ANESTHESIOLOGY

Early Childhood General Anesthesia and Neurodevelopmental Outcomes in the Avon Longitudinal Study of Parents and Children Birth Cohort

Graham J. Walkden, M.B.Ch.B., Hannah Gill, F.R.C.A., Ph.D., Neil M. Davies, Ph.D., Alethea E. Peters, B.M.B.Ch., Ingram Wright, D.Clin.Psychol., Ph.D., Anthony E. Pickering, F.R.C.A., Ph.D.

ANESTHESIOLOGY 2020; 133:1007–20

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In preclinical studies many general anesthetic agents cause accelerated neuronal apoptosis after extended periods of exposure in early development
- In most human studies, there is good evidence that brief exposure to general anesthesia in infancy does not result in poorer neurocognitive outcome when tested in early childhood
- There is mixed but generally poor evidence for an association between exposure in early childhood and a range of other neurodevelopmental or behavioral outcomes

What This Article Tells Us That Is New

- In a large longitudinal human birth cohort comparing children who were exposed or not to anesthesia and surgery before 4 yr, there was no evidence for a global picture of clinically and statistically significant long-term neurotoxic effects in a comprehensive array of neurodevelopmental measures between 7 and 16 yr of age
- However, among the 46 neurodevelopmental outcomes assessed, there was evidence of an increased risk of poorer motor function measured by dynamic balance in multiply exposed children and lower manual dexterity in multiply and singly exposed children, whereas social communication scores were also lower in multiply and singly exposed children

ABSTRACT

Background: Most common anesthetic agents have been implicated in causing neurodegeneration in the developing animal brain, leading to warnings regarding their use in children. The hypothesis of this study was that exposure to general anesthesia and surgery before 4 yr would associate with adverse neurodevelopmental outcomes at age 7 to 16 yr.

Methods: This cohort study comprised 13,433 children enrolled in the Avon Longitudinal Study of Parents and Children, a prospective, population-based birth cohort born between 1991 and 1993 in southwest England. Children were grouped by none, single, or multiple exposures to general anesthesia and surgery by 4 yr. Motor, cognitive, linguistic, educational, social, and behavioral developmental outcomes were evaluated at 7 to 16 yr using school examination results, validated parent/teacher questionnaires, or clinic assessments. Continuous outcomes were z-scored. *P*-value thresholds were corrected using false discovery rate procedures.

Results: This study compared 46 neurodevelopmental outcomes in 13,433 children: 8.3% (1,110) exposed singly and 1.6% (212) exposed multiply to general anesthesia and surgery. Of these, the following reached predefined levels of statistical significance (corrected $P < 0.00652$): dynamic balance scores were 0.3 SD (95% CI, 0.1, 0.5; $P < 0.001$) lower in multiply exposed children; manual dexterity performance was 0.1 SD (95% CI, 0.0, 0.2; $P = 0.006$) lower in singly and 0.3 SD (95% CI, 0.1, 0.4; $P < 0.001$) lower in multiply exposed children; and social communication scores were 0.1 SD (95% CI, 0.0, 0.2; $P = 0.001$) and 0.4 SD (95% CI, 0.3, 0.5; $P < 0.001$) lower in singly and multiply exposed children, respectively. General anesthesia and surgery were not associated with impairments in the remaining neurodevelopmental measures including: general cognitive ability; attention; working memory; reading, spelling, verbal comprehension and expression; behavioral difficulties; or national English, mathematics, and science assessments (all ≤0.1 SD; corrected $P \geq 0.00652$).

Conclusions: Early childhood general anesthesia and surgery were not associated with a global picture of clinically and statistically significant neurodegenerative effects, providing reassurance about the neurotoxic potential of general anesthesia. Exposure to anesthesia and surgery was associated with significantly lower motor and social linguistic performance.

(ANESTHESIOLOGY 2020; 133:1007–20)

ALL commonly used intravenous and inhalational anesthetic agents have been shown to increase neuronal apoptosis in immature animals, including nonhuman primates, with some drugs adversely affecting long-term learning and behavior.[1,2] Although long-term neurotoxic risks in humans remain uncertain, the U.S. Food and Drug Administration recently cautioned against lengthy or repeated general anesthesia or sedation in the third trimester of pregnancy and children aged less than 3 yr.[3] Defining the risk of anesthetic-induced neurotoxicity is a pressing public health issue because 5% of children aged less than 6 yr in the United Kingdom undergo general anesthesia annually.[4,5]

Concerns that fetuses, babies, and young children exposed to general anesthesia may experience long-lasting neurotoxic

effects has motivated a number of clinical studies, predominantly in Europe, North America, and Australia, over the last decade.[6] Most have employed retrospective study designs because of ethical and practical challenges associated with randomization to omit general anesthesia and the need for lengthy follow-up. These observational studies are heterogeneous in their methodologies, limited by residual confounding and often analyze small samples. Although some studies have offered reassurance,[7–10] others have reported long-term neurodevelopmental deficits after single exposures[11–18] and larger deficits after multiple exposures.[18–22] Pooled effect estimates from observational studies indicate at least a modest risk of impaired neurodevelopment after general anesthesia and surgery in childhood.[23,24] To date, one randomized controlled trial of 722 children undergoing spinal *versus* general anesthesia for herniorrhaphy before 60 weeks postmenstrual age has reported equivalent cognitive scores at age 2[25] and 5 yr.[26] However, the authors caution that more comprehensive cognitive assessment, possible in later childhood, may yet detect latent neurotoxic effects and that repeated or prolonged exposures remain concerning.

We hypothesized that exposure to general anesthesia (single or multiple) and any surgery before 4 yr of age would associate with adverse neurodevelopmental outcomes at age 7 to 16 yr. We tested this hypothesis in a large, population-based, representative birth cohort from the United Kingdom that contains a rich description of confounding factors and detailed, prospective assessment of multiple neurodevelopmental domains into adolescence.

Materials and Methods

Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children is a prospective population-based birth cohort that invited enrollment of all pregnant women in the Avon area of southwest England with estimated delivery dates between April 1, 1991, and December 31, 1992 (participation rate, 75.3%).[27,28] Informed consent for the use of data collected *via* questionnaires/clinics was obtained from participants following the recommendations of the Avon Longitudinal Study of Parents and Children Ethics and Law Committee at the time. Ethical approval for the current study was obtained from the Avon Longitudinal Study of Parents and Children Ethics and Law Committee and local Research Ethics Committees (proposal B3105). A data-processing and statistical-analysis plan was written and filed with the Avon Longitudinal Study of Parents and Children Ethics and Law Committee and approved on May 1, 2018, before the data were accessed. The study website contains full details of approved proposals (http://proposals.epi.bristol.ac.uk; accessed September 11, 2019), and all data are available through a fully searchable data dictionary and variable search tool (http://bristol.ac.uk/alspac/researchers/our-data/; accessed September 11, 2019).

