"The use of general anesthetics and sedation drugs in young children and pregnant women"

Andrew Davidson

Disclosures

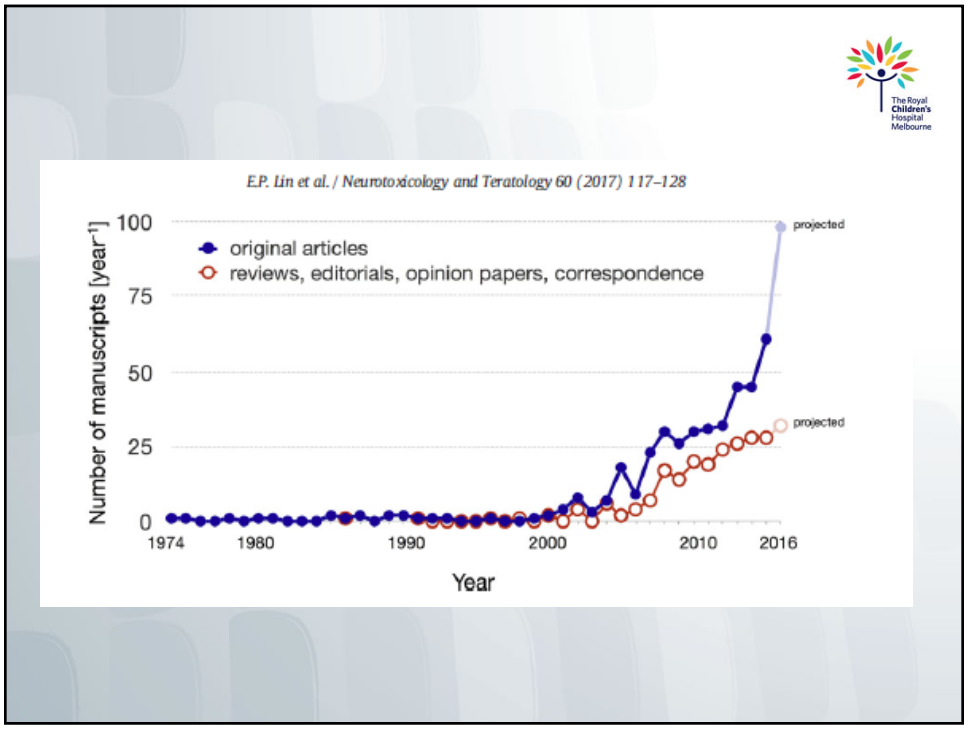
- I have no conflicts of interest except being PI for GAS trial and being recipient of ongoing research grants investigating this topic

Outline

- FDA statement
- Animal data
- Human clinical data
- What next

http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm

The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains.


E.P. Lin et al. / Neurotoxicology and Teratology 60 (2017) 117–128
Number of manuscripts [year⁻¹]
100
75
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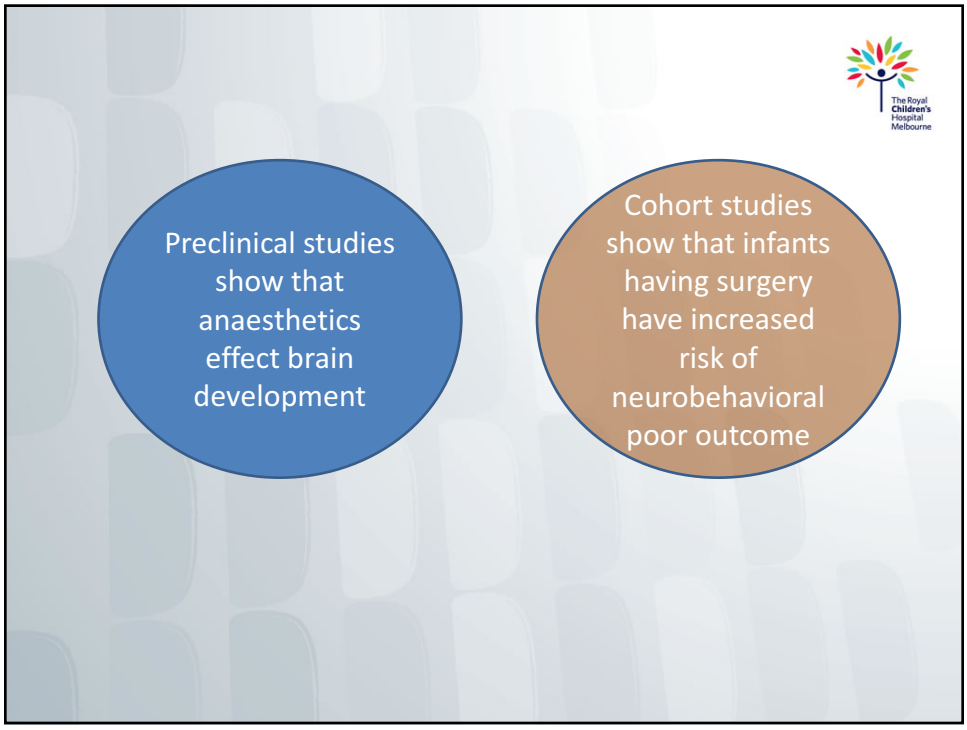
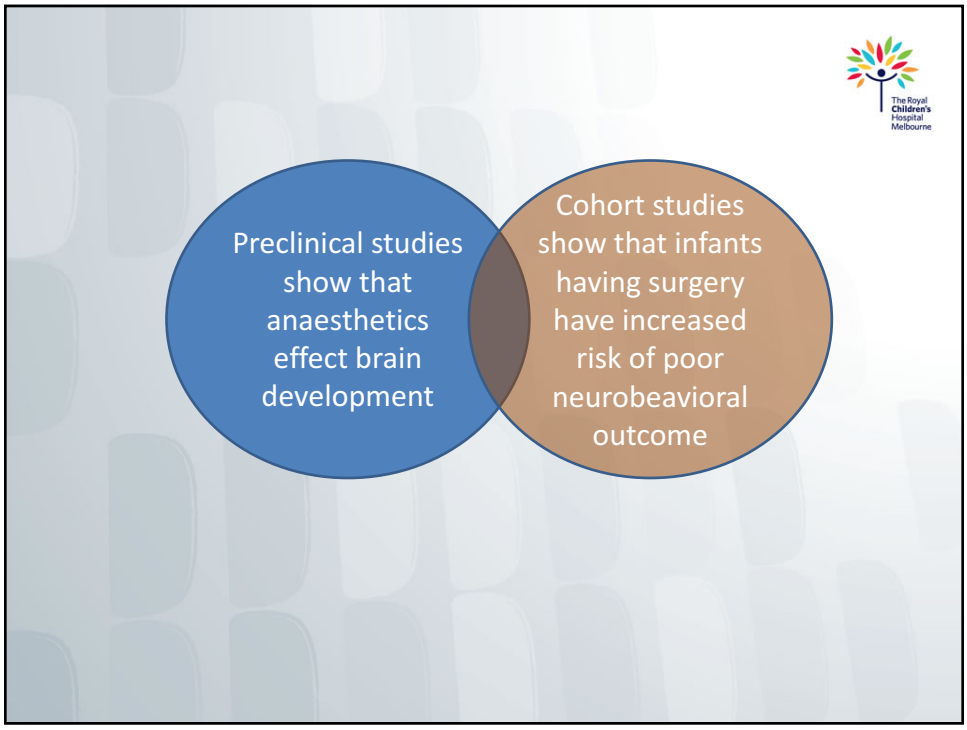

Preclinical studies show that anaesthetics effect brain development
Cohort studies show that infants having surgery have increased risk of neurobehavioral poor outcome


The Royal Children's Hospital Melbourne
Preclinical studies show that anaesthetics effect brain development
Cohort studies show that infants having surgery have increased risk of poor neurobeavioral outcome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Smart tots *versus* safetots

- Neurotoxicity is irrelevant
- If there had been a problem we would have seen it
- Concentrate of physiologic homeostasis

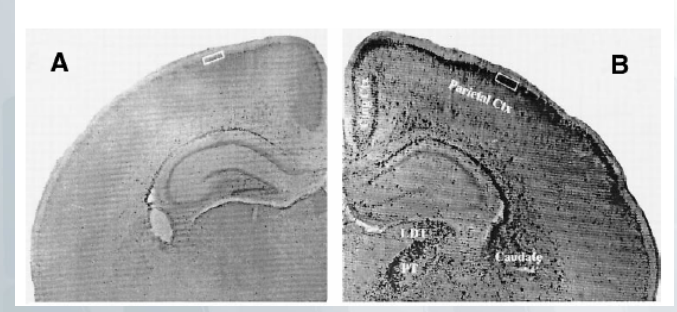
> Despite the inherent differences in the above-mentioned cohort studies, why are there such striking differences between the epidemiologic studies from North America and the epidemiologic studies generated (mainly) in Europe? Private/insurance based health care vs. mainly national health care systems with access for everyone? Differences in the access to and quality of the school systems between the continents? Or rather a desperate desire to keep and expand the NIH funding for the research group?

Animal data

Ikonomidou et al. Blockade of NMDA Receptors and Apoptotic Neurodegeneration in the Developing Brain. *Science 1999; 283, 5398*

- 7-day old rat

Saline Treatment MK-801 (0.5 mg/kg)



Ketamine (20 mg/kg x7)

Morphologic changes

- Apoptosis
  - 3 - 6 hours after anaesthesia exposure
  - Cortical layer 2/3 and layer 5 pyramidal neurons, also interneurons, oligodendrocytes
  - ~ 2% of all neurons
- Impaired hippocampal neurogenesis
  - Impact determined by cell age
  - Explain variable regions affected with age of animal
- Changes in dendritic spines and synaptic density
  - Occurs rapidly and persists

Mechanisms

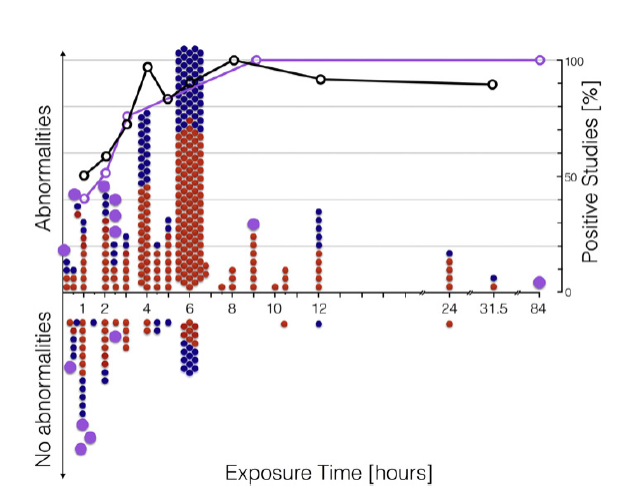
- "the anaesthetic state" – use it or lose it

- Altered neurtrophin signalling
- Mitochondrial dysfunction
- Neuroinflammation
- Changes in interneuron phenotype
- Tau phosphorylation

