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; XXX:00–00

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 ≥ 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.

(AНЕSTHESIOLOGY 2020; XXX:00–00)
effects has motivated a number of clinical studies, predominantly in Europe, North America, and Australia, over the last decade. 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, others have reported long-term neurodevelopmental deficits after single exposures and larger deficits after multiple exposures. Pooled effect estimates from observational studies indicate at least a modest risk of impaired neurodevelopment after general anesthesia and surgery in childhood. 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 and 5 yr. 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%). 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, neurologic or neuromuscular, or complex cardiac 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. 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. 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 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 tests were used to examine neurodevelopmental outcomes.
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 Digital Content, methods (http://links.lww.com/ALN/C468), after identifying associations in those domains in age-adjusted and complete case analyses.

---

**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.
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 |
| 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) |
| 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) |
| 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) |
| Social and behavioral outcomes | Continuous scores | Behavioral problems | 6.8 (6.8, 6.8; 6.7, 8.4) | Maternal and teacher questionnaires | Most difficulties: highest tertile |
| Strengths and Difficulties Questionnaire score | Continuous score | Sociocognitive dysfunction | 7.6 (7.6, 7.7; 7.5, 9.3) | Maternal questionnaire | - |
| Skuse sociocognitive dysfunction score | Continuous score | Sociocognitive dysfunction | 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) |
| Reading and language skills | Continuous score | Word recognition | 7.5 (7.4, 7.5; 6.8, 9.4) | Psychologists and speech therapists | - |
| Basic reading test         | Continuous score | Spelling ability | 7.5 (7.4, 7.5; 6.8, 9.4) | Psychologists and speech therapists | - |
| Spelling test              | Continuous score | Phonological awareness | 7.5 (7.4, 7.5; 6.8, 9.4) | Psychologists and speech therapists | - |
| Phoneme deletion task      | Continuous score | Verbal comprehension | 8.6 (8.5, 8.7; 7.4, 10.6) | Psychologists and speech therapists | - |
| Wechsler Objective Language Dimensions comprehension task | Continuous score | Verbal expression | 8.6 (8.5, 8.7; 7.4, 10.6) | Psychologists and speech therapists | - |
| Wechsler Objective Language Dimensions verbal expression task | Continuous score | Word recognition | 9.8 (9.7, 10.0; 8.8, 11.7) | Psychologists and speech therapists | - |
| Real-word reading test     | Continuous score | Decoding ability | 9.8 (9.7, 10.0; 8.8, 11.7) | Psychologists and speech therapists | - |
| Non–real-word reading test | Continuous score | Word recognition | 9.8 (9.7, 10.0; 8.8, 11.7) | Psychologists and speech therapists | - |

(Continued)
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. 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 β × 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. 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 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
Walkden et al. 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.

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 exposed multiple times.

