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Association of Anesthesia and Surgery During Childhood With Long-term Academic Performance

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Editorial

Supplemental content

IMPORTANCE The results of preclinical studies suggest that anesthetic drugs administered to neonatal animals cause widespread neuronal apoptosis and later neurocognitive impairment. Adequately powered studies in the pediatric surgical population are scarce, and it is unclear whether such preclinical findings are relevant for the pediatric setting.

OBJECTIVE To examine the association of anesthesia and surgery before age 4 years with long-term academic and cognitive performance indexed by school grades at age 16 years and IQ test scores at military conscription.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a cohort study among all children born in Sweden between January 1973 and December 1993. The dates of analysis were April 2013 to October 2015. Among all 2 174 073 Swedish children born between 1973 and 1993, we identified a primary study cohort of 33 514 children with 1 anesthesia and surgery exposure before age 4 years and no subsequent hospitalization and 159 619 matched unexposed control children. In addition, 3640 children with multiple surgical procedures before age 4 years were studied.

EXPOSURE Having at least 1 surgical procedure in the Swedish Patient Register before age 4 years.

MAIN OUTCOMES AND MEASURES The mean school grades at age 16 years and IQ test scores at military conscription at age 18 years. The mean difference between the exposed cohort and unexposed cohort was estimated in a model that included sex, month of birth during the same year, gestational age at delivery, Apgar score at 5 minutes, maternal and paternal educational levels, annual taxable household income, cohabiting parents, and number of siblings.

RESULTS Among 33 514 exposed children (22 484 male and 11 030 female) and 159 619 unexposed children (105 812 male and 53 807 female) in the primary study cohort, 1 exposure before age 4 years was associated with a mean difference of 0.41% (95% CI, 0.12%-0.70%) lower school grades and 0.97% (95% CI, 0.15%-1.78%) lower IQ test scores. The magnitude of the difference was the same after multiple exposures. There was no difference in school grades with 1 exposure before ages 6 months, 7 to 12 months, 13 to 24 months, or 25 to 36 months. The overall difference was markedly less than the differences associated with sex, maternal educational level, or month of birth during the same year.

CONCLUSIONS AND RELEVANCE Exposure to anesthesia and surgery before age 4 years has a small association with later academic performance or cognitive performance in adolescence on a population level. While more vulnerable subgroups of children may exist, the low overall difference in academic performance after childhood exposure to surgery is reassuring. These findings should be interpreted in light of potential adverse effects of postponing surgery.

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There is global concern regarding the effect of exposure to anesthesia and surgery during early life and the risk for later neurocognitive deficits and impaired school achievements.[1,2] After pioneering studies[3,4] in rodents, it is now established that exposure to commonly used anesthetics during critical time points in the neonatal period consistently leads to structural, functional, and later behavioral deficits in animals ranging from nematodes to primates.[4-11] Such anesthetic neurotoxicity, typically seen as apoptosis, cell death, reduced synaptic sprouting, and impaired neurogenesis, is affected by age and the cumulative dose of anesthetics and has been demonstrated in rodents and primates for an array of anesthetic agents.[12-14]

The findings in neonatal animal models have triggered a series of epidemiological studies[15-26] focusing on long-term cognitive development in young children undergoing anesthesia and surgery. While retrospective investigations have failed to identify an association with later academic performance after 1 exposure to anesthesia and surgery, multiple exposures are consistently associated with an increased risk for learning or cognitive disabilities.[17,18,24] Reasons for these divergent results have been proposed,[1,2,27,28] including confounding by indication and the effect of comorbidities driven by the underlying disorder. Nevertheless, a major challenge has been to obtain a large enough sample size to provide adequate statistical power and a sensitive and uniformly applied outcome measure of neurocognitive development or academic performance to detect long-term neurocognitive outcomes or impaired academic outcomes among children exposed to surgery in early life.

A recent clinical study[29] comparing children having 1 exposure to general anesthesia before age 36 months with unexposed siblings found no difference in IQ in later childhood. Another study[30] comparing the risk for cognitive decline in children exposed to either sevoflurane anesthesia or regional anesthesia while awake failed to identify any increased risk for negative cognitive outcomes associated with a cognitive test battery 2 years after surgery for hernia repair. On the other hand, while awaiting 5-year follow-up data on that study and other ongoing prospective trials,[31] health care professionals and parents are left with uncertainty as to whether early exposure to anesthesia and surgery per se leads to later behavioral deficits or poor academic achievements (http://www.smarttots.org).[32]

We undertook a nationwide cohort study of more than 2 million children born in Sweden between January 1973 and December 1993, combining an array of national health care databases, registries of school achievements, and the military conscription register with information on verbal and spatial cognitive testing. The dates of analysis were April 2013 to October 2015. Our objective was to examine the association of anesthesia and surgery before age 4 years with long-term academic and cognitive performance in adolescence.

