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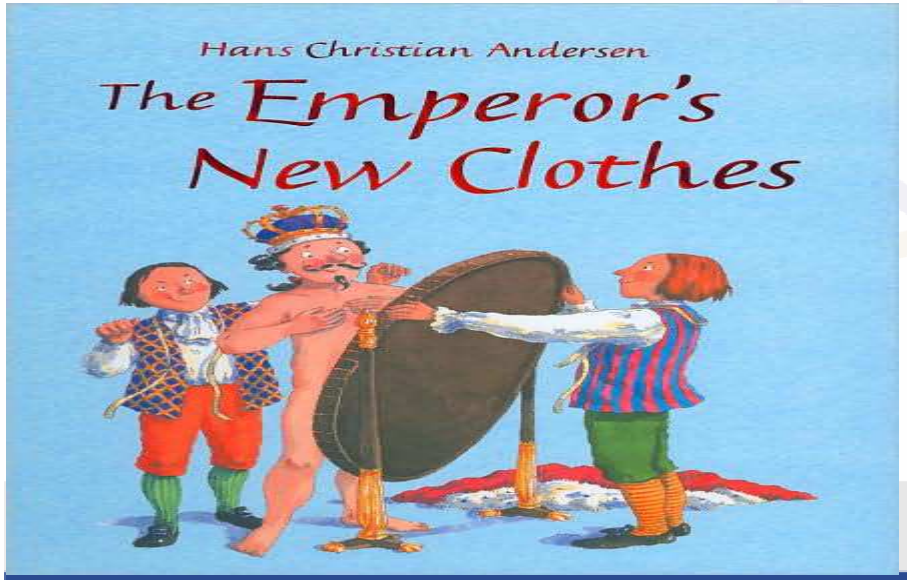
Anaesthesia-related neurotoxicity: the impact of surgery (and diagnosis) (Joint Meeting ADARPEF/ESPA, Bordeaux, France 2 April 2016)

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DENMARK
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OUH


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Hans Christian Andersen
The Emperor's New Clothes



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Covered Topics

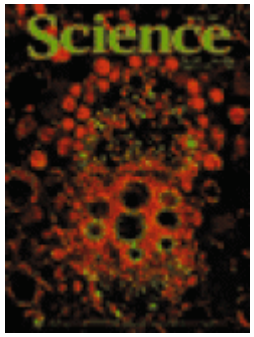
HOW CAN SURGERY IMPACT OUTCOME?

- TRAUMA (E.G. STRESS, INFLAMMATION)
- PAIN
- DIAGNOSIS /UNDERLYING CONDITIONS
- (ANAESTHESIA)

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Blockade of NMDA Receptors and Apoptotic Neurodegeneration in the Developing Brain

Chrysanthy Ikonomidou,* Friederike Bosch, Michael Miksa, Petra Bittigau, Jessica Vöckler, Krikor Dikranian, Tanya I. Tenkova, Vanya Stefovska, Lechoslaw Turski, John W. Olney



Science 1999;283:70-74

876 - The Journal of Neuroscience, February 1, 2003 - 23(3):876–882

Early Exposure to Common Anesthetic Agents Causes Widespread Neurodegeneration in the Developing Rat Brain and Persistent Learning Deficits

Vesna Jevtovic-Todorovic,[1] Richard E. Hartman,[2] Yukitoshi Izumi,[3] Nicholas D. Benshoff,[1] Krikor Dikranian,[3] Charles F. Zorumski,[3] John W. Olney,[3] and David F. Wozniak[3]
[1]Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia 22908, and Departments of [2]Neurology and [3]Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110

Repeated administration of ketamine may lead

to [1] Potential of ketamine and midazolam, individually or in

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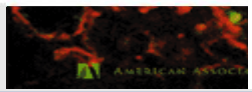
Rat brain

Chrysanth

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and Persistent Learning Deficits



Vesna Jevtovic-Todorovic,[1] Richard E. Hartman,[2] Yukitoshi Izumi,[3] Nicholas D. Benshoff,[3] Krikor Dikranian,[3] Charles F. Zorumski,[3] John W. Olney,[3] and David F. Wozniak[3]

[1]Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia 22908, and Departments of [2]Neurology and [3]Psychiatry, Washington University School of Medicine, St. Louis, Missouri 63110

SINGLE-DOSE KETAMINE ADMINISTRATION INDUCES APOPTOSIS IN NEONATAL MOUSE BRAIN

Michael Rudin,[1] Ron Ben-Abraham,[2] Vered Gazit,[3] Yevgeney Tendler,[3], Vadim Tashlykov,[3], and Yeshayahu Katz

[1]Dept. of Anesthesiology, HaEmek Medical Center, Afula, Israel; [2]Dept. of Anesthesiology and Critical Care, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [3]Laboratory of Anesthesia, Pain and Neural Research, The Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia

Juraj Sprung, MD, PhD; Randall P. Flick, MD, MPH; Slavica K. Katusic, MD; Robert C. Colligan, PhD; William J. Barbaresi, MD; Katarina Bojanić, MD; Tasha L. Welch, MD; Michael D. Olson, PA-C; Andrew C. Hanson, BS; Darrell R. Schroeder, MS; Robert T. Wilder, MD, PhD; and David O. Warner, MD

