulative frequency of ADHD at 18 yr of age by Kaplan–Meier analysis was 11.7% (95% CI, 9.3 to 14.8%) for unexposed children, 17.7% (95% CI, 14.3 to 21.9%) for singly exposed children, and 33.6% (95% CI, 25.1 to 44.0%) for multiply exposed children (fig. 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 to 120 min were significantly associated with ADHD in fully adjusted analysis, and durations of more than 121 min were significant 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 to 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 an LD, 72 (51%) met criteria for both LD and ADHD, whereas 70 met criteria for LD only. Of the 165 children with ADHD, 72 (44%) met criteria for both LD and ADHD, whereas 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

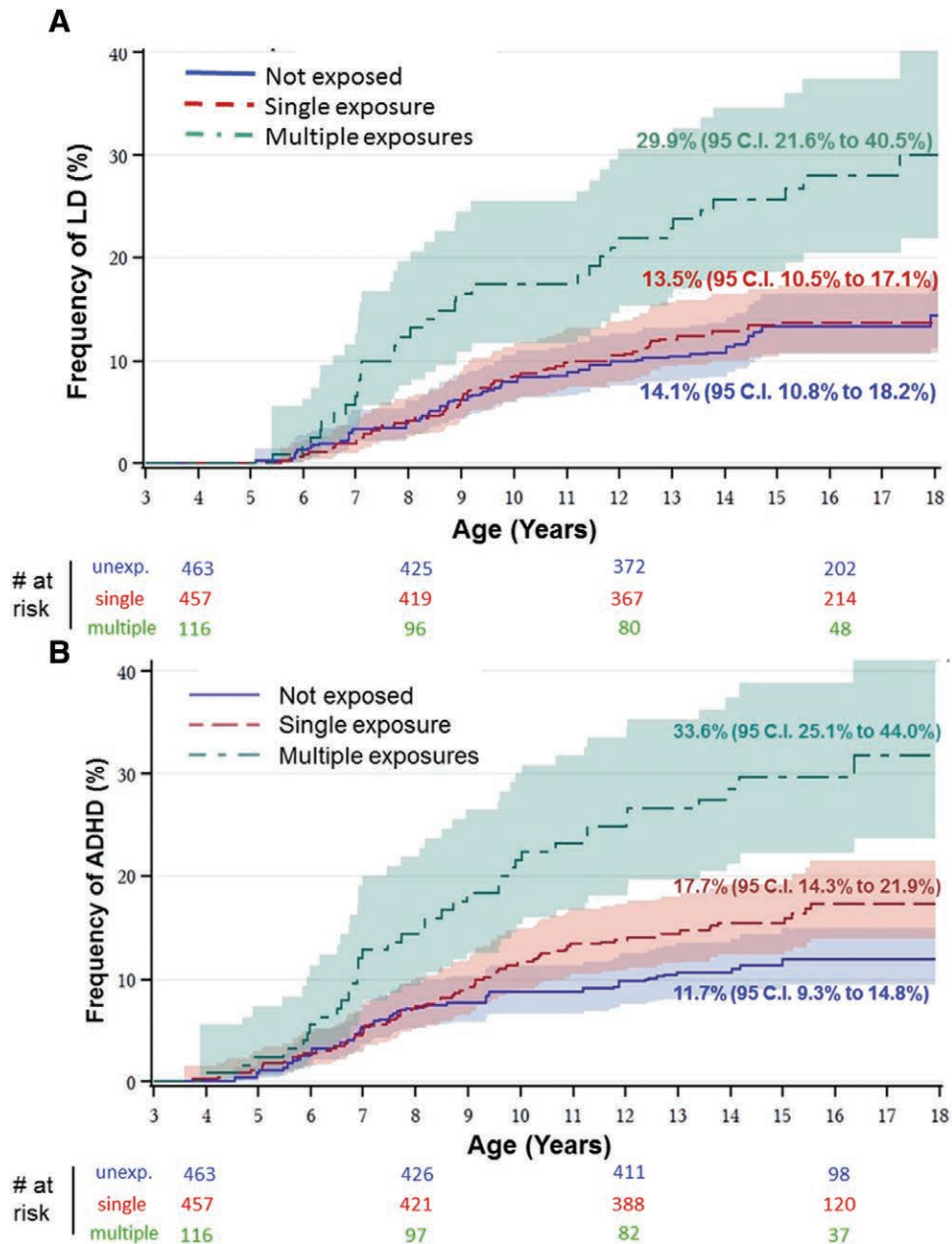


Fig. 1. Age of learning disability (LD; *A*) or attention-deficit/hyperactivity disorder (ADHD; *B*) diagnosis for children not exposed, singly exposed, or multiply exposed. Bands indicate 95% CIs. Cumulative incidence at age 18 yr estimated by Kaplan–Meier analysis with 95% CI is also indicated for 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 yr 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 yr of age). Unexp. = unexposed

may be more severe or that these children are at particular risk for the combination of ADHD and LD.

