University of Colorado
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The Effects of General Anesthesia on Very Young Brain

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Pediatric Anesthesia

- **Advances in pediatric and obstetric surgery have placed increased demands on anesthesia in terms of the complexity, duration and number of anesthetic interventions.**
- **In addition, since premature births (as young as 22 weeks post-conception) account for more than 10% of the overall birth rate more premature babies reach anesthesia providers daily.**
- **It would be overly simplistic to consider a child as small adult when it comes to anesthesia management.**

THE CNS IS NOT COMPLETELY DEVELOPED AT BIRTH

The brain weighs approximately 335 g at birth.

It doubles in size by 6 months.

It triples in size by 12 months.

The fundamental neuronal circuitries are not completed until about 4 years of age.

BRAIN DEVELOPMENT - SYNAPTOGENESIS

- Neuronal synapses formation,
- Neuronal migration,
- Neuronal maturation,
- Neuronal differentiation,
- Glial cells proliferation.

(Last trimester of pregnancy and first 3 years of life).

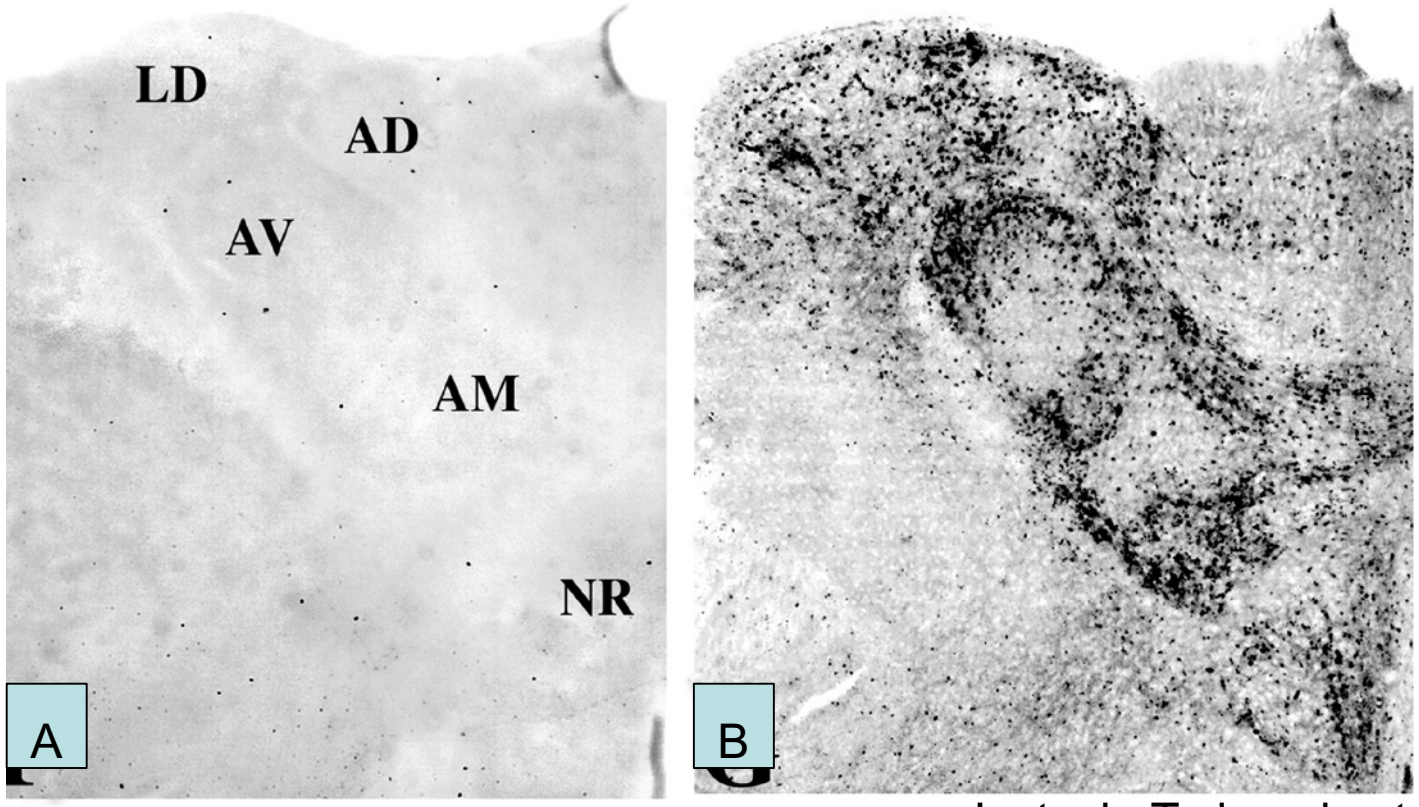
DEVELOPMENTAL NEUROAPOPTOSIS

- “Suicide” of redundant neurons;

- Approximately 0.5-2% of neuronal population.

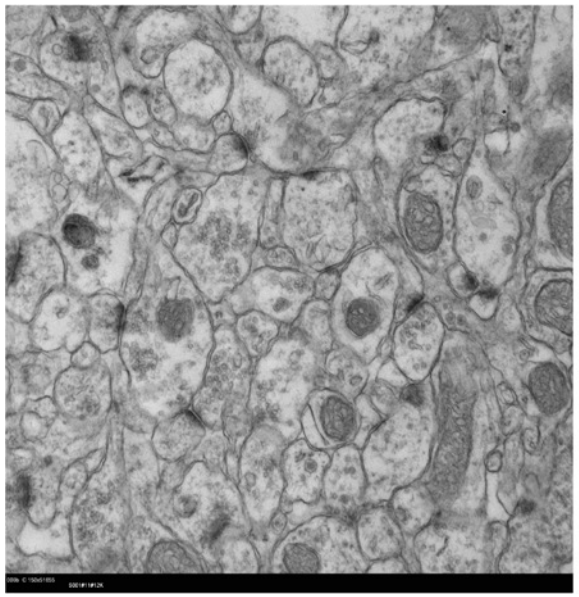
Commonly used general anesthetics induce massive neuronal suicide in the developing rat brain (PND 7 days)

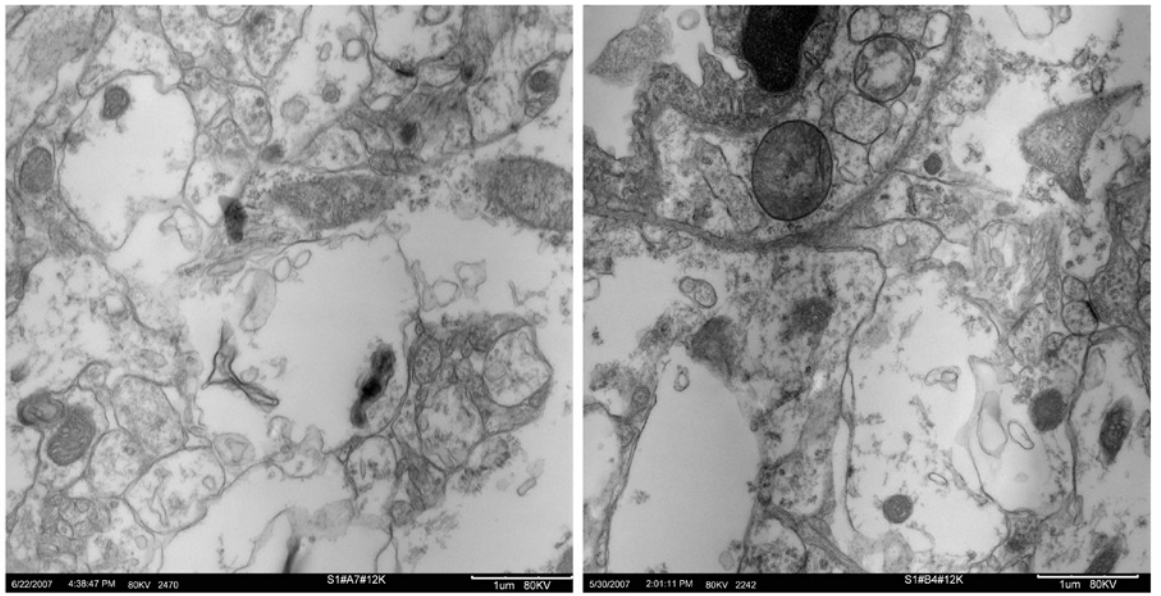
Isoflurane - alone or in combination with midazolam and nitrous oxide:



Jevtovic-Todorovic et al.,
J. Neurosci., 23(3):876-882, 2003

Anesthesia-induced scarcity of neuropil





control

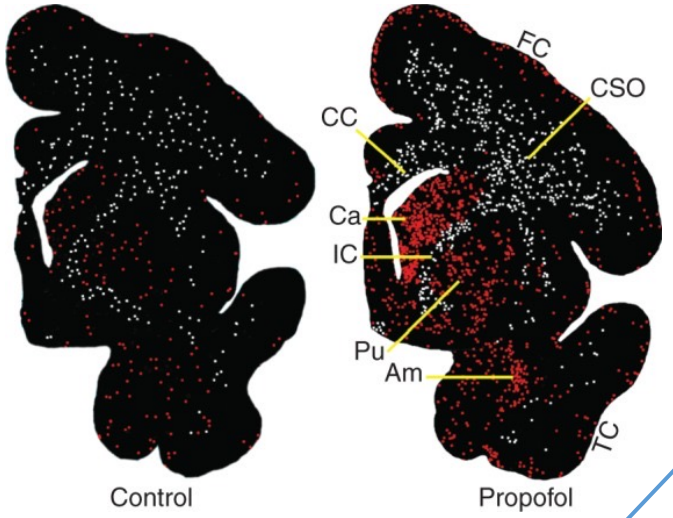
experimental

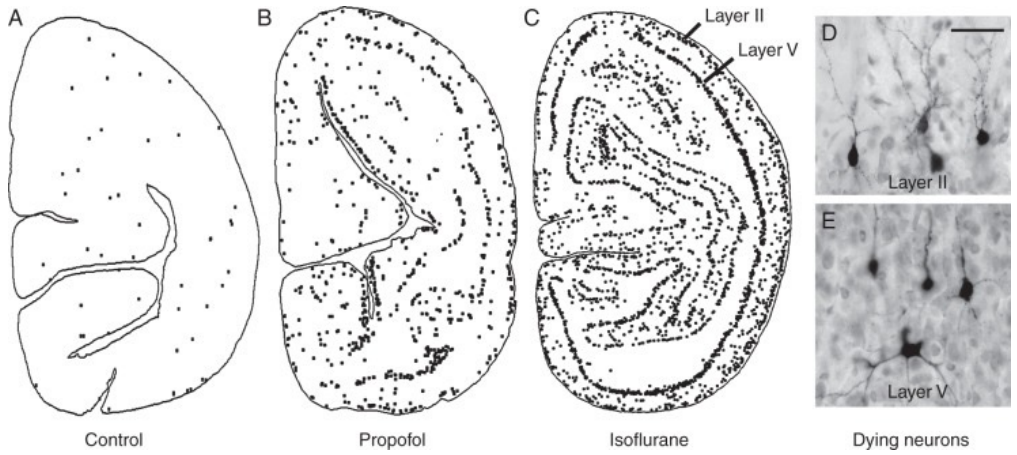
Lunardi N, Ori C, Erisir A, Jevtovic-Todorovic V.
Neurotoxicology Research, 2010, 17:179-88.

Propofol-induced Apoptosis of Neurons and Oligodendrocytes in Fetal and Neonatal Rhesus Macaque Brain

Fetal brain

Neonatal brain





Creeley et al., Br J Anaesth. 2013; 110(Suppl 1): i29–i38

Multiple Anesthetic Exposure in Infant Monkeys Alters Emotional Reactivity to an Acute Stressor

Raper et al. *Anesthesiology* 2015; 123(5): 1084–1092

- 4-hour exposures to sevoflurane anesthesia (at 2.5%) or brief maternal separations on postnatal day 6-10 that were repeated 14 and 28 days later
- Monkeys remained with their mothers in large social groups
- At 6 months of age, each monkey was tested on the human intruder paradigm, a common test for emotional reactivity in nonhuman primates
- The frequency of anxiety-related behaviors was significantly higher in monkeys that were exposed to anesthesia as neonates as compared to controls