Abstract

Objective: To study the association between exposure to procedures performed under general anesthesia before age 2 years and development of attention-deficit/hyperactivity disorder (ADHD).
Patients and Methods: Study patients included all children born between January 1, 1976, and December 31, 1982, in Rochester, MN, who remained in Rochester after age 5. Cases of ADHD diagnosed before age 19 years were identified by applying stringent research criteria. Cox proportional hazards regression assessed exposure to procedures requiring general anesthesia (none, 1, 2 or more) as a predictor of ADHD using a stratified analysis with strata based on a propensity score including comorbid health conditions.
Results: Among the 5357 children analyzed, 341 ADHD cases were identified (estimated cumulative incidence, 7.6%; 95% confidence interval [CI], 6.8%-8.4%). For children with no postnatal exposure to procedures requiring anesthesia before the age of 2 years, the cumulative incidence of ADHD at age 19 years was 7.3% (95% CI, 6.5%-8.1%). For single and 2 or more exposures, the estimates were 10.7% (95% CI, 6.8%-14.4%) and 17.9% (95% CI, 7.2%-27.4%), respectively. After adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to multiple (hazard ratio, 1.95; 95% CI, 1.03-3.71), but not single (hazard ratio,1.18; 95% CI, 0.79-1.77), procedures requiring general anesthesia was associated with an increased risk for ADHD.
Conclusion: Children repeatedly exposed to procedures requiring general anesthesia before age 2 years are at increased risk for the later development of ADHD even after adjusting for comorbidities.

© 2012 Mayo Foundation for Medical Education and Research ■ Mayo Clin Proc. 2012;87(2):129-129

Cognitive and Behavioral Outcomes After Early Exposure to Anesthesia and Surgery

AUTHORS: Randall P. Flick, MD, MPH,[a] Slavica K. Katusic, MD,[b] Robert C. Colligan, PhD,[c] Robert T. Wilder, MD, PhD,[a] Robert G. Voigt, MD,[d] Michael D. Olson, PhD,[a] Juraj Sprung, MD, PhD,[a] Amy L. Weaver, MS,[f] Darrell R. Schroeder, MS,[f] and David O. Warner, MD[e]

[a]Department of Anesthesiology, [b]Division of Epidemiology, Department of Health Sciences Research, [c]Department of Psychiatry and Psychology, [f]Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, and [d]Department of Pediatrics and Adolescent Medicine, and [e]Mayo Clinic Mayo Medical School, College of Medicine, Mayo Clinic, Rochester, Minnesota

WHAT'S KNOWN ON THIS SUBJECT: Exposure to virtually all anesthetic drugs has been shown to cause neurodegeneration in young animals. Studies of learning and cognition in children exposed to anesthesia and surgery have been few, have relied on single outcome measures, and have not controlled for comorbidity.

WHAT THIS STUDY ADDS: In this study of children exposed to anesthesia/surgery before the age of 2, multiple group and individual measures of learning and behavior are examined by using a matched design with adjustment for comorbidity using 2

Anesthesiology 2009; 110:796–804 Copyright © 2009, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

Early Exposure to Anesthesia and Learning Disabilities in a Population-based Birth Cohort

Robert T. Wilder, M.D., Ph.D., Randall P. Flick, M.D., M.P.H.,† Juraj Sprung, M.D., Ph.D.,‡ Slavica K. Katusic, M.D.,§ William J. Barbaresi, M.D.,‖ Christopher Mickelson, M.D.,# Stephen J. Gleich, M.D.,** Darrell R. Schroeder, M.S.,†† Amy L. Weaver, M.S.,†† David O. Warner, M.D.‡*

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Anesthesia for Cesarean Delivery and Learning Disabilities in a Population-based Birth Cohort

Juraj Sprung, M.D., Ph.D., Randall P. Flick, M.D., M.P.H.,† Robert T. Wilder, M.D., Ph.D.,‡ Slavica K. Katusic, M.D.,§ Tasha L. Fike, M.S.,‖ Mariella Dingli, M.D.,# Stephen J. Gleich, M.D.,** Darrell R. Schroeder, M.S.,†† William J. Barbaresi, M.D.,‡‡ Andrew C. Hanson, B.S.,§§ David O. Warner, M.D.**



Are Anesthesia and Surgery durin with Altered Academic Performan

Robert I. Block, Ph.D.,* Joss J. Thomas, M.D.,† Emine O. E
Karolie K. Kimble, R.N., B.A.,§ Michael M. Todd, M.D.‖

Anesth Analg. 2011 Nov;113(5):1143-51. Epub 2011 Mar 17.

Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort.

DiMaggio C, Sun LS, Li G.
Department of Anesthesiology, Columbia University, 622 West 168 St., New York, NY 10032, USA. cjd11@columbia.edu

Anesthesiology 2009; 11

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Cor J. Kalkman,
Marcel Bruens, F

A

Long-term Differences in Language and Cognitive Function After Childhood Exposure to Anesthesia

WHAT'S KNOWN ON THIS SUBJECT: Immature animals exposed to anesthetics display apoptotic neurodegeneration and long-term cognitive deficiencies. In children, studies of cognitive deficits associated with anesthesia exposure have yielded mixed results. No studies to date have used directly administered neuropsychological assessments as outcome measures.

WHAT THIS STUDY ADDS: This study examines the association between exposure to anesthesia in children under age 3 and deficits at age 10 by using a battery of directly administered neuropsychological assessments, with deficits found in language and abstract reasoning associated with exposure.