IEPs for Emotional/Behavioral Disorders and Speech/Language. Ninety-three children (9%) had an IEP for speech/language (SL), and 32 (3%) had an IEP for emotional/behavioral disorder (EBD). Exposures were not associated with the need for an IEP-SL or IEP-EBD (table 7) in either unadjusted or adjusted analyses.

Group-administered Ability and Achievement Tests. The median (minimum, maximum) age at the time of the last

available Stanford/OLSAT test was 14 yr (7, 15 yr) 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 of the 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

Table 4. Association of Anesthetic Exposure before the Age of 3 yr with Any Learning Disability (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
<i>A priori analyses</i>						
No. of anesthesia exposures		0.004		0.005		0.006
0 (n = 463)	Reference		Reference		Reference	
1 (n = 457)	1.03 (0.70–1.50)	0.896	1.02 (0.70–1.49)	0.913	1.06 (0.72–1.57)	0.767
≥2 (n = 116)	2.13 (1.32–3.43)	0.002	2.10 (1.30–3.40)	0.003	2.17 (1.32–3.59)	0.002
Total duration of exposure						
Continuous (per 30 min)	1.06 (1.02–1.10)	0.003	1.05 (1.01–1.10)	0.007	1.06 (1.02–1.10)	0.005
Categorical (30-min intervals)		0.179		0.325		0.162
0 (n = 463)	Reference		Reference		Reference	
1–30 (n = 152)	1.04 (0.61–1.77)	0.891	1.10 (0.64–1.89)	0.726	0.97 (0.55–1.73)	0.930
31–60 (n = 107)	0.79 (0.41–1.52)	0.483	0.81 (0.42–1.57)	0.527	0.85 (0.44–1.66)	0.631
61–90 (n = 119)	1.23 (0.70–2.14)	0.470	1.17 (0.67–2.06)	0.573	1.31 (0.75–2.31)	0.345
91–120 (n = 82)	1.77 (1.01–3.09)	0.045	1.70 (0.97–2.97)	0.063	1.82 (1.03–3.21)	0.039
≥ 121 (n = 113)	1.55 (0.93–2.59)	0.093	1.45 (0.86–2.43)	0.164	1.62 (0.94–2.77)	0.080
<i>Post hoc exploratory analyses</i>						
No. of anesthesia exposures‡		0.063		0.048		0.074
0 (n = 463)	Reference		Reference		Reference	
1 (n = 457)	1.00 (0.66–1.50)	0.980	1.01 (0.67–1.53)	0.954	1.04 (0.68–1.58)	0.864
≥ 2 (n = 116)	1.95 (1.01–3.79)	0.048	2.05 (1.05–4.00)	0.034	2.04 (1.02–4.06)	0.043
No. of anesthesia exposures§						
1 (n = 151)			Reference		Reference	
≥ 2 (n = 50)			2.65 (1.32–5.34)	0.006	2.78 (1.37–5.64)	0.005

*Data were adjusted for sex, birth weight, gestational age, and mother’s education.

†Data were adjusted for sex, birth weight, gestational age, mother’s education, and socioeconomic status.

‡Data were adjusted for total duration of anesthesia exposure. In all of these models, the duration of exposure was not statistically significant.

§This analysis was limited to the 201 patients with total duration of exposure of 61 to 120 min. 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 yr with Three Subtypes of LDs

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

*Data were adjusted for sex, birth weight, gestational age, and mother’s education.

†Data were adjusted for sex, birth weight, gestational age, mother’s education, and socioeconomic status.

