HHS Public Access
Author manuscript
Anesth Analg. Author manuscript; available in PMC 2022 July 01.

Published in final edited form as:
Anesth Analg. 2021 July 01; 133(1): 160–167. doi:10.1213/ANE.0000000000005180.

Association between behavioral and learning outcomes and single exposures to procedures requiring general anesthesia prior to age 3: Secondary analysis of data from Olmsted County, Minnesota

David O. Warner, M.D.[1], **Danqing Hu, M.D., Ph.D.**[1], **Michael J. Zaccariello, Ph.D., L.P.**[2], **Darrell R. Schroeder, M.S.**[3], **Andrew C. Hanson, B.S.**[3], **Robert T. Wilder, M.D.**[1], **Juraj Sprung, M.D., Ph.D.**[1], **Randall P. Flick, M.D., M.P.H.**[1]

[1]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota

[2]Department of Psychiatry Psychology, Mayo Clinic, Rochester, Minnesota

[3]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

Abstract

Background: Two prior population-based (children born in Olmsted County, MN), retrospective cohort studies both found that multiple exposures to anesthesia prior to age 3 were associated with a significant increase in the frequency of attention deficit hyperactivity disorder (ADHD) and learning disabilities (LD) later in life. The primary purpose of this secondary analysis of these data was to test the hypothesis that a single exposure to anesthesia prior to age 3 was associated with an increased risk of ADHD. We also examined the association of single exposures with LD and the need for individualized educational plans as secondary outcomes.

Methods: This analysis includes 5,339 children who were unexposed to general anesthesia prior to age 3 (4,876 born from 1976–1982 and 463 born from 1996–2000), and 1,054 children who had a single exposure to anesthesia prior to age 3 (481 born from 1976–1982 and 573 born from 1996–2000). The primary outcome of interest was ADHD. Secondary outcomes included learning

Corresponding Author: David O. Warner, M.D., Mayo Clinic, Department of Anesthesiology and Perioperative Medicine, 200 1st St SW, Rochester, MN 55905, Ph: 507-255-4288; warner.david@mayo.edu.

Author contributions:
David Warner: The author conceived of the study, obtained funding, directed study conduct and data analysis, drafted the manuscript, and approved the final version;
Danquing Hu: The author participated in study design, obtained much of the data, helped direct the analysis, edited the manuscript for important intellectual content, and approved the final version
Michael Zaccariello: The author participated in study design, obtained much of the data, helped direct the analysis, edited the manuscript for important intellectual content, and approved the final version.
Andrew Hanson: The author designed and conducted the statistical analysis, helped draft the manuscript, and approved the final version.
Darrell Schroeder: The author designed and conducted the statistical analysis, helped draft the manuscript, and approved the final version.
Robert Wilder: The author helped conceive the study, helped obtain the underlying data, edited the manuscript for important intellectual content, and approved the final version.
Juraj Sprung: The author helped conceive the study, helped obtain the underlying data, edited the manuscript for important intellectual content, and approved the final version.
Randall Flick The author helped conceive the study and obtain funding, edited the manuscript for important intellectual content, and approved the final version.

Conflicts of interest: None

disabilities (reading, mathematics, and written language) and the need for individualized educational programs (speech/language and emotion/behavior). To compare the incidence of each outcome between those who were unexposed and singly-exposed to anesthesia prior to the age of 3 years an inverse probability of treatment weighted proportional hazards model was used.

Results: For children not exposed to anesthesia, the estimated cumulative frequency (95% CI) of ADHD at age 18 was 7.3% (95% CI 6.5% to 8.1%) and 13.0% (95% CI 10.1% to 16.8%) for the 1976–1982 and 1996–2000 cohorts respectively. For children exposed to a single anesthetic prior to age 3, the cumulative frequency of ADHD was 8.1% (95% CI 5.3% to 12.4%) and 17.6% (95% CI 14.0% to 21.9%) for the 1976–1982 and 1996–2000 cohorts respectively. In weighted analyses, single exposures were not significantly associated with an increased frequency of ADHD (hazard ratio [HR] 1.21, 95% CI 0.91 to 1.60, p=0.184). Single exposures were also not associated with an increased frequency of any LD (HR 0.98, 95% CI 0.78 to 1.23), or the need for individualized education plans

Conclusion: This analysis did not find evidence that single exposures to procedures requiring general anesthesia prior to age three are associated an increased risk of developing ADHD, LD, or the need for individualized educational plans in later life.

Introduction

Two series of retrospective studies involving separate cohorts of children born in Olmsted County, MN (from 1976–1982 or 1996–2000, dates both inclusive) found that those who were exposed to two or more anesthetics at a young age (i.e., were multiply-exposed) were approximately twice as likely to develop attention-deficit hyperactivity disorder (ADHD) or a learning disability (LD) by adolescence, compared with those not exposed to anesthesia.[1–4] In another cohort of children born in Olmsted County from 1994 to 2007 who were recruited for prospective neuropsychological testing, children exposed to multiple anesthetics prior to age 3 exhibited deficits in fine motor skills with more modest processing speed impairment, without deficits in other neuropsychological domains such as general intelligence and memory, compared with children who were not exposed.[5,6] Furthermore, parents of children who were multiply-exposed reported a higher frequency of behavioral/emotional problems (including ADHD-like problems) and difficulties with executive function. This constellation of findings is consistent with evidence linking problems with fine motor skills and processing speed with ADHD, LD, and behavioral difficulties in the general population.[7,8]