AUTHORS: Caleb Ing, MD,[a] Charles DiMaggio, PhD,[a,b,c] Andrew Whitehouse, PhD,[d] Mary K. Hegarty, MBBS, FANZCA,[e] Joanne Brady, MS,[a,b,c] Britta S. von Ungern-Sternberg, ProfPhD,[e,f] Andrew Davidson, MD,[g] Alastair J.J. Wood, MD,[h] Guohua Li, MD,[a,b,c] and Lena S. Sun, MD[a,i]

Departments of [a]Anesthesiology, [b]Epidemiology, and [i]Pediatrics, Columbia University College of Physicians and Surgeons, New York, New York; [c]Mailman School of Public Health, New York, New York; [d]Centre for Child Health Research and Neurocognitive Development Unit, School of Psychology, and [f]School of Medicine and Pharmacology, The University of Western Australia, Perth, Australia [e]Department of Anaesthesia and Pain Management, Princess Margaret Hospital for Children, Perth, Australia; [g]Department of Anaesthesia, Murdoch Childrens Research Institute & Royal Children's Hospital, Melbourne, Australia; and [h]Department of Medicine, Weill Cornell College of Medicine, and Symphony Capital LLC, New York, New York

Abstra
used anesthetic agents may have serious neurotoxic effects on the developing brain. The purpose of this study was to assess the association between surgery for hernia repair and the risk of behavioral and developmental disorders in young children. We performed a retrospective cohort analysis of children who were enrollees of the New York State Medicaid program. Our

Key Words: anesthesia, surgery, behavior, development
(*J Neurosurg Anesthesiol* 2009;21:286–291)

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Cohort studies - Limitations

- Small sample size
- Single center studies
- Multiple types of surgeries
- Large age span
- No anaesthetic details
- Protected and/or single center cohorts
- Outcome measures (LD, ADHD, Autism, academic achievements, neuropsychological tests)
- Known and unknown confounders
- Migration problems

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Cohort studies - Outcome measures

- Developmental deficits (preschool)
- Learning disabilities (elementary school)
- Behavioural oucomes (mental retardation, Autism/ADHD)
- Psychiatric disorders
- Language/speech disorders
- Educational outcome or IQ?
- Group vs Individual cognitive testing

BMJ

BMJ 2014;348:g3387 doi: 10.1136/bmj.g3387 (Published 30 May 2014)

ANALYSIS

Is animal research sufficiently evidence based to be a cornerstone of biomedical research?

Public acceptance of the use of animals in biomedical research is conditional on it producing benefits for humans. **Pandora Pound** and **Michael Bracken** argue that the benefits remain unproved and may divert funds from research that is more relevant to doctors and their patients

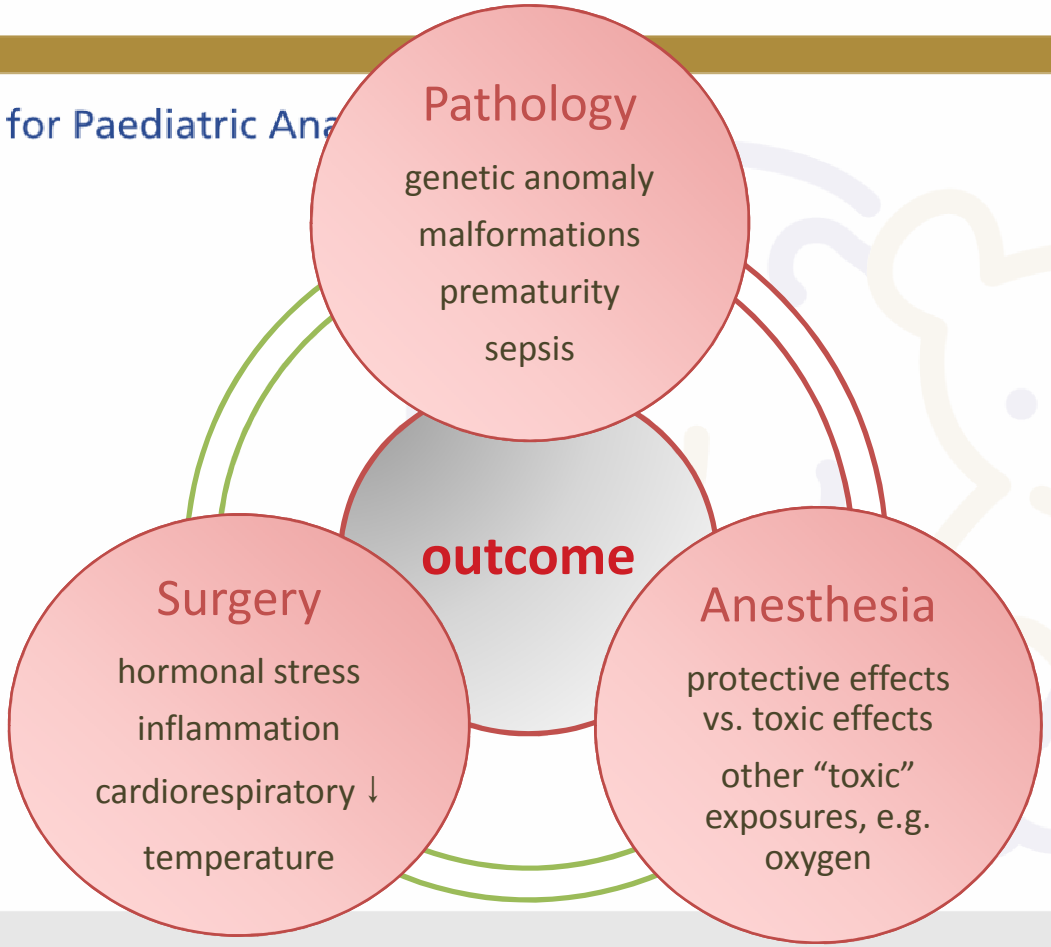
Pandora Pound *medical sociologist*[1], Michael B Bracken *Susan Dwight Bliss professor of epidemiology*[2]