LD = learning disability.

in the fully adjusted model. Associations with single exposures were significant in the subdomain of reading for all of the 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

Table 6. Association of Anesthetic Exposure before the Age of 3 yr 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
<i>A priori analyses</i>						
No. of anesthesia exposures		< 0.001		< 0.001		< 0.001
0 (n = 463)	Reference		Reference		Reference	
1 (n = 457)	1.38 (0.97–1.97)	0.075	1.36 (0.95–1.95)	0.091	1.33 (0.92–1.94)	0.134
≥ 2 (n = 116)	2.69 (1.70–4.27)	< 0.001	2.68 (1.68–4.26)	< 0.001	2.59 (1.59–4.21)	< 0.001
Total duration of anesthesia exposure						
Continuous (per 30 min)	1.05 (1.02–1.09)	0.004	1.05 (1.01–1.09)	0.007	1.05 (1.01–1.09)	0.022
Categorical (30-min intervals)		0.023		0.038		0.027
0 (n = 463)	Reference		Reference		Reference	
1–30 (n = 152)	1.37 (0.84–2.24)	0.203	1.43 (0.87–2.34)	0.161	1.30 (0.77–2.20)	0.325
31–60 (n = 107)	1.35 (0.77–2.35)	0.295	1.34 (0.76–2.36)	0.307	1.34 (0.75–2.39)	0.331
61–90 (n = 119)	1.47 (0.88–2.47)	0.14	1.41 (0.84–2.37)	0.196	1.57 (0.93–2.65)	0.091
91–120 (n = 82)	2.39 (1.44–3.98)	< 0.001	2.33 (1.40–3.88)	0.001	2.57 (1.51–4.36)	< 0.001
≥ 121 (n = 113)	1.73 (1.05–2.84)	0.031	1.64 (0.99–2.71)	0.056	1.41 (0.81–2.45)	0.23
<i>Post hoc exploratory analyses</i>						
No. of anesthesia exposures‡		0.003		0.002		0.003
0 (n = 463)	Reference		Reference		Reference	
1 (n = 457)	1.43 (0.97–2.10)	0.070	1.43 (0.97–2.12)	0.071	1.42 (0.95–2.13)	0.091
≥ 2 (n = 116)	2.98 (1.59–5.56)	< 0.001	3.09 (1.64–5.82)	< 0.001	3.11 (1.62–5.99)	< 0.001
No. of anesthesia exposures§						
1 (n = 151)			Reference		Reference	
≥ 2 (n = 50)			3.22 (1.70–6.13)	< 0.001	3.27 (1.70–6.30)	< 0.001

*Data were adjusted for sex, birth weight, gestational age, and mother's education.

†Data were adjusted for sex, birth weight, gestational age, mother's education, and socioeconomic status.

‡Data were adjusted for total duration of anesthesia exposure. In all of 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 min. Due to the restricted subset of patients analyzed, models were not stratified, and only covariate adjusted models were reported.

ADHD = attention-deficit/hyperactivity disorder

Table 7. Association of Anesthetic Exposure before the Age of 3 yr with Need for an IEP for EBD or 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 (0.28–1.30)	0.194	0.60 (0.27–1.34)	0.213	0.60 (0.25–1.45)	0.258
≥ 2 (n = 116)	0.99 (0.32–3.09)	0.991	0.93 (0.29–3.01)	0.906	0.83 (0.23–3.04)	0.784
IEP-SL		0.194		0.184		0.220
0 (n = 463)	Reference		Reference		Reference	
1 (n = 457)	0.77 (0.49–1.20)	0.250	0.76 (0.49–1.18)	0.222	0.81 (0.50–1.29)	0.366
≥ 2 (n = 116)	1.40 (0.72–2.75)	0.324	1.38 (0.71–2.71)	0.342	1.52 (0.75–3.10)	0.248

*Data were adjusted for sex, birth weight, gestational age, and mother's education.

†Data were adjusted for sex, birth weight, gestational age, mother's education, and socioeconomic status.

EBD = emotional/behavioral disorder; IEP = individual educational plan; SL = speech/language disorder.

between exposures and LD or ADHD, because 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

Table 8. Association of Anesthetic Exposure before the Age of 3 yr 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		0.00		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‡

*Data were adjusted for sex, birth weight, gestational age, and mother's education.

†Data were adjusted for sex, birth weight, gestational age, mother's education, and socioeconomic status.

‡Statistically significant ($P < 0.05$) differences in effect estimates for z scores are indicated.

