Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Neuropsychological Battery: Instruments, Outcome Measures and Scoring

I. In-Person Assessments

Instrument	Outcome Measure(s)	Type of Scores	Range	Mean	Standard Deviation	Clinical Cutoff
Wechsler Abbreviated Scale of Intelligence (WASI)	IQ	Composite Score	40–160	100	15	<70
California Verbal Learning Test-Children (CVLT-C)	Verbal Memory	T-score	20–80	50	10	NA
Wechsler Abbreviated Scale of Intelligence (WASI): Block Design and Matrix Reasoning	Visuospatial	T-score	20–80	50	10	NA
Wechsler Abbreviated Scale of Intelligence (WASI): Vocabulary and Similarities	Expressive Language and Verbal Reasoning	T-score	20–80	50	10	NA
Delis-Kaplan Executive Function System (DKEFS): Trail Making Subtest	Executive Function	Scaled Score	1–19	10	3	NA
Grooved Pegboard Test	Motor Speed	Time (seconds)	NA	NA	NA	NA
NEPSY-II Comprehension of Instructions	Receptive Language	Scaled Score	1–19	10	3	NA
NEPSY-II Speeded Naming	Language-Speeded Naming	Scaled Score	1–19	10	3	
NEPSY-II Word Generation	Executive Function	Scaled Score	1–19	10	3	
NEPSY-II Memory for Faces/ Delayed Memory	Visual Memory & Delayed Learning	Scaled Score	1–19	10	3	
Wechsler Intelligence Scale for Children-4th edition (WISC-IV): Digit Span	Executive Function	Scaled Score	1–19	10	3	NA
Wechsler Intelligence Scale for Children-4th edition (WISC-IV): Coding	Processing Speed	Scaled Score	1–19	10	3	
Continuous Performance Test-II (CPT-II)	Attention	T-Score	30–90	50	10	>60

eTable 1. Neuropsychological Battery: Instruments, Outcome Measures and Scoring (continued)

II. Parental Reports/Interviews

Instrument	Outcome Measure(s)	Type of Scores	Range	Mean	Standard Deviation	Clinical Cutoff
Behavior Rating Inventory of Executive Functions (BRIEF)	Executive Function	T-score	30–100	50	10	>60
Child Behavior Checklist (CBCL)	Internalizing Externalizing & Total Problems Behavior	T-score	20–100	50	10	>60
Adaptive Behavior Assessment System, Second Edition (ABAS-II)	Adaptive Function	Sum Score	40–130	100	15	< 70

Ranges, Means and Standard Deviations shown for each instrument are **POPULATION** ranges, means and standard deviations.
Clinical Cutoffs (if Available) for Instruments in the Neuropsychological Battery are shown. Clinical cutoff refers to the score that represents the boundary between "normal" and the "clinical range" for abnormal. Only those instruments with defined cutoffs are shown.
< cutoff score denotes scores below the cutoff are abnormal
> cutoff score denotes scores above the cutoff are abnormal

eTable 2. Summary of Variables and Models Used for Analysis

1. Pre-specified variables evaluated in combined exposed and unexposed cohort (by mixed ANOVA).

For analysis of primary outcomes, pre-specified variables included both those shared by sibling pairs and not shared by sibling pairs. For analysis of secondary outcomes, only those variables not shared by sibling pairs were analyzed.