Because these associations were determined in observational studies, it is not possible to conclude that they are caused by exposure to the anesthetic medications themselves, although this is a plausible interpretation given the specificity of the pattern of deficits, evidence from preclinical models, and proposed biologically-plausible mechanisms.[9–13] If anesthesia is causal, there should be a biological gradient (i.e., a dose-response relationship) between exposure and outcomes – a necessary, but not sufficient, condition to make causal inferences.[14] In the Olmsted County study involving prospective assessment, the estimates for the effect of single exposures on fine motor skills, processing speed, and parent reports of behavioral problems (compared with no exposures) were intermediate between the estimates for multiple exposures and 0, but the 95% confidence intervals (CI) did not exclude 0.[5] Parents of singly-exposed children reported significantly more problems with executive function and reading. In the two retrospective Olmsted County studies, the estimates for the hazard ratios (HR) for ADHD comparing children with single and no exposures were greater than 1, but the 95% CI for these estimates did not exclude unity (HR 1.18 [95% CI 0.79 to 1.77] and 1.33 [95% CI 0.92 to 1.94]).[1,2,4] If single exposures are associated with a small effect on the frequency of ADHD, the number of subjects in available studies may not provide sufficient precision of effect estimates to conclude statistical significance. Two prior studies utilizing large administrative datasets found estimated hazard ratios of 1.11 (95% CI 0.88 to 1.41)[15] and 1.31 (95% CI 1.25 to 1.37)[16] for the association between single exposures to anesthesia and ADHD, suggesting that the magnitude of any association is small.

For the two birth cohorts employed in the retrospective Olmsted County studies, the available underlying data were identical, including anesthesia exposure histories, birth and parental characteristics, and outcomes.[1–4,17] Some details of analytic procedures differed between studies, including the method used to account for imbalances in child and parental characteristics between exposed and unexposed groups, and the age threshold to define exposure. However, the availability of similar underlying data provides the opportunity to perform a combined analysis of the two cohorts, increasing the precision of effect estimates.

The primary purpose of this secondary analysis of data from retrospective studies of two birth cohorts from Olmsted County, MN was to search for evidence of a biological gradient between exposure and outcomes by testing the hypothesis that a single exposure to anesthesia prior to age 3 was associated with an increased risk of ADHD. We also examined the association of a single exposure with LD and the need for individualized educational plans as secondary outcomes.

METHODS

The studies incorporated in this secondary analysis were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards (Rochester, Minnesota). 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 according to Minnesota Statutes Section 144.295. As a part of this process, the Institutional Review Boards waived the requirement for written informed consent. Methods used to construct the birth cohorts have been previously described in detail and are here summarized.[1,17] Both included children born to mothers resident in Olmsted County, MN who were still resident in the local school district at age 5. For children born from 1976–1982, the study cohort consisted of all children meeting these two requirements. For children born from 1996–2000, a study cohort that included children unexposed, singly-exposed, and multiply exposed to anesthesia prior to age 3 was selected based on their propensity for receiving general anesthesia. For both study cohorts, children with severe intellectual disability were excluded as primary outcomes could not be ascertained.

For the present report, analyses were restricted to cohort members who were either unexposed or singly exposed to anesthesia prior to the age of 3 years. The primary outcome of interest was ADHD and secondary outcomes included learning disabilities (reading, mathematics, and written language) and the need for individualized educational programs (speech/language and emotion/behavior). Diagnostic criteria for these outcomes have been described previously.[1–4] For each outcome, children were considered at risk from birth until the date at which they met criteria for the given outcome, with censoring occurring at age 19 or at the date of last follow-up for children who emigrated out of Olmsted County prior to the age of 19. In order to account for potential confounding variables, inverse probability of treatment weighting (IPTW) was used. Treatment weights were calculated using propensity scores which were obtained separately for each study cohort using logistic regression with anesthesia exposure prior to the age of 3 as the dependent variable. Covariates used for the calculation of the propensity scores included: mother's and father's age, years of education, and marital status, estimated gestational age, birth weight, date of birth, and aggregated diagnostic groups (ADG), a method of quantifying overall health status. APGAR scores at 1 and 5 minutes, and the HOUSES index[18] (a measure of socioeconomic status) were included as covariates in the propensity model for the 1996–2000 study cohort.

For each of the study cohorts, weighted estimates of the cumulative incidence of each outcome at age 18 were obtained using the Kaplan-Meier method. To compare the incidence of each outcome between those who were unexposed and singly-exposed to anesthesia prior to the age of 3 years a weighted proportional hazards model was used. In all cases, exposure to anesthesia prior to age three (unexposed vs singly exposed) was the explanatory variable of interest and study cohort (1976–1982, 1996–2000) was included as a stratification variable. The strata-by-exposure interaction term was used to assess whether the effect of anesthesia exposure differed between cohorts. In order to accommodate missing data for some of the variables included in the calculation of the propensity scores, the calculation of propensity scores and IPTW analyses were performed with multiple-imputation, using 20 imputed datasets. In all cases, two-tailed p-values < 0.05 are considered statistically significant.