OLSAT = Otis-Lennon School Ability Test.

received by children with multiple exposures to anesthesia is provided as Supplemental Digital Content 1 (<http://links.lww.com/ALN/B473>). If physical status is used as a crude measure of burden of illness, for children exposed to multiple anesthetics, 66 (66%) of the 100 children classified as physical status I or II did not develop an LD or ADHD, and 8 (50%) of the 16 children classified as physical status III or IV did not develop an LD or ADHD ($P = 0.26$, Fisher's exact test; Supplemental Digital Content 2 [<http://links.lww.com/ALN/B474>], which is a table listing the maximum ASA physical status among exposed children who had an LD and/or ADHD). Of the 42 multiply exposed children who developed LD or ADHD, 23 (55%) were assessed as healthy (physical status I), 11 (26%) were classified as physical status II, and 8 (19%) were classified as physical status III or IV, respectively.

At the request of the peer reviewers for this article, 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, <http://links.lww.com/ALN/B475>, which is a table providing the results of this sensitivity analysis). In other models, children receiving neurologic or cardiovascular surgery (a total of 16

children) were excluded from the analyses of group-administered ability and achievement tests (Supplemental Digital Content 4, <http://links.lww.com/ALN/B476>, 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 neurologic or cardiovascular surgery had little effect on the relationship between exposure and LD or ADHD (Supplemental Digital Content 5, <http://links.lww.com/ALN/B477>, 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 independent school district 535 and were exposed to GA (50 singly exposed and 20 multiply exposed) were not included into the study cohort 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

Table 9. Analysis of Variables that Potentially Moderate Association of Anesthesia Exposures with LDs, ADHD, and Stanford/OLSAT Test Scores

	Moderator Variable			
	Sex	Gestational Age	Birth Weight	HOUSES Index
LD				
1 exp. × mod.	0.818	0.867	0.442	0.658
≥ 2 exp. × mod.	0.199	0.675	0.513	0.555
ADHD				
1 exp. × mod.	0.066	0.809	0.645	0.653
≥ 2 exp. × mod.	0.107	0.915	0.986	0.597
OLSAT total battery				
1 exp. × mod.	0.123	0.127	0.129	0.290
≥ 2 exp. × mod.	0.817	0.344	0.080	0.989
Stanford reading				
1 exp. × mod.	0.091	0.583	0.853	0.446
≥ 2 exp. × mod.	0.935	0.367	0.145	0.907
Stanford mathematics				
1 exp. × mod.	0.013*	0.639	0.929	0.696
≥ 2 exp. × mod.	0.554*	0.711	0.232	0.343
Stanford language				
1 exp. × mod.	0.307	0.397	0.255†	0.620
≥ 2 exp. × mod.	0.763	0.075	0.013†	0.654
Stanford spelling				
1 exp. × mod.	0.381	0.510	0.437	0.499
≥ 2 exp. × mod.	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 generalized estimating equation (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 with 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 versus no exposure was -0.22 (-0.41 to -0.04) and -0.38 (-0.70 to -0.07) for males, and +0.12 (-0.08 to +0.33) and -0.25 (-0.57 to +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 to +0.03) and -0.39 (-0.86 to +0.08) for those with body weight ≤ 2880 g, -0.34 (-0.69 to +0.00) and -0.71 (-1.14 to -0.27) for 2881 g ≤ body weight ≤ 3270 g, -0.25 (-0.60 to 0.09) and -0.69 (-1.32 to -0.07) for 3271 g ≤ body weight ≤ 3544 g, and 0.05 (-0.31 to 0.41) and -0.26 (-0.76 to 0.025) for 3545 g ≤ body weight ≤ 3870 g, and -0.03 (-0.38 to 0.33) and 0.46 (-0.10 to 1.01) for body weight >3870 g.

ADHD = attention-deficit/hyperactivity disorder; exp. = exposure; HOUSES = a housing-based socioeconomic index; LD = learning disabilities; mod. = moderator; OLSAT = Otis-Lennon School Ability Test.

study cohort. Comparing those who were and were not included in the study cohort, 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, <http://links.lww.com/ALN/B478>, which is a table showing this comparison).

Discussion

Multiple, but not single, exposures before age 3 yr 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 between 1996 and 2000) are largely consistent with and extend the main results from a previous cohort (born between 1976 and 1982).⁹⁻¹¹

Comparison with the Previous Cohort

Although the designs of the current and previous studies are similar, two major differences are notable. First, the current study used 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 previous articles,^{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 following: (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 previous and current cohorts^{9,11} (Supplemental Digital Content 7, <http://links.lww.com/ALN/B479>, 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 previous 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 with the previous 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 Minnesota (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 United States.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.