No statistical power calculation was conducted before the study. The sample size was based on the available data. The final data set comprised 13,433 children, as shown in figure 1. From an initial sample of 15,643 fetuses ever enrolled in the Avon Longitudinal Study of Parents and Children, we excluded withdrawn children, pregnancies that miscarried, children who died before 1 yr of age, children of indeterminate anesthetic exposure status, and children with independent risk factors for poor neurodevelopmental outcome (birth asphyxia,[29] neurologic or neuromuscular,[15,30] or complex cardiac[30–32] or genetic disorders).

General Anesthetic Exposure

The brain is thought to be particularly vulnerable to anesthetic-induced neurotoxicity during a period of peak synaptogenesis that is important for later cognitive development including use of language and social behavior.[1,13] This period of vulnerability is poorly defined in humans, which may explain why exposure to anesthesia has been heterogeneously defined in the literature. We defined the exposure as general anesthesia and surgery before 4 yr of age in line with a number of large observational studies.[12,14,20,33] Exposure was coded from questionnaire/clinic responses as none, one, or multiple general anesthetics and surgery by age 4 yr in a three-level categorical exposure variable. Age at exposure was determined from questionnaire/clinic responses or the time of questionnaire/clinic completion where not specified (Supplemental Digital Content, table 1, http://links.lww.com/ALN/C468).

Neurodevelopmental Outcomes

Neurodevelopmental outcomes (table 1; Supplemental Digital Content, methods, http://links.lww.com/ALN/C468) were selected *a priori* if they used validated tools and methods and were assessed after 6 yr of age, to distinguish

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 967. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented at the Anesthetic Research Society and British Journal of Anesthesia Research Forum, Royal College of Anaesthetists in London, United Kingdom, May 9, 2019.

Submitted for publication September 11, 2019. Accepted for publication July 27, 2020. Published online first on September 4, 2020. From the School of Physiology, Pharmacology and Neuroscience (G.J.W., H.G., A.E. Peters, A.E. Pickering), the Medical Research Council Integrative Epidemiology Unit (N.M.D.), the Department of Population Health Sciences (N.M.D.), and the School of Psychological Science (I.W.), University of Bristol, Bristol, United Kingdom; the Department of Anaesthesia, Pain and Critical Care Sciences, Translational Health Sciences, Bristol Medical School, Bristol Royal Infirmary, Bristol, United Kingdom (G.J.W., H.G., A.E. Peters, A.E. Pickering); the Department of Paediatric Anaesthesia, Bristol Royal Hospital for Children, Bristol, United Kingdom (H.G.); and the K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, Norwegian University of Science and Technology, Trondheim, Norway (N.M.D.).

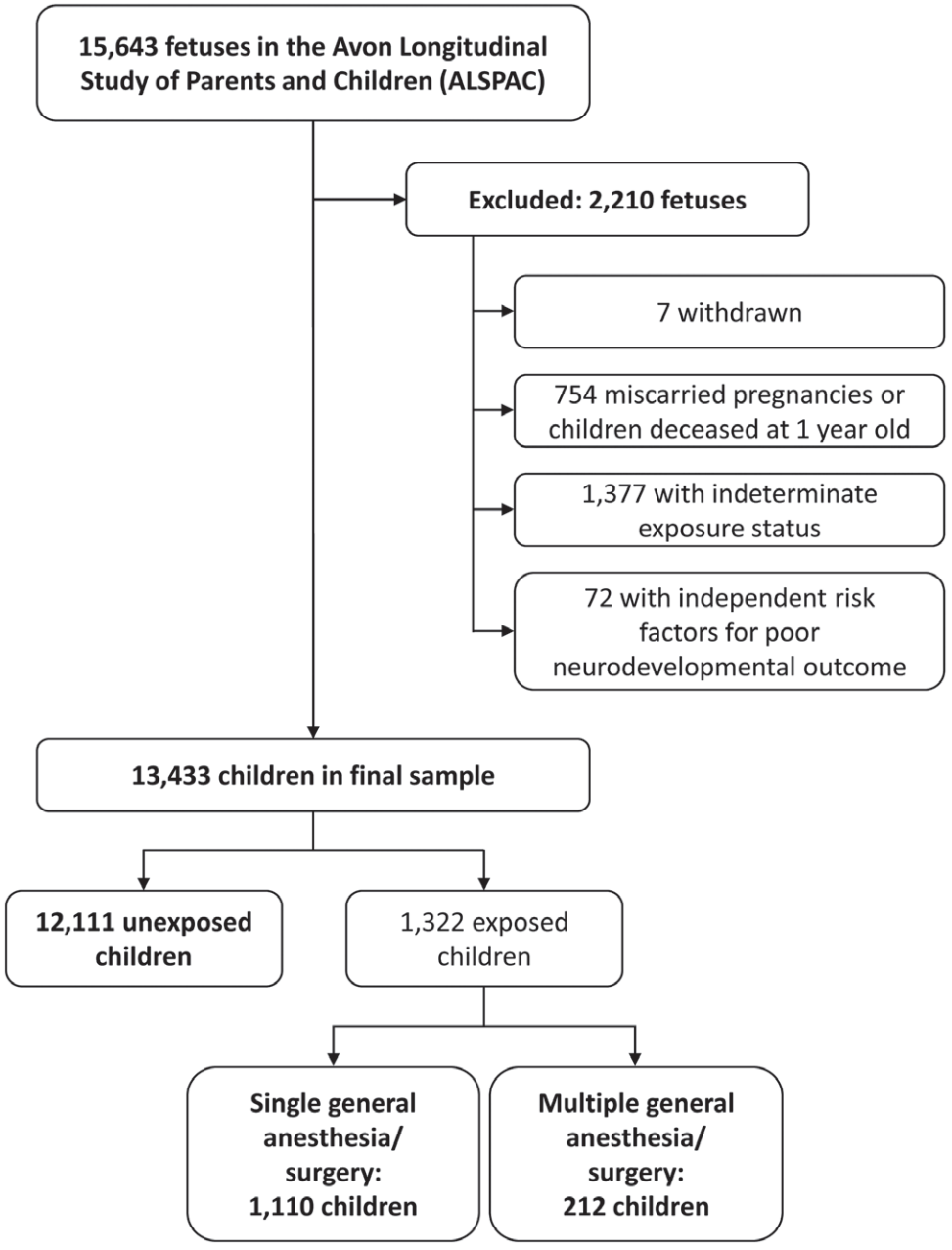

Fig. 1. Flowchart of study participants. The 15,643 fetuses enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC) includes 14,541 initially enrolled in phase I, as well as enrichment at phases II (at age 7 yr) and III (at age 8 yr). The 1,377 excluded with indeterminate exposure status comprised those who (1) identified as having undergone general anesthesia for gynecological (8), urological (81), ophthalmic surgery (1,021), appendectomy (177), or fracture fixation (90) at some point in the Avon Longitudinal Study of Parents and Children timeline but (2) underwent no other general anesthesia and surgery by 4 yr of age. This is because questionnaire/clinic data sources for these operations all date from a time point after 4 yr of age, and age of exposure was not sought (see Supplemental Digital Content, table 1, http://links.lww.com/ALN/C468). Had we retained these children with their age of exposure set to the clinic or questionnaire completion age, then we would have misclassified exposed children as unexposed and null-biased estimates of neurotoxic effect. The 72 excluded with independent risk factors for poor neurodevelopmental outcome suffered birth asphyxia,[29] neurologic or neuromuscular,[15,30] complex cardiac,[30–32] or genetic disorders.