RESULTS

This analysis includes 5,339 children who were unexposed to general anesthesia prior to age 3 (4,876 born from 1976–1982 and 463 born from 1996–2000), and 1,054 children who had a single exposure to anesthesia prior to age 3 (481 born from 1976–1982 and 573 born from 1996–2000). Most characteristics of unexposed and singly-exposed children were well-matched after IPTW, with standardized differences <0.1 for birth and parent characteristics (Table 1). Some aggregated diagnostic group (ADG) categories had residual standardized differences of >0.1 after weighting (Table 2).

In the 1976–1982 cohort, the estimated cumulative frequency (95% CI) of ADHD at age 18 was 7.3% (95% CI 6.5% to 8.1%) for unexposed children and 8.1% (95% CI 5.3% to 12.4%) for singly-exposed children. In the 1976–1982 cohort, the estimated cumulative frequency of ADHD at age 18 was 13.0% (95% CI 10.1% to 16.8%) for unexposed children and 17.6% (95% CI 14.0% to 21.9%) for singly-exposed children. In IPTW-weighted analyses, single exposures were not significantly associated with an increased frequency of ADHD (hazard ratio [HR] 1.21, 95% CI 0.91 to 1.60, p=0.18)(Table 3).

In the 1996–2000 cohort, the estimated cumulative frequency (95% CI) of any LD at age 18 was 20.0% (95% CI 18.8% to 21.3%) for unexposed children and 18.6% (95% CI 14.2% to 24.2%) for singly-exposed children. In the 1996–2000 cohort, the estimated cumulative frequency (95% CI) of any LD at age 18 was 14.3% (95% CI 10.1% to 19.9%) for unexposed children and 13.8% (95% CI 10.7% to 17.6%) for singly-exposed children. In IPTW-weighted analyses, single exposures were also not associated with an increased frequency of any LD (HR 0.98, 95% CI 0.78 to 1.23, p=0.87), or any individual LD (Table 3).

The cumulative frequency of needing any individual educational plan for children who were not exposed to anesthesia was 8.1% (7.3% to 9.0%) and 14.5% (11.4% to 18.3%) for the 1976–1982 and 1996–2000 cohorts respectively; for those exposed to a single anesthetic prior to age 3 the cumulative frequency at age 18 was 8.0% (5.2% to 12.2%) and 10.3% (7.8% to 13.7%). From IPTW-weighted proportional hazards regression analysis, single exposures were not associated with a change in the frequency of children requiring an individualized educational plan for either speech and language or emotional and behavioral disorders (Table 3).

For all outcomes, the interaction term in the adjusted model between cohort membership and hazard ratio was not significant (i.e., the association with anesthesia exposure did not differ between cohorts) (Table 3), indicating that the magnitude of associations were not different in the two cohorts.

DISCUSSION

The main finding of this secondary analysis that combined data from two studies examining separate birth cohorts is that exposure to a single general anesthetic prior to the age of three was not significantly associated with the risk of developing ADHD, LD, or the need for an individualized education plan later in life.

The multiple challenges of determining a phenotype associated with anesthesia exposure have been thoroughly discussed and reviewed, including the strengths and limitations of ADHD and LD as potential phenotypes.[14,19–21] We here note that unique among investigations of anesthesia neurotoxicity, the two series of studies used in this secondary analysis applied consistent research criteria to make both diagnoses, employing both medical and school record information that was identical in both series.[1–4] Several differences between the two studies are notable. First, the characteristics of the unexposed comparator groups differed among studies as noted in the Methods, such that there were more unexposed children available for analysis in the first cohort. Second, the analytic methods used to adjust for differences in parental and child characteristics differed in the original analyses. Third, as previously noted overall secular trends in the incidence of ADHD (increasing over time) and LD (decreasing over time) were reflected in these cohorts.[2,22,23] Finally, there were several advances in anesthesia practice after 1985, including the discontinuation of halothane use, the adoption of pulse oximetry and capnography as standard monitors, and increased use of subspecialty-trained pediatric anesthesiologists at Mayo Clinic. Despite these differences, children receiving multiple exposures were approximately twice as likely to develop either ADHD or LD in the original analysis of both series of studies, demonstrating a reproducible association.

Two other studies have utilized the diagnosis of ADHD as a phenotype for anesthesia-associated injury, ascertained by diagnostic codes in administrative datasets. Ko et al[15] utilized a large national sample of children in Taiwan, matching children with exposure prior to 3 years with unexposed children on birth year and gender, and adjusting for 4 variables (residence, parental occupation, perinatal conditions, and congenital anomalies). The adjusted HR for the association of single exposures was 1.11 (95% CI 0.88 to 1.41). The major limitation of this analysis was that children were between ages 5–10 at conclusion of follow up, insufficient to diagnose many eventual ADHD cases. Indeed, the cumulative incidence of ADHD in this cohort was 3.9%, considerably less than contemporaneous population estimates in Taiwan.[15] Given that the data from the Olmsted County cohorts shows that anesthesia-associated differences in ADHD frequency develop at later ages,[2,4] this limited follow up biases against finding differences. Ing et al[16] utilized Medicaid datasets from the states of Texas and New York, using propensity matching based on 50 variables to identify unexposed controls for children undergoing one of 4 common procedures requiring general anesthesia at less than 5 years of age. The HR for the association of single exposures was 1.31 (95% CI 1.25 to 1.37). In a subsequent analysis of this same cohort that used persistent use of ADHD medication as the outcome, the HR was similar (1.37 [95% CI 1.30 to 1.44]).[24]