Variables	Variable Shared by Siblings	Significantly Associated with Primary Outcome	Significant Secondary Outcomes Associated with Variable
Study site	Yes	FIQ, PIQ, VIQ	NA
Race	Yes	FIQ, PIQ, VIQ	NA
Socioeconomic Status Indices			NA
Maternal income	Yes	FIQ, PIQ, VIQ	NA
Maternal marital status	Yes	FIQ, PIQ, VIQ	NA
Maternal housing	Yes	FIQ, PIQ, VIQ	NA
Maternal education	Yes	FIQ, PIQ, VIQ	NA
Maternal insurance type	Yes	FIQ, PIQ, VIQ	NA
Paternal income	Yes	FIQ, PIQ, VIQ	NA
Paternal marital status	Yes	FIQ, PIQ, VIQ	NA
Paternal housing	Yes	FIQ, PIQ, VIQ	NA
Paternal education	Yes	FIQ, PIQ, VIQ	NA
Paternal insurance type	Yes	FIQ, PIQ, VIQ	NA
Age at testing (Age)	No	No	Visual memory Verbal Memory Motor speed (Dominant Hand) Attention (Omission)
Appropriateness for gestational age DEFINED as normal birth weight for gestational age	No	PIQ	Motor speed (Non-dominant Hand) Visuospatial (matrix reasoning) Executive function (cognitive flexibility)
Sex	No	No	Verbal memory Processing speed Sensorimotor Attention (Commission) Verbal fluency CBCL (internalizing, total problems) ABAS (Conceptual composite, Social composite, Practical composite, GAC composite)
Birth order	No	No	Attention (Omission)

Abbreviations: FIQ=Full-scale IQ; PIQ=Performance IQ; VIQ=Verbal IQ

2. Linear mixed effect model

Outcomes that were found to be significant by paired t-test were further analyzed using the linear mixed effect model, variable(s) included in model must be: (1) not shared by siblings, and (2) significant by mixed ANOVA in the combined cohort.

Since no **Primary Outcome** was found to be significant by paired t-test, no further analysis using the linear mixed effect model was performed for the primary outcome.

Secondary Outcomes that were found to be significant by paired t-tests included verbal fluency, CBCL (internalizing and total problems scores), and ABAS (social composite scores). Sex was the variable that was found to be significant for all of these secondary outcomes, and was incorporated in the analysis using the linear mixed effect model.

A summary of the coefficient estimates and p-values for the effect of exposure and covariates from linear mixed effect models are summarized in table below.

Secondary Outcomes	Δ (95% CI)	Variable included in Model	Coefficient After Adjustment for Variable	P After Adjustment for Variable[a]
Verbal fluency	-1 (-1.7 to -0.3)	Sex	0.5	0.3
CBCL				
Internalizing behavior	3.2 (1.1-5.3)	Sex	-2	0.2
Total problems	2.7 (0.6-4.7)	Sex	-1	0.3
ABAS				
Social composite	-3.3 (-6.1 to -0.6)	Sex	-0.1	0.9

[a]After adjusting for sex, the only significant covariate, there were no statistically significant differences between sibling pairs in any of the secondary outcomes.

eTable 2. Summary of Variables and Models Used for Analysis (continued)

3. Mixed effect logistic regression model

The pre-specified criteria for categorical analysis using the mixed effect logistic regression model were: (1) significant by paired t-test, and (2) availability of clinical cutoffs. Only CBCL scores and ABAS social composite scores fulfilled these criteria

Secondary Outcomes	Clinical Cutoff	Abnormal Score		Variable included in Model	P After Adjustment for Variable[a]
		Exposed No. (%)	Unexposed No. (%)		
CBCL					
Internalizing	>60	21 (21%)	10 (10%)	Sex	0.02
Total problems	>60	15 (15%)	12 (12%)	Sex	0.5
ABAS					
Social composite	<70	7 (7%)	0	Sex	0.9

[a]After adjustment for sex, the only secondary outcome significant by the categorical analysis was CBCL internalizing scores.

eTable 3A. Numbers of Sibling Pairs With Complete Data Available for Analysis by Outcome Measures and Reasons for Exclusion

Domains	Neurocognitive Outcomes	Assessment Instrument(s)	No. of sibling pairs enrolled	Reason for exclusion (n)	No. of sibling pairs with complete data for analysis
Global	Global Cognitive	WASI	116	Wrong surgical procedure in exposed (5) Missing anesthesia record in exposed (1) Did not meet age requirement for testing (1) Age between sibling >36 months (3) Incomplete data in one of the siblings (1)	105