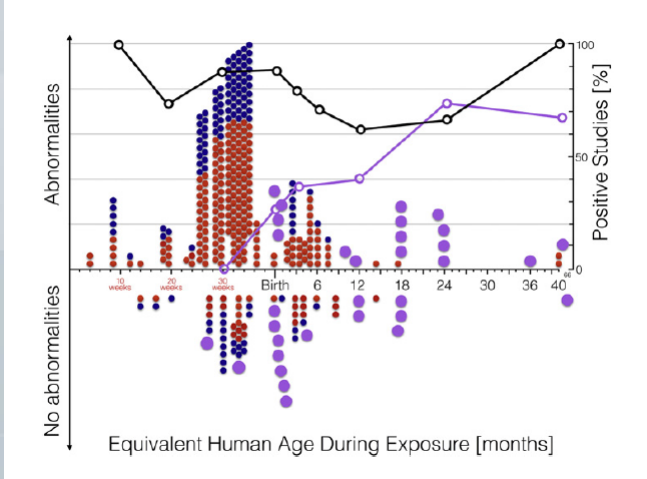
Agent

- All general anaesthetics and benzodiazepines
- Probably not the α2-adrenergic receptor agonist dexmedetomidine
- ? Not Xenon

Duration of exposure

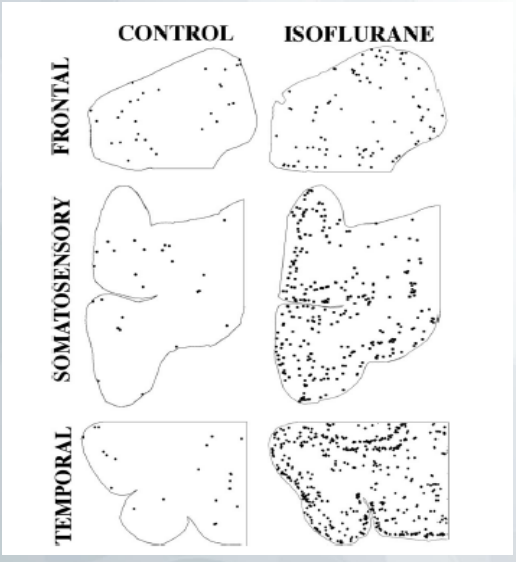


Age at exposure



What we know – animal studies

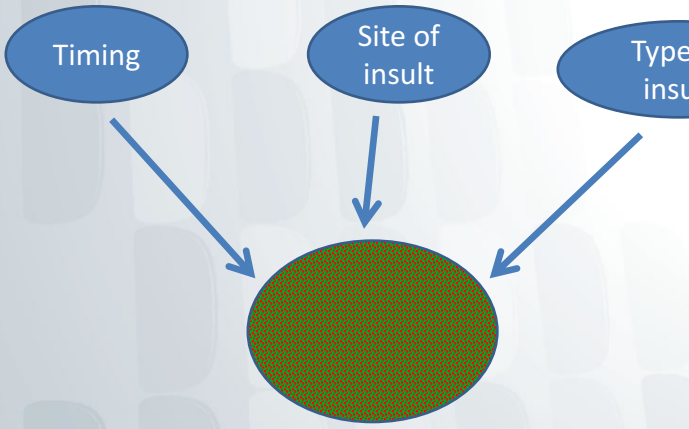
- In animal experiments many general anaesthetics have a variety of effects on the developing brain; including apoptosis.
- The effects and regions affected vary with *dose*, *agent* and *age* of exposure.
- The strongest evidence for morphologic change is for agents that are *GABA agonists* or *NMDA antagonists*.
- The changes are greatest with *longer* exposure.
- There are multiple mechanisms described.
- Increasing evidence for long term neurodevelopmental changes in rodents and *non-human primates*.

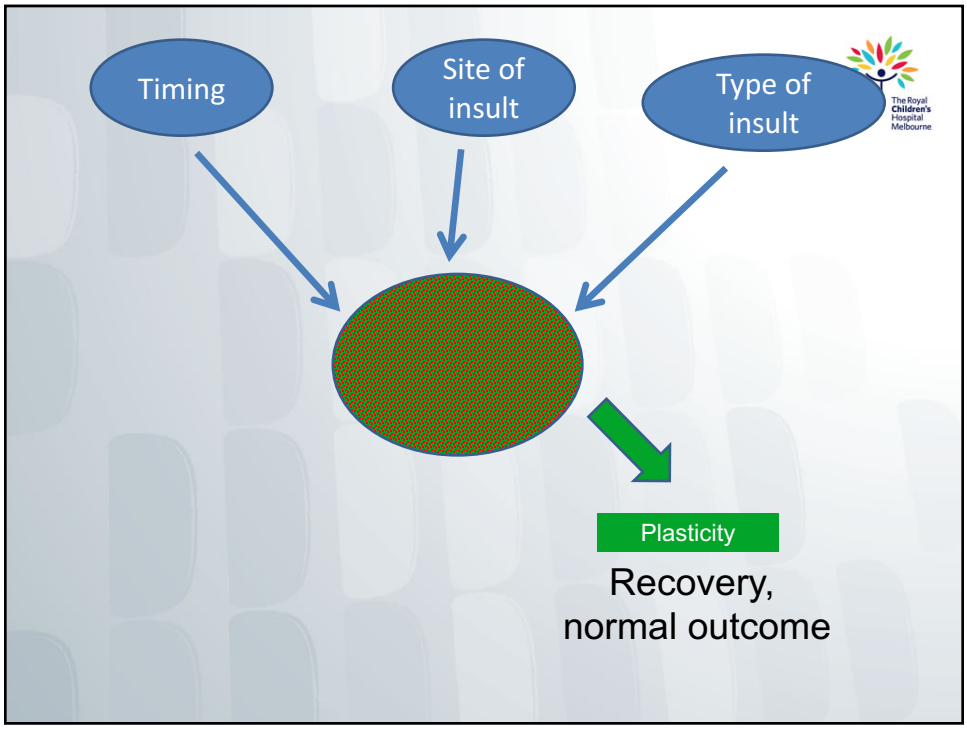


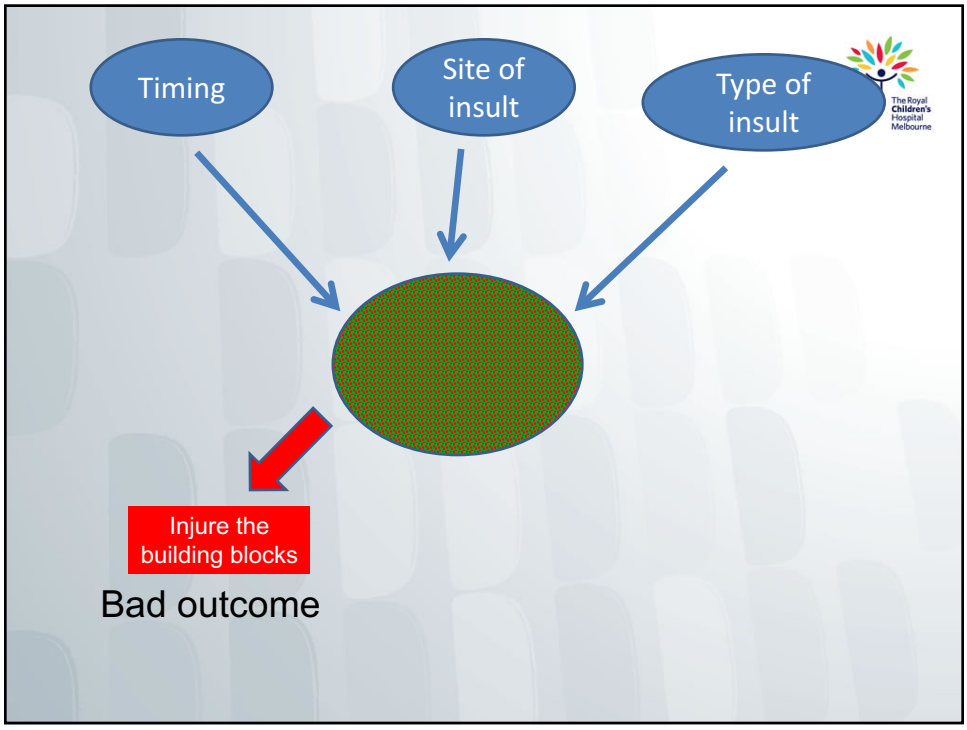
?

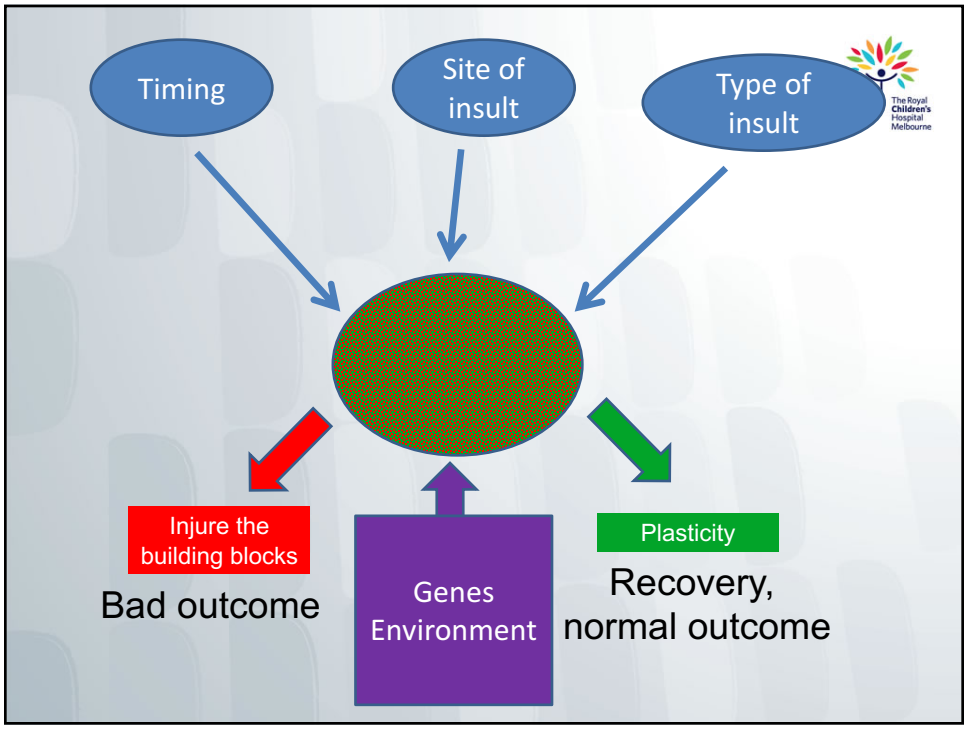
Translation

- *There is no reason to suggest these changes in animals would not occur when the developing human brain is exposed to sufficient doses of general anaesthetics.*
- But, there are precedents for animal models being irrelevant to humans.
- Hard to predict what age, or at what dose, children are at risk.
- We have incomplete data on which neurological domains in humans are likely to be affected, if any.
- We don't know the impact of surgery.
- There are many modifying factors when translating animal to humans.