Key Points

Question Does exposure to anesthesia and surgery during early childhood affect academic and cognitive performance in adolescence?

Findings In this cohort study among 33 514 exposed children, exposure to surgery with anesthesia before age 4 years was associated with 0.41% lower school grades and 0.97% lower IQ test scores, with no difference in school grades with regard to age. The overall difference was markedly less than the differences associated with sex, maternal educational level, or month of birth during the same year.

Meaning Exposure to anesthesia and surgery before age 4 years has a small association with later academic performance or cognitive performance in adolescence on a population level.

Methods

The study was approved by the regional ethical review board in Stockholm, Sweden. Because this study was based on secondary analysis of national registry data, this approval did not require any informed consent. Information was retrieved and cross-linked from 8 different registers as described in eTable 1 in the Supplement.

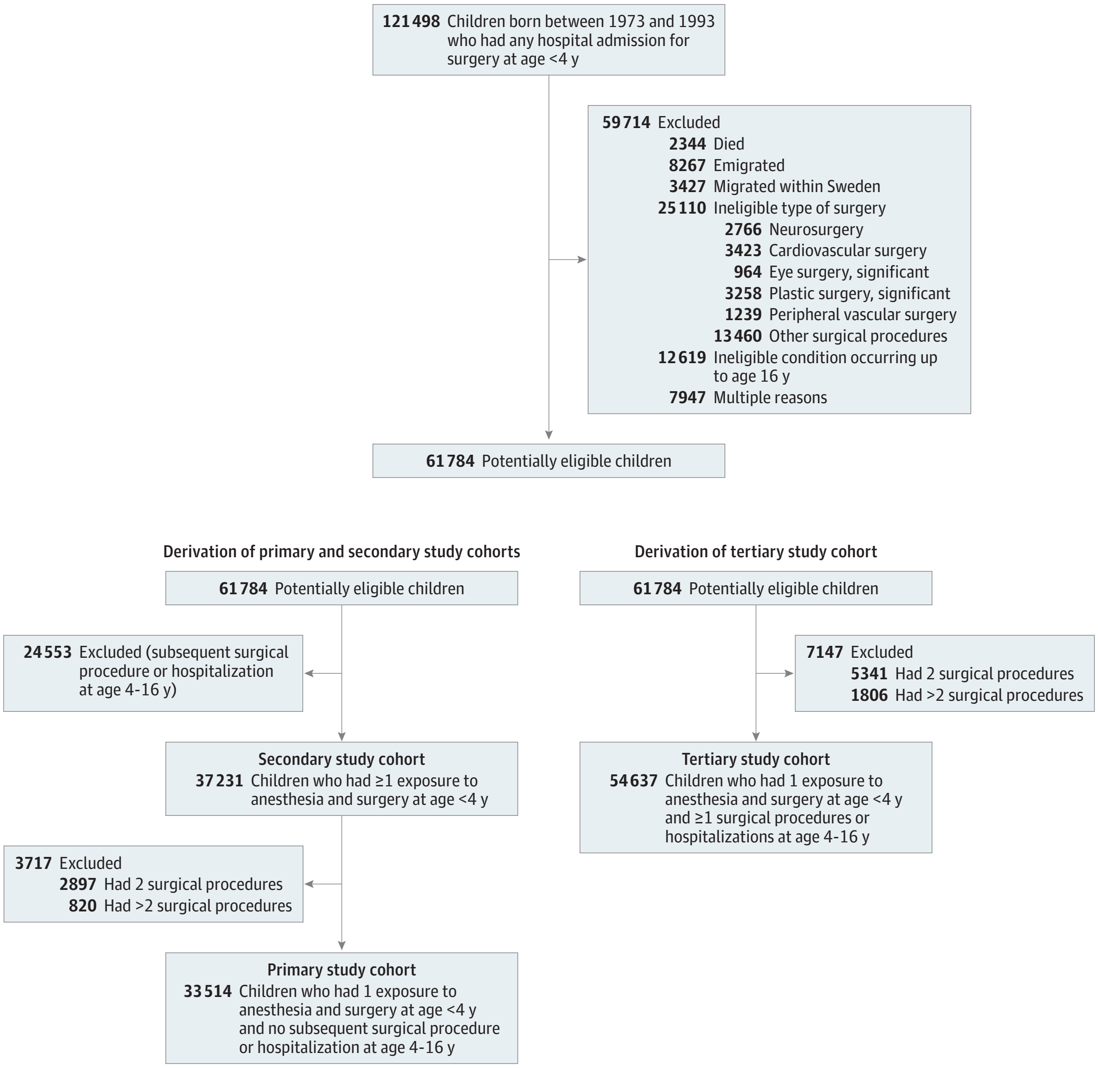
Surgery Cohorts

Among all 2 174 073 children born in Sweden between 1973 and 1993, the exposed surgery cohort comprised all 121 498 children who had any hospital admission for surgery before age 4 years. Exposed and unexposed children were identified by cross-linking the Swedish Medical Birth Register with the Swedish Patient Register, both administered by the National Board of Health and Welfare in Stockholm (http://www.socialstyrelsen.se). In 1973, the Swedish Patient Register included counties covering 80% of the Swedish population, and complete coverage was reached in 1987. As a consequence, exposure status for children born in counties without coverage between 1973 and 1986 could not be ascertained and was excluded. Children migrating to counties without register coverage and children who died or emigrated before obtaining their final school grades at age 16 years were excluded (**Figure 1**). Premature children were not excluded; however, for all outcomes, the estimated difference between exposed and unexposed children was adjusted for gestational age at delivery.

The remaining exposed children were classified according to 14 groups of surgical procedures (eTable 2 in the Supplement). Children deemed to have a high risk of residual cognitive impairment because of the reason for surgery or the procedure per se, such as neurosurgery, cardiothoracic surgery, or cancer surgery, were excluded, leaving 8 types of surgery for analysis. In addition, children with predefined diagnoses occurring up to age 16 years (eg, serious malformation or cancer disorders without surgery) were excluded (Figure 1 and eTable 3 in the Supplement).

The primary cohort (n = 33 514) was defined as children having 1 anesthesia and surgery exposure before age 4 years and no subsequent surgery or hospitalization until age 16 years. A secondary cohort included the children with multiple surgical procedures before age 4 years (n = 3640). A tertiary cohort also included the children with in-hospital care from ages 4 to 16 years (Figure 1 and eTable 4 in the Supplement).

Figure 1. Flowchart for Surgery Cohorts



The primary, secondary, and tertiary study cohorts are shown.

Control Cohort

For each individual in the surgery cohorts, 5 control children having no surgery or hospitalization before age 16 years were selected from the Swedish Medical Birth Register. Controls were matched for sex, month of birth during the same year, and maternal parity and county of residence at delivery.