Thus, each extant analysis found HR of >1 for the association of a single exposure to anesthesia at a young age with developing ADHD later in life, but the CI for the estimate excluded one only for the Ing study, which included the greatest number of ADHD cases in exposed children (1,223 in the Ing study [personal communication, 9/24/19], vs. 152 in the Ko study and 106 in the current analysis). These findings would be consistent with either a small effect size that requires a larger sample to demonstrate statistical significance or with no consistent association across the three analyses. Indeed, for a matched cohort design, a total of 944 events are required to have statistical power (two-tailed, alpha=0.05) of 80% to detect a hazard ration of 1.2. Assuming an incidence of ADHD among singly-exposed of approximately 17% by age 19, this would require approximately 2900 subjects per group in a matched cohort design.

Studies from the Olmsted County birth cohorts are the only investigations to utilize LD as an outcome, likely because ascertainment requires access to educational records which may be difficult to obtain. LD is an educational label used in practice to provide additional educational resources to children with difficulty in communication and/or academic skills development that impair learning.[20] This combined analysis provided no evidence that single exposures are associated with any form of LD. This finding implies either that any association is very small and not detectable with the available sample size, or that any learning impairment associated with single exposures is below the threshold for LD designation.

The need for individualized educational plans, either for emotional and behavioral disorders or speech and language disorders, was used in these studies as an indicator of potential concerns by school personnel for problems with language abilities or behavior.[2,3] Multiple exposures were associated with plans for speech and language disorders in the 1976–1982 cohort but not the 1996–2000 cohort; there was no association with plans for emotional and behavioral disorders in either cohort. When combined with the lack of association with single exposure, these findings suggest that there is little evidence that anesthesia exposure is associated with alterations in these domains sufficient to prompt school intervention. This finding would be consistent with prior studies showing only very small or no associations between anesthesia exposure and teacher-assessed readiness for school.[25,26]

As discussed extensively in prior work, there are several potential explanations for any associations between exposure and outcomes other than a causal effect of anesthesia.[2,5,21] Recognizing these limitations, it still is instructive to consider the implications of a small HR for a relatively common environmental exposure in a relatively prevalent condition such as ADHD. According to the National Survey of Child Health, a parent survey, in 2016 9.4% of children 2–17 years of age (6.1 million children) had been diagnosed with ADHD in the United States (US).[27] According to our prior work, 11.5% of children in Olmsted County have a single exposure to anesthesia prior to age 3.[28] If that proportion is extrapolated to the approximately 4 million children born annually in the US, ~480,000 will require a single general anesthetic prior to age 3. If the expected cumulative incidence of ADHD diagnosis is 9.4% in the general population, 45,000 of these children would be expected to develop ADHD in the absence of exposure. If the true HR for developing ADHD after single exposures is 1.21, an additional ~9,450 children would be expected to develop ADHD (0.24% of the underlying population of 4 million). Thus, for this effect size, single exposures to anesthesia would have only a small effect on the population ADHD incidence, increasing the cumulative incidence of ADHD in the US by approximately 2.5% (0.24/9.4). So even if there was a small causal effect of anesthesia on ADHD, it would have little impact on the population prevalence of ADHD.

In conclusion, this secondary analysis of two cohorts of children born in Olmsted County, MN provides a more precise estimate of association, but did not find evidence that single exposures to procedures requiring general anesthesia prior to age three are associated an increased risk of developing ADHD, LD, or the need for individualized educational plans in later life.

Acknowledgments

This work was supported by R01 HD071907 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health, and also utilized the resources of the Rochester Epidemiology Project, supported by R01 AG034676 from the National Institute on Aging of the National Institutes of Health.

Glossary of Terms

ADHD	Attention deficit hyperactivity disorder
LD	Learning disability
CI	Confidence interval

HR	Hazard ratio
IPTW	Inverse probability of treatment weighting
ADG	Aggregated diagnostic group
US	United States