long-term neurotoxic effects from short-term postoperative cognitive–behavioral changes. Only those tests that had data for more than 6,000 children were included. A number of sensitivity analyses were performed in cognitive and linguistic domains on further outcomes (containing 6,000 observations or less), as detailed in table 1 and Supplemental

Table 1. Summary of Neurodevelopmental Outcomes

Neurodevelopmental Outcome	Variable Type	Domain Measured	Age (Median), yr (IQR, range)	Assessment	Dichotomization
Educational outcomes					
Key stage 2 English, mathematics, and science	Continuous scores	Educational performance	11.2 (10.9, 11.4; 10.7, 11.7)	Standardized national test	-
Nonentry to key stage 2 exams*	Binary variable	Educational performance	11.2 (10.9, 11.4; 10.7, 11.7)	Standardized national test	-
Key stage 3 English, mathematics, and science	Continuous scores	Educational performance	14.1 (13.8, 14.4; 13.6, 14.7)	Standardized national test	-
Nonentry to key stage 3 exams*	Binary variable	Educational performance	14.1 (13.8, 14.4; 13.6, 14.7)	Standardized national test	-
Key stage 4 total points score	Continuous score	Educational performance	15.4 (15.2, 15.8; 15.0, 16.9)	Standardized national test	-
Number of key stage 4 exam entries*	Continuous score	Educational performance	15.4 (15.2, 15.8; 15.0, 16.9)	Standardized national test	-
Key stage 4 English and mathematics A*, A, B, or C grade	Binary variables	Educational performance	15.4 (15.2, 15.8; 15.0, 16.9)	Standardized national test	-
Key stage 4 science 2 "good" passes (C grade or above)	Binary variable	Educational performance	15.4 (15.2, 15.8; 15.0, 16.9)	Standardized national test	-
Cognitive function					
Wechsler Intelligence Scale for Children global intelligence quotient	Continuous score	General cognitive ability	8.6 (8.5, 8.7; 7.4, 10.5)	Psychology team in clinics	-
Wechsler Intelligence Scale for Children verbal intelligence quotient*	Continuous score	Linguistic ability	8.6 (8.5, 8.7; 7.4, 10.5)	Psychology team in clinics	-
Sky search task	Continuous score	Attention	8.6 (8.5, 8.7; 7.4, 10.6)	Psychologists in clinics	-
Opposite worlds task	Continuous score	Attention	8.6 (8.5, 8.7; 7.4, 10.6)	Psychologists in clinics	-
Counting span task	Continuous score	Working memory	10.6 (10.5, 10.8; 9.8, 12.3)	Psychologists in clinics	-
Wechsler Abbreviated Scale of Intelligence global intelligence quotient*	Continuous score	General cognitive ability	15.3 (15.3, 15.5; 14.3, 17.1)	Psychology team in clinics	-
Motor ability					
Heel-to-toe walking task	Continuous score	Dynamic balance	7.5 (7.4, 7.5; 6.8, 9.4)	Trained assessors in clinics	Fail: <15 successful steps[47]
Preferred hand peg placing	Continuous score	Manual dexterity	7.5 (7.4, 7.5; 6.8, 9.4)	Trained assessors in clinics	Fail: ≥23 seconds (below median average)[47]
Nonpreferred hand peg placing	Continuous score	Manual dexterity	7.5 (7.4, 7.5; 6.8, 9.4)	Trained assessors in clinics	Fail: ≥26 seconds (below median average)[47]
Bean bag throwing task	Continuous score	Ball skills	7.5 (7.4, 7.5; 6.8, 9.4)	Trained assessors in clinics	Fail: 0–3 accurate throws (less than 1 SD from the mean)[47]
Social and behavioral outcomes					
Strengths and Difficulties Questionnaire score	Continuous scores	Behavioral problems	6.8 (6.8, 6.8; 6.7, 8.4) 8.6 (8.5, 8.7; 7.4, 10.6) 11.2 (11.2, 11.7; 10.4, 13.5)	Maternal and teacher questionnaires	Most difficulties: highest tertile[48]
Skuse sociocognitive dysfunction score	Continuous score	Sociocognitive dysfunction	7.6 (7.6, 7.7; 7.5, 9.3)	Maternal questionnaire	-
Child's Communication Checklist score	Continuous score	Social communication	9.6 (9.6, 9.7; 9.5, 11.0)	Maternal questionnaire	Impairment: ≤134 points (at least 2 SD below the mean average)[49]
Reading and language skills					
Basic reading test	Continuous score	Word recognition	7.5 (7.4, 7.5; 6.8, 9.4)	Psychologists and speech therapists	-
Spelling test	Continuous score	Spelling ability	7.5 (7.4, 7.5; 6.8, 9.4)	Psychologists and speech therapists	-
Phoneme deletion task	Continuous score	Phonological awareness	7.5 (7.4, 7.5; 6.8, 9.4)	Psychologists and speech therapists	-
Wechsler Objective Language Dimensions comprehension task	Continuous score	Verbal comprehension	8.6 (8.5, 8.7; 7.4, 10.6)	Psychologists and speech therapists	-
Wechsler Objective Language Dimensions verbal expression task	Continuous score	Verbal expression	8.6 (8.5, 8.7; 7.4, 10.6)	Psychologists and speech therapists	-
Real-word reading test	Continuous score	Word recognition	9.8 (9.7, 10.0; 8.8, 11.7)	Psychologists and speech therapists	-
Non–real-word reading test	Continuous score	Decoding ability	9.8 (9.7, 10.0; 8.8, 11.7)	Psychologists and speech therapists	-

(*Continued*)

Table 1. (Continued)

Neurodevelopmental Outcome	Variable Type	Domain Measured	Age (Median), yr (IQR, range)	Assessment	Dichotomization
Spelling test	Continuous score	Spelling ability	9.8 (9.7, 10.0; 8.8, 11.7)	Psychologists and speech therapists	-
Test of Word Reading Efficiency word-reading test*	Continuous score	Word recognition	13.8 (13.8, 13.9; 8.8, 11.7)	Psychologists and speech therapists	-
Test of Word Reading Efficiency non-word–reading test*	Continuous score	Decoding ability	13.8 (13.8, 13.9; 8.8, 11.7)	Psychologists and speech therapists	-

A full description of neurodevelopmental outcomes is available in Supplemental Digital Content, methods (http://links.lww.com/ALN/C468).

*Sensitivity analyses.

IQR, interquartile range.

Digital Content, methods (http://links.lww.com/ALN/C468), after identifying associations in those domains in age-adjusted and complete case analyses.