Isoflurane Anesthesia Has Long-term Consequences on Motor and Behavioral Development in Infant Rhesus Macaques

Coleman et al., Anesthesiology 2017;126(1):74-84

- Infant monkeys were exposed to isoflurane once for 5 hrs or 3 times
- Repeated isoflurane exposures resulted in motor reflex deficits at 1 month of age
- Repeated isoflurane exposures resulted in increased anxiety in new social environment and affiliative/appeasement behavior

Contents lists available at ScienceDirect

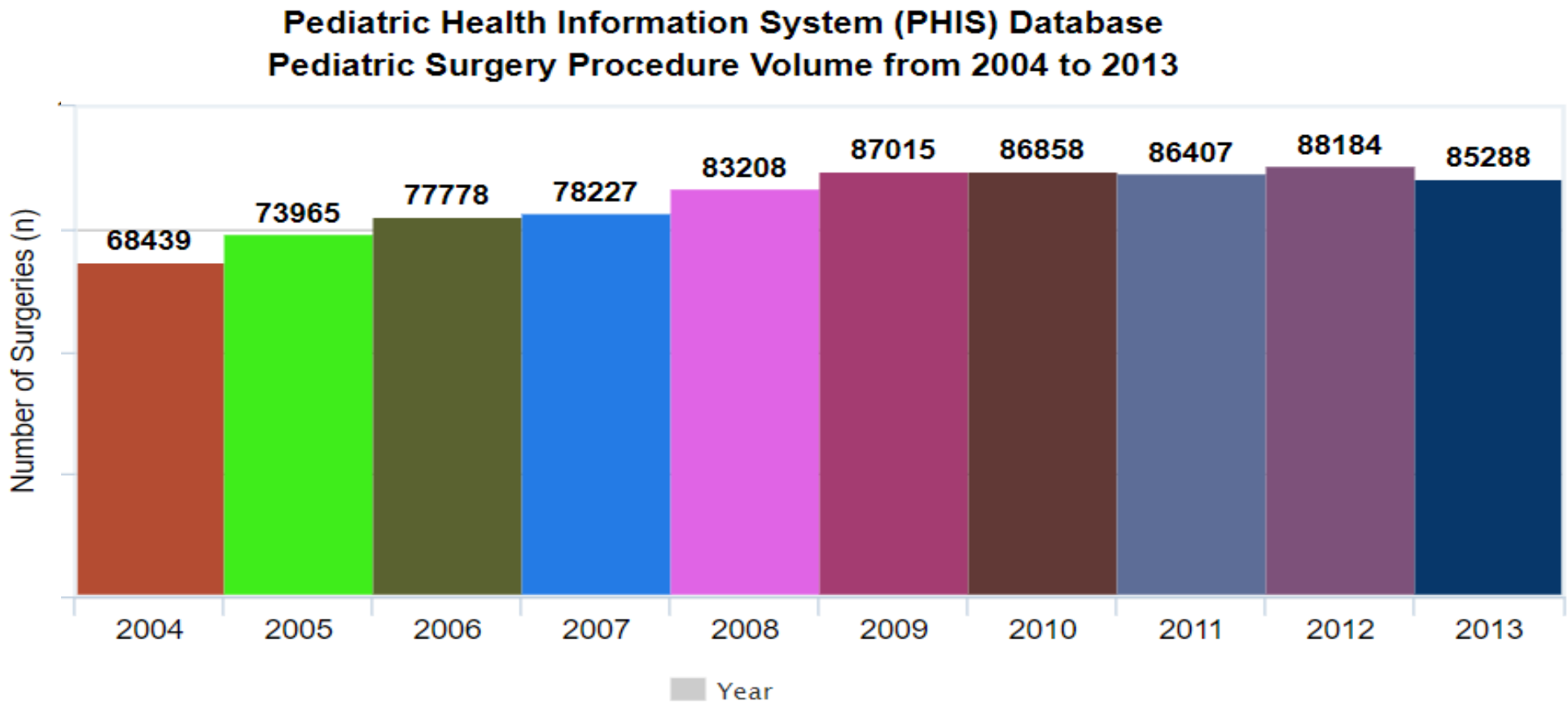
Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