Individualized Education Program. Exposure was not associated with the need for either an 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 previous 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 previous 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 previous cohort⁹). Regarding achievement tests, multiple exposures were associated with significant decreases in only mathematics scores in the previous cohort, which may reflect a limited number of available scores. Unlike the previous 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 previous cohorts) or the greater numbers of available test scores in the current cohort, enhancing the power to detect differences. Any potential effects of single exposure on these domains were not sufficient to cause formally diagnosed LDs, 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 used in other studies.^{25,26} This multiplicity of outcomes, as well as other differences in experimental design, makes direct comparisons among studies problematic, because 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 used the Early Developmental Index, a questionnaire completed by kindergarten teachers, as the outcome.^{12,13} Both found that exposure was associated with a small but significant reduction in Early Developmental Index 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 Early Developmental Index domains (broadly divided into categories of general/language/cognitive development and well-being/social competence/maturity) affected by exposure differed between the two studies. Although the Early Developmental Index 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. Although 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 trial²³ and a sibling-matched study using detailed neuropsychologic 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 previous studies using 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 with 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, because 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 neurologic surgery (3% of procedures in this study) can be associated with abnormalities in neurodevelopment.^{47,48} Sensitivity analyses eliminating these 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 LDs and ADHD were not affected. Myringotomy was frequent, and it is possible that hearing deficits could contribute to LDs. 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 the following: (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 U.S. population as a whole³³; and (3) there was a lack of group test data in 21% of cohort members.

Conclusions

Multiple, but not single, exposures to procedures requiring GA before the age of 3 yr 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 previous observations in children anesthetized before 1985 and provide additional 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.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Warner: Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, 200 First St. SW, Rochester, Minnesota 55905. warner.david@mayo.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