Timing
Site of insult
Type of insult
Plasticity
Recovery, normal outcome


Timing
Site of insult
Type of insult
Injure the building blocks
Bad outcome


Timing
Site of insult
Type of insult
Injure the building blocks
Bad outcome
Genes
Environment
Plasticity
Recovery, normal outcome

Human data

Surgery in neonates

- Congenital diaphragmatic hernia
- Oesophageal atresia
- Laparotomy for necrotising enterocolitis
- Congenital heart disease
- Hernia repair in the ELBW infants
- Pyloric stenosis

- All have increased risk of poor neurobehavioural outcome

Human studies specifically addressing the problem

- Birth cohorts
- Retrospective population based studies
- Ambi-directional cohort studies
- One prospective trial

- Diagnosis of learning or developmental disorder
- School grades
- Psychometric testing
- MRI imaging

Learning disability or ADHD

- Mayo group
  - Increased risk with multiple exposures <2yr of age
  - No risk with single exposure
  - Similar results in a more recent cohort exposed <3yr
- New York. Di Maggio *et al.*
  - Weak evidence for an association between hernia repair and diagnosis of a disorder
  - Greater if multiple exposure

Age at Exposure to Surgery and Anesthesia in Children and Association With Mental Disorder Diagnosis

Caleb Ing, MD, MS,*† Ming Sun, MS,*‡ Mark Olfson, MD, MPH,§ Charles J. DiMaggio, PhD, MPH, PA-C,‖ Lena S. Sun, MD,*¶ Melanie M. Wall, PhD,‡§ and Guohua Li, MD, DrPH*†

BACKGROUND: Animals exposed to anesthetics during specific age periods of brain development experience neurotoxicity, with neurodevelopmental changes subsequently observed during adulthood. The corresponding vulnerable age in children, however, is unknown.
METHODS: An observational cohort study was performed using a longitudinal dataset constructed by linking individual-level Medicaid claims from Texas and New York from 1999 to 2010. This dataset was evaluated to determine whether the timing of exposure to anesthesia ≤5 years of age for a single common procedure (pyloromyotomy, inguinal hernia, circumcision outside the perinatal period, or tonsillectomy and/or adenoidectomy) is associated with increased subsequent risk of diagnoses for any mental disorder, or specifically developmental delay (DD) such as reading and language disorders, and attention deficit hyperactivity disorder (ADHD). Exposure to anesthesia and surgery was evaluated in 11 separate age at exposure categories: ≤28 days old, >28 days and ≤6 months, >6 months and ≤1 year, and 6-month age intervals between >1 year old and ≤5 years old. For each exposed child, 5 children matched on propensity score calculated using sociodemographic and clinical covariates were selected for comparison. Cox proportional hazards models were used to measure the hazard ratio of a mental disorder diagnosis associated with exposure to surgery and anesthesia.
RESULTS: A total of 38,493 children with a single exposure and 192,465 propensity score-matched children unexposed before 5 years of age were included in the analysis. Increased risk of mental disorder diagnosis was observed at all ages at exposure with an overall hazard ratio of 1.26 (95% confidence interval [CI], 1.22–1.30), which did not vary significantly with the timing of exposure. Analysis of DD and ADHD showed similar results, with elevated hazard ratios distributed evenly across all ages, and overall hazard ratios of 1.26 (95% CI, 1.20–1.32) for DD and 1.31 (95% CI, 1.25–1.37) for ADHD.
CONCLUSIONS: Children who undergo minor surgery requiring anesthesia under age 5 have a small but statistically significant increased risk of mental disorder diagnoses and DD and ADHD diagnoses, but the timing of the surgical procedure does not alter the elevated risks. Based on these findings, there is little support for the concept of delaying a minor procedure to reduce long-term neurodevelopmental risks of anesthesia in children. In evaluating the influence of age at exposure, the types of procedures included may need to be considered, as some procedures are associated with specific comorbid conditions and are only performed at certain ages.
(Anesth Analg 2017;XXX:00–00)

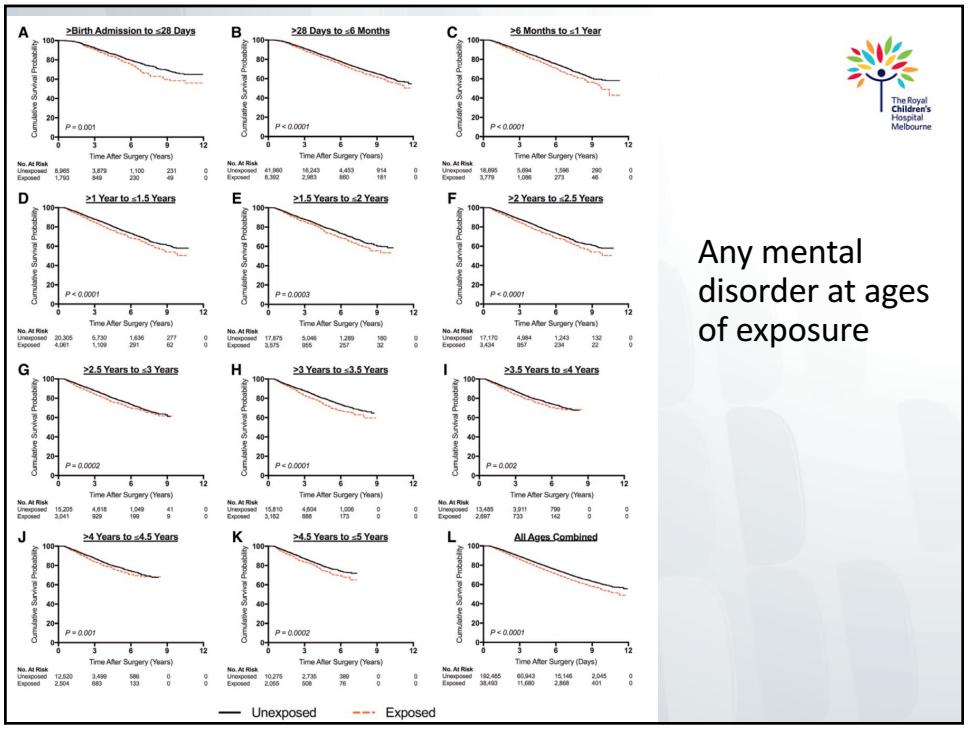
Ing et al., Anesth Analg 2017

- 38,493 children surgery before 5 yrs
  - Pyloromyotomy
  - Inguinal hernia
  - Circumcision
  - Tonsillectomy and/or adenoidectomy
- 192, 465 matched controls

- Diagnosis of any mental disorder
  - Developmental delay
  - ADHD

- Overall hazard ratio of mental disorder 1.26 (95% CI 1.22–1.30)

- Developmental Delay 1.26 (95% CI, 1.20–1.32)
- ADHD 1.31 (95% CI, 1.25–1.37)



Any mental disorder at ages of exposure

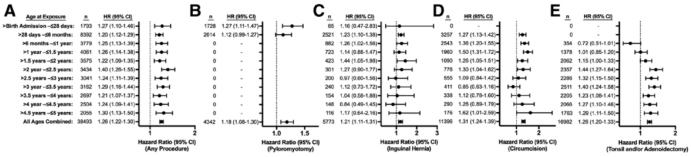


Figure 2. Hazard of an *ICD-9* coded mental disorder diagnosis after a single exposure to surgery and anesthesia in Texas and New York. Hazard ratios (HRs) for diagnosis of mental disorder are displayed for exposed versus matched unexposed children. The number (n) of exposed children in each age at exposure group is also displayed. A shows HRs for children who had any of the 4 procedures of interest versus unexposed children. B, C, D, and E show HRs for children who had pyloromyotomy, inguinal hernia repair, circumcision, and tonsillectomy and/or adenoidectomy, respectively, compared to unexposed children. CI indicates confidence interval.

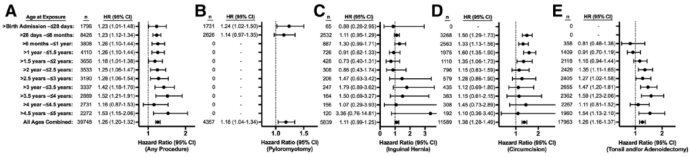


Figure 3. Hazard of an *ICD-9* coded developmental delay diagnosis after a single exposure to surgery and anesthesia in Texas and New York. Hazard ratios (HRs) for diagnosis of a developmental delay are displayed for exposed versus matched unexposed children. The number (n) of exposed children in each age at exposure group is also displayed. A shows HRs for children who had any of the 4 procedures of interest versus unexposed children. B, C, D, and E show HRs for children who had pyloromyotomy, inguinal hernia repair, circumcision, and tonsillectomy and/or adenoidectomy, respectively, compared to unexposed children. CI indicates confidence interval.

Risk for each disorder, By surgery type

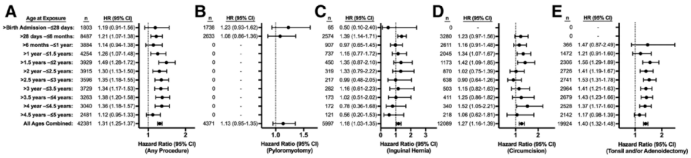


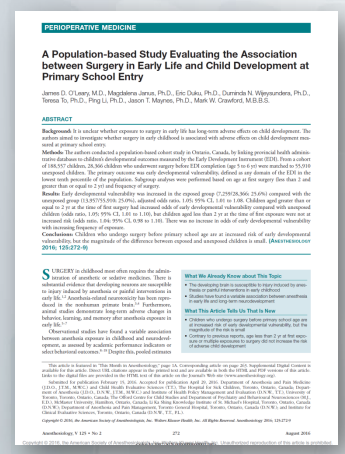
Figure 4. Hazard of an *ICD-9* coded attention deficit hyperactivity disorder diagnosis after a single exposure to surgery and anesthesia in Texas and New York. Hazard ratios (HRs) for diagnosis of an attention deficit hyperactivity disorder are displayed for exposed versus matched unexposed children. The number (n) of exposed children in each age at exposure group is also displayed. A shows HRs for children who had any of the 4 procedures of interest versus unexposed children. B, C, D, and E show HRs for children who had pyloromyotomy, inguinal hernia repair, circumcision, and tonsillectomy and/or adenoidectomy, respectively, compared to unexposed children. CI indicates confidence interval.

School grades

- Denmark. Hansen *et al.*
- Iowa. Block *et al.*

- Weak evidence for an association between surgery in infancy and poor school grades
- Very little if any evidence for an association when control for confounding

- Higher incidence of “non-attainers”



PERIOPERATIVE MEDICINE

A Population-based Study Evaluating the Association between Surgery in Early Life and Child Development at Primary School Entry

James D. O'Leary, M.D., Magdalena Janus, Ph.D., Eric Duku, Ph.D., Duminda N. Wijeysundera, Ph.D., Teresa To, Ph.D., Ping Li, Ph.D., Jason T. Maynes, Ph.D., Mark W. Crawford, M.B.B.S.

ABSTRACT

Background: It is unclear whether exposure to surgery in early life has long-term adverse effects on child development. The authors aimed to investigate whether surgery in early childhood is associated with adverse effects on child development measured at primary school entry.

Methods: The authors conducted a population-based cohort study in Ontario, Canada, by linking provincial health administrative databases to children's developmental outcomes measured by the Early Development Instrument (EDI). From a cohort of 188,557 children, 28,366 children who underwent surgery before EDI completion (age 5 to 6 yr) were matched to 55,910 unexposed children. The primary outcome was early developmental vulnerability, defined as any domain of the EDI in the lowest tenth percentile of the population. Subgroup analyses were performed based on age at first surgery (less than 2 and greater than or equal to 2 yr) and frequency of surgery.

Results: Early developmental vulnerability was increased in the exposed group (7,259/28,366; 25.6%) compared with the unexposed group (13,937/55,910; 25.0%; adjusted odds ratio, 1.05; 95% CI, 1.01 to 1.08. Children aged greater than or equal to 2 yr at the time of first surgery had increased odds of early developmental vulnerability compared with unexposed children (odds ratio, 1.09; 95% CI, 1.01 to 1.18), but children aged less than 2 yr at the time of first exposure were not at increased risk (odds ratio, 1.04; 95% CI, 0.98 to 1.10). There was no increase in odds of early developmental vulnerability with increasing frequency of exposure.