[1]Bath, UK; [2]Yale University Schools of Public Health and Medicine, New Haven CT, USA

Key messages

- The conduct, reporting, and synthesis of much animal research continues to be inadequate
- This current situation is unethical since animals and humans participate in research that cannot produce reliable results
- There is insufficient systematic evidence for the clinical benefits of animal research
- Greater rigour and accountability is needed to ensure best use of public funds

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Pathology
genetic anomaly
malformations
prematurity
sepsis
outcome
Surgery
hormonal stress
inflammation
cardiorespiratory ↓
temperature
Anesthesia
protective effects
vs. toxic effects
other "toxic"
exposures, e.g.
oxygen

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Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

REVIEW ARTICLE

Anesthesia-related neurotoxicity and the developing animal brain is not a significant problem in children

Tom G. Hansen[1,2]

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2 Clinical Institute – Anesthesiology, University of Southern Denmark, Odense C, Denmark

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Sample size?

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Behavior and Development in Children and Age at the Time of First Anesthetic Exposure

Cor J. Kalkman, M.D., Ph.D., Linda Peelen, M.Sc.,† Karel G. Moons, Ph.D.,* Monna Veenhuizen, M.D.,‡ Marcel Bruens, R.N.,§ Gerben Sinnema, Ph.D.,|| Tom P. de Jong, M.D., Ph.D.#*

The child behavioural checklist

N=243 (0-6 yrs) urology: no difference

Post hoc sample calculation

Children > 2 years => n > 6.000

Children < 6 months => n > 2.200

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Age, sample size, surgery?

PERIOPERATIVE MEDICINE

Academic Performance in Adolescence after Inguinal Hernia Repair in Infancy

A Nationwide Cohort Study

Tom G. Hansen, M.D., Ph.D.,* Jacob K. Pedersen, M.Sc.,† Steen W. Henneberg, M.D., Ph.D.,‡
Dorthe A. Pedersen, M.Sc.,† Jeffrey C. Murray, M.D.,§ Neil S. Morton, M.D.,‖
Kaare Christensen, M.D., Ph.D., D.M.Sc.#

Anesthesiology 2011; 114:1076–85

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Outcome Measures Danish Cohort Studies

1. **Academic achievements 9th Grade**
   (0-13; mean= 8, SD=1)
   Average Tests and Teacher Rating
   (Danish, Foreign Languages, Mathematics, Hard Sciences & Social Sciences)
2. **Non-attainments**

Adjustment: e.g.: gender, age, birth weight, congenital malformations, parental age and level of education

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Statistics Denmark - Registers

The Danish Demographic Database

The Danish National Hospital Register

The Integrated Database for Labour Market Research

The Register of Compulsory School Completion Assessments and Test Scores

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Table 1. Characteristics of Early Anesthetic Exposure *versus* Control Group: Denmark, 1986–1990 Birth Cohort

Characteristic	Exposure Group (n = 2,689)	Control Group (n = 14,575)
Death	34 (1.3)	183 (1.3)
1–365 d after birth	6 (0.2)	109 (0.7)
>365 d after birth	28 (1.0)	74 (0.5)
Migration	109 (4.1)	752 (5.2)
Study base	2,547 (94.7)	13,640 (93.6)
Congenital malformation	316 (12.4)	624 (4.6)
Deceased	8 (23.5)	39 (21.3)
Migrant	9 (8.3)	33 (4.4)
Birth weight	2,541 (99.8)	13,616 (99.8)
<1,500 g	152 (6.0)	70 (0.5)
Birth weight, g	3,000 ± 798	3,437 ± 556
≤1,499	25 (16.4)	11 (15.7)
≥1,500	291 (12.2)	610 (4.5)
Sex (boy)	2,266 (89.0)	6,955 (51.0)
Paternal age, yr	30.3 ± 5.4	30.7 ± 5.4
Maternal age, yr	27.8 ± 4.9	28.1 ± 4.8
Paternal education	1.49 ± 1.71	1.68 ± 1.78
Maternal education	1.53 ± 1.66	1.77 ± 1.74
Average test score	7.73 ± 1.09	7.99 ± 1.08
Boy	7.68 ± 1.08	7.83 ± 1.08
Girl	8.08 ± 1.06	8.14 ± 1.06
Average teacher score	7.71 ± 1.11	8.03 ± 1.09
Boy	7.65 ± 1.11	7.80 ± 1.10
Girl	8.20 ± 1.01	8.25 ± 1.04
Test score	2,016 (79.2)	11,850 (86.9)
Boy	1,771 (78.2)	5,843 (84.0)
Girl	245 (87.2)	6,007 (89.9)
Teacher score	2,028 (79.6)	11,893 (87.2)
Boy	1,782 (78.6)	5,876 (84.5)
Girl	246 (87.5)	6,017 (90.0)

All data are presented as No. (%) or mean ± SD unless otherwise specified.