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

| Covariates                              | No General Anesthesia/Surgery (N = 12,111) | Single General Anesthesia/Surgery (N = 1,110) | Multiple General Anesthesia/Surgery (N = 212) |
|-----------------------------------------|-------------------------------------------|---------------------------------------------|---------------------------------------------|
|                                        | N   | Statistic | N   | Statistic | N   | Statistic |
| Female sex, %*                         | 6,154 | 50.8      | 424  | 38.2      | 58  | 27.4      |
| Maternal education, %*                 | 2,320 | 19.2      | 180  | 16.2      | 32  | 15.1      |
| None/certificate of secondary education | 1,076 | 8.9       | 99   | 8.9       | 13  | 6.1       |
| Vocational                             | 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, %*                 | 4,736 | 39.1      | 320  | 28.8      | 60  | 28.3      |
| None/certificate of secondary education | 906   | 7.5       | 73   | 6.6       | 16  | 7.5       |
| Vocational                             | 2,123 | 17.5      | 239  | 21.5      | 55  | 25.9      |
| O level                                | 2,687 | 22.2      | 260  | 23.4      | 55  | 25.9      |
| A level                                | 1,659 | 13.7      | 218  | 19.6      | 26  | 12.3      |
| Degree+                                 | 795   | 6.6       | 142  | 12.8      | 30  | 14.2      |
| Nonfebrile convulsions, %*             | 9,228 | 2 (1–3)   | 1,057 | 3 (2–3)   | 193 | 3 (2–3)   |
| Traumatic life events, median (interquartile range)* | 24 yr | 2.928 | 24.2 | 218 | 19.6 | 38 | 17.9 |
|                                        | 25–29 yr | 4,496 | 40.8 | 425 | 38.3 | 89 | 42.0 |
|                                        | 30–34 yr | 3,060 | 25.4 | 364 | 32.8 | 67 | 31.6 |
|                                        | 35+ yr | 1,157 | 10.6 | 103 | 9.3  | 18 | 8.5     |
| Maternal self-rated health in pregnancy, %* | 195     | 6.3     | 64  | 5.8     | 14  | 6.6     |
| Always well                             | 7,789 | 64.3     | 641  | 57.7     | 120 | 56.6     |
| Rarely or sometimes unwell              | 3,564 | 29.4     | 405  | 36.5     | 78  | 36.8     |
| Often or always unwell                  | 8,094 | 66.8     | 736  | 66.3     | 159 | 74.5     |
| Maternal hospitalization in pregnancy, %** | 8,118 | 6.8 | 115 | 10.4 | 25 | 11.8 |
| Nonroutine screening for fetal abnormalities, %***| 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, %*                    | 10,573 | 85.6     | 891  | 80.3     | 158 | 74.5     |
| Normal                                  | 952   | 7.9       | 79   | 7.1       | 18  | 8.5       |
| Prolonged stay or transitional care ward | 786 | 6.5       | 140  | 12.6     | 36  | 17.0      |
| Same/other hospital special care baby unit | 1,537    | 24.4     | 135  | 21.4     | 16  | 13.2      |
| Abnormal placenta or cord, %***        | 527   | 8.4       | 91   | 14.6     | 27  | 22.5      |
| Non–breast/bottle fed at 24 h, %*      | 4,625 | 38.2     | 516  | 46.5     | 102 | 48.1      |
| Neonatal jaundice, %*                  | 327   | 2.7       | 44   | 4.0      | 13  | 6.1       |
| Multiple gestation, %*                 | 514   | 7.8       | 84   | 12.6     | 11  | 8.3       |
| Induction of labor, %***               | 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.
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 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-toe walking\textsuperscript{15} (dynamic balance) and peg-placing tasks\textsuperscript{15} (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.36 However, measures of neurocognitive function are unreliable in young children37 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.3–22,23 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.,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{36} 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,\textsuperscript{39} including the intensity of educational support.\textsuperscript{10} Although some large, retrospective anesthetic-induced neurotoxicity studies have provided reassurance concerning academic achievement,\textsuperscript{9} others offer contrary evidence.\textsuperscript{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.\textsuperscript{30} 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.\textsuperscript{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.\textsuperscript{32} 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,\textsuperscript{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\textsuperscript{10} or the General Anesthesia versus Spinal trial.\textsuperscript{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.\textsuperscript{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 or because they have craniofacial abnormalities associated with impaired neurodevelopment. Children referred for adenotonsillectomy for obstructive sleep apnea are also at risk of impaired neurodevelopment. 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. 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), 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 neurodevelopmental impairment 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,
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. Anesthesiology’s articles are made freely accessible to all readers on www.anesthesiology.org, for personal use only, 6 months from the cover date of the issue.