Domains	Neurocognitive Outcomes	Assessment Instrument(s)	No. of sibling pairs with available data	Reason for exclusion (n)	No. of sibling pairs with complete data for analysis
Memory/ Learning	Visual memory	NEPSY-II	105	Incomplete data (1)	104
			105	Incomplete data (2)	103
	Verbal memory	CVLT-C	105	Incomplete data (2)	103
Motor/ Processing speed	Motor speed	Grooved pegboard (dominant)	105	Incomplete data (3)	102
		Grooved pegboard (non-dominant)	105	Incomplete data (1)	104
	Processing speed	WISC-IV	105	Incomplete data (2)	103
Visuospatial	Visuospatial	WASI	105		105
Attention	Attention	CPT-II	105	Incomplete data (5)	100
Executive Function	Executive Function	BRIEF	105	Incomplete data (1)	104
	Working memory	WISC-IV	105	Incomplete data (1)	104
	Cognitive flexibility	DKEFS Trail Making	105	Incomplete data (1)	104
	Verbal fluency	NEPSY-II	105	Incomplete data (1)	104
Language	Expressive	WASI	105	-	105
	Verbal reasoning			-	105
	Receptive	NEPSY-II	105	Incomplete data (1)	104
	Speeded naming		105	Incomplete data (8)	97
Behavior	Internalizing	CBCL	105	Incomplete data (3)	102
	Externalizing		105	Incomplete data (4)	101
	Total Problems		105	Incomplete data (4)	101
	Adaptive behavior	ABAS-II	105	Incomplete data (3)	102
			105	-	105
			105	Incomplete data (4)	101
			105	Incomplete data (6)	99

eTable 3B. Comparative Demographics and Parental Socioeconomic Status Between Sibling Pairs Included and Excluded in Data Analysis

Exposed and Unexposed Siblings Demographics				
	INCLUDED Exposed (n=105) No. (%)	**EXCLUDED Exposed (n=11) No. (%)**	**INCLUDED Unexposed (n=105) No. (%)**	**EXCLUDED Unexposed (n=11) No. (%)**
Age of anesthesia exposure Mean (SD) (months)	n=105 17.3 (10.9)	n=11 21.2 (9.6)	-	-
0-11 months Mean (SD) (months)	n=33 (31%) 3.7 (2.4)	n=1 (9%) 4	-	-
12-23 months Mean (SD) (months)	n=39 (37%) 17.1 (3.0)	n=7 (74%) 18.3 (3.3)	-	-
24-36 months Mean (SD) (months)	n=33 (31%) 30.5 (3.8)	n=3 (27%) 35.7 (2.0)	-	-
ASA Physical Status (at surgery)				
1	85 (81%)	9 (82%)	-	-
2	20 (19%)	2 (18%)	-	-
Duration of Anesthesia Mean (SD) (minutes)	n=105 84 (33)	n=11 78 (24)	-	-
Age at testing Mean (SD) (years)	n=105 10.6 (2.0)	n=11 10.3 (1.6)	n=105 10.9 (1.7)	n=11 11 (2)
Sex				
Males	95 (90%)	10 (91%)	59 (56%)	4 (36%)
Females	10 (10%)	1 (9%)	46 (44%)	7 (64%)
Birth order				
Older sib	44 (42%)	4 (36%)	61 (58%)	7 (64%)
Younger sib	61 (58%)	7 (64%)	44 (42%)	4 (36%)
Appropriateness for Gestational Age				
SGA	10 (9.5%)	1 (9%)	6 (6%)	1 (9%)
AGA	84 (80%)	9 (82%)	89 (85%)	8 (73%)
LGA	11 (10%)	1 (9%)	10 (9.5%)	2 (18%)
Race				
White	90 (86%)	10 (91%)	90 (86%)	10 (91%)
Non-white	14 (13%)	1 (9%)	14 (13%)	1 (9%)
Missing	1 (1%)	0	1 (1%)	0
Ethnicity				
Hispanic	4 (4%)	0	4 (4%)	0
Non-Hispanic	98 (93%)	11 (100%)	98 (93%)	11 (100%)
Missing	3 (3%)	0	3 (3%)	0
Anesthesia or surgery after 36 months	18 (17%)	0	23 (22%)	0
Enrolled in special education program	16 (15%)	3 (27%)	14 (13%)	0

eTable 3B. Comparative Demographics and Parental Socioeconomic Status Between Sibling Pairs Included and Excluded in Data Analysis (continued)