Conclusions: Children who undergo surgery before primary school age are at increased risk of early developmental vulnerability, but the magnitude of the difference between exposed and unexposed children is small. (ANESTHESIOLOGY 2016; 125:272-9)

SURGERY in childhood most often requires the administration of anesthetic or sedative medicines. There is substantial evidence that developing neurons are susceptible to injury induced by anesthesia or painful interventions in early life.[1,2] Anesthesia-related neurotoxicity has been reproduced in the nonhuman primate brain.[3,4] Furthermore, animal studies demonstrate long-term adverse changes in behavior, learning, and memory after anesthesia exposure in early life.[5–7]

Observational studies have found a variable association between anesthesia exposure in childhood and neurodevelopment, as assessed by academic performance indicators or select behavioral outcomes.[8–10] Despite this, pooled estimates

What We Already Know about This Topic

- The developing brain is susceptible to injury induced by anesthesia or painful interventions in early childhood
- Studies have found a variable association between anesthesia in early life and long-term neurodevelopment

What This Article Tells Us That Is New

- Children who undergo surgery before primary school age are at increased risk of early developmental vulnerability, but the magnitude of the risk is small
- Children who undergo surgery at age less than 2 yr at first exposure or multiple exposures to surgery did not increase the risk of adverse child development

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 263. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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Anesthesiology, V 125 • No 2 272 August 2016

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PERIOPERATIVE MEDICINE

Neurodevelopmental Assessment in Kindergarten in Children Exposed to General Anesthesia before the Age of 4 Years

A Retrospective Matched Cohort Study

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ABSTRACT

Background: Animal studies demonstrate general anesthetic (GA) toxicity in the developing brain. Clinical reports raise concern, but the risk of GA exposure to neurodevelopment in children remains uncertain.

Methods: The authors undertook a retrospective matched cohort study comparing children less than 4 yr of age exposed to GA to those with no GA exposure. The authors used the Early Development Instrument (EDI), a 104-component questionnaire, encompassing five developmental domains, completed in kindergarten as the outcome measure. Mixed-effect logistic regression models generated EDI estimates for single versus multiple GA exposure and compared both single and multiple exposure by the age of 0 to 2 or 2 to 4 yr. Known sociodemographic and physical confounders were incorporated as covariates in the models.

Results: A total of 18,056 children were studied; 3,858 exposed to a single GA and 620 exposed to two or more GA, who were matched to 13,586 unexposed children. In children less than 2 yr of age, there was no independent association between single or multiple GA exposure and EDI results. Paradoxically, single exposure between 2 and 4 yr of age was associated with deficits, most significant for communication/general knowledge (estimate, −0.71; 95% CL, −0.93 to −0.47; $P < 0.0001$) and language/cognition (estimate, −0.34; 95% CL, −0.52 to −0.16; $P < 0.0001$) domains. Multiple GA exposure before the age of 4 yr was not associated with any developmental deficits.

Conclusions: These findings refute the assumption that the earlier the GA exposure in children, the greater the likelihood of long-term neurocognitive risk. The authors cannot confirm an association between multiple GA exposure and increased risk of neurocognitive impairment, increasing the probability of confounding to explain the results. (ANESTHESIOLOGY 2016; XXX:00-00)

ANIMAL studies provide convincing evidence that general anesthesia (GA) is toxic to the developing brain during a species-specific vulnerable period and is associated with long-term neurocognitive deficits.[1–4] These findings have generated considerable concern, but the clinical relevance continues to be uncertain.[5–7] The period of potential vulnerability for human brain development is longer than it is for animals, but an age of specific risk has not been clearly defined. Dose, duration, and frequency of anesthetic exposure that may be detrimental to humans are unknown. A specific outcome measure that describes a human correlate to the histopathologic and behavioral impairments observed in animals remains undefined, and confounders are present

What We Already Know about This Topic

- The risk of general anesthesia and surgery to neurodevelopment in children remains uncertain

What This Article Tells Us That Is New

- In a Canadian retrospective cohort review of 3,600 children exposed to a single general anesthetic, ED assessed to two or more, and over 13,000 nonexposed children, there was no increased risk of developmental deficits in less than 2 yr and the Early Development Instrument assessment.
- In children between 2 and 4 yr of age, single and multiple anesthetic exposures were associated with decreases in the Early Development Instrument score although this might be related to confounding.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

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Anesthesiology, V XXX • No X 1 XXX 2016

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Anesthesiology 2016

Outcome measure: Early Development Index (EDI)

- Measure of child development at entry to primary school
- 103 item teacher completed questionnaire to assess child's readiness for school
- 5 domains:
  - physical health and well being
  - social knowledge and competence
  - emotional health and maturity
  - language and cognitive development
  - communication skills and general knowledge

O'Leary *et al.* Ontario

- 28,366 surgery before EDI completion
- 55,910 matched controls

- Excluded; physical disability, health related causes of impaired development, diagnosis of behavioural learning or developmental problem
- Matching: (1:2) gestational age at birth, mother's age at birth, rurality, gender, year and quarter of birth

- Primary outcome: "vulnerability" (any EDI domain in lowest 10%)
- Regression adjusted for: aboriginal status, age, household income

Results

Table 2. Unadjusted Early Development Instrument Domain Scores and Vulnerability in Exposed and Unexposed Groups in the Matched Cohort

Outcomes	Cohort Groups: No Surgery (n = 55,910)	Surgery (n = 28,366)	SMD or ARD	*P* Value
EDI domain scores, mean (SD)				
Physical health and well-being	8.96 ± 1.21	8.92 ± 1.23	−0.03	< 0.001
Social knowledge and competence	8.44 ± 1.71	8.38 ± 1.73	−0.04	< 0.001
Emotional health and maturity	8.13 ± 1.43	8.09 ± 1.46	−0.03	< 0.001
Language and cognitive development	8.77 ± 1.57	8.77 ± 1.57	0.00	0.58
Communication skills and general knowledge	7.97 ± 2.36	8.00 ± 2.32	0.01	0.06
Early developmental vulnerability, N (%)	13,957 (25.0)	7,259 (25.6)	0.6	0.047
Multiple challenge index, N (%)	1,453 (2.6)	771 (2.7)	0.1	0.31
EDI domains ≤ tenth percentile, N (%)				
Physical health and well-being	6,568 (11.7)	3,546 (12.5)	0.7	0.003
Social knowledge and competence	4,505 (8.1)	2,367 (8.3)	0.2	0.36
Emotional health and maturity	5,162 (9.2)	2,898 (10.2)	1.0	< 0.001
Language and cognitive development	4,023 (7.2)	2,004 (7.1)	−0.1	0.009
Communication skills and general knowledge	5,303 (9.5)	2,514 (8.9)	−0.6	0.01

ARD = absolute risk difference; EDI = Early Development Instrument; SMD = standardized mean difference.

- Weak evidence for a small difference

Results: age at exposure

Table 3. Adjusted Odds of Vulnerability for Children Exposed to Surgery Compared with Children Not Exposed to Surgery, Stratified According to Age at the Time of First Surgery

Outcomes	Age at First Exposure: Any Age (n = 28,366) OR (95% CI)	*P* Value	< 2 yr (n = 10,937) OR (95% CI)	*P* Value	≥ 2 yr (n = 17,429) OR (95% CI)	*P* Value
Early developmental vulnerability	1.05 (1.01–1.08)	0.009	1.04 (0.98–1.10)	0.19	1.05 (1.01–1.10)	0.02
Multiple Challenge Index	1.06 (0.97–1.16)	0.18	0.94 (0.82–1.09)	0.42	1.15 (1.03–1.29)	0.02
EDI domains ≤ tenth percentile:						
Physical health and well-being	1.09 (1.04–1.14)	< 0.001	1.09 (1.01–1.17)	0.02	1.09 (1.03–1.15)	0.004
Social knowledge and competence	1.05 (1.00–1.11)	0.07	1.02 (0.93–1.11)	0.72	1.08 (1.00–1.15)	0.04
Emotional health and maturity	1.13 (1.07–1.18)	< 0.001	1.13 (1.04–1.22)	0.003	1.13 (1.06–1.20)	< 0.001
Language and cognitive development	0.99 (0.94–1.05)	0.79	0.92 (0.84–1.01)	0.07	1.04 (0.97–1.12)	0.25
Communication skills and general knowledge	0.94 (0.89–0.99)	0.01	0.88 (0.81–0.96)	0.003	0.98 (0.91–1.04)	0.45

- Difference only detected in >2 yr group
- Insufficient power to comment on <2 yr group

Graham *et al.* Manitoba

- 4,470 surgery before age 4
- 13,586 matched controls

- Excluded; diagnosis of developmental disability,
- Matching: (1:3) gestational age at birth, mother's age at birth, rurality, income quintile, gender, year of birth

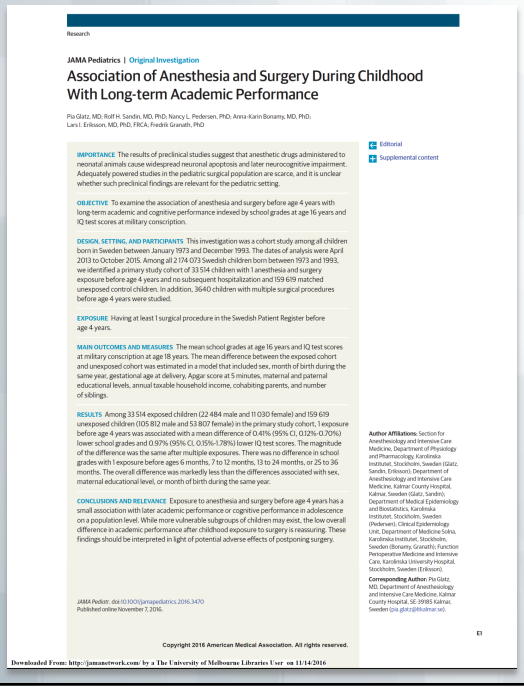
- Regression adjusted for: ever received welfare, gestational age, small or large for dates, mothers age at birth, child's age, John Hopkins Resource Utilisation Band

Results

Table 3. Early Development Instrument Results: Single *versus* Multiple GA

			Single GA (n = 3,850)					Multiple GA (n = 620)			
	No GA		Mixed-effect Model					Mixed-effect Model			
Domain	EDI Score (SD)	EDI Score (SD)	Estimate	95% CI	*t* Value	*P* Value	EDI Score (SD)	Estimate	95% CI	*t* Value	*P* Value
Com/gen knowl	7.6 (2.6)	7.1 (2.8)	−0.35	−0.45 to 0.26	−7.6	< 0.0001	6.9 (2.8)	−0.49	−0.69 to −0.28	−4.6	< 0.0001
Emotional maturity	7.8 (1.6)	7.6 (1.6)	−0.06	−0.12 to −0.007	−2	0.03	7.6 (1.6)	−0.04	−0.17 to 0.08	−0.68	0.49
Lang/cogn development	8.1 (2.0)	7.7 (2.3)	−0.23	−0.3 to −0.16	−6.37	< 0.0001	7.6 (2.4)	−0.3	−0.46 to −0.14	−3.62	< 0.0001
Physical well-being	8.7 (1.4)	8.4 (1.6)	−0.14	−0.19 to −0.09	−5.59	< 0.0001	8.3 (1.7)	−0.25	−0.36 to −0.13	−4.23	< 0.0001
Social competence	8.2 (1.8)	8.0 (2.0)	−0.1	−0.17 to −0.04	−3.06	0.002	7.9 (2.0)	−0.14	−0.29 to 0.009	−1.84	0.06
Total score	40.2 (7.7)	38.7 (8.4)	−0.87	−1.13 to −0.6	−6.45	< 0.0001	38.3 (8.6)	−1.2	−1.83 to −0.61	−3.94	< 0.0001

- Strong evidence for a small difference
- No evidence for a difference between single and multiple exposures
- Difference greater in older children



Research

JAMA Pediatrics | Original Investigation

Association of Anesthesia and Surgery During Childhood With Long-term Academic Performance

Pia Glatz, MD; Rolf H. Sandin, MD, PhD; Nancy L. Pedersen, PhD; Anna-Karin Bonamy, MD, PhD; Lars I. Eriksson, MD, PhD, FRCA; Fredrik Granath, PhD

IMPORTANCE The results of preclinical studies suggest that anesthetic drugs administered to neonatal animals cause widespread neuronal apoptosis and later neurocognitive impairment. Adequately powered studies in the pediatric surgical population are scarce, and it is unclear whether such preclinical findings are relevant for the pediatric setting.