Potential Confounders

The data were obtained from the Avon Longitudinal Study of Parents and Children concerning a rich pool of covariates based on *a priori* consideration of potential confounders.[6] These potential confounders included demographic variables, socioeconomic status, childhood health status, adverse childhood experiences, school cohort, neurotoxic exposures, maternal factors in childhood, maternal health in pregnancy, neonatal condition, and course and complications of labor and delivery. They were coded as presented in table 2 and Supplemental Digital Content, table 2 (http://links.lww.com/ALN/C468). Depression symptoms, being bullied, and number of hospital admissions in childhood were not included as they were measured after exposure and considered potential mediators of the relationship between general anesthesia and surgery and neurodevelopmental outcome.

Statistical Analyses

Parametric descriptive statistics are reported where histograms and standardized normal probability plots demonstrated a normal distribution. Two-tailed hypothesis testing was used for all statistical tests. Analyses were performed using STATA, version 15.1 (StataCorp, USA).

Missing data rates are shown in Supplemental Digital Content, table 2 (http://links.lww.com/ALN/C468). Across the 79 variables used in our analyses, 635 (4.7%) children had no missing values, 3,387 (25.2%) had 1 to 10 missing values, 3,117 (23.2%) had 11 to 20 missing values, and 6,294 (46.9%) had more than 20 missing values. Therefore, multivariate multiple imputation was used to impute missing values in 100 stacked data sets with the aim of reducing the bias and imprecision in neurotoxic effect estimates, which may specifically arise from missing data (Supplemental Digital Content, methods, table 3, http://links.lww.com/ALN/C468).

Neurodevelopmental outcomes were expressed using a variety of different units or scores. Continuous outcomes were z-scored (*i.e.* standardized to a mean of 0 and SD of 1) based on the mean and SD of all the individuals in the study sample. Linear regression coefficients (β) then represent a change of $\beta \times 1$ SD in outcome score in the single or multiple general anesthesia and surgery group *versus* the unexposed group. Removing the unit of measurement and presenting effect estimates in multiples of SD simplifies interpretation and permits comparison of effect sizes across multiple heterogeneous outcome measures. Where possible, outcome scores were also dichotomized into clinically meaningful categories as described above and analyzed in parallel in logistic regression models to further aid interpretation. Dichotomized or binary outcomes are presented as odds ratios. Minimum clinically meaningful effect sizes were not defined before data access. For each outcome, neurotoxic effects were (1) adjusted for age of outcome assessment and (2) fully adjusted for all confounders in complete case and multiply imputed data sets. Potential confounders selected from Supplemental Digital Content, table 2 (http://links.lww.com/ALN/C468) for inclusion in multivariable confounder-adjusted models were age of outcome assessment and those significant at the 5% level in univariate analyses (Supplemental Digital Content, table 4, http://links.lww.com/ALN/C468).

This study performed hypothesis testing on 46 neurodevelopmental outcomes. As the number of hypotheses tested increases, the proportion of type I errors (false positives) can be expected to increase.[34] One can define a "false discovery rate" as the ratio of the number of false-positive results to the number of total positive results arising from multiple hypothesis testing. False discovery rate procedures calculate corrected critical *P*-value thresholds (that account for multiple hypothesis testing), which replace the standard (uncorrected) critical *P*-value thresholds of $P < 0.05$, $P < 0.01$, and $P < 0.001$. We compared the *P* values generated by individual hypothesis tests with these corrected critical *P*-value thresholds: individual null hypotheses can be rejected where their *P* values are greater than the corrected critical *P*-value threshold. A corrected *P*-value threshold

Table 2. Characteristics of Children with No, One, or Multiple General Anesthetic Exposures by Age 4 yr

	No General Anesthesia/ Surgery (N = 12,111)		Single General Anesthesia/ Surgery (N = 1,110)		Multiple General Anesthesia/Surgery (N = 212)	
Covariates	**N**	**Statistic**	**N**	**Statistic**	**N**	**Statistic**
Female sex, %*	6,154	50.8	424	38.2	58	27.4
Maternal education, %*						
None/certificate of secondary education	2,320	19.2	180	16.2	32	15.1
Vocational	1,076	8.9	99	8.9	13	6.1
O level	5,301	43.8	402	36.2	99	46.7
A level	2,185	18	272	24.5	49	23.1
Degree+	1,229	10.1	157	14.1	19	9.0
Paternal education, %*						
None/certificate of secondary education	4,736	39.1	320	28.8	60	28.3
Vocational	906	7.5	73	6.6	16	7.5
O level	2,123	17.5	239	21.5	55	25.9
A level	2,687	22.2	260	23.4	55	25.9
Degree+	1,659	13.7	218	19.6	26	12.3
Nonfebrile convulsions, %*	795	6.6	142	12.8	30	14.2
Traumatic life events, median (interquartile range)*	9,228	2 (1–3)	1,057	3 (2–3)	193	3 (2–3)
Maternal age at delivery, %*						
<24 yr	2,928	24.2	218	19.6	38	17.9
25–29 yr	4,946	40.8	425	38.3	89	42.0
30–34 yr	3,080	25.4	364	32.8	67	31.6
35+ yr	1,157	9.6	103	9.3	18	8.5
Maternal self-rated health in pregnancy, %*						
Always well	758	6.3	64	5.8	14	6.6
Rarely or sometimes unwell	7,789	64.3	641	57.7	120	56.6
Often or always unwell	3,564	29.4	405	36.5	78	36.8
Maternal hospitalization in pregnancy, %**	8,094	66.8	736	66.3	158	74.5
Nonroutine screening for fetal abnormalities, %***						
No tests	2,878	23.8	240	21.6	50	23.6
Tested	8,415	69.5	755	68.0	137	64.6
Abnormal test	818	6.8	115	10.4	25	11.8
Gestation (median), weeks (IQR)*	12,111	40 (39–41)	1,110	40 (38–40)	212	40 (39–40)
Birthweight (median), g (IQR)*	12,111	3,400 (3,120–3,710)	1,110	3,400 (3,030–3,720)	212	3,400 (3,040–3,760)
Apgar score at 5 min, median (IQR)**	6,289	10 (9–10)	628	10 (9–10)	120	10 (9–10)
Postnatal course, %*						
Normal	10,373	85.6	891	80.3	158	74.5
Prolonged stay or transitional care ward	952	7.9	79	7.1	18	8.5
Same/other hospital special care baby unit	786	6.5	140	12.6	36	17.0
Abnormal placenta or cord, %***	1,537	24.4	135	21.4	16	13.2
Non–breast/bottle fed at 24 h, %*	527	8.4	91	14.6	27	22.5
Neonatal jaundice, %*	4,625	38.2	516	46.5	102	48.1
Multiple gestation, %*	327	2.7	44	4.0	13	6.1
Induction of labor, %***						
No labor	514	7.8	84	12.6	11	8.3
Spontaneous	4,785	72.6	461	68.9	83	62.4
Artificial rupture of membranes or pharmacologic	1,291	19.6	124	18.5	39	29.3

Statistically significant differences between groups: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
IQR, interquartile range.

of $P < 0.00652$ (corresponding to $P < 0.05$, uncorrected) was the threshold for statistical significance in this study. This approach to mitigating against false-positive results is less conservative than the Bonferroni method but does not reduce statistical power to the same extent. A *post hoc* analysis to investigate the potential effects of confounding by indication within children undergoing otorhinolaryngeal procedures is explained in eMethods.