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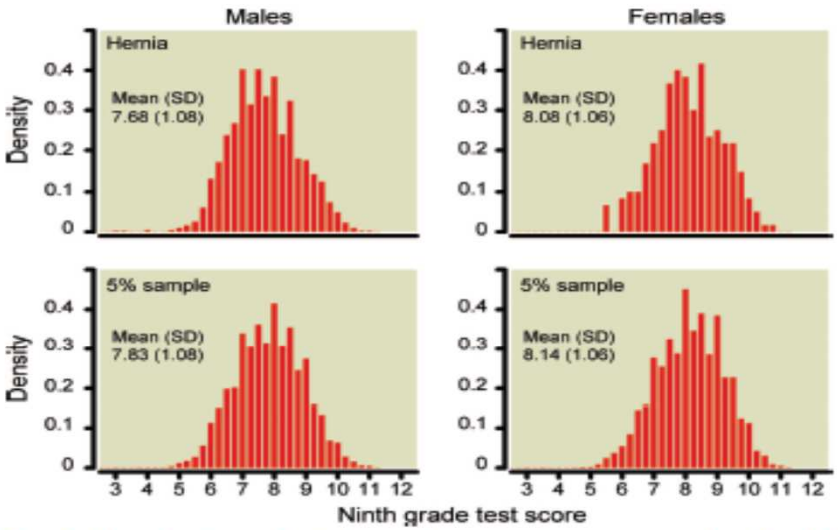


Fig. 1. Distribution of ninth grade mean test scores for Danish adolescents (born 1986–1990) who underwent inguinal hernia repair in infancy (n = 2,547) *versus* a control group composed of a randomly selected 5% population sample of age-matched cohorts (n = 14,575).

What We Already Know about This Topic

- Animal studies have raised concerns about the potential for neurocognitive impairment from general anesthesia in human newborns, but clinical studies are inconclusive.

What This Article Tells Us That Is New

- In more than 2,500 children who underwent inguinal hernia repair as infants in Denmark, academic test scores in ninth grade were not different than those of a randomly selected sample after adjusting for known confounders.

Odds Ratio for test score non-attainments: 1.13 (95%CI: 0.98-1.31)

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Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study

Tom G. Hansen[1,2], Jacob K. Pedersen[3], Steen W. Henneberg[4], Neil S. Morton[5] & Kaare Christensen[3,6,7]

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2 Clinical Institute – Anesthesiology, University of Southern Denmark, Odense C, Denmark
3 Institute of Public Health – Epidemiology, University of Southern Denmark, Odense C, Denmark
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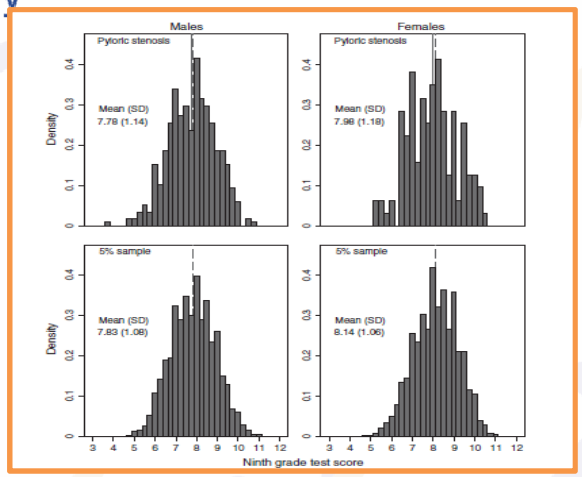
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Table 1 Characteristics of pyloric stenosis patients and 5% population sample from the 1986–90 birth cohorts in Denmark

	Pyloric stenosis		5%-Population sample	
	n	Percent (%)	n	Percent (%)
No of live births	779		14 665	
Deaths (days after birth)	6	0.8	195	1.3
1–365	3	0.4	110	0.8
>365	3	0.4	75	0.5
Migrations	25	3.2	757	5.2
Cong. malf. among deceased[a]	6	100.0	40	21.6
Cong. malf. among migrants[a]	21	84.0	31	4.1
Study base	748	96.0	13 723	93.6
Congenital malformations[a]	674	90.1	595	4.3
Among birth weights −1499	2	33.3	12	14.8
Among birth weights 1500+	671	90.6	581	4.3
Congenital malformations excl. Pyl. Sten.[b]	51	6.8	583	4.4
Among birth weights −1499	0	0.0	12	14.8
Among birth weights 1500+	50	6.7	569	4.3
Known birth weight	747	99.9	13 700	99.8
Birth weight <1500 (g)	6	0.8	81	0.6
Males	603	80.6	7032	51.2
	Mean	sd	Mean	sd
Birth weight (g)	3345	624	3434	560
Maternal age	27.9	4.9	28.0	4.8
Paternal age	30.7	5.6	30.7	5.4
Maternal education	1.57	1.68	1.77	1.74
Paternal education	1.49	1.74	1.67	1.78
Average test score	7.82	1.15	7.99	1.08
Males	7.78	1.14	7.83	1.08
Females	7.98	1.18	8.14	1.06
Average teachers' score	7.81	1.17	8.03	1.09
Males	7.74	1.19	7.80	1.10
Females	8.06	1.06	8.25	1.04
	n	Percent (%)	n	Percent (%)
Available test score	586	79.7	11 910	86.8
Males	470	77.9	5898	83.9
Females	126	86.9	6012	89.9
Available teachers' score	605	80.9	11 964	87.1
Males	478	79.3	5932	84.4
Females	127	87.6	6022	90.0

All available individuals included.
[a]Any congenital malformation as expressed by an ICD-8 code of 740–759.99 or an ICD-10 code of Q00.0–Q99.9.
[b]Any congenital malformation other than Pyloric Stenosis, as expressed by an ICD-8 code of 740–759.99 excluding 750.10–750.19 or an ICD-10 code of Q00.0–Q99.9 excluding Q40.0.