OBJECTIVE To examine the association of anesthesia and surgery before age 4 years with long-term academic and cognitive performance indexed by school grades at age 16 years and IQ test scores at military conscription.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a cohort study among all children born in Sweden between January 1973 and December 1993. The dates of analysis were April 2013 to October 2015. Among all 2 174 073 Swedish children born between 1973 and 1993, we identified a primary study cohort of 33 514 children with 1 anesthesia and surgery exposure before age 4 years and no subsequent hospitalization and 159 619 matched unexposed control children. In addition, 3640 children with multiple surgical procedures before age 4 years were studied.

EXPOSURE Having at least 1 surgical procedure in the Swedish Patient Register before age 4 years.

MAIN OUTCOMES AND MEASURES The mean school grades at age 16 years and IQ test scores at military conscription at age 18 years. The mean difference between the exposed cohort and unexposed cohort was estimated in a model that included sex, month of birth during the same year, gestational age at delivery, Apgar score at 5 minutes, maternal and paternal educational levels, annual taxable household income, cohabiting parents, and number of siblings.

RESULTS Among 33 514 exposed children (22 484 male and 11 030 female) and 159 619 unexposed children (105 812 male and 53 807 female) in the primary study cohort, 1 exposure before age 4 years was associated with a mean difference of 0.41% (95% CI, 0.12%-0.70%) lower school grades and 0.97% (95% CI, 0.15%-1.78%) lower IQ test scores. The magnitude of the difference was the same after multiple exposures. There was no difference in school grades with 1 exposure before ages 6 months, 7 to 12 months, 13 to 24 months, or 25 to 36 months. The overall difference was markedly less than the differences associated with sex, maternal educational level, or month of birth during the same year.

CONCLUSIONS AND RELEVANCE Exposure to anesthesia and surgery before age 4 years has a small association with later academic performance or cognitive performance in adolescence on a population level. While more vulnerable subgroups of children may exist, the low overall difference in academic performance after childhood exposure to surgery is reassuring. These findings should be interpreted in light of potential adverse effects of postponing surgery.

Editorial
Supplemental content

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Glatz et al., JAMA pediatrics 2016

The cohort

- 2,174,073 Swedish children born between 1973 and 1993,
- 33,514 children with 1 anaesthesia and surgery exposure before age 4 years and no subsequent hospitalization
- 159,619 matched unexposed control children.
- In addition, 3640 children with multiple surgical procedures

Outcomes

- The mean school grades at age 16 years
- IQ test scores at military conscription at age 18 years

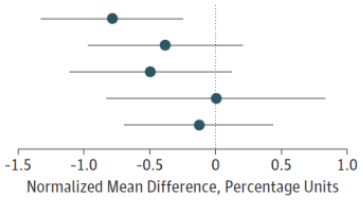
- Adjusted for sex, month of birth, gestational age at delivery, Apgar score at 5 min, parental education, household income, cohabiting parents, and number of siblings

Results

- One exposure before age 4 years was associated with:
  - mean difference of 0.41% (95%CI, 0.12-0.70) lower school grades
  - and 0.97% (95%CI, 0.15-1.78) lower IQ test scores.

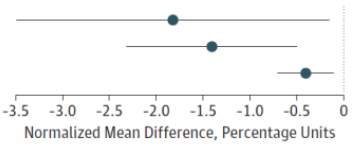
Age at exposure

Age at Surgery, mo	No. of Surgical Procedures	Mean (95% CI)
37-48	8321	-0.79 (-1.33 to -0.25)
25-36	6943	-0.38 (-0.97 to 0.20)
13-24	6202	-0.50 (-1.11 to 0.12)
7-12	3420	0.00 (-0.82 to 0.83)
0-6	7971	-0.13 (-0.69 to 0.43)



Number of exposures

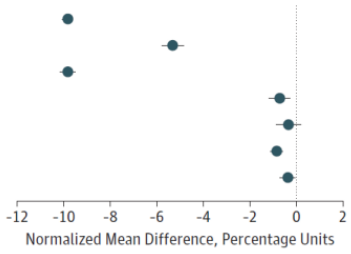
Multiple Surgical Procedures	No. of Surgical Procedures	Mean (95% CI)
≥3	799	-0.82 (-3.49 to -0.15)
2	2841	-1.41 (-2.31 to -0.50)
1	32857	-0.41 (-0.70 to -0.12)



Impact of exposure compared to other factors

A Mean school grades

	Mean (95% CI)
Boys vs girls	-9.88 (-9.69 to -10.10)
Born in December vs January of the same year	-5.34 (-4.89 to -5.80)
Maternal educational level, 10-12 vs >12 y	-9.89 (-9.61 to -10.20)
Inguinal hernia, operated children vs controls[a]	-0.75 (-1.17 to -0.34)
Inguinal hernia, operated children vs controls	-0.36 (-0.86 to 0.15)
All operations, operated children vs controls[a]	-0.87 (-1.11 to -0.64)
All operations, operated children vs controls	-0.41 (-0.70 to -0.12)



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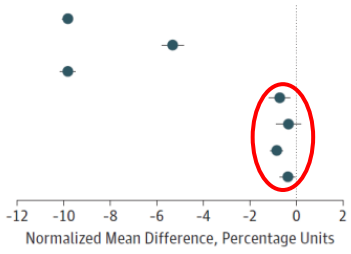

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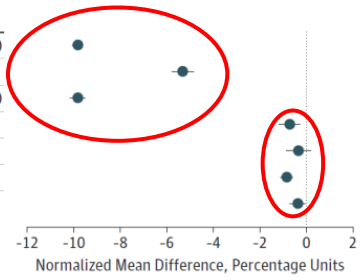
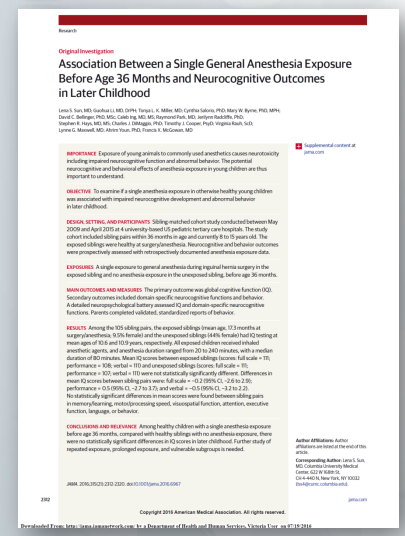


Psychometric testing

- Perth/New York. Ing *et al.*
- UCSF. Stratmann *et al.*
- Cincinnati. Backeljauw *et al.*

- Association between exposure and cognitive, memory, listening comprehension and language deficits



Research

Original Investigation

Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood

Lena S. Sun, MD; Guohua Li, MD, DrPH; Tonya L. K. Miller, MD; Cynthia Salorio, PhD; Mary W. Byrne, PhD, MPH; David C. Bellinger, PhD, MSc; Caleb Ing, MD, MS; Raymond Park, MD; Jaclynn Radcliffe, PhD; Stephen R. Hays, MD, MS; Charles J. DiMaggio, PhD; Timothy J. Cooper, PsyD; Virginia Rauh, ScD; Lynne G. Maxwell, MD; Ahnim Yoon, PhD; Francis X. McGowan, MD

IMPORTANCE Exposure of young animals to commonly used anesthetics causes neurotoxicity including impaired neurocognitive function and abnormal behavior. The potential neurocognitive and behavioral effects of anesthesia exposure in young children are thus important to understand.

OBJECTIVE To examine if a single anesthesia exposure in otherwise healthy young children was associated with impaired neurocognitive development and abnormal behavior in later childhood.

DESIGN, SETTING, AND PARTICIPANTS Sibling-matched cohort study conducted between May 2009 and April 2015 at 4 university-based US pediatric tertiary care hospitals. The study cohort included sibling pairs within 36 months in age and currently 8 to 15 years old. The exposed siblings were healthy at surgery/anesthesia. Neurocognitive and behavior outcomes were prospectively assessed with retrospectively documented anesthesia exposure data.

EXPOSURES A single exposure to general anesthesia during inguinal hernia surgery in the exposed sibling and no anesthesia exposure in the unexposed sibling, before age 36 months.

MAIN OUTCOMES AND MEASURES The primary outcome was global cognitive function (IQ). Secondary outcomes included domain-specific neurocognitive functions and behavior. A detailed neuropsychological battery assessed IQ and domain-specific neurocognitive functions. Parents completed validated, standardized reports of behavior.

RESULTS Among the 105 sibling pairs, the exposed siblings (mean age, 17.3 months at surgery/anesthesia; 9.5% female) and the unexposed siblings (44% female) had IQ testing at mean ages of 10.6 and 10.9 years, respectively. All exposed children received inhaled anesthetic agents, and anesthesia duration ranged from 20 to 240 minutes, with a median duration of 80 minutes. Mean IQ scores between exposed siblings (scores: full scale = 111; performance = 108; verbal = 111) and unexposed siblings (scores: full scale = 111; performance = 107; verbal = 111) were not statistically significantly different. Differences in mean IQ scores between sibling pairs were: full scale = −0.2 (95% CI, −2.6 to 2.9); performance = 0.5 (95% CI, −2.7 to 3.7); and verbal = −0.5 (95% CI, −3.2 to 2.2). No statistically significant differences in mean scores were found between sibling pairs in memory/learning, motor/processing speed, visuospatial function, attention, executive function, language, or behavior.

CONCLUSIONS AND RELEVANCE Among healthy children with a single anesthesia exposure before age 36 months, compared with healthy siblings with no anesthesia exposure, there were no statistically significant differences in IQ scores in later childhood. Further study of repeated exposure, prolonged exposure, and vulnerable subgroups is needed.