REFERENCES

1. Wilder RT, Flick RP, Sprung J, et al. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009;110(4):796–804. [PubMed: 19293700]
2. Hu D, Flick RP, Zaccariello MJ, et al. Association between exposure of young children to procedures requiring general anesthesia and aearning and Bbehavioral outcomes in a population-based birth cohort. Anesthesiology. 2017;127(2):227–240. [PubMed: 28609302]
3. Flick RP, Katusic SK, Colligan RC, et al. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics. 2012;128(5):e1053–1061.
4. Sprung J, Flick RP, Katusic SK, et al. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc. 2012;87(2):120–129. [PubMed: 22305025]
5. Warner DO, Zaccariello MJ, Katusic SK, et al. Neuropsychological and behavioral butcomes after exposure of young children to procedures requiring general anesthesia: The Mayo Anesthesia Safety in Kids (MASK) Study. Anesthesiology. 2018;129(1):89–105. [PubMed: 29672337]
6. Zaccariello MJ, Frank RD, Lee M, et al. Patterns of neuropsychological changes after general anaesthesia in young children: secondary analysis of the Mayo Anesthesia Safety in Kids study. Br J Anaesth. 2019;122(5):671–681. [PubMed: 30982593]
7. Piek JP, Dyck MJ, Nieman A, et al. The relationship between motor coordination, executive functioning and attention in school aged children. Arch Clin Neuropsychol. 2004;19(8):1063–1076. [PubMed: 15533697]
8. Kaiser ML, Schoemaker MM, Albaret JM, Geuze RH. What is the evidence of impaired motor skills and motor control among children with attention deficit hyperactivity disorder (ADHD)? Systematic review of the literature. Res Dev Disabil. 2014;36C:338–357. [PubMed: 25462494]
9. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. Nat Rev Neurosci. 2016;17(11):705–717. [PubMed: 27752068]
10. Disma N, Mondardini MC, Terrando N, Absalom AR, Bilotta F. A systematic review of methodology applied during preclinical anesthetic neurotoxicity studies: important issues and lessons relevant to the design of future clinical research. Paediatr Anaesth. 2016;26(1):6–36. [PubMed: 26530523]
11. Lee JH, Zhang J, Wei L, Yu SP. Neurodevelopmental implications of the general anesthesia in neonate and infants. Exp Neurol. 2015;272:50–60. [PubMed: 25862287]
12. Lin EP, Lee JR, Lee CS, Deng M, Loepke AW. Do anesthetics harm the developing brain? An integrative analysis of animal and human studies. Neurotoxicol Teratol. 2017;60:117–128. [PubMed: 27793659]
13. Xu L, Hu Y, Huang L, et al. The association between attention deficit hyperactivity disorder and general anaesthesia - a narrative review. Anaesthesia. 2019;74(1):57–63. [PubMed: 30511754]
14. Flick RP, Warner DO. A users' guide to interpreting observational studies of pediatric anesthetic neurotoxicity: The lessons of Sir Bradford Hill. Anesthesiology. 2012;117(3):459–462. [PubMed: 22797284]
15. Ko WR, Liaw YP, Huang JY, et al. Exposure to general anesthesia in early life and the risk of attention deficit/hyperactivity disorder development: a nationwide, retrospective matched-cohort study. Paediatr Anaesth. 2014;24(7):741–748. [PubMed: 24612161]
16. Ing C, Sun M, Olfson M, et al. Age at exposure to surgery and anesthesia in children and association with mental disorder diagnosis. Anesth Analg. 2017;125:1988–1998. [PubMed: 28857799]

17. Hu D, Flick RP, Gleich SJ, et al. Construction and characterization of a population-based cohort to study the association of anesthesia exposure with neurodevelopmental outcomes. PLoS One. 2016;11(5):e0155288. [PubMed: 27167371]

18. Juhn YJ, Beebe TJ, Finnie DM, et al. Development and initial testing of a new socioeconomic status measure based on housing data. J Urban Health. 2011;88(5):933–944. [PubMed: 21499815]

19. Walkden GJ, Pickering AE, Gill H. Assessing long-term neurodevelopmental outcome following general anesthesia in early childhood: Challenges and opportunities. Anesth Analg. 2019;128(4):681–694. [PubMed: 30883414]

20. Beers SR, Rofey DL, McIntyre KA. Neurodevelopmental assessment after anesthesia in childhood: review of the literature and recommendations. Anesth Analg. 2014;119(3):661–669. [PubMed: 25137001]

21. Davidson AJ, Sun LS. Clinical evidence for any effect of anesthesia on the developing brain. Anesthesiology. 2018;128(4):840–853. [PubMed: 29210706]

22. Cortiella C, Horowitz SH. The State of Learning Disabilities: Facts, Trends, and Emerging Issues. New York: National Center for Learning Disabilities, 2014.

23. Prevention CfDCa. Key Findings: Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD: United States, 2003—2011. Centers for Disease Control and Prevention http://www.cdc.gov/ncbddd/adhd/features/key-findings-adhd72013.html. Published 2014, accessed 7/10/20..

24. Ing C, Ma X, Sun M, et al. Exposure to surgery and anesthesia in early childhood and subsequent use of attention deficit hyperactivity disorder medications. Anesth Analg. 1 8 2020 published ahead of print

25. 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(4):667–677. [PubMed: 27655179]

26. O'Leary JD, Janus M, Duku E, et al. A population-based study evaluating the association between surgery in early life and child development at primary school entry. Anesthesiology. 2016;125(2):272–279. [PubMed: 27433745]

27. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. J Clin Child Adolesc Psychol. 2018;47(2):199–212. [PubMed: 29363986]

28. Shi Y, Hu D, Rodgers EL, et al. Epidemiology of general anesthesia prior to age 3 in a population-based birth cohort. Paediatr Anaesth. 2018;28(6):513–519. [PubMed: 29532559]

Author Manuscript

Author Manuscript

Author Manuscript

Key points

Question:

Is a single exposure to anesthesia prior to age 3 associated with an increased frequency of attention deficit hyperactivity disorder later in life?

Findings:

In weighted analyses, single exposures were not significantly associated with an increased frequency of ADHD (hazard ratio [HR] 1.21, 95% CI 0.91 to 1.60, p=0.184).

