Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship. Are the Conclusions Justified by the Data?

Reply to Flick et al., 2009

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We thank Flick and colleagues for their thoughts and their comments on our article. Although we agree that the published study has limitations, we think that many of the limitations might be overstated. Flick et al. assert that the conclusion that 'there is no evidence for a causal relationship between anesthesia administration and later learning-related outcomes' should be qualified due to limitations of the study design and the data. We disagree and welcome the opportunity to clarify how the design and the results of our study support this conclusion.

First, we agree that we do not have systematic information on the duration of the anesthetics or the reason for surgery in the NTR sample. It is certainly the case, from the work of Wilder et al. (2009), that that duration of exposure could have an effect. We would note, however, that duration of the anesthetics is positively correlated with the reason for surgery. A more severe health problem in the child is often related to more intense surgery with longer use of anesthetics. From the work that we presented, we would suggest that a sicker child is also a more vulnerable child who, with or without anesthesia, may have a higher chance of developing learning disabilities. This is demonstrated by our finding that the non-exposed child of a discordant MZ twin pair scores as low on educational attainment as the exposed child.

Second, it is important to note that in our study the between-subjects comparison (on all available data) showed the expected outcome, that is, the exposed children did worse than the non-exposed children even when using a simple measure of exposure that did not take into account frequency.

Next, we agree that anesthetic exposure *per se* is not the only environmental factor that could influence later learning problems. The impact of hospitalization and other environmental influences could play a role. However, our study demonstrates that there are no differences between identical co-twins when one of the pair is exposed and the other is not and that the NON-exposed individual of the pair scores as low as the exposed co-twin (both score lower than twins of nonexposed pairs). Therefore, we suggest that there are other (possibly genetic) factors that influence learning disabilities. These factors are likely to be comorbid with anesthetic exposure.

Response rates of the data collection of the Netherlands Twin Register have been published elsewhere. The NTR has an average response rate of about 80% for survey research with attrition being random, with respect to childhood psychopathology and dropout from the study (see Bartels et al., 2007). We apologize for the incompleteness of Table 2. Flick and colleagues were correct, the first two columns are for males and the second are for females.

Sample sizes vary by outcome variable due to the history of data collection. Questions on anesthetics have been collected since the start of the twin register (1986). Data collection for Educational Achievement (EA) data started in 2000. Moreover, twins have to reach age 12 before information on EA becomes available. Data on Cognitive Problems (CP) were collected from the Conners' Teacher Rating Scale (CTRS-RS; Conners, 2001) and were also added to the data collection procedure in later years.

Sample sizes for the between-individual analyses (Table 4 in the original paper) were indeed not presented. We apologize for this oversight. The number of children is added to Table 1 below between parentheses (note these are not pairs but individuals). The between-individual analyses were carried out using data from children concordant exposed (CON-E) and non-exposed (CON-NE) pairs as well as children from

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Table 1

Educational Achievement (EA) and Cognitive Problems (CP): Means for Subjects From Four Exposure Groups (Twins From Concordant or Discordant Pairs); Tests Were Done for Males and Females and for Exposure Under Age 3 and Exposure Ever Under Age 12

EA exposure	CON-NE	DIS_NE	DIS_E	CON-E
Under 3 years: males*	539.48 (575)	536.76 (62)	536.4 (62)	537.5 (132)
Ever exposed: males**	540.11 (396)	538.54 (99)	538.83 (98)	537.38 (301)
Under 3 years: females***	537.49 (876)	534.43 (49)	534.36 (50)	538.21 (98)
Ever exposed: females	537.6 (591)	536.26 (129)	535.69 (127)	537.82 (276)
CP				
Under 3 years: males	2.69 (270)	2.98 (31)	2.75 (29)	2.63 (63)
Ever exposed: males	2.92 (192)	2.9 (40)	2.73 (41)	2.57 (146)
Under 3 years: females*	1.85 (411)	4.26 (28)	3.44 (31)	2.85 (55)
Ever exposed: females*	1.74 (292)	2.86 (63)	2.67 (64)	2.38 (127)

Note: * Concordant non-exposed twins score significantly higher on EA and lower on CP.

** Concordant non-exposed twins score significantly higher than concordant exposed twins on EA.

*** Concordant non-exposed and concordant exposed twins score significantly higher than discordant twins on EA.

discordant pairs (DIS-E and DIS-NE). Please note that samples sizes change over time (under 3 years vs. ever exposed before age 12).

Flick et al. express concerns about statistical power. Across the analyses performed for boys and girls, assuming power of .80, and an alpha of .05 we are able to detect small to medium effect sizes (with Cohen's d from .17–.40, depending on the analysis).

Finally, we indicated in the paper that the measures of EA and CP are not direct measures of learning disability, but are indicators of cognitive performance. The correlation between Full-Scale WISC IQ and the EA measure is .63 (Bartels et al., 2002), which is identical to the correlation between IQ and the EA measure (r = .62) used by Wilder et al. (2009).

Thus, our results support the conclusion that there is no direct causal effect of childhood anesthetic exposure on cognitive performance. We favor the hypothesis that there is an overall (genetic) vulnerability that underlies both the reason for anesthetic exposure and cognitive problems. However, in order to gain more insight into this important topic we are currently expanding our project to collect information on the reason for and outcome of the surgeries and more detailed information on anesthetic use within our sample.

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