Results

Of the 13,433 children in the sample, 1,322 (9.8%) were exposed to general anesthesia and surgery by 4 yr of age; 1,110 (8.3%) were exposed once, and 212 (1.6%) were exposed multiple times. The cumulative frequency of childhood exposure to general anesthesia by surgical indication is shown in figure 2.

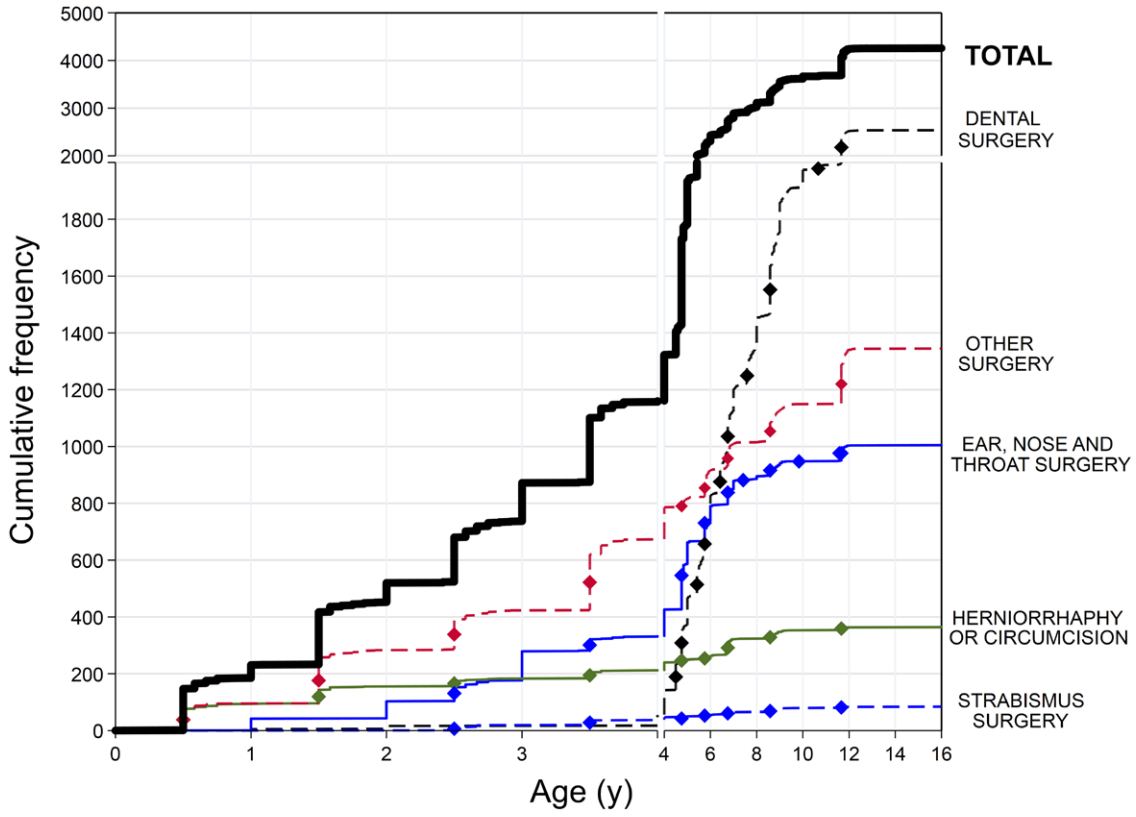

Fig. 2. Anesthetic exposures throughout childhood. Shown are the cumulative numbers of exposures to general anesthesia and surgery for herniorrhaphy; circumcision; dental; strabismus; ear, nose, and throat; or other undefined procedures. The majority of otorhinolaryngology procedures were grommet insertions (70.7%) or adenoidectomy and/or tonsillectomy procedures (27.8%). *Superimposed diamonds* indicate the time points at which questionnaires/clinics provided information regarding particular operations. Children undergoing any general anesthesia and surgery by 4 yr of age were classified as exposed. The cumulative number of children undergoing any procedure is shown by the *thick black line* (1,322 exposures by 4 yr of age: 1,110 singly exposed and 212 multiply exposed).

As anticipated for the surgical population, there were significant differences in the demographics between unexposed and exposed groups (table 2; Supplemental Digital Content, table 2, http://links.lww.com/ALN/C468). Children undergoing general anesthesia and surgery were predominantly male, carried in multiple gestation pregnancies, and born at lower gestational age and birthweight. Mothers of exposed children reported worse health status and more hospital admissions in pregnancy, underwent more nonroutine fetal anomaly screening, were more often artificially induced into labor, and were older at delivery. Exposed children experienced a more complicated postnatal course in hospital with more frequent jaundice and artificial feeding. In childhood, these exposed children were admitted to the hospital more frequently, had more nonfebrile convulsions, had a greater burden of depressive symptoms, and were more often bullied. Exposed children were generally born to mothers of higher occupational status and parents of higher educational achievement.

Example univariate associations between general anesthesia and surgery and potential confounders tested in the models are shown in Supplemental Digital Content table 4 (http://links.lww.com/ALN/C468). In general, female sex, having more educated parents, and older maternal age at delivery were associated with improved neurodevelopmental outcome. Neurodevelopmental outcomes were generally worse in children who experienced a complex postnatal course and more traumatic life events in childhood and whose mothers reported worse health status in pregnancy.

The key findings from the fully adjusted and multiply imputed analyses are summarized in figure 3. We did not find that general anesthesia and surgery were associated with a picture of clinically and statistically significant global deficits in general cognitive ability; attention; sociocognitive function; working memory; reading and spelling performance; phonological awareness; verbal comprehension or expression; behavioral difficulties; or national assessments of English, mathematics, and science ability at key stages 2