Meaning:

This analysis did not find evidence that single exposures to procedures requiring general anesthesia prior to age three are associated an increased risk of developing attention deficit hyperactivity disorder.

Table 1 -

Birth and parental characteristics *

Characteristic	'76-'82 cohort						'96-'00 cohort					
	Unweighted statistics			*Weighted statistics*			*Unweighted statistics*			*Weighted statistics*		
	Unexposed (n=4,876)	*Singly exposed (n=375)*	*SD*	*Unexposed*	*Singly exposed*	*SD*	*Unexposed (n=463)*	*Singly exposed (n=457)*	*SD*	*Unexposed*	*Singly exposed*	*SD*
Mother's age (yeats)	26.5 (4.7)	26.9 (4.7)	0.08	26.5 (4.7)	26.5 (4.5)	<.01	29.3 (5.5)	29.2 (5.7)	<.01	29.3 (5.5)	29.3 (5.6)	<.01
Father's age (yeats)	28.5 (5.4)	29.1 (5.3)	0.10	28.6 (5.4)	28.5 (5.3)	0.02	31.5 (6.5)	31.3 (6.1)	0.03	31.4 (6.4)	31.4 (6.0)	<.01
Mother's education (yeats)												
<12	343 (7%)	22 (6%)	0.05	(7%)	(6%)	0.04	38 (8%)	45 (10%)	0.06	(9%)	(9%)	0.01
12	1584 (32%)	120 (32%)	0.01	(32%)	(33%)	<.01	80 (17%)	80 (18%)	<.01	(17%)	(17%)	0.01
13–15	1684 (35%)	129 (34%)	<.01	(35%)	(34%)	<.01	125 (27%)	120 (26%)	0.02	(27%)	(27%)	0.01
≥16	1265 (26%)	104 (28%)	0.04	(26%)	(27%)	0.02	220 (48%)	212 (46%)	0.02	(47%)	(47%)	<.01
Father's education (years)												
<12	337 (7%)	20 (5%)	0.07	(7%)	(6%)	0.02	31 (7%)	33 (7%)	0.02	(7%)	(7%)	<.01
12	1394 (29%)	102 (27%)	0.03	(28%)	(27%)	0.02	104 (22%)	100 (22%)	0.01	(22%)	(22%)	<.01
13–15	1262 (26%)	91 (24%)	0.04	(26%)	(28%)	0.04	110 (24%)	120 (26%)	0.06	(25%)	(25%)	0.01
≥16	1883 (39%)	162 (43%)	0.09	(39%)	(39%)	<.01	218 (47%)	204 (45%)	0.05	(46%)	(46%)	0.02
Parents married at time of birth	4522 (93%)	353 (94%)	0.06	(93%)	(93%)	<.01	383 (83%)	379 (83%)	<.01	(83%)	(83%)	0.02
Male sex	2469 (51%)	253 (67%)	0.35	(52%)	(51%)	0.01	272 (59%)	275 (60%)	0.03	(59%)	(59%)	<.01
Estimated gestational age (weeks)	40.0 (2.0)	39.9 (2.4)	0.06	40.0 (2.0)	40.1 (2.1)	0.05	38.5 (2.6)	38.6 (2.5)	0.06	38.6 (2.5)	38.6 (2.5)	<.01
Birth weight (g)	3474 (532)	3418 (629)	0.10	3471 (536)	3496 (576)	0.05	3336 (737)	3356 (647)	0.03	3356 (726)	3353 (648)	<.01
Apgar (1 min)							8 (7, 9)	8 (7, 9)	0.08	8 (7, 9)	8 (7, 9)	<.01
Apgar (5 min)							9 (9, 10)	9 (9, 10)	0.15	9 (9, 10)	9 (9, 10)	<.01
HOUSES (quartile)												
1st							115 (25%)	109 (24%)	0.02	(26%)	(25%)	0.03
2nd							123 (27%)	98 (21%)	0.12	(24%)	(24%)	0.01
3rd							117 (25%)	111 (24%)	0.02	(24%)	(24%)	<.01
4th							108 (23%)	139 (30%)	0.16	(26%)	(27%)	<.01

*Exposure status is according to number of exposures prior to age 3. Numbers are n (%) for categorical variables and mean (standard deviation, SD) for continuous variables except for APGAR scores which are median (Q1, Q3). Both weighted and unweighted samples are summarized in both time-frames. Unweighted characteristics differ across time-frames due to sample selection methods. The. HOUSES index (a measure of socioeconomic status) was not available for ‘76-’82 cohort. APGAR scores were missing for 70% of subjects in the ‘76-’82 cohort and therefore were not included in the propensity models or summary statistics. To account for missing data, multiple-imputation was used. This table summarizes a single imputation and therefore has no missing data. In the ‘76-’82 cohort, data were missing for father’s age (n=271, 5.2%), mother’s education (n=447, 8.5%), father’s education (n=718, 13.7%), gestational age (n=327, 6.2%), and birth weight (n=10, 0.2%). In the ‘96-’00 cohort, data were missing for father’s age (n=41, 4.5%), mother’s education (n=16, 1.7%), father’s education (n=78, 8.5%), and HOUSES (n=88, 9.6%).