Outcomes

The primary outcome variables were academic performance based on school grades at age 16 years and general intelligence test scores. School grades were retrieved from the Swedish Ninth Grade Register, which only includes children receiving grades after completing 9 years in the regular schooling system and does not include information on children in need of special education because of severe disabilities. Therefore, study individuals having no recorded school grades are those leaving the regular schooling system or those never entering this system because of severe disabilities.

School grades are based on a uniform school curriculum and academic performance evaluation system for all schools and students throughout Sweden, calibrated annually by a compulsory nationwide individual-level test in mathematics, Swedish, and English. Children in Sweden start school in the fall the year they become 7 years old. The 3 academic performance outcomes were the mean school grades, grades below the 10th percentile of the matched control group, or no recorded school grades. Two different grading systems were used during the study period, one with the mean school grades ranging from 1 to 5 for children born between 1973 and 1981 and the other with the mean school grades ranging from 0 to 320 for children born between 1982 and 1993.

The data on general intelligence test scores based on verbal and spatial cognitive testing (hereafter IQ test scores) were available for the boys born before 1986 who completed the national military conscription review process, typically performed at age 18 years. Details are given in eMethods 1 in the Supplement.

Table. Characteristics of Children Exposed and Unexposed to Surgery Before Age 4 Years

Characteristic	No. (%) Exposed (n = 33 514)	No. (%) Unexposed (n = 159 619)	*P* Value[a]
Sex			
Boys	22 484 (67.1)	105 812 (66.3)	.005
Girls	11 030 (32.9)	53 807 (33.7)	
Year of birth			
1973-1978	5826 (17.4)	29 223 (18.3)	<.001
1979-1983	6856 (20.5)	32 975 (20.7)	
1984-1988	9270 (27.7)	44 335 (27.8)	
1989-1993	11 562 (34.5)	53 086 (33.3)	
No. of siblings			
0	11 238 (33.5)	54 639 (34.2)	<.001
1	11 781 (35.2)	57 033 (35.7)	
2	6463 (19.3)	30 271 (19.0)	
3	2475 (7.4)	10 836 (6.8)	
4	896 (2.7)	4165 (2.6)	
≥5	661 (2.0)	2675 (1.7)	
Gestational age at delivery			
Postterm, ≥42 wk	420 (1.3)	2208 (1.4)	<.001
Term, 37-41 wk	30 092 (89.8)	149 863 (93.9)	
Moderately preterm, 32-36 wk	2494 (7.4)	6655 (4.2)	
Very preterm, 28-31 wk	362 (1.1)	362 (0.2)	
Extremely preterm, <28 wk	47 (0.1)	49 (0.0)	
Missing	99 (0.3)	482 (0.3)	
Apgar score at 5 min			
0-3	82 (0.2)	293 (0.2)	<.001
4-6	265 (0.8)	867 (0.5)	
≥7	30 516 (91.1)	146 162 (91.6)	
Missing	2651 (7.9)	12 297 (7.7)	
Maternal educational level			
≤9 y	5615 (16.8)	25 587 (16.0)	<.001
10-12 y	16 858 (50.3)	78 456 (49.2)	
Higher education <3 y	5058 (15.1)	25 156 (15.8)	
Higher education ≥3 y	5422 (16.2)	27 485 (17.2)	
Research education	136 (0.4)	789 (0.5)	
Missing	425 (1.3)	2146 (1.3)	
Paternal educational level			
≤9 y	7832 (23.4)	35 514 (22.2)	<.001
10-12 y	15 766 (47.0)	74 041 (46.4)	
Higher education <3 y	3910 (11.7)	19 130 (12.0)	
Higher education ≥3 y	4266 (12.7)	22 464 (14.1)	
Research education	429 (1.3)	2402 (1.5)	
Missing	1311 (3.9)	6068 (3.8)	
Annual taxable household income quartile			
≤1	8036 (24.0)	36 012 (22.6)	<.001
>1 to 2	8441 (25.2)	40 592 (25.4)	
>2 to 3	8462 (25.2)	41 035 (25.7)	
>3	8529 (25.4)	41 602 (26.1)	
Missing	46 (0.1)	378 (0.2)	