Supplemental content at jama.com

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2312 jama.com

Sun et al., JAMA 2016

Pediatric Anesthesia Neurodevelopment Assesment (PANDA)

- Sibling matched ambidirectional cohort study
- 105 Sibling pairs – 8-15 years old, and siblings similar age
- Healthy at time of exposure

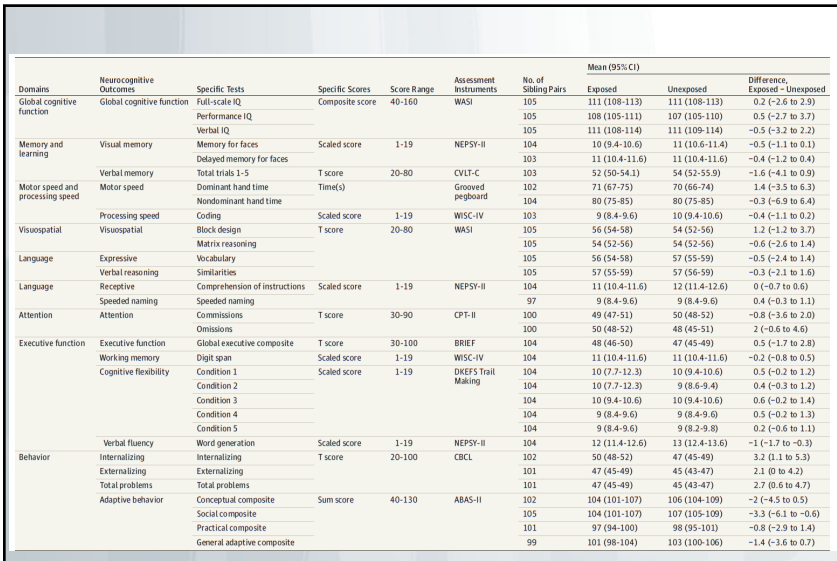
- Exposure – GA for inguinal hernia surgery before 36 months of age
- Median duration of anaesthesia 80 minutes

- Primary outcome – IQ
- Range of secondary outcomes – behaviour and other neurocognitive tests

Results

	Exposed	Unexposed	Difference
Full scale IQ	111 (108-113)	111 (108-113)	0.2 (-2.6 to 2.9)
Performance IQ	108 (105-111)	107 (105-110)	0.5 (-2.7 to 3.7)
Verbal IQ	111 (108-114)	111 (109-114)	-0.5 (-3.2 to 2.2)

Data as mean (95% CI)



Domains	Neurocognitive Outcomes	Specific Tests	Specific Scores	Score Range	Assessment Instruments	No. of Sibling Pairs	Mean (95% CI) Exposed	Unexposed	Difference, Exposed − Unexposed
Global cognitive function	Global cognitive function	Full-scale IQ	Composite score	40-160	WASI	105	111 (108-113)	111 (108-113)	0.2 (−2.6 to 2.9)
		Performance IQ				105	108 (105-111)	107 (105-110)	0.5 (−2.7 to 3.7)
		Verbal IQ				105	111 (108-114)	111 (109-114)	−0.5 (−3.2 to 2.2)
Memory and learning	Visual memory	Memory for faces	Scaled score	1-19	NEPSY-II	104	10 (9.4-10.6)	11 (10.6-11.4)	−0.5 (−1.1 to 0.1)
		Delayed memory for faces				103	11 (10.4-11.6)	11 (10.4-11.6)	−0.4 (−1.2 to 0.4)
	Verbal memory	Total trials 1-5	T score	20-80	CVLT-C	103	52 (50-54.1)	54 (52-55.9)	−1.6 (−4.1 to 0.9)
Motor speed and processing speed	Motor speed	Dominant hand time	Time(s)		Grooved pegboard	102	71 (67-75)	70 (66-74)	1.4 (−3.5 to 6.3)
		Nondominant hand time				104	80 (75-85)	80 (75-85)	−0.3 (−6.9 to 6.4)
	Processing speed	Coding	Scaled score	1-19	WISC-IV	103	9 (8.4-9.6)	10 (9.4-10.6)	−0.4 (−1.1 to 0.2)
Visuospatial	Visuospatial	Block design	T score	20-80	WASI	105	56 (54-58)	54 (52-56)	1.2 (−1.2 to 3.7)
		Matrix reasoning				105	54 (52-56)	54 (52-56)	−0.6 (−2.6 to 1.4)
Language	Expressive	Vocabulary				105	56 (54-58)	57 (55-59)	−0.5 (−2.4 to 1.4)
	Verbal reasoning	Similarities				105	57 (55-59)	57 (56-59)	−0.3 (−2.1 to 1.6)
Language	Receptive	Comprehension of instructions	Scaled score	1-19	NEPSY-II	104	11 (10.4-11.6)	12 (11.4-12.6)	0 (−0.7 to 0.6)
	Speeded naming	Speeded naming				97	9 (8.4-9.6)	9 (8.4-9.6)	0.4 (−0.3 to 1.1)
Attention	Attention	Commissions	T score	30-90	CPT-II	100	49 (47-51)	50 (48-52)	−0.8 (−3.6 to 2.0)
		Omissions				100	50 (48-52)	48 (45-51)	2 (−0.6 to 4.6)
Executive function	Executive function	Global executive composite	T score	30-100	BRIEF	104	48 (46-50)	47 (45-49)	0.5 (−1.7 to 2.8)
	Working memory	Digit span	Scaled score	1-19	WISC-IV	104	11 (10.4-11.6)	11 (10.4-11.6)	−0.2 (−0.8 to 0.5)
	Cognitive flexibility	Condition 1	Scaled score	1-19	DKEFS Trail Making	104	10 (7.7-12.3)	10 (9.4-10.6)	0.5 (−0.2 to 1.2)
		Condition 2				104	10 (7.7-12.3)	9 (8.6-9.4)	0.4 (−0.3 to 1.2)
		Condition 3				104	10 (9.4-10.6)	10 (9.4-10.6)	0.6 (−0.2 to 1.4)
		Condition 4				104	9 (8.4-9.6)	9 (8.4-9.6)	0.5 (−0.2 to 1.3)
		Condition 5				104	9 (8.4-9.6)	9 (8.2-9.8)	0.2 (−0.6 to 1.1)
	Verbal fluency	Word generation	Scaled score	1-19	NEPSY-II	104	12 (11.4-12.6)	13 (12.4-13.6)	−1 (−1.7 to −0.3)
Behavior	Internalizing	Internalizing	T score	20-100	CBCL	102	50 (48-52)	47 (45-49)	3.2 (1.1 to 5.3)
	Externalizing	Externalizing				101	47 (45-49)	45 (43-47)	2.1 (0 to 4.2)
	Total problems	Total problems				101	47 (45-49)	45 (43-47)	2.7 (0.6 to 4.7)
	Adaptive behavior	Conceptual composite	Sum score	40-130	ABAS-II	102	104 (101-107)	106 (104-109)	−2 (−4.5 to 0.5)
		Social composite				105	104 (101-107)	107 (105-109)	−3.3 (−6.1 to −0.6)
		Practical composite				101	97 (94-100)	98 (95-101)	−0.8 (−2.9 to 1.4)
		General adaptive composite				99	101 (98-104)	103 (100-106)	−1.4 (−3.6 to 0.7)

- no evidence for differences in secondary outcomes that included memory and learning, motor and processing speed, visuospacial function, attention, executive function, or language

Age at exposure, length of exposure

Table 4. IQ Scores in Exposed and Unexposed Siblings at Different Ages and at Different Durations of Anesthesia Exposure

	No. of Sibling Pairs	Verbal IQ Score			Performance IQ Score			Full-Scale IQ Score		
		Mean (95% CI)		Difference, Exposed – Unexposed (95% CI)	Mean (95% CI)		Difference, Exposed – Unexposed (95% CI)	Mean (95% CI)		Difference, Exposed – Unexposed (95% CI)
		Exposed	Unexposed		Exposed	Unexposed		Exposed	Unexposed	
Age at anesthesia exposure, mo										
0-11	33	113 (109-117)	113 (109-117)	0 (−5.1 to 5.1)	108 (103-113)	107 (101-113)	1 (−4.8 to 6.8)	112 (108-116)	111 (106-116)	1 (−4.1 to 6.1)
12-23	39	111 (107-115)	110 (106-114)	0 (−4.4 to 4.4)	108 (104-112)	107 (102-112)	1 (−4.0 to 6.0)	111 (107-115)	110 (106-114)	1 (−3.5 to 5.4)
24-36	33	109 (104-114)	111 (107-115)	−2 (−6.4 to 2.4)	107 (102-112)	108 (104-112)	−1 (−6.8 to 4.8)	110 (105-115)	111 (107-115)	−1 (−5.8 to 3.8)
Duration of anesthesia exposure, min										
0-59	24	117 (111-123)	113 (108-118)	4 (−1.6 to 9.6)	113 (108-118)	113 (107-119)	0 (−6.8 to 6.8)	117 (112-122)	115 (110-120)	2 (−4 to 8)
60-119	64	110 (107-113)	112 (109-115)	−3 (−6.4 to 0.4)	108 (104-112)	106 (103-109)	2 (−1.9 to 5.9)	110 (107-113)	110 (107-113)	0 (−3.4 to 3.4)
≥120	17	106 (98-114)	105 (101-109)	1 (−5.2 to 7.2)	100 (94-106)	104 (96-112)	−4 (−8.5 to 4.5)	103 (96-110)	105 (99-111)	−2 (−8.2 to 4.2)

- No difference with age of exposure
- No difference with duration of anaesthetic – up to 120 minutes

MRI data

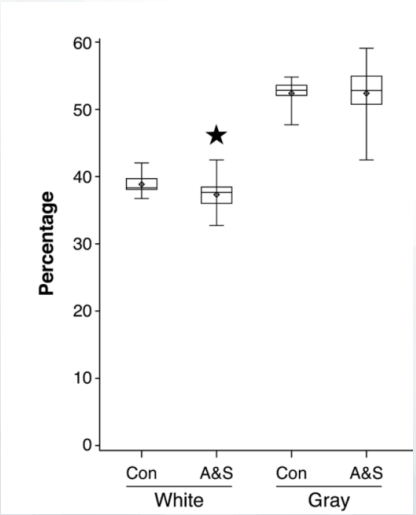
- Backeljauw (*Pediatrics 2015)*

- Anesthesia < 4yrs, matched control group
- MRI aged 5-18
- 53 subjects each group
- No loss of total white matter
- No loss of grey matter in thalamus or retrosplenium
- Lower IQ and listening comprehension associated with loss of grey matter in occipital cortex and cerebellum

MRI data

- Block (*Anesthesiology* 2017)

- Anesthesia in infancy
- MRI aged 12-15
- 17 subjects each group
- Lower total white matter
- No difference in grey matter



Summary of human cohort data

- Good evidence for an association between major surgery in neonates and increased risk or poor neurodevelopmental outcome

- Good evidence for an association between exposure in early childhood and a *very* small difference in school grades

- Good evidence for an association between single and multiple exposures and learning disability and diagnosed disorder

- Mixed evidence for an association with deficits in cognition, memory and language

- Poor evidence that the effects are greater with multiple exposures

- Little, if any, evidence that the effects *are greater* in infants

Limitations of human cohort data

- Confounding – children have anaesthetics because they are having a procedure
  - Procedure itself may cause harm
  - Illness requiring the procedure may be associated with poor neurodevelopmental outcome
- *If find an association in cohort studies cannot assume it is due to causation*
- Multiple different outcome measures
  - Using apical outcomes cannot exclude an association in sub domains
  - Detailed assessments – can't test all domains, & increased risk of chance associations
- Heterogeneous or selective populations – cannot exclude an association in smaller at risk groups
- *Lack of evidence in cohort studies does not rule out an association*

GAS trial

Articles

Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

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Summary

Background Preclinical data suggest that general anaesthetics affect brain development. There is mixed evidence from cohort studies that young children exposed to anaesthesia can have an increased risk of poor neurodevelopmental outcome. We aimed to establish whether general anaesthesia in infancy has any effect on neurodevelopmental outcome. Here we report the secondary outcome of neurodevelopmental outcome at 2 years of age in the General Anaesthesia compared to Spinal anaesthesia (GAS) trial.