Table 2 -

Health status*

Characteristic	'76-'82 cohort: Unweighted statistics: Unexposed (n=4,876)	'76-'82 cohort: Unweighted statistics: Singly exposed (n=375)	'76-'82 cohort: Unweighted statistics: SD	'76-'82 cohort: Weighted statistics: Unexposed	'76-'82 cohort: Weighted statistics: Singly exposed	'76-'82 cohort: Weighted statistics: SD	'96-'00 cohort: Unweighted statistics: Unexposed (n=463)	'96-'00 cohort: Unweighted statistics: Singly exposed (n=457)	'96-'00 cohort: Unweighted statistics: SD	'96-'00 cohort: Weighted statistics: Unexposed	'96-'00 cohort: Weighted statistics: Singly exposed	'96-'00 cohort: Weighted statistics: SD
Johns Hopkins ADGs												
Time Limited: Minor	2382 (49%)	214 (57%)	0.17	(49%)	(53%)	0.08	422 (91%)	423 (93%)	0.05	(92%)	(92%)	0.02
Time Limited: Minor-Primary Infections	4092 (84%)	335 (89%)	0.16	(84%)	(84%)	<.01	458 (99%)	454 (99%)	0.03	(99%)	(99%)	0.02
Time Limited: Major	565 (12%)	88 (23%)	0.32	(12%)	(16%)	0.11	155 (33%)	154 (34%)	<.01	(34%)	(35%)	<.01
Time Limited: Major-Primary Infections	796 (16%)	98 (26%)	0.24	(16%)	(24%)	0.18	172 (37%)	175 (38%)	0.02	(38%)	(37%)	0.02
Allergies	390 (8%)	46 (12%)	0.14	(8%)	(12%)	0.14	105 (23%)	128 (28%)	0.12	(24%)	(28%)	0.10
Asthma	395 (8%)	36 (10%)	0.05	(8%)	(9%)	0.03	63 (14%)	80 (18%)	0.11	(14%)	(17%)	0.09
Likely to Recur: Discrete	492 (10%)	59 (16%)	0.17	(10%)	(14%)	0.11	234 (51%)	238 (52%)	0.03	(51%)	(52%)	0.01
Likely to Recur: Discrete Infections	3918 (80%)	331 (88%)	0.22	(81%)	(86%)	0.16	441 (95%)	448 (98%)	0.15	(96%)	(98%)	0.15
Likely to Recur: Progressive	10 (<1%)	1 (<1%)	<.01	(0%)	(0%)	<.01	0 (0%)	2 (<1%)	0.03	(0%)	(0%)	0.03
Chronic Medical: Stable	390 (8%)	58 (15%)	0.23	(8%)	(14%)	0.20	143 (31%)	127 (28%)	0.07	(32%)	(28%)	0.08
Chronic Medical: Unstable	514 (11%)	58 (15%)	0.15	(11%)	(12%)	0.05	123 (27%)	116 (25%)	0.03	(28%)	(26%)	0.05
Chronic Specialty: Stable-Orthopedic	115 (2%)	14 (4%)	0.08	(2%)	(4%)	0.10	15 (3%)	14 (3%)	0.01	(3%)	(3%)	0.03
Chronic Specialty: Stable-Ear, Nose, Throat	47 (1%)	12 (3%)	0.14	(1%)	(2%)	0.08	127 (27%)	156 (34%)	0.15	(29%)	(34%)	0.11
Chronic Specialty: Stable-Eye	1153 (24%)	116 (31%)	0.16	(24%)	(29%)	0.11	142 (31%)	138 (30%)	0.01	(32%)	(30%)	0.04
Chronic Specialty: Unstable-Orthopedic	0 (0%)	0 (0%)		(0%)	(0%)		1 (<1%)	2 (<1%)	0.01	(0%)	(0%)	0.01
Chronic Specialty: Unstable-Ear, Nose, Throat	1 (<1%)	1 (<1%)	0.02	(0%)	(0%)	0.02	71 (15%)	116 (25%)	0.25	(18%)	(23%)	0.12