(continued)

Table. Characteristics of Children Exposed and Unexposed to Surgery Before Age 4 Years (continued)

Characteristic	No. (%) Exposed (n = 33 514)	No. (%) Unexposed (n = 159 619)	*P* Value[a]
Cohabiting parents			
No	12 068 (36.0)	53 793 (33.7)	<.001
Yes	21 446 (64.0)	105 826 (66.3)	
Type of surgery			
Abdominal	4411 (13.2)	NA	NA
ENT	6365 (19.0)	NA	NA
Eye, minimal	1145 (3.4)	NA	NA
Inguinal hernia	9812 (29.3)	NA	NA
Orthopedics	3839 (11.5)	NA	NA
Plastic, minimal	3230 (9.6)	NA	NA
Tympanic membrane	1184 (3.5)	NA	NA
Urology	3528 (10.5)	NA	NA
Age at surgery, mo			
0-6	8119 (24.2)		NA
7-12	3490 (10.4)	NA	NA
13- 24	6313 (18.8)	NA	NA
25-36	7090 (21.2)	NA	NA
37-48	8502 (25.4)	NA	NA

Abbreviations: ENT, ear, nose, and throat; NA, not applicable.

[a] χ^2 Test for homogeneity between exposed vs unexposed.

Statistical Analysis

Analysis of variance was used to test effects on the mean school grades and was performed separately for the 2 grading systems. The mean difference between the exposed cohort and unexposed cohort was estimated in a model that included sex, month of birth during the same year, gestational age at delivery, Apgar score at 5 minutes, maternal and paternal educational levels, annual taxable household income, cohabiting parents, and number of siblings. All variables were categorized as listed in the **Table** (including children hospitalized between ages 4 and 16 years) (eTable 4 in the Supplement). Details are given in eMethods 2 in the Supplement.

The adjusted mean differences between the exposed and unexposed cohorts for the 2 grading systems were normalized by the mean school grade in the unexposed cohort in each grading system (3.21 and 205.22, respectively), and a pooled estimate was obtained by weighting with the reciprocal variance using the following equation:

$$\Delta_{pooled} = \frac{\sum_{i=1}^{2} w_i \frac{\Delta_i}{\bar{Y}_i}}{\sum_{i=1}^{2} w_i},$$

where $\bar{Y}_i$ indicates mean grade in the control cohort for system i, Δ_i mean grade surgery cohort − mean grade control cohort, and w_i

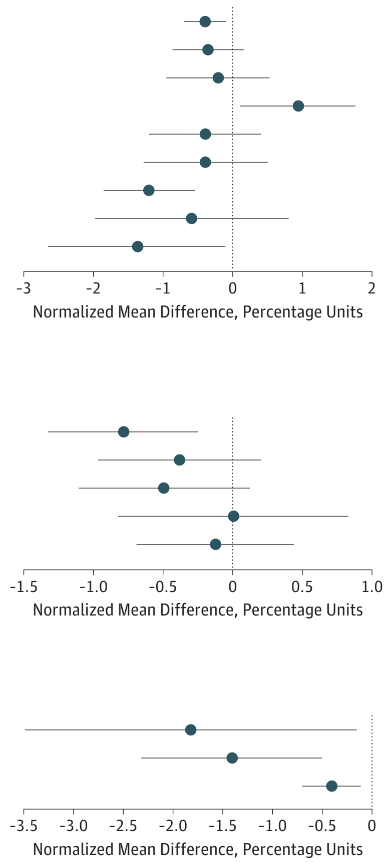
$$\frac{\bar{Y}_i^2}{Var(\Delta_i)}.$$

Figure 2. Differences in the Mean Grades Between Surgery Cohorts and Controls With Respect to School Performance