Odds Ratio for test score non-attainments: 1.37 (95% CI: 1.11-1.68)

E-mail:

ESPA

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

*Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium**

www.thelancet.com Vol 387 January 16, 2016

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.

Pediatric Anesthesia
Pediatric Anesthesia ISSN 1155-5645

ORIGINAL ARTICLE

Neurosurgical conditions and procedures in infancy are associated with mortality and academic performances in adolescence: a nationwide cohort study

Tom G. Hansen[1,2], Jacob K. Pedersen[3], Steen W. Henneberg[4], Neil S. Morton[5] & Kaare Christensen[3,6,7]

Pediatric Anesthesia 25 (2015) 186–192

9th grade test score Neurosurgery in infancy Danish birth cohorts 1986-1990	Mortality (%)	Non-attainment (%)	Test scores
All neurosurgeries (n=228)	15.8	48.7	7.57
Hydrocephalus (n=130)	18.5	59.7	7.51
Craniotomy (n=43)	18.6	40.0	7.32
Myelo/encephaloceles (n=55)	7.3	32.7	7.78
Controls (n=14,703)	1.3	13.2	7.99

ESPA

Outcome after oral cleft surgery

Danish birth cohorts 1986-1990 (age 15-16y)	Age at surgery	Mortality (%)	9th grade exam (%)	Test score (SD)
Oral cleft (n=588)	2m – 22 m	1.5	81.5	7.93 (1.09)
Cleft lip (n=171)	**2m**-6m	1.2	88.4	8.10 (1.04)
Cleft palate (n=195)	14m-**22m**	1.0	72.1	7.85 (1.10)
Cleft lip + palate (n=222)	**2m**-6m 14-**22m**	2.3	84.4	7.83 (1.12)
Controls (n=14,677)	-	1.3	86.8	7.99 (1.09)



Compensating factors ? CL parents better educated? Fewer preterms ? More caring environment? Different sex-distribution?

ACTA OTO-LARYNGOLOGICA, 2016
http://dx.doi.org/10.3109/00016489.2016.1146412

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RESEARCH ARTICLE

School performance in cholesteatoma-operated children in Denmark: a nationwide population-based register-study

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Table 1. Characteristics of children surgically treated for middle ear cholesteatoma before 15 years of age (cholesteatoma group) and a 5% population sample (control group) from the Danish 1986–1991 birth cohorts.

	Cholesteatoma group		Control group		
	n	%	*n*	%	*p*-value[c]
Total number	702		17 757		
Exclusions					
Congenital malformations[a]	114	16.2	1362	7.7	<0.001
Emigrated before 17 years	16	2.7	774	4.7	0.024
Died before 17 years	1	0.2	121	0.8	0.067
Unknown birth weight	1	0.2	27	0.2	1.000
Different grading scale	18	3.2	346	2.2	0.147
Unknown parental education	3	0.5	21	0.1	0.051
Study base	549	78.2	15 106	85.1	<0.001
Sex					
Males	343	62.5	7627	50.6	<0.001
Females	206	37.5	7479	49.5	<0.001
	Mean	SD	Mean	SD	*p*-value[d]
Age at first cholesteatoma surgery	9.4	3.1	–	–	–
Birth weight (g)	3393	578	3448	587	0.015
Maternal education[b]	2.1	0.8	2.1	0.7	0.217
Paternal education[b]	1.9	0.7	2.0	0.7	0.015
Average grade					
Males	7.7	1.1	7.8	1.1	0.110
Females	8.1	1.1	8.2	1.1	0.140
9th grade marks registered	*N*	%	*n*	%	*p*-value[c]
Males	290	84.6	6708	88.0	0.060
Females	182	88.4	6915	92.5	0.029

Table 3. Results from three different linear regressions adjusting for the same confounders as in Table 2 (not shown).

	Coefficient	95% CI		*p*-value
Mathematics				
Sex				
Male	Ref	–		–
Female	0.12	0.08;	0.16	<0.001
No. cholesteatoma surgeries				
0	Ref	–		–
1	−0.06	−0.19;	0.08	0.413
≥2	−0.02	−0.19;	0.16	0.869
Danish				
Sex				
Male	Ref	–		–
Female	0.61	0.5;	0.65	<0.001
No. cholesteatoma surgeries				
0	Ref	–		–
1	−0.01	−0.12;	0.10	0.876
≥2	−0.12	−0.27;	0.02	0.101
English				
Sex				
Male	Ref	–		–
Female	0.35	0.30;	0.40	<0.001
No. cholesteatoma surgeries				
0	Ref	–		–
1	−0.12	−0.29;	0.04	0.148
≥2	−0.26	−0.48;	−0.03	0.024

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Neurocognition after neonatal surgery?

Neurodevelopmental Outcomes After Neonatal Surgery for Major Noncardiac Anomalies

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CONCLUSIONS: Cognitive and motor developmental delay was found in 23% of patients with NCCA. Meta-analysis showed that the mean neurodevelopmental outcome scores were 0.5 SD below the normative score of the healthy population.