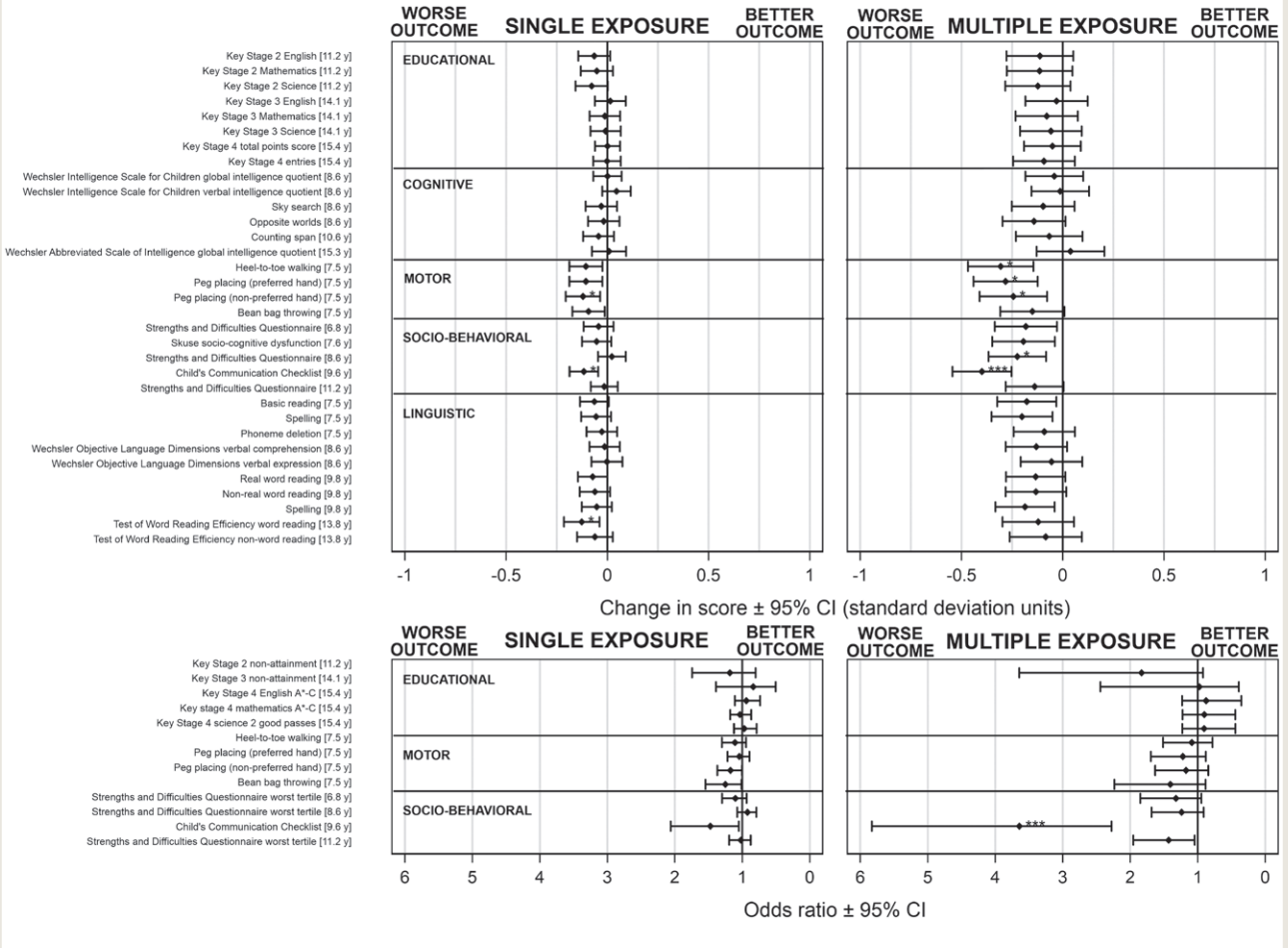

Fig. 3. Confounder-adjusted associations between general anesthesia and surgery by age 4 yr and neurodevelopmental outcomes in older childhood. Effect sizes derived from the multiply imputed data set (N = 13,433). (*Upper*) Mean differences ± 95% CI in SD units for continuous outcomes. (*Lower*) Odds ratios ± 95% CI for dichotomized outcomes. Statistical significance after correcting for type I errors associated with multiple testing is indicated by *asterisks*: *$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$. Outcomes are assessed at median ages as indicated in the legend.

and 3. The longitudinal picture across neurodevelopmental domains is therefore one of reassuringly limited impact. Nonetheless, we found some evidence of impairments in several specific neurodevelopmental subdomains. The evidence for and against an association in each domain is described in detail below.

Educational Outcomes

We did not find that general anesthesia and surgery were associated with meaningful and statistically significant lowering of performance in standardized educational tests of English, mathematics, and science ability across the entire age range of the study. Lower CI limits on the key stage 4 results suggest that early childhood general anesthesia and surgery are unlikely to be associated with anything greater than a 30% increase in the odds of impaired educational outcome. Exam nonentry, a proxy of whether children were below testing level, was similar between exposure groups at all ages in sensitivity analyses. However, lower confidence limits likely exceeded maximum clinically acceptable differences in exam nonentry. In addition, 23.1 and 28.8% of children who were exposed to single or multiple general anesthetics and surgery, respectively, received special educational needs provision in school as compared with 20.3% of those unexposed ($P = 0.001$).

Cognitive Function

Measures of intelligence quotient including the Wechsler Intelligence Scale for Children and, in a sensitivity analysis, the Wechsler Abbreviated Scale of Intelligence were similar between exposure groups. Measures of attention and working memory were also similar between exposure groups.

Motor Ability

Children who were singly exposed had scores for heel-to-toe walking[35] (dynamic balance) and peg-placing tasks[35] (manual dexterity) that were in the order of 0.1 SD (95% CI, 0.0, 0.2) lower, and children who were multiply exposed had scores that were 0.3 SD (95% CI, 0.1, 0.5) lower (fig. 3). These differences were statistically significant and present after confounder-adjustment and correction for multiple outcome testing (Supplemental Digital Content, table 5, http://links.lww.com/ALN/C468). To illustrate the real-world magnitude of effects, the standardized differences were back-transformed into original units (Supplemental Digital Content, figure 2, http://links.lww.com/ALN/C468). This corresponded to a difference of at most one step in the heel-to-toe walking test (median score, 15 correct steps; interquartile range, 13, 15). In the peg-placing tasks (preferred hand median time taken, 22 s; interquartile range, 20, 24; nonpreferred hand median time taken, 25 s; interquartile range, 22, 28), this corresponds to at most a 2-s increase in the time required to complete a task. No differences were detected in bean bag throwing.

Social and Behavioral Outcomes

There was evidence for a lowering in pragmatic communication scores (tested at median age 9.6 yr) using the Child's Communication Checklist,[36] which remained after confounder adjustment and correction for multiple outcome testing (Supplemental Digital Content, table 5, http://links.lww.com/ALN/C468). This manifested as a 0.1 SD (95% CI, 0.0, 0.2) lower score after single exposure and a 0.4 SD (95% CI, 0.3, 0.5) lower score after multiple exposures. This corresponds to a 50% (95% CI, 10, 110) increase in the likelihood of meaningful impairment for singly exposed children and a 260% (95% CI, 130, 480) increase for multiply exposed children. Repeating the analysis after restricting the exposed children to those who underwent (1) nonotorhinolaryngology procedures or (2) otorhinolaryngology procedures did not appreciably alter associations between general anesthesia and surgery and lower the Child's Communication Checklist scores (Supplemental Digital Content, table 6, methods, http://links.lww.com/ALN/C468). This did not provide evidence that confounding by indication could explain this result.

Multiply exposed children had 0.2 SD (95% CI, 0.1, 0.4) more behavioral difficulties at median age 8.6 yr. This corresponds to a potential increase of two behavioral difficulties (median recorded difficulties, 2; interquartile range, 2, 9). Behavioral difficulties at median ages of 6.8 and 11.2 yr were not increased by exposure to general anesthesia and surgery early in childhood. No intergroup differences were detected in sociocognitive dysfunction.