Parental Socioeconomic Status (SES)				
	INCLUDED (n=105) Maternal No. (%)	**EXCLUDED (n=11) Maternal No. (%)**	**INCLUDED (n=105) Paternal No. (%)**	**EXCLUDED (n=11) Paternal No. (%)**
Income				
Unemployed	13 (12%)	0	1 (1%)	0
≤ $ 40,000	36 (34%)	4 (36%)	13 (12%)	1 (9%)
$40,0001-$80,000	22 (21%)	1 (9%)	27 (26%)	1 (9%)
$80,0001-$100,000	22 (21%)	2 (18%)	42 (40%)	2 (18%)
>$ 100,000	8 (8%)	1 (9%)	16 (15%)	6 (55%)
Missing	4 (4%)	3 (27%)	6 (6%)	1 (9%)
Education				
≤12 grade	18 (17%)	1 (9%)	24 (23%)	4 (36%)
2 year college	13 (12%)	3 (27%)	12 (11%)	1 (9%)
4 year college	32 (30%)	4 (36%)	32 (30%)	2 (18%)
Postgraduate	42 (40%)	3 (27%)	34 (32%)	4 (36%)
Missing	0		3 (3%)	
Housing				
Own	91 (87%)	9 (82%)	88 (84%)	9 (82%)
Rent	14 (13%)	2 (18%)	11 (10%)	2 (18%)
Other	0		2 (2%)	
Missing	0	0	4 (4%)	0
Marital Status				
Singe	5 (5%)	0	5 (5%)	0
Married	94 (90%)	9 (82%)	96 (91%)	9 (82%)
Divorced	4 (4%)	2 (18%)	1 (1%)	2 (18%)
Other	2 (2%)	0	2 (2%)	0
Missing	0	0	1 (1%)	0
Insurance				
No insurance	2 (2%)	0	2 (2%)	1 (9%)
Medicaid	7 (7%)	1 (9%)	2 (2%)	0
Other insurance	96 (91%)	10 (91%)	97 (92%)	9 (82%)
Missing	0	0	4 (4%)	1 (9%)

eTable 4. IQ Scores in Siblings With No Additional Anesthesia After Age 3 Years

No Further Exposure Cohort consisted of a total of 67 sibling pairs in which both exposed and unexposed siblings had no additional anesthesia exposure after age 3 years. The following illustrates how the cohort was constructed:

	Exposed (n)	**Unexposed (n)**
Anesthesia before age 36 months	105	0
No anesthesia before age 36 months	0	105
Anesthesia after age 36 months	18	23
Anesthesia after age 36 months in Exposed Sibling Only	14	0
Anesthesia after age 36 months in Unexposed Sibling Only	0	19
Anesthesia after age 36 months in Both Exposed and Unexposed Siblings	4	4
Single Exposure in Exposed Sibling and NO Exposure in Unexposed Sibling	67	67

IQ scores and Differences in IQ Scores (Δ [Exposed-Unexposed]) in the Entire Study Cohort and in the No Further Exposure Cohort are shown below[a]

	ENTIRE STUDY COHORT IQ Scores (95% CI) (n=105 sibling pairs)		**NO FURTHER EXPOSURE COHORT IQ Scores (95% CI)** (n=67 sibling pairs)	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Full-scale IQ	111(108-113)	111 (108-113)	112 (109-115)	110 (107-114)
Performance IQ	108 (105-111)	107 (105-110)	109 (106-113)	108 (104-112)
Verbal IQ	111 (108-114)	111 (109-114)	112 (109-115)	111 (108-114)
	ΔIQ (Exposed-Unexposed) (95% CI)			
Full-scale ΔIQ	0.2 (-2.6-2.9)		2 (-1.4-5.3)	
Performance ΔIQ	0.5 (-2.7-3.7)		1.6 (-2.8-5.9)	
Verbal ΔIQ	-0.5 (-3.2-2.2)		1.6 (-1.7-4.9)	