Type of Surgery	No. of Surgical Procedures	Mean (95% CI)
All operations	32 857	-0.41 (-0.70 to -0.12)
Inguinal hernia	9645	-0.36 (-0.86 to 0.15)
Abdominal	4326	-0.21 (-0.95 to 0.52)
Urology	3466	0.93 (0.12 to 1.75)
Orthopedics	3745	-0.41 (-1.20 to 0.38)
Plastic, minimal	3180	-0.40 (-1.27 to 0.47)
ENT	6212	-1.22 (-1.87 to -0.57)
Paracentesis	1155	-0.60 (-1.98 to 0.78)
Eye, minimal	1128	-1.37 (-2.67 to -0.08)

Age at Surgery, mo	No. of Surgical Procedures	Mean (95% CI)
37-48	8321	-0.79 (-1.33 to -0.25)
25-36	6943	-0.38 (-0.97 to 0.20)
13-24	6202	-0.50 (-1.11 to 0.12)
7-12	3420	0.00 (-0.82 to 0.83)
0-6	7971	-0.13 (-0.69 to 0.43)

Multiple Surgical Procedures	No. of Surgical Procedures	Mean (95% CI)
≥3	799	-0.82 (-3.49 to -0.15)
2	2841	-1.41 (-2.31 to -0.50)
1	32 857	-0.41 (-0.70 to -0.12)



Shown are the findings in operated children vs controls. The 2 upper panels apply to the primary cohort, whereas the lower panel applies to the secondary cohort. ENT indicates ear, nose, and throat.

Therefore, the surgery effect was estimated as percentage unit change in reference to the mean school grade. Heterogeneity in the normalized difference between the 2 systems was tested by a z test.

The IQ test scores at military conscription were analyzed in the same manner as the school grades. To facilitate comparisons with analyses of school grades, the difference between the exposed and unexposed cohorts was normalized by the mean test result in the unexposed cohort.

The risks of having grades below the 10th percentile, no recorded school grades, and no available cognitive test scores were analyzed by logistic regression with the same covariates as in the analysis of the mean school grades. The results from these analyses are presented as odds ratios with 95% CIs. Homogeneity of surgery effects with respect to the type of surgery, age at first surgery, and number of surgical procedures and sex, maternal educational level, and annual taxable household income was tested by χ^2 tests. Analyses were performed using a statistical software program (SAS, version 9.4; SAS Institute Inc).

Results

Academic Performance

Among 33 514 exposed children and 159 619 unexposed children in the primary study cohort, the data revealed a mean difference of 0.41% (95% CI, 0.12%-0.70%) lower school grades for 1 exposure before age 4 years. There was no difference in school grades with 1 exposure before age 6 months, between 7 to 12 months, between 13 to 24 months, or between 25 to 36 months (**Figure 2**). Despite no overall heterogeneity with respect to age at surgery, a small difference of 0.79%, (95% CI, 0.25%-1.33%) in academic performance was detected in children exposed at ages 37 to 48 months, which thus contributed to the overall association before age 4 years. The difference in the mean school grades associated with 1 exposure was several orders of magnitude less than the mean difference associated with sex, maternal educational level, and month of birth during the same year.

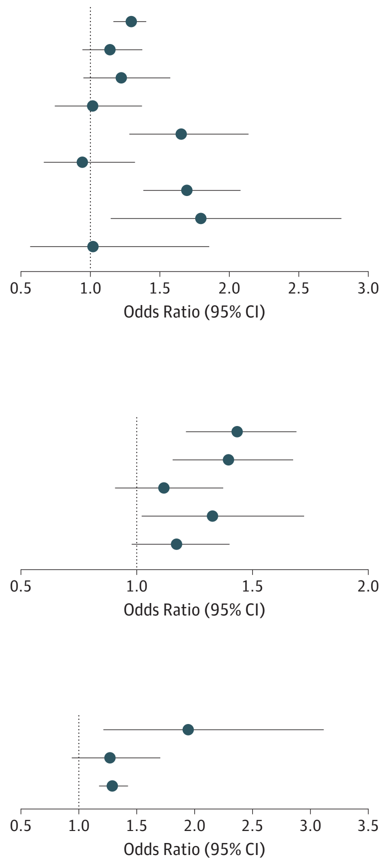
Significant heterogeneity between the different types of surgery was detected. This finding was mainly due to the 1.22%

Figure 3. Differences in the Probability of Obtaining No Grades Between Surgery Cohorts and Controls With Respect to School Performance