Reading and Language Skills

In a sensitivity analysis, the Test of Word Reading Efficiency score was 0.1 SD (95% CI, 0.0, 0.2) lower at median age 13.8 yr in singly exposed children (fig. 3). This statistically significant difference corresponded at most to a two-word difference in performance (median words read, 84; interquartile range, 77, 89). Multiple general anesthetic exposures and surgery were not associated with clinically and statistically significant differences in the Test of Word Reading Efficiency among multiply exposed children or in performance in the other nine linguistic outcomes.

Discussion

We have taken advantage of the deep phenotyping undertaken on the Avon Longitudinal Study of Parents and Children to examine the impact of early childhood general anesthesia and surgery on long-term neurodevelopment, correcting for multiple confounding factors that can hinder the interpretation of cohort studies. This large cohort study employs detailed, prospective assessment of multiple neurodevelopmental domains into adolescence and is the only such study based in the United Kingdom. Reassuringly, we did not find that general anesthesia and surgery were associated with a global picture of clinically and statistically significant long-term neurotoxic effects in a comprehensive array of neurodevelopmental measures between 7 and 16 yr of age. However, there was evidence of lower motor function (corroborated by multiple neurodevelopmental metrics) and, uniquely, lower pragmatic communication ability.

After confounder adjustment, we found that general anesthesia and surgery were not associated with clinically and statistically significant neurodevelopmental impairments in general cognitive ability; attention; sociocognitive function; working memory; reading and spelling performance; phonological awareness; verbal comprehension or expression; behavioral difficulties; or national assessments of English, mathematics, and science ability at key stages 2 and 3. Lower confidence limits on these null results suggest that neurodevelopmental metrics are unlikely to be lowered by more than 0.3 SD after general anesthesia and surgery. Associations for academic performance at key stage 4 were not statistically significant, with lower confidence limits suggesting that anything greater than a 30% increase in the odds of impaired educational outcome was unlikely. Lower confidence limits likely exceeded maximum clinically acceptable differences in exam nonentry at key stages 2 and 3.

The General Anesthesia *versus* Spinal trial, an international equivalence trial of children undergoing inguinal herniorrhaphy before 60 weeks of age, randomized 363 to spinal anesthesia and 359 to relatively short duration general anesthesia with sevoflurane. Participants in the two arms of the trial had similar cognitive scores at ages 2[25] and 5 yr.[26] However, measures of neurocognitive function

are unreliable in young children[37] and follow-up into later childhood, as in the present study, is required for more reliable assessment.

A number of large observational studies have investigated altered neurodevelopment after surgery and anesthesia in early childhood.[7–22,33] Schneuer *et al.*[33] determined that children exposed to general anesthesia by 4 yr of age had poorer development at school entry (sample size, 82,156) and poorer reading and numeracy test performance at 8 to 9 yr old (sample size, 153,025). Effects on development and reading ability, but not numeracy, were attenuated in a subgroup analysis that sought to minimize confounding by indication by restricting to children undergoing single general anesthesia without subsequent hospitalizations. Ing *et al.*[11] used Medicaid data to construct a cohort containing 38,493 children exposed to a single general anesthetic for one minor surgery before 5 yr of age and 192,465 propensity-matched controls. It reported a small increased risk of childhood mental disorder diagnosis after exposure. However, there was no way to ascertain the source or accuracy of mental disorder diagnoses, and associations with major surgery or multiple exposures were not studied. Other retrospective cohort studies that have considered the role of early childhood general anesthesia in the diagnosis of mental disorders such as autism and attention deficit hyperactivity disorder have reported contradictory findings.[7,8,11]

Two large observational studies have followed children into adolescence. The Pediatric Anesthesia and NeuroDevelopment Assessment study comprised 105 sibling pairs, where one sibling received single general anesthesia for inguinal herniorrhaphy by age 3 yr.[10] It found little evidence of differences in intelligence quotient between sibling pairs (the primary outcome), as well as memory, motor or processing speed, visuospatial function, attention, executive function, language, or behavior (secondary outcomes), by ages 8 to 15 yr. The Mayo Anesthesia Safety in Kids observational study comprised a matched cohort of 997 children, 586 of whom underwent one or more general anesthetics before 3 yr of age.[22] It found no evidence that general anesthesia and intelligence quotient (the primary outcome) were associated at age 8 to 20 yr but reported tentative associations in some secondary outcomes including processing speed, fine motor function, and parentally reported executive function, behavior, and reading for multiply exposed children (as will be discussed later). A recent analysis of the Mayo Anesthesia Safety in Kids data found no evidence that general anesthesia was associated with impaired performance in the Operant Test Battery,[38] which measures aspects of motivation, visual discrimination, attention, response speed, time perception, learning, and memory and is analogous to tests in which infant macaques exposed to ketamine have demonstrated poor performance. The results of the present study are supportive of associations between general anesthesia and fine motor and linguistic development but not of those relating to executive function or behavior identified in the Mayo Anesthesia Safety in Kids study.

Standardized national tests of educational achievement are of interest to parents/guardians and permit whole-population data linkage studies. Performance reflects cognitive ability as well as the influence of multiple other factors,[39] including the intensity of educational support.[40] Although some large, retrospective anesthetic-induced neurotoxicity studies have provided reassurance concerning academic achievement,[9] others offer contrary evidence.[12,15,17] Although we did not find that general anesthesia and surgery were associated with any meaningful and statistically significant lowering of educational achievement, we found evidence that the number of children with special educational needs provision in schools increased with increasing exposure to general anesthesia and surgery. It therefore remains possible that any neurotoxic influence was compensated for by interventions from the education system.

An important finding of the present study is an association between general anesthesia and surgery and pragmatic ability in social communication, assessed by parents using the Child's Communication Checklist at the age 9.6 yr. Singly and multiply exposed children had graded 50 and 260% increases in the odds of clinically significant impairment in pragmatic communication ability. Similar impairments were evident in complete case, multiply imputed, age- and confounder-adjusted analyses. The Child's Communication Checklist highlights reported traits in social and pragmatic aspects of communication.[36] Although relying on parental report, the observed differences in Child's Communication Checklist score are unlikely to represent a reporting bias by hypervigilant parents (who may have a heightened awareness of communication/social function) in the anesthetic exposed groups because other parentally assessed metrics (*i.e.* Strengths and Difficulties Questionnaire scores) offered discordant results. To date, no other studies have considered the neurotoxic potential of general anesthesia on social aspects of communication, which are not readily assessed by conventional tests.

