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In Reply:

We thank Dr. Drummond for his interest in our work.[1] In response to his request, we have provided a table of surgical procedures performed in the restricted cohort of children who had data on all outcomes and covariates of interest (table 1). We also have applied the resource utilization band (RUB) comorbidity correction to our restricted cohort as requested and found that the risks of deficit in the restricted cohort were consistent with those reported in the full cohort. However, because of the smaller sample size of the restricted cohort, two of the outcomes could not be modeled after adding RUB, and the remaining outcomes had wider 95% CIs than those reported in the full cohort. We would emphasize again that the primary purpose of the restricted cohort analysis was not to quantify the relative risk of cognitive deficits associated with the exposure to anesthesia, but rather to assess whether certain outcome measures were more sensitive than others in measuring differences between the exposed and unexposed children.

Table 1. Procedures Performed on Children Exposed to Anesthesia in the Restricted Cohort (n = 781)

Procedure	n (%)
Myringotomy	38 (24.5)
Inguinal and umbilical hernia	16 (10.3)
Dental Procedure	14 (9.0)
Minor skin and nail procedure	10 (6.5)
Orchiopexy, hydrocele, and varicocele	10 (6.5)
Tonsillectomy and adenoidectomy	10 (6.5)
Circumcision	8 (5.2)
Procedure on extraocular muscles	7 (4.5)
Hypo/epispadias repair and chordee release	6 (3.9)
Finger and hand surgery	5 (3.2)
Procedures on month/tongue and cleft lip and palate repair	5 (3.2)
Nasolacrimal duct probe	4 (2.6)
Computed tomography scan	3 (1.9)
Foot and knee surgery	3 (1.9)
Lymph node excision	2 (1.3)
Minor rectal/anal procedure	2 (1.3)
Nasal airway procedure	2 (1.3)
Procedure on orbit, lens, or retina	2 (1.3)
Tracheostomy and removal	2 (1.3)
Bone marrow biopsy	1 (0.6)
Crainiectomy	1 (0.6)
Gastric and bowel repair and resection	1 (0.6)
Laparotomy and laparoscopy	1 (0.6)
Magnetic resonance imaging	1 (0.6)
PDA ligation	1 (0.6)
Total	155 (100)

Due to patients with multiple exposures, the number of procedures exceeds the number of exposed patients.

PDA = patent ductus arteriosus.

Comorbid illnesses including otitis media are potential confounders and may play a role in the cognitive outcome differences between children exposed and unexposed to anesthesia. Although 33% of the procedures in the full Raine cohort were otolaryngological in nature, they were unlikely to sufficiently explain the observed excess risk of cognitive deficits in the exposed children because similar results have been reported in children who underwent inguinal hernia surgery only.[2] In addition, the association between otitis media and developmental outcomes is disputed, with a meta-analysis of prospective studies finding the association to be negligible.[3]

As an alternative to restricting our analysis to specific procedures or illness profiles, we used RUB scores to account for comorbid illnesses in all children in the Raine cohort. The Johns Hopkins Adjusted Clinical Groups Case-Mix System was used to generate the RUB scores. The Adjusted Clinical Groups system is a widely accepted method for measuring health resource utilization and was used in this study after a comprehensive search to find the most appropriate comorbidity adjustment method available for children and adults. The reason that the RUB comorbidity correction had varying effects on the different outcomes is that different cognitive deficits may impact health services resource utilization differently. However, as emphasized in our Discussion, unmeasured and often unknown differences in exposed and unexposed children may still represent a source of residual confounding. Even the most rigorous adjustment technique in an observational study cannot match the ability of randomization to account for both known and unknown confounders between the two groups.

Regarding the adjustment for sex, all medical and demographic covariates were included as categorical variables in our modified multivariable Poisson regression model, which is a standard method in regression modeling. Per Dr. Drummond's request, we have evaluated the association between anesthetic exposure and cognitive deficit in boys in the restricted and full cohorts and found that the point estimates of the risk ratios were consistent with those reported in our article. Owing to decreased sample size in this subset analysis, however, some of the models did not converge and those that did provided wider CIs for the outcome variables. We also tested for possible interaction by sex, and found that there was no significant interaction with sex in any of the associations between exposure to anesthesia and cognitive outcomes.

We agree with Dr. Drummond that the question of whether exposure to anesthetics in early childhood has any significant long-term adverse effect on neurodevelopment in children is of clinical and public health importance yet extremely difficult to tackle. We are determined to continue our efforts to help answer this important question through rigorously designed and carefully performed studies.

Competing Interests

The authors declare no competing interests.

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Old Guidelines or Methods Cannot Insure Quality or Progress

To the Editor:

The recent article and editorial regarding the use of a proprietary Decision Support Tool extolled the need to quit memorizing data, favoring medical interactive applications in applying medical knowledge.[1,2] The Decision Support Tool was designed to increase adherence to an outdated yet still "current" 2007 American College of Cardiology/American Heart Association perioperative evaluation consensus guideline (PECG). It is clear that perioperative β blockade (PBB) and cost containment played a very large role in the underlying assumptions of that guideline. It is also clear that in 2008, the POISE study (PeriOperative ISchemic Evaluation trial [ClinicalTrials.gov Identifier: NCT00182039]) completely transformed the premise of PBB, finding PBB stroke morbidity outweighed any cardiac morbidity prevention. PBB guideline revisions followed rapidly in 2009, without corresponding PECG changes. Furthermore, the reporting of Dr. Poldermans ethical violations, as a world proponent of PBB, further publically raised significant questions undermining the 2007 PECG validity. Cardiac guidelines experience particularly rapid turnover for multiple reasons.* Medical reversal is a rapidly emerging reality, indicating guidelines have limits to application, as well as potentially short shelf-lives, as PBB clearly demonstrated.[3] This may directly compromise the usage of any Decision Support Tool, especially if failing to update rapidly while physician's life-long learning does facilitate updates.

Assuming the PECG is "correct" in 2014, is a fundamental problem. Similarly, testing "correct answers" based

* Boyles S: Cardiac Practice Guidelines Have High Turnover, May 27, 2014. Available at: http://www.medpagetoday.com/Cardiology/CHF/46004. Accessed June 13, 2014.