Type of Surgery	No. of Surgical Procedures	Odds Ratio (95% CI)
All operations	33514	1.29 (1.17-1.42)
Inguinal hernia	9812	1.14 (0.95-1.37)
Abdominal	4411	1.22 (0.95-1.57)
Urology	3528	1.02 (0.75-1.37)
Orthopedics	3839	1.66 (1.28-2.15)
Plastic, minimal	3230	0.94 (0.67-1.33)
ENT	6365	1.70 (1.38-2.08)
Paracentesis	1184	1.79 (1.15-2.81)
Eye, minimal	1145	1.02 (0.57-1.85)

Age at Surgery, mo	No. of Surgical Procedures	Odds Ratio (95% CI)
37-48	8502	1.44 (1.22-1.70)
25-36	7090	1.40 (1.16-1.68)
13-24	6313	1.12 (0.91-1.38)
7-12	3490	1.33 (1.02-1.73)
0-6	8119	1.17 (0.98-1.40)

Multiple Surgical Procedures	No. of Surgical Procedures	Odds Ratio (95% CI)
3 or more	820	1.95 (1.22-3.11)
2	2897	1.26 (0.94-1.70)
1	33514	1.29 (1.17-1.42)



Shown are the findings in operated children vs controls. The 2 upper panels apply to the primary cohort, whereas the lower panel applies to the secondary cohort. ENT indicates ear, nose, and throat.

lower grades in the ear, nose, and throat subgroup and the 0.93% higher grades in the urological surgery subgroup (Figure 2).

There was no association between having grades below the 10th percentile and exposure (odds ratio, 1.02; 95% CI, 0.98-1.07) (eFigure 1 in the Supplement). This risk was not modified by lower maternal educational level or lower socioeconomic status (eTable 5 in the Supplement).

Among the exposed children, 2.0% had no recorded school grades at age 16 years compared with 1.6% among the control children. The adjusted odds ratio was 1.29 (95% CI, 1.17-1.42). This association was significantly modified by the type of surgery, with the paracentesis, orthopedic surgery, and ear, nose, and throat subgroups having a higher probability of no recorded school grades than those undergoing other types of surgery (**Figure 3**). The odds ratios for having no recorded school grades were not significantly different with respect to age at first surgery or the number of surgical procedures (Figure 3).

The secondary cohort, which included children with multiple surgical procedures before age 4 years (ie, those exposed on 2 occasions [n = 2841] or ≥3 occasions [n = 799]), had 1.41% and 1.82% lower mean school grades, respectively (Figure 2). Heterogeneity with respect to the number of surgical procedures was statistically significant.

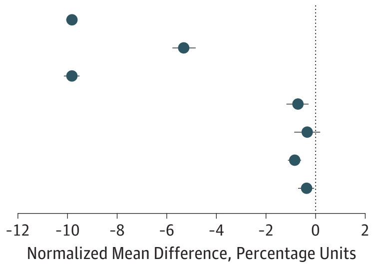
In the above analyses, exposed children and unexposed controls who were hospitalized between ages 4 and 16 years were excluded, assuming that the potential effect of anesthesia on cognitive function does not affect future hospitalization. However, there was an association between surgery at a young age and future hospitalization, with 18.3% of the exposed children hospitalized between ages 4 and 7 years compared with 12.5% of the controls. The corresponding proportions of hospitalized children between ages 8 and 16 years were 27.0% among exposed children and 22.9% among unexposed children (eTable 4 in the Supplement). When children hospitalized after age 4 years also were included, the exposed children had 0.87% (95% CI, 0.64%-1.11%) lower mean school grades, and the odds ratios for having grades below the 10th percentile and for having no recorded school grades were 1.09 (95% CI, 1.05-1.12) and 1.31 (95% CI, 1.23-1.40), respectively (eFigure 1 and eFigure 2 in the Supplement).

The associations with nonsurgical variables known to affect later academic performance are shown in **Figure 4**. The difference in the mean school grades associated with

Figure 4. Difference in the Mean School Grades and Probability of Having No Recorded School Grades in Relation to Nonsurgical Variables

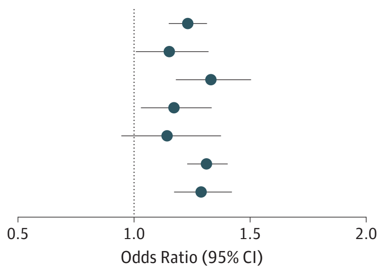
A Mean school grades

	Mean (95% CI)
Boys vs girls	-9.88 (-9.69 to -10.10)
Born in December vs January of the same year	-5.34 (-4.89 to -5.80)
Maternal educational level, 10-12 vs >12 y	-9.89 (-9.61 to -10.20)
Inguinal hernia, operated children vs controls[a]	-0.75 (-1.17 to -0.34)
Inguinal hernia, operated children vs controls	-0.36 (-0.86 to 0.15)
All operations, operated children vs controls[a]	-0.87 (-1.11 to -0.64)
All operations, operated children vs controls	-0.41 (-0.70 to -0.12)



