The effect of surgery on child development at primary school entry: a sibling-controlled cohort study

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Introduction

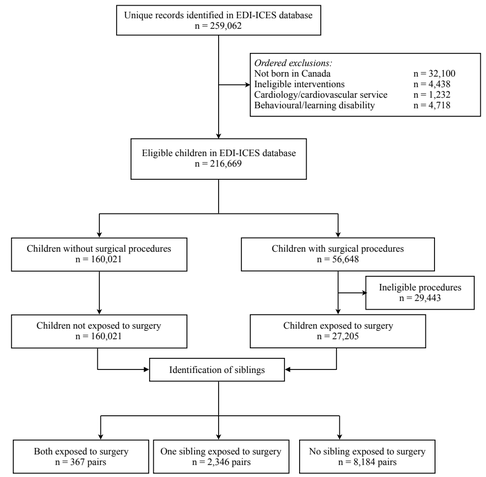
Clinical studies of pediatric anesthesia neurotoxicity have heterogeneous and mixed findings. Child development is a function of the complex interaction between *de novo* genetic, familial, and environmental risk and protective factors. We hypothesized that by examining differences between biological siblings we would mitigate risks of unmeasured confounding from biological vulnerability and environmental factors and provide a more accurate estimate of risk of adverse child development after exposure to surgical procedures that require anesthesia.

- The primary aim of this study was to examine whether anesthesia and surgery in early childhood are associated with adverse child development in biological siblings using the Early Development Instrument (EDI), a population-based measure of child development.

Methods

- With IRB approval, this was a sibling-controlled cohort study using the EDI and population-based health and demographic administrative databases, housed at the Institute for Clinical Evaluative Sciences (ICES), Ontario, Canada.
- The linkage and assembly of the Ontario EDI-ICES database has been previously described (O'Leary *et al.* Anesthesiology 2016).
- The EDI is a 103-item teacher-completed questionnaire used to assess child development at primary school entry (age 5-6 years) in five major domains (physical health and well-being, social knowledge and competence, emotional health and maturity, language and cognitive development, and communication skills and general knowledge).
- Cohort assembly for this study is described in the **Figure**.
- Siblings (maternal) were classified by exposure to surgery (both siblings had surgery, neither sibling had surgery, or one sibling had surgery).
- The primary outcome was early developmental vulnerability, defined as any major domain of the EDI in the lowest 10th percentile of a population.
- Secondary outcomes included i) performance in major EDI domains, and ii) the multiple challenge index, defined as vulnerability in ≥9 sub-domains of the EDI.
- Multivariable conditional logistic linear regression models were used to estimate the adjusted association between exposure to surgery (independent variable) and EDI outcomes.
- Statistical significance was defined as (two-tailed) $P < 0.005$, mitigating for multiple comparisons. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Figure. Cohort assembly



Characteristics and baseline EDI outcomes

- Among discordant siblings, children exposed to surgery were more likely to be male (65.9% vs. 37.6%) and be the eldest of their siblings (56.4% vs. 48.6%).
- Most children who underwent surgery were aged ≥2 years at the time of first surgery (60.6%), had a same day surgery and discharge (77.8%), had only one eligible surgery performed (83.7%), and the procedure was considered non-physiologically complex (i.e., OHIP basic units <8) (90.5%).
- The most common anatomical categories of surgical procedures performed, based on CCI and CCP codes, were ear and mastoid (33.9%), oral cavity and pharynx (31.2%), male genital organs (16.2%), and musculoskeletal (14.8%).

- When neither sibling was exposed to surgery there were no differences in the adjusted risks of early developmental vulnerability, multiple challenge index, vulnerability in major domain vulnerability, or major domain scores.
- When both children were exposed to surgery there were no differences in any EDI outcomes.

Table. Adjusted odds ratio (95%CI) of early developmental vulnerability, a multiple challenge index, or major EDI domains in the lowest tenth percentile for discordant siblings, i.e., only one sibling was exposed to surgery.

	≤ tenth percentile		
EDI Outcomes	**Adjusted OR**	**95% confidence interval**	***P* value**
Overall, early developmental vulnerability	1.14	(0.98 to 1.32)	0.1
Multiple challenge index	1.50	(0.98 to 2.3)	0.06
Major EDI Domains:			
Language and cognitive development	0.92	(0.71 to 1.19)	0.5
Physical well-being	1.11	(0.91 to 1.35)	0.3
Social competence	1.09	(0.85 to 1.41)	0.5
Emotional maturity	1.06	(0.84 to 1.34)	0.6
Communication and general knowledge	1.02	(0.81 to 1.28)	0.9

Results

- After adjusting for potential confounding, the primary analysis found no differences among siblings for early developmental vulnerability when only one had been exposed to surgery before school age (**Table**).
- There were no differences in vulnerability (<10th percentile) or performance scores in major EDI domains (**Table**).
- For children exposed to surgery (n = 2,346) among discordant sibling-pairs, age category at first exposure (age <2 vs. ≥2 years), multiple exposures (1 vs. >1), and physiologically complexity (<8 vs. ≥8 OHIP basic units) did not alter the risk of adverse EDI outcomes after adjusting for other covariates.

Conclusions

Children who had surgery prior to primary school entry were not found to be at increased risk of adverse child development compared to their biological siblings who did not have surgery. This sibling-controlled cohort mitigated for unmeasured biological vulnerability and home environmental influences on child development, and the negative findings are consistent with other clinical studies of anesthesia exposure in siblings. This study further supports that anesthesia exposure in early childhood is not associated with adverse child development.