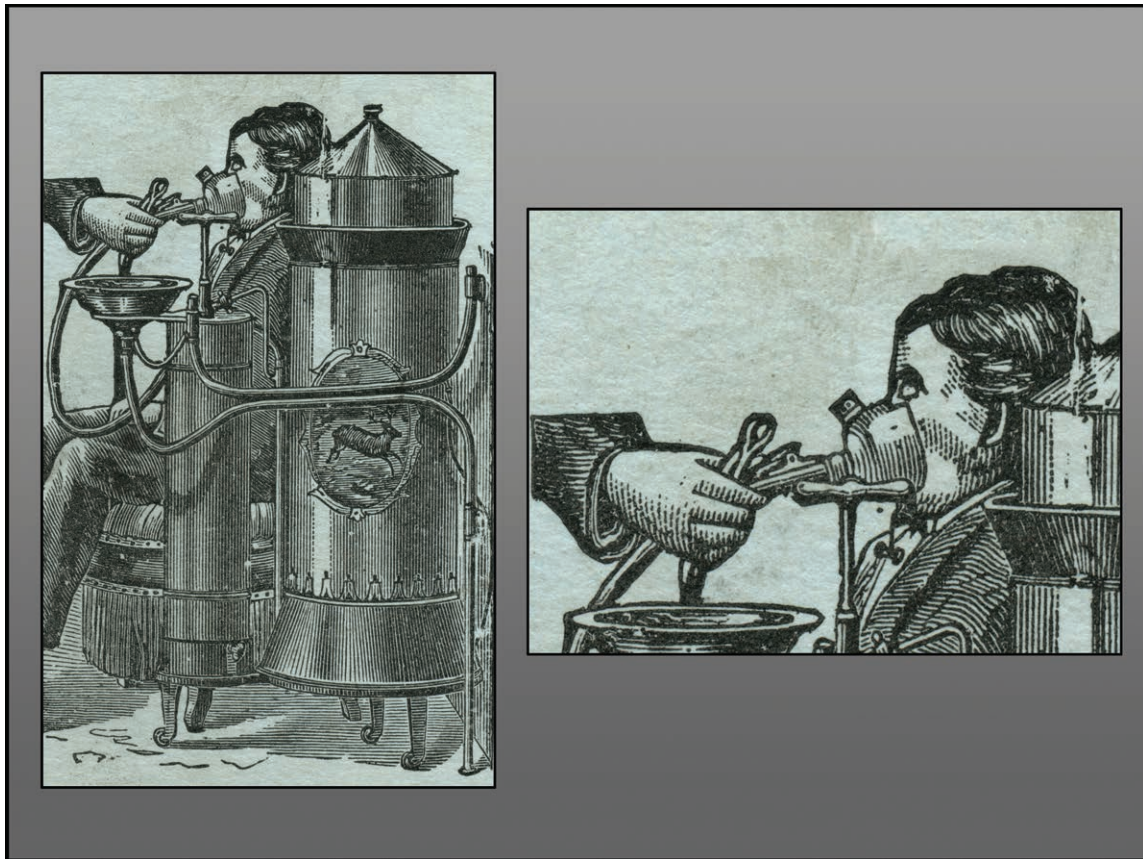
- Jevtovic-Todorovic V, Hartman RE, Izumi Y, Benshoff ND, Dikranian K, Zorumski CF, Olney JW, Wozniak DF: Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; 23:876–82
- Sanchez V, Feinstein SD, Lunardi N, Joksovic PM, Boscolo A, Todorovic SM, Jevtovic-Todorovic V: General anesthesia causes long-term impairment of mitochondrial morphogenesis and synaptic transmission in developing rat brain. *ANESTHESIOLOGY* 2011; 115:992–1002
- Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, Zhang X, Dissen GA, Creeley CE, Olney JW: Isoflurane-induced neuroapoptosis in the neonatal rhesus macaque brain. *ANESTHESIOLOGY* 2010; 112:834–41
- Disma N, Mondardini MC, Terrando N, Absalom AR, Bilotta F: A systematic review of methodology applied during pre-clinical anesthetic neurotoxicity studies: Important issues and lessons relevant to the design of future clinical research. *Paediatr Anaesth* 2016; 26:6–36
- Jevtovic-Todorovic V, Absalom AR, Blomgren K, Brambrink A, Crosby G, Culley DJ, Fiskum G, Giffard RG, Herold KF, Loepke AW, Ma D, Orser BA, Planel E, Slikker W Jr, Soriano SG, Stratmann G, Vutskits L, Xie Z, Hemmings HC Jr: Anaesthetic neurotoxicity and neuroplasticity: An expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth* 2013; 111:143–51
- Kodama M, Satoh Y, Otsubo Y, Araki Y, Yonamine R, Masui K, Kazama T: Neonatal desflurane exposure induces more robust neuroapoptosis than do isoflurane and sevoflurane and impairs working memory. *ANESTHESIOLOGY* 2011; 115:979–91
- Paule MG, Li M, Allen RR, Liu F, Zou X, Hotchkiss C, Hanig JP, Patterson TA, Slikker W Jr, Wang C: Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. *Neurotoxicol Teratol* 2011; 33:220–30
- DiMaggio C, Sun LS, Li G: Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. *Anesth Analg* 2011; 113:1143–51
- Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO: Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. *Pediatrics* 2011; 128:e1053–61
- Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO: Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *ANESTHESIOLOGY* 2009; 110:796–804
- Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT, Warner DO: Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. *Mayo Clin Proc* 2012; 87:120–9
- O'Leary JD, Janus M, Duku E, Wijeyesundera DN, To T, Li P, Maynes JT, Crawford MW: A population-based study evaluating the association between surgery in early life and child development at primary school entry. *ANESTHESIOLOGY* 2016; 125:272–9
- Graham MR, Brownell M, Chateau DG, Dragan RD, Burchill C, Fransoo RR: Neurodevelopmental assessment in kindergarten in children exposed to general anesthesia before the age of 4 years: A retrospective matched cohort study. *ANESTHESIOLOGY* 2016; 125:667–77
- Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F: Association of anesthesia and surgery during childhood with long-term academic performance. *JAMA Pediatr* 2016; 171:e163470
- DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G: A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. *J Neurosurg Anesthesiol* 2009; 21:286–91
- Stratmann G, Lee J, Sall JW, Lee BH, Alvi RS, Shih J, Rowe AM, Ramage TM, Chang FL, Alexander TG, Lempert DK, Lin N, Siu KH, Elphick SA, Wong A, Schnair CI, Vu AF, Chan JT, Zai H,