B No recorded school grades

	Odds Ratio (95% CI)
Boys vs girls	1.23 (1.15 to 1.31)
Born in December vs January of the same year	1.15 (1.01 to 1.32)
Maternal educational level, 10-12 vs >12 y	1.33 (1.18 to 1.50)
Inguinal hernia, operated children vs controls[a]	1.17 (1.03 to 1.33)
Inguinal hernia, operated children vs controls	1.14 (0.95 to 1.37)
All operations, operated children vs controls[a]	1.31 (1.23 to 1.40)
All operations, operated children vs controls	1.29 (1.17 to 1.42)



[a] Children hospitalized between ages 4 and 16 years were included.

these variables (sex, maternal educational level, and month of birth during the same year) was several orders of magnitude greater than the mean difference associated with exposure to anesthesia and surgery before age 4 years.

IQ Test Scores From the National Military Conscription Review Process

The IQ test scores from the military conscription review were obtained from 9198 exposed boys and 45 115 unexposed boys (eTable 6 in the Supplement). The mean IQ test scores among boys with 1 exposure before age 4 years (normalized by the mean IQ test score in the unexposed cohort) were 0.97% (95% CI, 0.15%-1.78%) lower than the scores among unexposed boys (**Figure 5**). The fraction of boys without IQ test scores was slightly higher among the exposed vs unexposed individuals (odds ratio, 1.09; 95% CI, 1.02-1.15). The IQ test scores that include children having 1 or more hospitalizations between ages 4 and 16 years are shown in eFigure 2 in the Supplement.

School Grades Measured by the Old and New Grading Systems

The normalized difference between exposed and unexposed children for the 2 grading systems was not statistically significant for all surgical procedures as a group or for any procedural subgroup. Details are given in eTable 7, eFigure 3, and eMethods 2 in the Supplement.

Discussion

In this highly powered nationwide study, we found statistically significant but minimally lower school grades at age 16 years among children exposed to 1 surgical procedure with anesthesia before age 4 years. The association indicates a mean reduction in the mean school grades of 0.41% (95% CI, 0.12%-0.70%), which is at most less than 0.70% considering the 95% CI. The magnitude of this reduction is markedly less than the observed differences in school grades between children born in January or December of the same year, between those born to mothers with intermediate vs high educational levels, or between boys and girls. Because school grades may not fully reflect all aspects of cognitive function, we also investigated IQ test scores in the subcohort of boys who were included in military conscription at age 18 years. Boys who underwent 1 surgical procedure before age 4 years had a 0.97% reduction in the mean IQ test scores at conscription, confirming the small extent of the exposure effect seen on school grades.

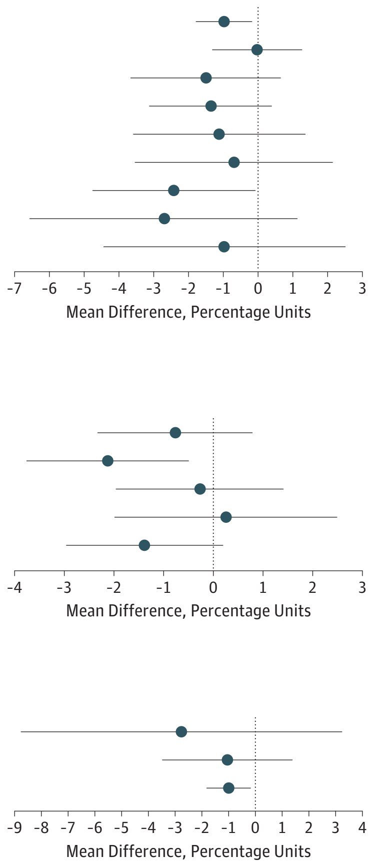
While there is evidence from experimental animal models that a single exposure to anesthetics for several hours in the early postnatal period produces neuroapoptosis, impaired synaptic sprouting, and later neurocognitive deficits over a wide range of species,[4-6] recent findings after brief exposures of less than 1 hour fail to demonstrate such effects.[13] In rats, the most pronounced postexposure neuronal apoptosis is seen around postnatal day 7, corresponding to the most intense period of synaptogenesis.[14] Although these experimental observations have fueled a general controversy of increased vulnerability among children in the neonatal period and before age 12 months, there was no reduction in school grades among children with surgery before age 1 year in this study. Because the observed effect was not significantly modified by age at surgery, our findings do not support hypotheses that the youngest children would be more vulnerable.