Risk factors:
Birth weight
Prematurity
Congenital anomalies
Syndromes
Chromosomal disorders
Duration of hospital stay
Duration of IPPV
Need for supplementary O2
Growth delay
Level of parental education

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Neurocognition after congenital cardiac surgery

Neurodevelopmental Outcomes After Cardiac Surgery in Infancy

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PEDIATRICS Volume 135, number 5, May 2015

A Systematic Review of Motor and Cognitive Outcomes After Early Surgery for Congenital Heart Disease

AUTHORS: Suzanne H. Snookes, BS,[a,b] Julia K. Gunn, MBBS, FRACP,[c,d,e] Bev J. Eldridge, BS, PhD,[a] Susan M. Donath, BS, MA,[d,f,g] Rod W. Hunt, BMBS, MMed, PhD, FRACP, MRCP,[c,d,e] Mary P. Galea, BS, BA, PhD,[b] and Lara Shekerdemian, MD, MRCP, FRACP[c,d,h]

CONCLUSIONS: With this review we identified a limited number of prospective studies that systematically addressed outcome in patients at the highest risk. These studies consistently revealed cognitive and motor delay in children after cardiac surgery during early infancy. Additional investigation is required to ascertain the consequences of such impairment during later childhood and into adult life. *Pediatrics* 2010; 125:e818–e827

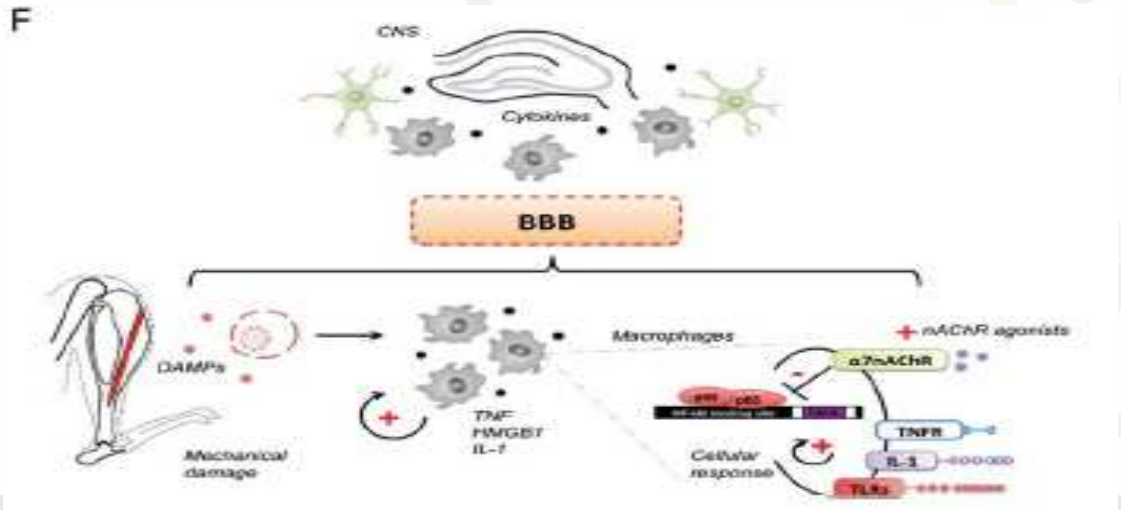
Risk factors:
Birth weight
Prematurity
Congenital anomalies and syndromes
Chromosomal disorders
Complexity of CHD
Lenght of hospital/ICU stay
Preoperative IPPV
APGAR
Socioeconomic status
Level of parental education
Ethnicity
CPB techniques (DHCA)
Hct↓
B-glucose

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Resolving Postoperative Neuroinflammation and Cognitive Decline

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Ting Yang, MD, PhD,[1] Claudia Monaco, MD, PhD,[4] Marc Feldmann, FMedSci, FAA, FRS,[4]
Malin Jonsson Fagerlund, MD, PhD,[2] Israel F. Charo, MD, PhD,[5]
Katerina Akassoglou, PhD,[3,6] and Mervyn Maze, MB, ChB[1]

ANN NEUROL 2011;70:986–995



Detection of Postoperative Cognitive Decline After Coronary Artery Bypass Graft Surgery is Affected by the Number of Neuropsychological Tests in the Assessment Battery

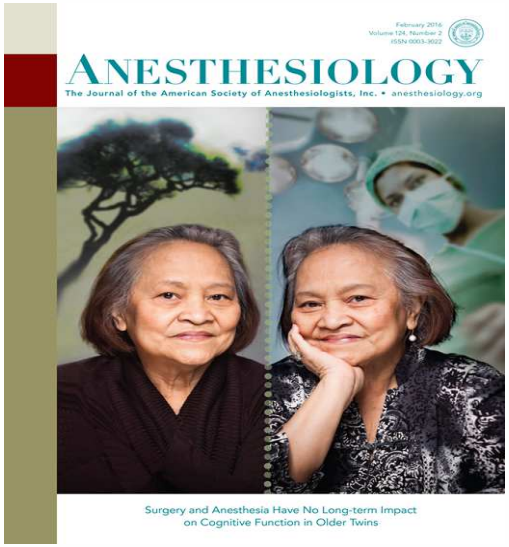
Matthew S. Lewis, BAppSc Hons, Paul Maruff, PhD, Brendan S. Silbert, MBBS, FANZCA, Lis A. Evered, BS, and David A. Scott, MBBS, FANZCA, PhD

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(Ann Thorac Surg 2006;81:2097–104)
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No reliable tools available for assessing POCD

Increasing number of tests to classify POCD ⇒ ↑ sensitivity to change in both exposure and control groups



PERIOPERATIVE MEDICINE

Cognitive Functioning after Surgery in Middle-aged and Elderly Danish Twins

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ABSTRACT

Background: Postoperative cognitive dysfunction is common, but it remains unclear whether there are long-term adverse cognitive effects of surgery combined with anesthesia. The authors examined the association between exposure to surgery and level of cognitive functioning in a sample of 8,503 middle-aged and elderly twins.