- Wong MK, Anthony AM, Barbour KC, Ben-Tzur D, Kazarian NE, Lee JY, Shen JR, Liu E, Behniwal GS, Lammers CR, Quinones Z, Aggarwal A, Cedars E, Yonelinas AP, Ghetti S: Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. *Neuropsychopharmacology* 2014; 39:2275–87
17. Backeljauw B, Holland SK, Altaye M, Loepke AW: Cognition and brain structure following early childhood surgery with anesthesia. *Pediatrics* 2015; 136:e1–12
 18. Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, Davidson A, Wood AJ, Li G, Sun LS: Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; 130:e476–85
 19. Bong CL, Allen JC, Kim JT: The effects of exposure to general anesthesia in infancy on academic performance at age 12. *Anesth Analg* 2013; 117:1419–28
 20. Block RI, Thomas JJ, Bayman EO, Choi JY, Kimble KK, Todd MM: Are anesthesia and surgery during infancy associated with altered academic performance during childhood? *ANESTHESIOLOGY* 2012; 117:494–503
 21. Hansen TG, Pedersen JK, Henneberg SW, Pedersen DA, Murray JC, Morton NS, Christensen K: Academic performance in adolescence after inguinal hernia repair in infancy: A nationwide cohort study. *ANESTHESIOLOGY* 2011; 114:1076–85
 22. Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K: Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: A nationwide cohort study. *Paediatr Anaesth* 2013; 23:883–90
 23. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME; GAS consortium: Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): An international multicentre, randomised controlled trial. *Lancet* 2016; 387:239–50
 24. Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC, Ing C, Park R, Radcliffe J, Hays SR, DiMaggio CJ, Cooper TJ, Rauh V, Maxwell LG, Youn A, McGowan FX: Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA* 2016; 315:2312–20
 25. Beers SR, Rofey DL, McIntyre KA: Neurodevelopmental assessment after anesthesia in childhood: Review of the literature and recommendations. *Anesth Analg* 2014; 119:661–9
 26. Ing CH, DiMaggio CJ, Malacova E, Whitehouse AJ, Hegarty MK, Feng T, Brady JE, von Ungern-Sternberg BS, Davidson AJ, Wall MM, Wood AJ, Li G, Sun LS: Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. *ANESTHESIOLOGY* 2014; 120:1319–32
 27. Murphy KL, Baxter MG: Long-term effects of neonatal single or multiple isoflurane exposures on spatial memory in rats. *Front Neurol* 2013; 4:87
 28. Amrock LG, Starner ML, Murphy KL, Baxter MG: Long-term effects of single or multiple neonatal sevoflurane exposures on rat hippocampal ultrastructure. *ANESTHESIOLOGY* 2015; 122:87–95
 29. Flick RP, Wilder RT, Sprung J, Katusic SK, Voigt R, Colligan R, Schroeder DR, Weaver AL, Warner DO: Hyperoxia in pediatric anesthesia: Time for reconsideration? *ANESTHESIOLOGY* 2009; 111:1384–6
 30. Bartels M, Althoff RR, Boomsma DI: Anesthesia and cognitive performance in children: No evidence for a causal relationship. *Twin Res Hum Genet* 2009; 12:246–53
 31. Gleich SJ, Flick R, Hu D, Zaccariello MJ, Colligan RC, Katusic SK, Schroeder DR, Hanson A, Buenvenida S, Wilder RT, Sprung J, Voigt RG, Paule MG, Chelonis JJ, Warner DO: Neurodevelopment of children exposed to anesthesia: Design of the Mayo Anesthesia Safety in Kids (MASK) study. *Contemp Clin Trials* 2015; 41:45–54
 32. Hu D, Flick RP, Gleich SJ, Scanlon MM, Zaccariello MJ, Colligan RC, Katusic SK, Schroeder DR, Hanson AC, Buenvenida SL, Wilder RT, Sprung J, Warner DO: Construction and characterization of a population-based cohort to study the association of anesthesia exposure with neurodevelopmental outcomes. *PLoS One* 2016; 11:e0155288
 33. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Pankratz JJ, Brue SM, Rocca WA: Data resource profile: The Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol* 2012; 41:1614–24
 34. Katusic SK, Colligan RC, Barbaresi WJ, Schaid DJ, Jacobsen SJ: Incidence of reading disability in a population-based birth cohort, 1976–1982, Rochester, Minn. *Mayo Clin Proc* 2001; 76:1081–92
 35. Barbaresi W, Katusic S, Colligan R, Weaver A, Pankratz V, Mrazek D, Jacobsen S: How common is attention-deficit/hyperactivity disorder? Towards resolution of the controversy: Results from a population-based study. *Acta Paediatr Suppl* 2004; 93:55–9
 36. Katusic SK, Barbaresi WJ, Colligan RC, Weaver AL, Leibson CL, Jacobsen SJ: Case definition in epidemiologic studies of AD/HD. *Ann Epidemiol* 2005; 15:430–7
 37. Katusic SK, Colligan RC, Beard CM, O'Fallon WM, Bergstralh EJ, Jacobsen SJ, Kurland LT: Mental retardation in a birth cohort, 1976–1980, Rochester, Minnesota. *Am J Ment Retard* 1996; 100:335–44
 38. Juhn YJ, Beebe TJ, Finnie DM, Sloan J, Wheeler PH, Yawn B, Williams AR: Development and initial testing of a new socioeconomic status measure based on housing data. *J Urban Health* 2011; 88:933–44
 39. Sexton CC, Gelhorn HL, Bell JA, Classi PM: The co-occurrence of reading disorder and ADHD: Epidemiology, treatment, psychosocial impact, and economic burden. *J Learn Disabil* 2012; 45:538–64
 40. Mayes SD, Calhoun SL, Crowell EW: Learning disabilities and ADHD: Overlapping spectrum disorders. *J Learn Disabil* 2000; 33:417–24
 41. Seidman LJ, Biederman J, Monuteaux MC, Doyle AE, Faraone SV: Learning disabilities and executive dysfunction in boys with attention-deficit/hyperactivity disorder. *Neuropsychology* 2001; 15:544–56
 42. Cortiella C, Horowitz SH: The state of learning disabilities: Facts, trends, and emerging issues. New York: National Center for Learning Disabilities, 2014
 43. Centers for Disease Control and Prevention: Key findings: trends in the parent-report of health care provider-diagnosis and medication treatment for ADHD: United States, 2003–2011. Atlanta: Centers for Disease Control and Prevention, 2014
 44. Guhn M, Gadermann AM, Almas A, Schonert-Reichl KA, Hertzman C: Associations of teacher-rated social, emotional, and cognitive development in kindergarten to self-reported wellbeing, peer relations, and academic test scores in middle childhood. *Early Child Res Quart* 2016; 35: 76–84
 45. Hansen TG: Anesthesia-related neurotoxicity and the developing animal brain is not a significant problem in children. *Paediatr Anaesth* 2015; 25:65–72
 46. Davidson AJ, Becke K, de Graaff J, Giribaldi G, Habre W, Hansen T, Hunt RW, Ing C, Loepke A, McCann ME, Ormond GD, Pini Prato A, Salvo I, Sun L, Vutskits L, Walker S, Disma N: Anesthesia and the developing brain: A way forward for clinical research. *Paediatr Anaesth* 2015; 25:447–52
 47. Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K: Neurosurgical conditions and procedures in