Figure 5. Differences in the Mean Score in Conscription IQ Test Between Surgery Cohorts and Controls With Respect to School Performance

Type of Surgery	No. of Surgical Procedures	Mean (95% CI)
All operations	9198	-0.97 (-1.78 to -0.15)
Inguinal hernia	3222	-0.02 (-1.31 to 1.28)
Abdominal	1103	-1.49 (-3.65 to 0.68)
Urology	1708	-1.35 (-3.11 to 0.41)
Orthopedics	838	-1.09 (-3.57 to 1.38)
Plastic, minimal	650	-0.67 (-3.52 to 2.17)
ENT	928	-2.40 (-4.76 to -0.05)
Paracentesis	341	-2.70 (-6.55 to 1.14)
Eye, minimal	408	-0.96 (-4.45 to 2.54)

Age at Surgery, mo[a]	No. of Surgical Procedures	Mean (95% CI)
37-48	2166	-0.75 (-2.31 to 0.80)
25-36	1962	-2.11 (-3.74 to -0.47)
13-24	1882	-0.26 (-1.94 to 1.41)
7-12	1035	0.27 (-1.96 to 2.50)
0-6	2153	-1.37 (-2.95 to 0.21)

Multiple Surgical Procedures	No. of Surgical Procedures	Mean (95% CI)
3 or more	149	-2.74 (-8.73 to 3.25)
2	887	-1.02 (-3.43 to 1.39)
1	9198	-0.97 (-1.78 to -0.15)



Shown are the findings in operated children vs controls. The 2 upper panels apply to the primary cohort, whereas the lower panel applies to the secondary cohort. ENT indicates ear, nose, and throat.

It may be argued that that the measure of school grades at age 16 years is insufficiently sensitive to detect an effect from an intervention in early childhood. However, given the nationwide school curriculum, combined with a uniform school grade system, we were able to detect an effect even by month of birth during the same year, which indicates that the outcome variable is sensitive enough to detect a subtle association between chronological age at school start and school grades at age 16 years and that the school system per se is unable to fully compensate a difference in cognitive function relating to age at school start. Furthermore, the magnitude of the association was similar to that for cognitive performance indexed by the IQ test scores during military conscription 2 years later.

The largest caveat with this investigation and similar studies[15-26] is the inability to disentangle the potential effects of anesthesia per se, the influence of perioperative management, and the possible sequelae of surgery (including the duration of surgery per se) or its underlying cause. To reduce confounding by indication as much as possible, we excluded surgical procedures associated with serious comorbidity and successive contact with the health care system, such as neurosurgery, cardiothoracic surgery, and cancer surgery. In spite of this effort, we found differences between the types of surgery, which could reflect not only associations between the underlying condition and future cognitive function but also differences in the type and duration of anesthesia. It may be argued that the lower school grades associated with ear, nose, and throat surgery at ages 37 to 48 months could be due to confounding from hearing impairment or delayed speech development,[32] while reasons for higher school grades among children with urological procedures seem more speculative and cannot be resolved by our data. Furthermore, we excluded all children hospitalized between ages 4 to 16 years, thereby reducing the potential effect of comorbidities relating to the indication for surgery or its potential sequelae. As an illustration of the effect on the data by hospitalization after age 4 years, the reduction in school grades was twice as high in the exposed group when children with later hospitalizations were included compared with the unexposed group.

Two previous studies[22,23] have shown an increased probability of having no recorded school grades (nonattainment) among children undergoing surgery at young ages (odds ratios, 1.19 and 1.37, respectively), despite a lack of difference in test results compared with unexposed controls. We also observed an increased probability of nonattainment at age 16 years in the surgery group herein (adjusted odds ratio, 1.29).

We could not determine whether the reason for having no recorded school grades was because of leaving the school system early or never entering the regular school system, a limitation of the present study. However, because the association between exposure and school grades in the 10th percentile was weak, it seems unlikely that the relationship with nonattainment reflects a dramatic effect of anesthesia and surgery in particularly sensitive individuals.

Several studies[16-18] have confirmed an association between multiple exposures to anesthesia and surgery and later learning disabilities and poor academic performance. Wilder et al[18] found learning disabilities among 144 children having 2 or more procedures with anesthesia but not among 449 children having a single procedure. We also observed a larger reduction in the mean school grades with increasing numbers of surgical procedures. Even with exposure to 3 or more surgical procedures, the reduction is small compared with the difference in grades between children born in January or December of the same year. While this observation may reflect a dose response with respect to the exposure, the risk of confounding by indication is also likely to increase with increasing numbers of surgical procedures. Another limitation is that this study lacked any data on the duration of surgery, although historical data indicate that it was unlikely to exceed 60 minutes (eMethods 2 in the Supplement).

Conclusions

Exposure to anesthesia and surgery before age 4 years is associated with a small difference in academic performance or cognitive performance in adolescence on a population level. The magnitude of this association should be interpreted in light of potential adverse effects of postponing surgery.

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