Methods: Results from five cognitive tests were compared in twins exposed to surgery, classified as major, minor, hip and knee replacement, or other, with those of a reference group without surgery using linear regression adjusted for sex and age. Genetic and shared environmental confounding was addressed in intrapair analyses of 87 monozygotic and 124 dizygotic same-sexed twin pairs in whom one had a history of major surgery and the other did not.

Results: Statistically significantly lower composite cognitive score was found in twins with at least one major surgery compared with the reference group (mean difference, −0.27; 95% CI, −0.48 to −0.06), corresponding to one tenth of an SD, that is, a negligible effect size. In the intrapair analysis, the surgery-exposed co-twin had the lower cognitive score in 49% (95% CI, 42 to 56%) of the pairs. None of the other groups differed from the reference group except the knee and hip replacement group that tended to have higher cognitive scores (mean difference, 0.35; 95% CI, −0.18 to 0.87).

Conclusions: A history of major surgery was associated with a negligibly lower level of cognitive functioning. The supplementary analyses suggest that preoperative cognitive functioning and underlying diseases were more important for cognitive functioning in mid- and late life than surgery and anesthesia. (ANESTHESIOLOGY 2016; 124:312-21)

Pediatric Anesthesia

EDITORIAL

Anesthetists rather than anesthetics are the threat to baby brains

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Infantile Postoperative Encephalopathy: Perioperative Factors as a Cause for Concern

Mary Ellen McCann, A.N.J. Schouten, Nicole Dobija, Carlos Munoz, Lianne Stephenson, Tina Y. Poussaint, C.J. Kalkman, Paul R. Hickey, Linda S. de Vries and Robert C. Tasker

Pediatrics 2014;133;e751; originally published online February 10, 2014;
DOI: 10.1542/peds.2012-0973

But what about:

Hypocarbia/hypercarbia?
Hypoxia/hyperoxia?
Blood pressure/perfusion?
Hypo/hyper-glycemia?
hyponatriemia?
Hypo/hyperthemia?
Training/competencies/vol

REVIEW

CURRENT OPINION

Safe Anesthesia For Every Tot – The SAFETOTS initiative

Markus Weiss[a,b], Laszlo Vutskits[c], Tom G. Hansen[d,e], and Thomas Engelhardt[f]

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Conclusions

Surgery and underlying conditions (far) more important re: periopreative neurocognitive outcome than anaesthetic exposures

Animal studies do not reliably predict human outcomes

Europe vs. USA?

No more inflammatory and non-evidence based papers, please.

Alternatives??

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ACADEMIC PERFORMANCE AFTER ANESTHESIA AND SURGERY DURING CHILDHOOD: A LARGE-SCALE NATION-WIDE STUDYGlatz, Sandin, Bonamy, Pedersen, Eriksson Granath
ANESTH ANALG 2015; 120; S289

~ 2,000,000 children 1973-1993
107,460 exposed children < 4 yrs
34,480 exposed x 1 children < 4 yrs

Fig. 1

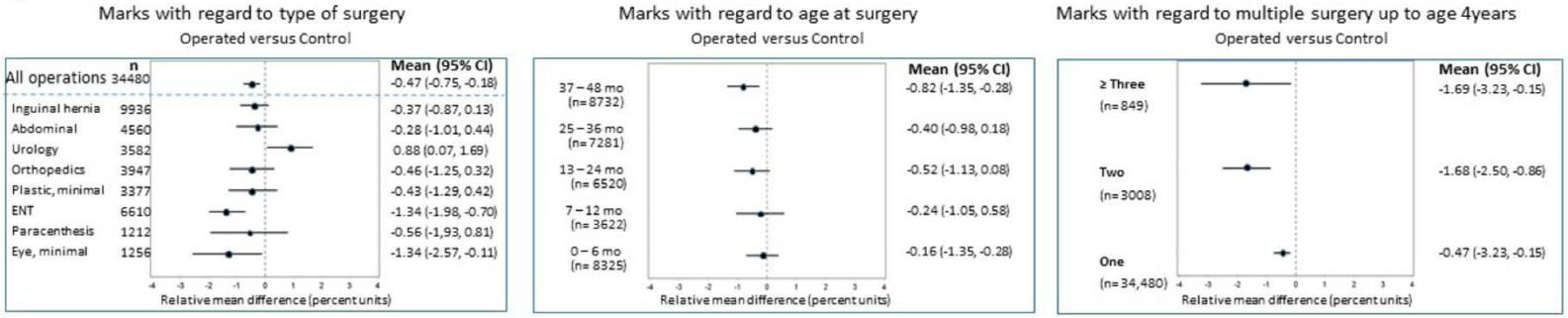


Fig 2

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ACADEMIC PERFORMANCE AFTER ANESTHESIA AND SURGERY DURING CHILDHOOD: A LARGE-SCALE NATION-WIDE STUDYGlatz, Sandin, Bonamy, Pedersen, Eriksson Granath ANESTH ANALG 2015; 120; S289

Fig 2