References

1. Fredriksson A, Pontén E, Gordh T, Eriksson P: Neonatal exposure to a combination of N-methyl-d-aspartate and γ-aminobutyric acid type A receptor anesthetic agents potentiates apoptotic neurodegeneration and persistent behavioral deficits. Anesthesiology 2007; 107:427–36
2. Walters JL, Paule MG: Review of preclinical studies on pediatric general anesthesia-induced developmental neurotoxicity. Neurotoxicol Teratol 2017; 60:2–23
3. U.S. Food and Drug Administration: Drug safety communication: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women. 2016. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-results-new-warnings-about-using-general-anesthetics-and. Accessed September 11, 2019.
4. Humby P: Overview of the UK population: February 2016. Overview of the UK population, its size, characteristics and the causes of population change including national and regional variation. Office for National Statistics. 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/headlinepopulations/overviewoftheukpopulation/february2016. Accessed September 11, 2019.
5. Sury MR, Palmer JH, Cook TM, Pandit JJ: The state of UK anaesthesia: A survey of National Health Service activity in 2013. Br J Anaesth 2014; 113:575–84
6. Walkden GJ, Pickering AE, Gill H: Assessing long-term neurodevelopmental outcome following general anesthesia in early childhood: Challenges and opportunities. Anesth Analg 2019; 128:681–94
7. Ko WR, Huang JY, Chiang YC, Nfor ON, Ko PC, Jan SR, Lung CC, Chang HC, Lin LY, Liaw YP: Risk of autistic disorder after exposure to general anesthesia and surgery: A nationwide, retrospective matched cohort study. Eur J Anaesthesiol 2015; 32:303–10
8. Ko WR, Liaw YP, Huang JY, Zhao DH, Chang HC, Ko PC, Jan SR, Nfor ON, Chiang YC, Lin LY: 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; 24:741–8
9. Hansen TG, Pedersen JK, Henneberg SW, Pedersen DA, Murray JC, Morton NS, Christensen K: Academic performance in adolescence after inguinal hernia repair in infancy: A nationwide cohort study. Anesthesiology 2011; 114:1076–85
10. Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC, Ing C, Park R, Radcliffe J, Hays SR, DiMaggio CJ, Cooper TJ, Raulh V, Maxwell LG, Youn A, McGowan FX: Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. JAMA 2016; 315:2312–20
11. Ing C, Sun M, Olsson M, DiMaggio CJ, Sun LS, Wall MM, Li G: Age at exposure to surgery and anesthesia...
in children and association with mental disorder diagnosis. Anesth Analg 2017; 125:1988–98

12. Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F: Association of anesthesia and surgery during childhood with long-term academic performance. JAMA Pediatr 2017; 171:e163470

13. O’Leary JD, Janus M, Duku E, Wijeysundera DN, T o et al. Anesthesiology 2016; 125:272–9

14. Graham MR, Brownell M, Chateau DG, Dragan et al. Anesthesiology 2009; 110:796–804

15. Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K: Neurosurgical conditions and procedures in infancy are associated with mortality and academic performances in adolescence: A nationwide cohort study. Paediatr Anaesth 2015; 25:186–92

16. Morriss FH Jr, Saha S, Bell EF, Colaizy TT, Stoll BJ, Hintz SR, Shankaran S, Vohr BR, Hamrick SE, Pappas A, Jones PM, Carlo WA, Laptook AR, Van Meurs KP, Sanzchez PJ, Hale EC, Newman NS, Das A, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network: Surgery and neurodevelopmental outcome of very low-birth-weight infants. JAMA Pediatr 2014; 168:746–54

17. Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K: Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: A nationwide cohort study. Paediatr Anaesth 2013; 23:883–90

18. DiMaggio C, Sun LS, Li G: Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg 2011; 113:1143–51

19. Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO: Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics 2011; 128:e1053–61

20. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO: Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology 2009; 110:796–804

21. Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, Welch TL, Olson MD, Hanson AC, Schroeder DR, Wilder RT, Warner DO: Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc 2012; 87:120–9

22. Warner DO, Zaccariello MJ, Katusic SK, Schroeder DR, Hanson AC, Schulte PJ, Buenvenida SL, Gleich SJ, Wilder RT, Sprung J, Hu D, Voigt RG, Paule MG, Chelonis JJ, Flick RP: Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: The Mayo Anesthesia Safety in Kids (MASK) study. Anesthesiology 2018; 129:89–105

23. DiMaggio C, Sun LS, Ing C, Li G: Pediatric anesthesia and neurodevelopmental impairments: A Bayesian meta-analysis. J Neurosurg Anesthesiol 2012; 24:376–81

24. Zhang H, Du L, Du Z, Jiang H, Han D, Li Q: Association between childhood exposure to single general anesthesia and neurodevelopment: A systematic review and meta-analysis of cohort study. J Anesth 2015; 29:749–57

25. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME; GAS consortium: Neurodevelopmental outcome at 2 years of age after general anesthesia and awake-regional anesthesia in infancy (GAS): An international multicentre, randomised controlled trial. Lancet 2016; 387:239–50