Characteristic	'76-'82 cohort: Unweighted statistics: Unexposed (n=4,876)	'76-'82 cohort: Unweighted statistics: Singly exposed (n=375)	'76-'82 cohort: Unweighted statistics: SD	'76-'82 cohort: Weighted statistics: Unexposed	'76-'82 cohort: Weighted statistics: Singly exposed	'76-'82 cohort: Weighted statistics: SD	'96-'00 cohort: Unweighted statistics: Unexposed (n=463)	'96-'00 cohort: Unweighted statistics: Singly exposed (n=457)	'96-'00 cohort: Unweighted statistics: SD	'96-'00 cohort: Weighted statistics: Unexposed	'96-'00 cohort: Weighted statistics: Singly exposed	'96-'00 cohort: Weighted statistics: SD
Chronic Specialty: Unstable-Eye	103 (2%)	23 (6%)	0.20	(2%)	(5%)	0.17	37 (8%)	34 (7%)	0.02	(8%)	(8%)	0.02
Dermatologic	749 (15%)	81 (22%)	0.16	(15%)	(19%)	0.10	149 (32%)	148 (32%)	<.01	(33%)	(32%)	0.01
Injuries/Adverse Effects: Minor	2027 (42%)	199 (53%)	0.23	(42%)	(46%)	0.08	245 (53%)	251 (55%)	0.04	(54%)	(55%)	0.03
Injuries/Adverse Effects: Major	1215 (25%)	135 (36%)	0.24	(25%)	(36%)	0.23	208 (45%)	227 (50%)	0.10	(47%)	(50%)	0.06
Psychosocial: Time Limited: Minor	175 (4%)	20 (5%)	0.08	(4%)	(4%)	<.01	116 (25%)	119 (26%)	0.02	(27%)	(25%)	0.03
Psychosocial: Persistent/Recurrent, Stable	297 (6%)	43 (11%)	0.19	(6%)	(6%)	<.01	98 (21%)	98 (21%)	<.01	(21%)	(21%)	<.01
Psychosocial: Persistent/Recurrent, Unstable	0 (0%)	0 (0%)		(0%)	(0%)		9 (2%)	5 (1%)	0.05	(2%)	(1%)	0.05
Signs/Symptoms: Minor	1558 (32%)	148 (39%)	0.16	(32%)	(37%)	0.10	389 (84%)	396 (87%)	0.07	(84%)	(87%)	0.07
Signs/Symptoms: Uncertain	865 (18%)	97 (26%)	0.20	(18%)	(22%)	0.10	429 (93%)	442 (97%)	0.18	(93%)	(97%)	0.18
Signs/Symptoms: Major	1123 (23%)	120 (32%)	0.20	(24%)	(29%)	0.12	306 (66%)	307 (67%)	0.02	(67%)	(68%)	0.02
Discretionary	2454 (50%)	284 (76%)	0.55	(51%)	(69%)	0.37	323 (70%)	358 (78%)	0.20	(71%)	(79%)	0.18
See and Reassure	197 (4%)	20 (5%)	0.06	(4%)	(5%)	0.05	226 (49%)	225 (49%)	<.01	(51%)	(48%)	0.06
Prevention/ Administrative	4781 (98%)	370 (99%)	0.04	(98%)	(98%)	0.01	462 (100%)	457 (100%)	0.01	(100%)	(100%)	0.01
Malignancy	68 (1%)	2 (1%)	0.06	(1%)	(0%)	0.08	0 (0%)	2 (<1%)	0.03	(0%)	(0%)	0.03
Dental	188 (4%)	21 (6%)	0.08	(4%)	(5%)	0.05	5 (1%)	33 (7%)	0.31	(3%)	(6%)	0.14

* The John's Hopkins aggregated diagnostic groups (ADG) provide a means to quantify overall health status. Exposure status is according to number of exposures prior to age 3. Numbers are n (%). Both weighted and unweighted samples are summarized in both time-frames. Unweighted characteristics differ across time-frames due to sample selection methods. To account for missing data, multiple-imputation was used. This table summarizes a single imputation and therefore has no missing data. In the '76-'82 cohort, data were missing for some subjects (n=64, 1.2%).

Table 3 -

Results from weighted analyses*

	'76-'82 cohort		'96-'00 cohort			Combined cohorts	
Outcome	***Est. 95% CI***	***P***	***Est. 95% CI***	***P***	***Interaction P***	***Est. 95% CI***	***P***
ADHD	1.12 (0.73, 1.70)	0.610	1.29 (0.86, 1.92)	0.215	0.632	1.21 (0.91, 1.60)	0.184
Learning disability	0.93 (0.70, 1.25)	0.644	1.08 (0.74, 1.60)	0.679	0.542	0.98 (0.78, 1.23)	0.870
Reading LD	0.98 (0.69, 1.39)	0.925	0.96 (0.59, 1.57)	0.876	0.942	0.98 (0.73, 1.30)	0.872
Mathematics LD	0.93 (0.67, 1.29)	0.667	0.93 (0.58, 1.49)	0.762	0.997	0.93 (0.71, 1.22)	0.600
Written language LD	0.98 (0.71, 1.35)	0.890	1.39 (0.84, 2.29)	0.200	0.251	1.07 (0.83, 1.39)	0.596
IEP-SL	1.10 (0.66, 1.85)	0.713	0.82 (0.52, 1.30)	0.408	0.409	0.93 (0.65, 1.34)	0.716
IEP-EBD	0.89 (0.47, 1.68)	0.718	0.56 (0.23, 1.39)	0.212	0.418	0.72 (0.40, 1.30)	0.280

*Results are from inverse probability for treatment weighted (IPTW) stratified proportional hazards regression. Robust sandwich estimates for covariance were used to account for the weighted approach. Estimates are hazard ratios associated with single exposure to anesthesia prior to age 3 compared to no exposure. For each outcome, one model was run to assess the interaction effect between cohort membership and anesthesia exposure and a second model was run without the interaction effect to estimate the effect of anesthesia in the combined cohort. The interaction p-value is testing the hypothesis that the effect of single exposure is equal between the 2 cohorts. Stabilized weights were calculated according to sex and cohort membership. Missing data was accounted for by using multiple imputation. Twenty imputed datasets were generated and analysis results were combined using Rubin's rules to account for uncertainty in the imputed values. Est, estimate; CI, confidence interval; ADHD, attention-deficit hyperactivity disorder; LD, learning disability; IEP, individualized education plan; SL, speech/language; EBD, emotional/behavioral disorder.