[a]There were no statistically significant differences between exposed and unexposed siblings who had no further anesthesia exposures after age 3 years. The ΔIQ scores for the 67 sibling pairs were comparable to the findings in the 105 sibling pairs that made up the entire cohort.

eTable 5A. Differences Between Exposed-Unexposed Scores in All Children and in Same-Sex Siblings[a]

	Δ IQ Scores (95% CI)			Δ CBCL (95% CI)			Δ ABAS-II Social Composite (95% CI)[c]	Δ Verbal Fluency (95% CI)[d]
	Full-scale	Performance	Verbal	Internalizing[b]	Externalizing	Total Problems[b]		
All Children	0.2 (-2.6–2.9) (n=105)	0.5 (-2.7–3.7) (n=105)	-0.5 (-3.2–2.2) (n=105)	3.2 (1.1–5.3) (n=102)	2.1 (0–4.2) (n=101)	2.7 (0.6–4.7) (n=101)	-3.3 (-6.1 to -0.6) (n=105)	-1 (-1.7 to -0.3) (n=104)
Same-Sex Sibling Pairs	-0.5 (-4.4–3.3) (n=42)	-0.9 (-5.9–4.1) (n=42)	-0.4 (-4.7–3.9) (n=42)	-0.1 (-3.1–2.8) (n=41)	0.9 (-2.4–4.2) (n=41)	-0.8 (-3.8–2.2) (n=41)	-0.9 (-3.9–2.2) (n=42)	-0.6 (-1.7–0.5) (n=41)

Δ = Differences of scores between exposed and unexposed siblings

[a]Differences between exposed and unexposed sibling pairs in full-scale IQ scores, performance IQ scores and verbal IQ scores in same-sex sibling pairs are comparable to the entire study cohort of 105 sibling pairs.

[b]Internalizing and total problems CBCL scores were statistically significantly different between sibling pairs for the entire cohort when analyzed using the paired t-test. In the analysis of the combined cohort, sex was found to be a significant, and the only significant, covariate. Therefore, sex was included in the linear mixed effect model to analyze the difference between siblings. The results found there was no statistically significant difference between exposed and unexposed siblings in internalizing or total problems CBCL scores. For all CBCL scores, the difference between same-sex siblings was small, and non-significant.

[c]Adaptive behavior as assessed using ABAS-II was found to be significantly different between sibling pairs in social composite scores by paired t-test. The only significant covariate by mixed ANOVA in the combined cohort was sex. Sex was therefore included in the linear mixed effect model and the results indicate that there was no statistically significant difference between exposed and unexposed siblings. Comparison of same-sex siblings showed a small and non-significant difference between siblings in ABAS social composite scores.

[d]Verbal fluency was found to be statistically significantly different between exposed and unexposed siblings by paired t-test. After adjustment for sex, the only significant covariate, there was no longer any statistically significant difference between sibling pairs in verbal fluency. Differences in verbal fluency scores in same-sex sibling pairs were small and non-significant.

eTable 5B. All Children and Same-Sex Siblings With CBCL Scores Considered to Be Abnormal (>60)[a]

All Children with Scores >60 No. (%)			
	Internalizing (n=102)	**Externalizing (n=101)**	**Total Problems (n=101)**
Exposed	21 (21%)	11 (11%)	15 (15%)
Unexposed	10 (10%)	8 (8%)	12 (12%)
Same-Sex Siblings with Scores >60 No. (%)			
	Internalizing (n=41)	**Externalizing (n=41)**	**Total Problems (n=41)**
Exposed	6 (15%)	3 (7%)	3 (7%)
Unexposed	6 (15%)	5 (12%)	7 (17%)

[a]CBCL scores above 60 are considered clinically abnormal. Among exposed children (total n=102), there were proportionally more exposed children who scored >60 in internalizing CBCL scores compared to unexposed children, even after adjustment for sex. There was no statistically significant difference in the proportion of exposed and unexposed children who scored >60 in externalizing and total problems scores. When the analysis was restricted to only same-sex sibling pairs (n=41), similar proportions of exposed and unexposed children scored >60 in internalizing, externalizing and total problems CBCL scores.