At median age 7.5 yr, we detected lower clinic-assessed dynamic balance and manual dexterity scores, primarily in multiply exposed children. However, the magnitude of the differences in motor scores in the present study are smaller than the definitions of moderate fine motor impairment (at least 1 SD below mean) used in prenatal alcohol exposure literature.[41] Anesthetic-induced neurotoxicity studies that have examined motor outcomes offer conflicting evidence. The Mayo Anesthesia Safety in Kids study reported that a fine motor composite score used as a secondary outcome was lower in multiply but not singly exposed children.[22] Subsequent reanalysis of the Mayo Anesthesia Safety in Kids study, this time accounting for multiple testing, supported this conclusion: a factor representing motor skills, visual–motor integration, and processing speed was 0.35 (95% CI, 0.13, 0.57) SD units lower in multiply exposed

children,[42] in keeping with the findings of the present study. In contrast, general anesthesia was not found to be associated with impaired motor development in the Pediatric Anesthesia and NeuroDevelopment Assessment study[10] or the General Anesthesia *versus* Spinal trial.[25] However, the differences in motor scores found in our study are comparable with the clinical equivalence margin of 0.3 SD units, which was selected as being clinically meaningful for the primary outcome of the General Anesthesia *versus* Spinal trial.[25] These effects merit further investigation, ideally using an experimental design with assessment in this domain as a key outcome.

Strengths and Limitations

This is a large cohort study based on 13,433 children, which provides the statistical power to detect potentially subtle neurotoxic effects. The study benefits from a diverse battery of sensitive, validated neurodevelopmental outcomes that were assessed prospectively by trained assessors or parents/teachers, as well as linkage to standardized national academic test results. Follow-up extended through adolescence.

An inherent criticism of observational studies of anesthetic-induced neurotoxicity is the inability to delineate the neurodevelopmental effects of anesthesia from those of surgery. "Confounding by indication" can occur where the disease or the surgery itself is an independent risk factor for poor neurodevelopmental outcome. In the present study, children with middle ear effusions who were referred for grommet insertion were at risk of delayed speech/language development, either because they may have prolonged bilateral hearing loss[43] or because they have craniofacial abnormalities associated with impaired neurodevelopment.[44] Children referred for adenotonsillectomy for obstructive sleep apnea are also at risk of impaired neurodevelopment.[45] This source of bias tends to cause false-positive findings, *i.e.* if surgery were harmful, we would misattribute these effects to anesthesia. Although *post hoc* analyses that (1) excluded or (2) restricted children undergoing otorhinolaryngology procedures did not seem to alter associations for the Child's Communication Checklist, associations that we detect between general anesthesia and surgery and lowered performance in motor and social communication outcomes may still be explained by confounding by indication. In contrast, the generally negative findings of our study are unlikely to be undermined by this source of bias.

Confounding in the analysis was addressed by excluding children with independent risk factors for impaired neurodevelopment and by adjusting for multiple factors throughout the life course. More educated parents were more likely to have children that (1) underwent general anesthesia and surgery and (2) had better neurodevelopmental outcomes. More educated parents are also more likely to successfully pursue special educational needs provision for their children.[46] Residual confounding through either mechanism may mask a harmful effect of general anesthesia and surgery if parental education is not adequately controlled for. Data concerning preexisting health conditions and perioperative factors (*e.g.*, child distress, coadministered drugs, duration, oxygenation, cardiovascular status, complications, postoperative pain scores) were unavailable in the present study. Confounding by such factors could in part explain the consistent pattern toward lowered performance in neurodevelopment outcomes after general anesthesia and surgery (evident in number of previous cohort studies[18–21]), as well as our findings concerning motor function and pragmatic communication ability.

Another limitation of our work is insufficient detail in the ascertainment of exposure in a birth cohort that was not designed for this specific purpose. First, the exact timing of general anesthesia and surgery was frequently unknown, being set to the timing of the later questionnaire or clinic, and therefore a minority of children exposed before the age of 4 yr may have been misclassified as undergoing general anesthesia and surgery after age 4 yr (unexposed) in the final data set. Second, except for otorhinolaryngology procedures, it was not possible to determine whether children had one or multiple procedures within each surgical specialty. The definition of exposure may thus have underestimated the number of multiply exposed children, potentially biasing the neurotoxic effect estimates. This may result in an overestimate of the effects of single exposure and underestimate the effects of multiple exposures. Third, we have no estimate of dose or duration of anesthetic exposure, limiting our ability to make inferences about dose-response.

Finally, children in this cohort would have undergone general anesthesia and surgery between 1991 and 1997. Since then there have been widespread changes in the anesthetic techniques and the level of monitoring and training of the clinicians providing care. Such changes are likely to have improved pediatric anesthetic care, so the generally reassuring conclusions from the present study probably remain generalizable to current pediatric anesthetic practice in developed countries.

Conclusions

This study provides a further degree of reassurance to parents/guardians and to all care providers, especially surgeons and anesthesiologists, that pediatric anesthesia and surgery is unlikely to be associated with long-term neurodegenerative effects in a developed world setting. However, we provide evidence of association between general anesthesia and surgery and impaired motor development and complex linguistic development. We suggest that researchers studying possible anesthetic harms examine motor and complex linguistic outcomes *a priori* in addition to the intelligence quotient and educational outcomes, which have been the primary focus of previous studies. Our results do not provide a clear phenotype of anesthetic-induced neurodevelopmental impairment and do not warrant a change in care

but do provide target outcomes for future trials concerning this most pressing issue in modern pediatric anesthetic practice.

Acknowledgments

The authors are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole Avon Longitudinal Study of Parents and Children team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The authors thank George Davey Smith, M.A., M.D., B.Chir., M.Sc., University of Bristol Medical Research Council Integrative Epidemiology Unit, Population Health Sciences, University of Bristol, Bristol, United Kingdom, for helping to develop our study protocol and Amanda Hill, M.A., Population Health Sciences, University of Bristol, Bristol, United Kingdom, for enabling our access to data.

Research Support

United Kingdom Medical Research Council (London, United Kingdom) and Wellcome Trust (London, United Kingdom) grant No. 102215/2/13/2 and the University of Bristol (Bristol, United Kingdom) provide core support for the Avon Longitudinal Study of Parents and Children. A comprehensive list of grants funding is available on the study website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf; accessed September 11, 2019). Record linkage to the National Pupil Database was specifically funded by the Department for Education and Skills (London, United Kingdom) through grant No. EOR/SBU/2002/121. The Medical Research Council and the University of Bristol support the Medical Research Council Integrative Epidemiology Unit (Bristol, United Kingdom) through grant No. MC_UU_00011/1. Dr. Walkden is supported by a National Institute for Health Research (United Kingdom) badged Academic Clinical Fellowship. Dr. Gill is supported by grant No. CL-2014-25-003 from the National Institute for Health Research and grant No. AMS-SGCL13-Gill from the Academy of Medical Sciences (London, United Kingdom).

Competing Interests

Dr. Pickering is a member of the Lateral Pharma Pty. Ltd. (Melbourne, Australia) scientific advisory board and has received a speaker honorarium from Eli Lilly and Company Ltd. (Hampshire, United Kingdom), although neither are related to this study. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Walkden: School of Physiology, Pharmacology and Neuroscience, Biomedical Sciences Building, University Walk, Bristol BS8 1TD, United Kingdom. g.walkden@bristol.ac.uk.

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