Methods In this international assessor-masked randomised controlled equivalence trial, we recruited infants younger than 60 weeks postmenstrual age, born at greater than 26 weeks' gestation, and who had inguinal herniorrhaphy, from 28 hospitals in Australia, Italy, the USA, the UK, Canada, the Netherlands, and New Zealand. Infants were randomly assigned (1:1) to receive either awake-regional anaesthesia or sevoflurane-based general anaesthesia. Web-based randomisation was done in blocks of two or four and stratified by site and gestational age at birth. Infants were excluded if they had existing risk factors for neurological injury. The primary outcome of the trial will be the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at age 5 years. The secondary outcome, reported here, is the composite cognitive score of the Bayley Scales of Infant and Toddler Development III, assessed at 2 years. The analysis was as per protocol adjusted for gestational age at birth. A difference in means of five points (1/3 SD) was predefined as the clinical equivalence margin. This trial is registered with ANZCTR, number ACTRN12606000441516 and ClinicalTrials.gov, number NCT00756600.

Findings Between Feb 9, 2007, and Jan 31, 2013, 363 infants were randomly assigned to receive awake-regional anaesthesia and 359 to general anaesthesia. Outcome data were available for 238 children in the awake-regional group and 294 in the general anaesthesia group. In the as-per-protocol analysis, the cognitive composite score (mean [SD]) was 98·6 (14·2) in the awake-regional group and 98·2 (14·7) in the general anaesthesia group. There was equivalence in mean between-group (awake-regional minus general anaesthesia) 0·169, 95% CI −2·30 to 2·64). The median duration of anaesthesia in the general anaesthesia group was 54 min.

Interpretation For this secondary outcome, we found no evidence that just less than 1 h of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia.

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Introduction

Substantial preclinical evidence exists that describes how general anaesthetic drugs change brain development in young animals.[1] These changes include accelerated apoptosis and other effects such as changes to dendritic morphology.[2–4] Findings have also shown that exposure to general anaesthesia in young animals is associated with long-term cognitive and behavioural changes.[5–7] These effects have been described in various species including non-human primates.[7–9] The changes are seen with several different general anaesthetic drugs, are greater with longer exposure, and are less severe in older animals.[10] The clinical relevance of these findings is unknown and much debated.[11–13]

In human beings, there is conflicting evidence for an association between exposure to anaesthesia in early childhood and adverse long-term neurodevelopmental outcome; however, confounding restricts any assumption of causality.[14–16] Young children who receive anaesthesia are inevitably having surgery or an investigative procedure.

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*See appendix for a full list of study investigators

Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet 2016;387(10015):239-50.

Design

- Randomised, assessor blinded, multisite, equivalence trial
- Infants hernia repair < 60 weeks post menstrual age
- Exclusions: previous GA, born < 26 weeks, risk of for poor neurodevelopmental outcome
- Awake – regional anesthesia, *versus*
- Sevoflurane

Neurodevelopmental outcomes

- Primary outcome:
  - WPPSI-III Full Scale IQ score at 5 years
- Secondary outcomes
  - Bayley III at 2 years

Bayley-III

- 5 scores
  - Cognitive
  - Motor
  - Language
  - Social emotional
  - Adaptive behaviour
- Composite score normalised to each country
  - Mean 100
  - SD 15

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  - Cognitive
  - Motor
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Analysis

- Primary: As per protocol
- Secondary: Intention to treat
- Adjusted for gestational age at birth
- Multiple imputation
- Complete case

Analysis

- Primary: As per protocol
- Secondary: Intention to treat

- Adjusted for gestational age at birth

- Multiple imputation
- Complete case

- 722 randomised

- RA failure rate: 19%
- Loss to follow up: 14%
- Incomplete assessment: 4%

- Average anaesthesia time 55 minutes

Composite cognitive score RA-GA

APP multiple imputation	0.169 (-2.30 to 2.64)

Data as difference in mean (95% CI)

Composite cognitive score RA-GA

APP multiple imputation	0.169 (-2.30 to 2.64)
APP complete case	0.458 (-2.02 to 2.94)

Data as difference in mean (95% CI)

Composite cognitive score RA-GA

APP multiple imputation	0.169 (-2.30 to 2.64)
APP complete case	0.458 (-2.02 to 2.94)
ITT multiple imputation	0.256 (-2.06 to 2.57)

Data as difference in mean (95% CI)

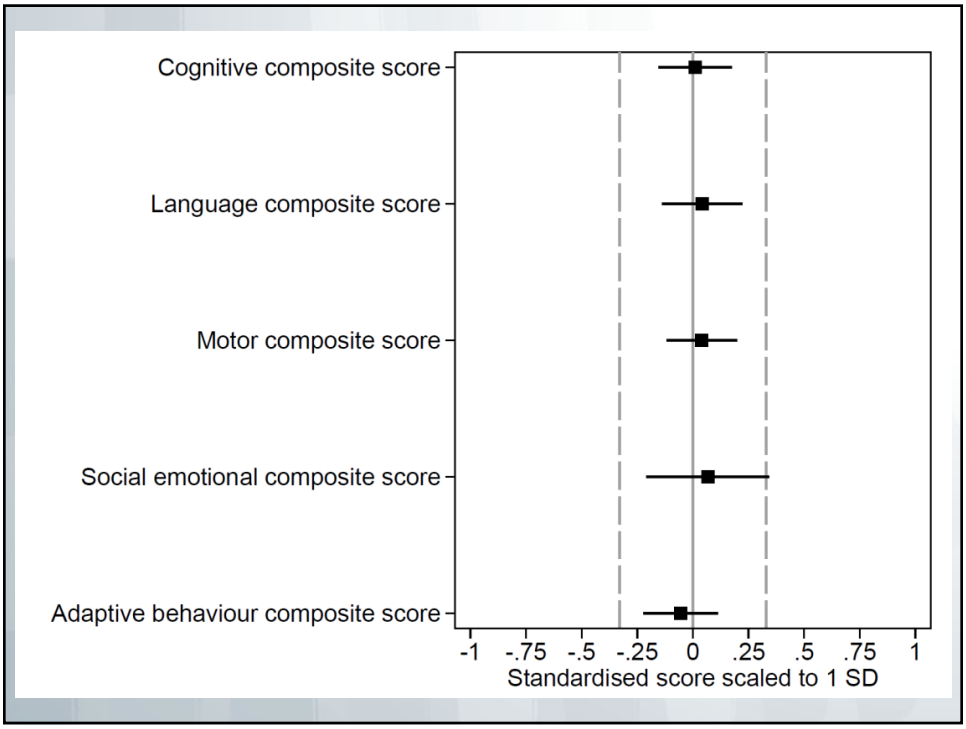
Composite cognitive score RA-GA

APP multiple imputation	0.169 (-2.30 to 2.64)
APP complete case	0.458 (-2.02 to 2.94)
ITT multiple imputation	0.256 (-2.06 to 2.57)
ITT complete case	0.430 (-1.90 to 2.76)

Data as difference in mean (95% CI)

Difference in means

Scale		RA - GA	95% CI for RA - GA	
Cognitive composite score	APP multiple imputation	0·169	-2·30	2·64
	APP complete case	0·458	-2·02	2·94
	ITT multiple imputation	0·256	-2·06	2·57
	ITT complete case	0·430	-1·90	2·76
Language composite score	APP multiple imputation	1·146	-1·59	3·88
	APP complete case	0·628	-2·07	3·32
	ITT multiple imputation	1·454	-1·14	4·05
	ITT complete case	0·942	-1·61	3·49
Motor composite score	APP multiple imputation	0·598	-1·77	2·97
	APP complete case	0·410	-1·92	2·74
	ITT multiple imputation	0·143	-1·08	3·37
	ITT complete case	1·031	-1·20	3·26
Social emotional composite score	APP multiple imputation	1·005	-3·12	5·13
	APP complete case	2·012	-1·32	5·35
	ITT multiple imputation	1·183	-2·82	5·19
	ITT complete case	2·015	-1·17	5·20
Adaptive behaviour composite score	APP multiple imputation	-0·893	-3·52	1·73
	APP complete case	-1·223	-3·83	1.38
	ITT multiple imputation	-0·502	-3·03	2·02
	ITT complete case	-0·830	-3·34	1·68



Limitations

- Duration of exposure – just under an hour
- 2 year outcome measure
  - Imperfect predictor of future function
  - No measure of higher executive function

Results in context

- Increasing evidence that 1 hour of exposure in infancy does not increase risk of poor neurodevelopmental outcome
- No human data relating to longer exposures

http://www.fda.gov/Drugs/DrugSafety/ucm532356.htm

The U.S. Food and Drug Administration (FDA) is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains.

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Multiple cases – confounding

- Assume 5% children have ADHD
- Assume all children have 10% chance of three different surgeries
- For one other surgery it is more likely to be needed in children at risk of later developing ADHD

Number of surgeries	RR if 4% vs 2%	RR if 10% vs 2%
>2	1.15	1.59
1	1.09	1.15
0	0.98	0.92

Recommendation

- No need to delay or avoid short procedures
- Should consider delay non essential lengthy procedures
  - We don't do "non essential" lengthy procedures
  - How long should the delay be?
- Do not generate a real risk by using an untested inadequate anaesthetic to avoid a still largely theoretical risk

What next

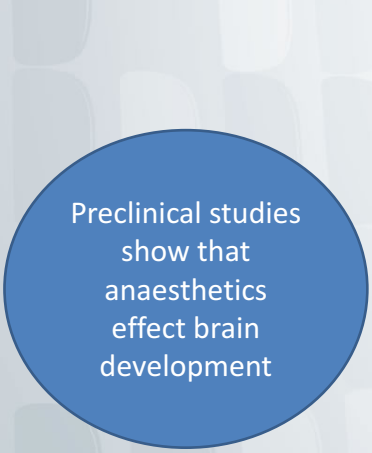
What next

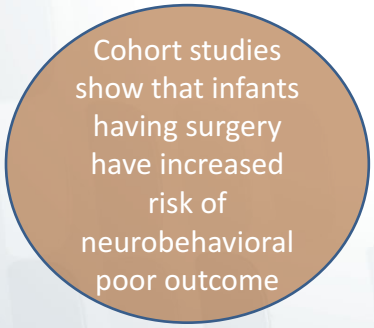
- Better understand mechanisms
- Identify “safe” agents, mitigating agents
- Better cohort data
  - Define those at risk
  - Identify the domains affected
- Biomarkers