- infancy are associated with mortality and academic performances in adolescence: A nationwide cohort study. *Paediatr Anaesth* 2015; 25:186–92
48. Sananes R, Manlhiot C, Kelly E, Hornberger LK, Williams WG, MacGregor D, Buncic R, McCrindle BW: Neurodevelopmental outcomes after open heart operations before 3 months of age. *Ann Thorac Surg* 2012; 93:1577–83
49. Roberts JE, Rosenfeld RM, Zeisel SA: Otitis media and speech and language: A meta-analysis of prospective studies. *Pediatrics* 2004; 113(3 pt 1):e238–48
50. Moser JJ, Veale PM, McAllister DL, Archer DP: A systematic review and quantitative analysis of neurocognitive outcomes in children with four chronic illnesses. *Paediatr Anaesth* 2013; 23:1084–96

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

A Hollywood Ending for a Master of the Laughing Gasometer, Dr. Frank C. Longnecker



Two upright cylindrical pieces of apparatus dominate the reverse of this dental trade card (*left*) distributed by Dr. Franklin C. “Frank” Longnecker (ca. 1839 to 1933) of Buffalo, New York. Compressed nitrous oxide is released gradually from the shorter cylinder into the taller one, the gasometer. After adulterating his nitrous oxide with a chloroformed elixir, Longnecker advertised that he “numbs the nerves to all the pain / While pulling teeth to the highest strain, / Go and breathe the Vital Air / In DR. F. C. LONGNECKER’S Dental Chair....” Closer examination (*right*) reveals that Longnecker is depicted holding both the dental forceps and the anesthetic inhaler in his right hand. Thus, he is acting simultaneously as both surgeon and anesthetist on the depicted lady patient, a practice later decried as risky. After passing away in his 92nd year, Dr. Longnecker was buried in Los Angeles’ Hollywood Forever Cemetery. This trade card is part of the Wood Library-Museum’s Ben Z. Swanson Collection. (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.