26. McCann ME, de Graaff JC, Dorris L, Disma N, Withington D, Bell G, Grobler A, Stargatt R, Hunt RW, Sheppard SJ, Marmor J, Giribaldi G, Bellinger DC, Hartmann PL, Hardy P, Frawley G, Izzo F, von Ungern Sternberg BS, Lynn A, Wilton N, Mueller M, Polaner DM, Absalom AR, Szmuk P, Morton N, Berde C, Soriano S, Davidson AJ; GAS Consortium: Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): An international, multicentre, randomised, controlled equivalence trial. Lancet 2019; 393:664–77

27. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, Henderson J, Macleod J, Molloy L, Ness A, Ring S, Nelson SM, Lawlor DA: Cohort profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol 2013; 42:97–110

28. Boyd A, Golding J, Macleod J, Lawlor DA, Fraser A, Henderson J, Molloy L, Ness A, Ring S, Davey Smith G: Cohort Profile: The “children of the 90s” : The index offspring of the Avon Longitudinal Study of Parents and Children. Int J Epidemiol 2013; 42:111–27

29. Halloran DR, McClure E, Chakraborty H, Chomba E, Wright LL, Carlo WA: Birth asphyxia survivors in a developing country. J Perinatol 2009; 29:243–9
30. Walker K, Badawi N, Halliday R, Stewart J, Sholler GF, Winlaw DS, Sherwood M, Holland AJ: Early developmental outcomes following major noncardiac and cardiac surgery in term infants: A population-based study. J Pediatr 2012; 161:748–52.e1

31. Sananes R, Manlhiot C, Kelly E, Hornberger LK, Williams WG, MacGregor D, Buncic R, McCrindle BW: Neurodevelopmental outcomes after major noncardiac and cardiac surgery in term infants: A population-based study. J Pediatr 2012; 161:748–52.e1

32. Hansen JH, Rotermann I, Logoteta J, Jung O, Dütschke P, Scheewe J, Kramer HH: Neurodevelopmental outcome in hypoplastic left heart syndrome: Impact of perioperative cerebral tissue oxygenation of the Norwood procedure. J Thorac Cardiovasc Surg 2016; 151:1358–66

33. Schneuer FJ, Bentley JP, Davidson AJ, Holland AJ, Badawi N, Martin AJ, Skowno J, Lain SJ, Nassar NJ: The impact of general anesthesia on child development and school performance: A population-based study. Pediatric Anesthesia 2018; 28:528–36

34. Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. J Royal Stat Soc B Methodol. 1995; 57:289–300

35. Henderson SE: Movement assessment battery for children. The Psychological Corporation, 1992

36. Bishop DV: Development of the Children's Communication Checklist (CCC): A method for assessing qualitative aspects of communicative impairment in children. J Child Psychol Psychiatry 1998; 39:879–91

37. Clausen NG, Köhler S, Hansen TG: Systematic review of the neurocognitive outcomes used in studies of paediatric anaesthesia neurotoxicity. Br J Anaesth 2018; 120:1255–73

38. Warner DO, Chelonis JJ, Paule MG, Frank RD, Lee M, Zaccariello MJ, Katusic SK, Schroeder DR, Hanson AC, Schulte PJ, Wilder RT, Sprung J, Flick RJ, Warner DO: Patterns of neuropsychological changes after general anaesthesia in young children: Secondary analysis of the Mayo Anesthesia Safety in Kids study. Br J Anaesth 2019; 122:671–81

39. Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ: Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev 2010; 10:CD001801

40. Gallagher ER, Collett BR: Neurodevelopmental and academic outcomes in children with orofacial clefts: A systematic review. Pediatrics 2019; 144:e20184027

41. Szumski G, Karwowski M: School achievement of children with intellectual disability: The role of socioeconomic status, placement, and parents’ engagement. Res Dev Disabil 2012; 33:1615–25

42. Taylor CM, Emond AM, Lingam R, Golding J: Prenatal lead, cadmium and mercury exposure and associations with motor skills at age 7 years in a UK observational birth cohort. Environ Int 2018; 117:40–7

43. Wiles NJ, Peters TJ, Heron J, Gunnell D, Emond A, Lewis G: Fetal growth and childhood behavioral problems: Results from the ALSPAC cohort. Am Journal of Epidemiol 2006; 163:829–37

44. Bishop DV, Baird G: Parent and teacher report of pragmatic aspects of communication: Use of the children’s communication checklist in a clinical setting. Dev Med Child Neurol 2001; 43:809–18