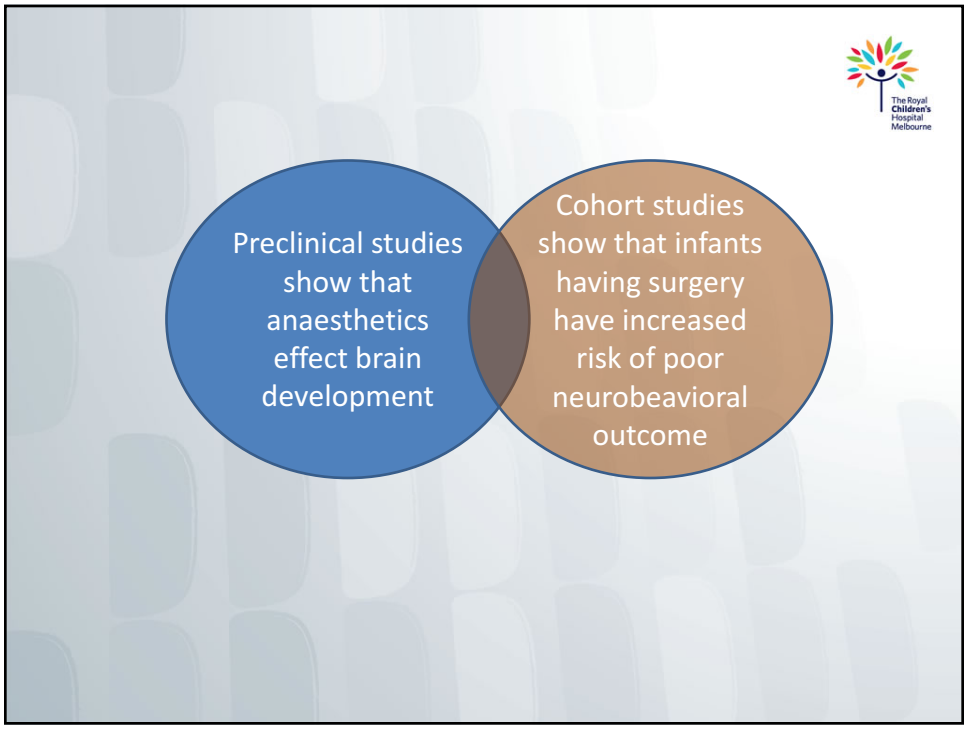
Next trial

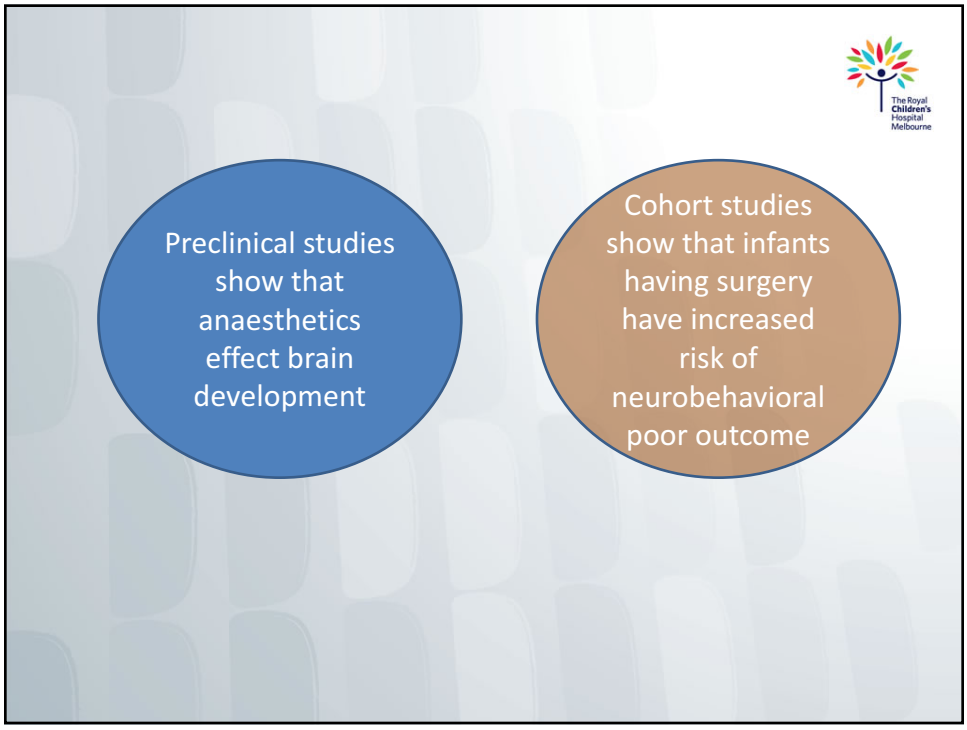
- Infants > 2.5 hrs anesthesia

- Dexmedetomidine/remifentanil/low dose sevoflurane,
- Standard dose sevoflurane






Preclinical studies show that anaesthetics effect brain development
Cohort studies show that infants having surgery have increased risk of poor neurobeavioral outcome


Preclinical studies show that anaesthetics effect brain development
Cohort studies show that infants having surgery have increased risk of neurobehavioral poor outcome

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Editorial Views

Anesthesiology
50:1, 1979

Dragons and Other Scientific Hazards

This brings me back to my initial point, the problem of discovering nonexistence. Obviously, when what you're searching for doesn't exist, you'll have trouble finding it even with an infinite number of experiments. Although halothane (or enflurane or diazepam or Innovar) may not be toxic, you cannot construct a study that will conclusively document nontoxicity. Long ago my father warned me that I could not disprove the existence of dragons.

Wider context

- If it isn't neurotoxicity then what is it that explains the association?
- What *is* the optimal anaesthetic for infants?

Neurotoxicity and the Need for Anesthesia in the Newborn

Does the Emperor Have No Clothes?

IN 2011 nearly half the pediatric papers in ANESTHESIOLOGY were related to neurotoxicity of general anesthetics to the developing brain. There is continued debate about the clinical relevance of the animal data, and the interpretation of human cohort studies. In this issue Shih *et al.* present a paper that moves us a significant step closer to translating the animal data to clinical situations.[1] But, as we slowly unravel the question of whether or not general anesthetics cause any clinically significant effect on brain development, we should perhaps address some wider-related issues that sometimes go unsaid.

Shih *et al.* provides further evidence that several hours of anesthesia exposure is associated with neuronal injury and subsequent neurobehavioural change in a rodent. At a mechanistic level it is difficult to argue that apoptosis would be triggered by sevoflurane in rodents but not in humans. The big question has always been how to translate this to human practice. Is it relevant clinically? This study helps address two important issues in translation: the effect of tissue injury, and the relative effect of anesthesia on neurobehavioural outcome when compared with other events that might influence outcome.

The study found that tissue injury neither worsens nor mitigates the effect. Rats with tail-clamp injury had the same histologic change and the same neurobehavioral changes compared with rats with no injury. This is interesting as previous animal studies have often been criticized as being invalid because they have no surgical stimulus. It had been argued that surgery provides an intense stimulus that would override any "use it or lose it" mechanism where apoptosis is due to neuronal traffic quiescence. In this respect findings from this study imply that previous studies are indeed a valid model whether there is a surgical stimulus or not. It has also been argued that the increased risk of poor outcome found in some human cohort studies is because of the inflammation and stress associated with the surgery rather than the anesthetic. Shih *et al.*'s study provides some indication that the surgery itself may not be a contributor to poor outcome; however, the degree of surgical stimulus in clinical practice varies considerably, and it is still possible that the stress of a major laparotomy or cardiac surgery has a greater chance of measurable impact on neurodevelopment than a tail clamp.

"... regardless of whether or not sevoflurane causes any clinically relevant toxicity, is it time to question the mantra that all babies need a hypnotic agent such as sevoflurane?"

Another aspect of Shih *et al.*'s study looked at whether or not the injured rats could be "treated" with environmental enrichment. They found that environmental enrichment did indeed reverse the effect of anesthetic, resulting in performance similar to environmentally enriched controls and superior to unenriched control and anesthesia-exposed animals. This is important for translation, perhaps not as a viable treatment modality (it is difficult to see how we could practically further enrich the environment for the average infant in the 21st century), but the finding is very important as it highlights that neurobehavioural outcome is dependent on multiple factors. A common criticism when translating animal to human data is that there are a multitude of influences on outcome in humans and that an anesthesia exposure may only be one minor insult compared with many other more significant events in childhood. Shih *et al.*'s findings might provide some hint that the

◆ This Editorial View accompanies the following article: Shih J, May LdV, Gonzalez HE, Lee EW, Alvi RS, Sall JW, Rau V, Bickler PE, Lalchandani GR, Yusupova M, Woodward E, Kang H, Wilk AJ, Carlston CM, Mendoza MV, Guggenheim JN, Schaefer M, Rowa AM, Stratmann G: Delayed environmental enrichment reverses sevoflurane-induced memory impairment in rats. ANESTHESIOLOGY 2012; 116:XXX–XXX.

Illustration: J. P. Rathmell, A. B. Johnson.

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The Royal Children's Hospital Melbourne

Pediatric Anesthesia

EDITORIAL

Do we actually need to anesthetize the neonate?

In this issue of *Pediatric Anesthesia*, authors discuss several key aspects of the theory and practice of neonatal anesthesia. Recurring themes are that neonatal physiology is substantially different to older children, that there are substantial gaps in our understanding of basic pharmacology and physiology, and there is a relative paucity of strong clinical evidence to guide practice. There are more questions than answers.

One fundamental question is do we actually need to anesthetize the neonate? Until relatively recently, neonates received little in the way of anesthesia due to concerns about their physiological capacity to survive the depressant effects of anesthetics and a belief that neonates have less capacity to feel pain. While we can still argue about what a neonate "feels," it is clear that neonates do respond adversely to nociceptive stimuli. Dr Walker's review illustrates that painful stimuli result in structural changes in the spinal cord, and untreated pain has adverse long-term consequences. Good pain relief not only improves outcome, it is now regarded as a basic human right, and there is no reason why this right should not be extended to the neonate. But anesthesia is more than just pain relief. Do they need to be anesthetized? One way to answer this is to ask what we are aiming to achieve with anesthesia. Rees and Gray described the triad of anesthesia as hypnosis, analgesia, and immobility (1). This was perhaps a simplistic approach, and practically the aims are closer to unconsciousness, immobility, and reduction in the stress and cardiovascular response associated with nociception. Amnesia may also be regarded as an aim; however, unconsciousness should result in amnesia.

Clearly neonates need to be immobilized for surgery. Do they need to be unconscious? Presence of consciousness is not easily defined in neonates, and defining consciousness in neonates, and indeed the fetus, can lead to fascinating psychological, physiological, philosophical, and theological debate. Rather than arguing about the theory, most practical anesthetists would be content if the neonate does not show signs of being distressed. Relieving distress can be seen a basic human right, and distressed neonates in the neonatal intensive care unit have poorer short-term and long-term outcomes. In an unparalyzed neonate, being unresponsive could be reasonably expected to be a sign of not being distressed. Similarly, a quiet neonate having an awake regional technique could be assumed to be not distressed. If the neonate is paralyzed, it is harder to identify distress. Giving 'enough' general anesthetic would result in unconsciousness and hence prevent distress, but we have no idea how much is required to produce unconsciousness. Alternatively, adequate analgesia might be sufficient. Does it matter if the neonate hears what's going on if they are pain free? Perhaps some added sedation is required to prevent distress even if the neonate is pain free, but how do we know how much sedation is needed?

Preventing the physiologic stress and cardiovascular response of anesthesia is an important aim of anesthesia in neonates. A number of papers demonstrate improved outcomes and lower stress hormones in neonates that had sufficient analgesia and/or anesthesia (2–4). While the importance of preventing physiologic stress is seen as increasingly important, we still have little idea how much anesthetic or which anesthetic is best at doing this.

One approach to anesthetizing neonates could be to treat them like little adults and give a standard cocktail of hypnotic, analgesic, and neuromuscular blocking agent. If we give 'enough,' this should achieve our aims. As discussed above, the major flaw with this approach is our inability to determine 'enough.' The problem of determining 'enough' has become more acute given the possible neurotoxicity of general anesthetics. More that 'enough' general anesthetic may cause more harm than good. While the clinical implications of neurotoxicity are still very unclear, and possibly may be clinically irrelevant, there is still a nagging concern that neonates that have surgery do have an increased risk of poor neurobehavioral outcome. If the elevated risk is not be due to neurotoxicity or concurrent pathology, it is still possibly due to other factors related to the anesthetic. One candidate cause is hypotension. As pointed out in this issue, very little is known about cerebral autoregulation in the neonate. What blood pressure is adequate to prevent cerebral ischemia in neonates – particularly in those with other risk factors for cerebral injury? Once again, more than 'enough' general anesthetic may cause more harm than good. It seems we have come full circle and we are once again concerned about the capacity of neonates to manage the depressant effects of *excessive* anesthesia.

Yes, we do need to anesthetize the neonate, but we have little idea how we should best do this. Anesthetizing neonates is different to anesthetizing adults or older children. To do this best, we need to start filling some of the gaps in our knowledge.

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