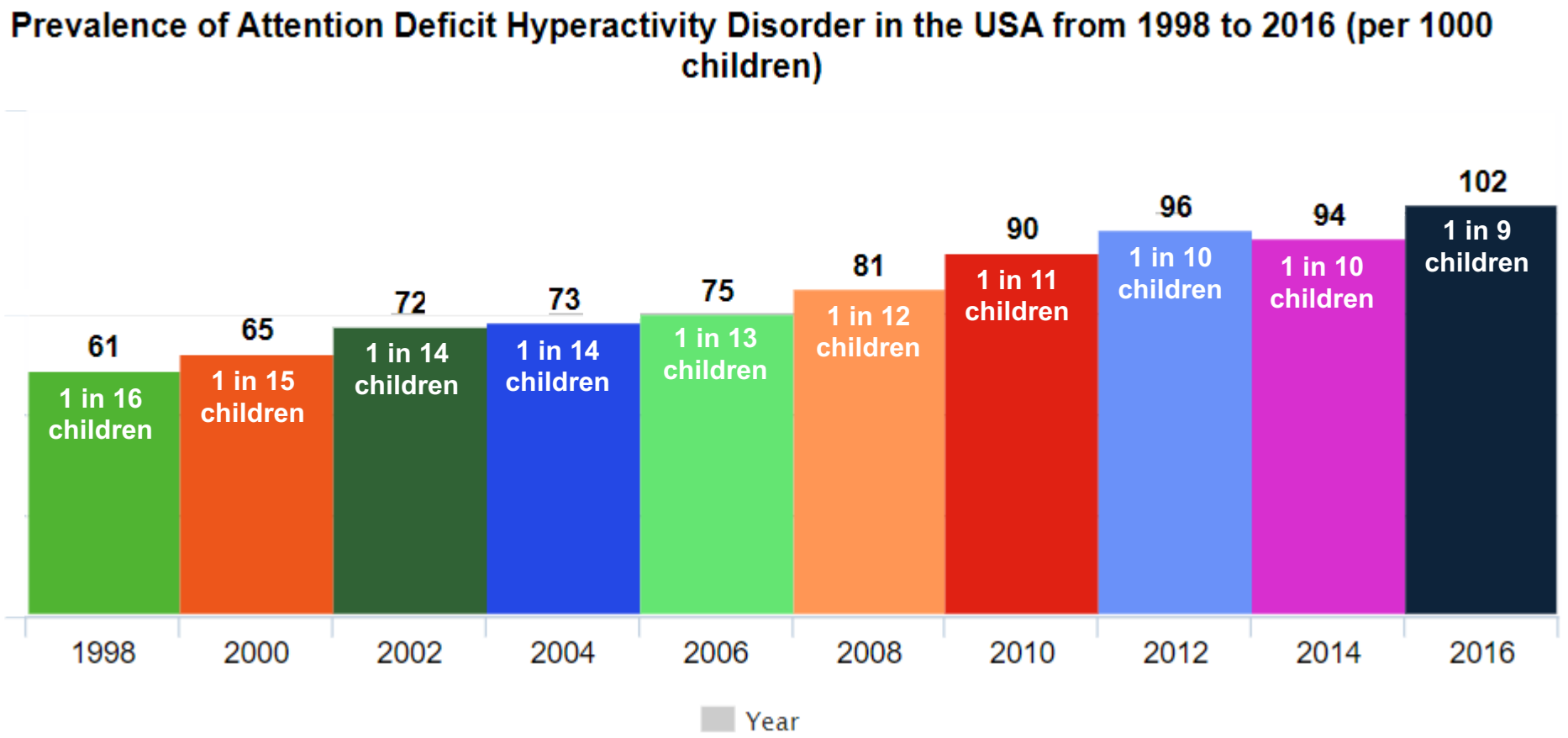
Pediatric surgery – a changing field: national trends in pediatric surgical practice

Nicholas E. Bruns [a], M. Abid Shah [b], Amelia N. Dorsey [a], Todd A. Ponsky [a], Oliver S. Soldes [a,*]

[a] Division of Pediatric Surgery, Akron Children's Hospital, Akron, OH, USA
[b] Department of Quality and Patient Safety, Akron Children's Hospital, Akron, OH, USA

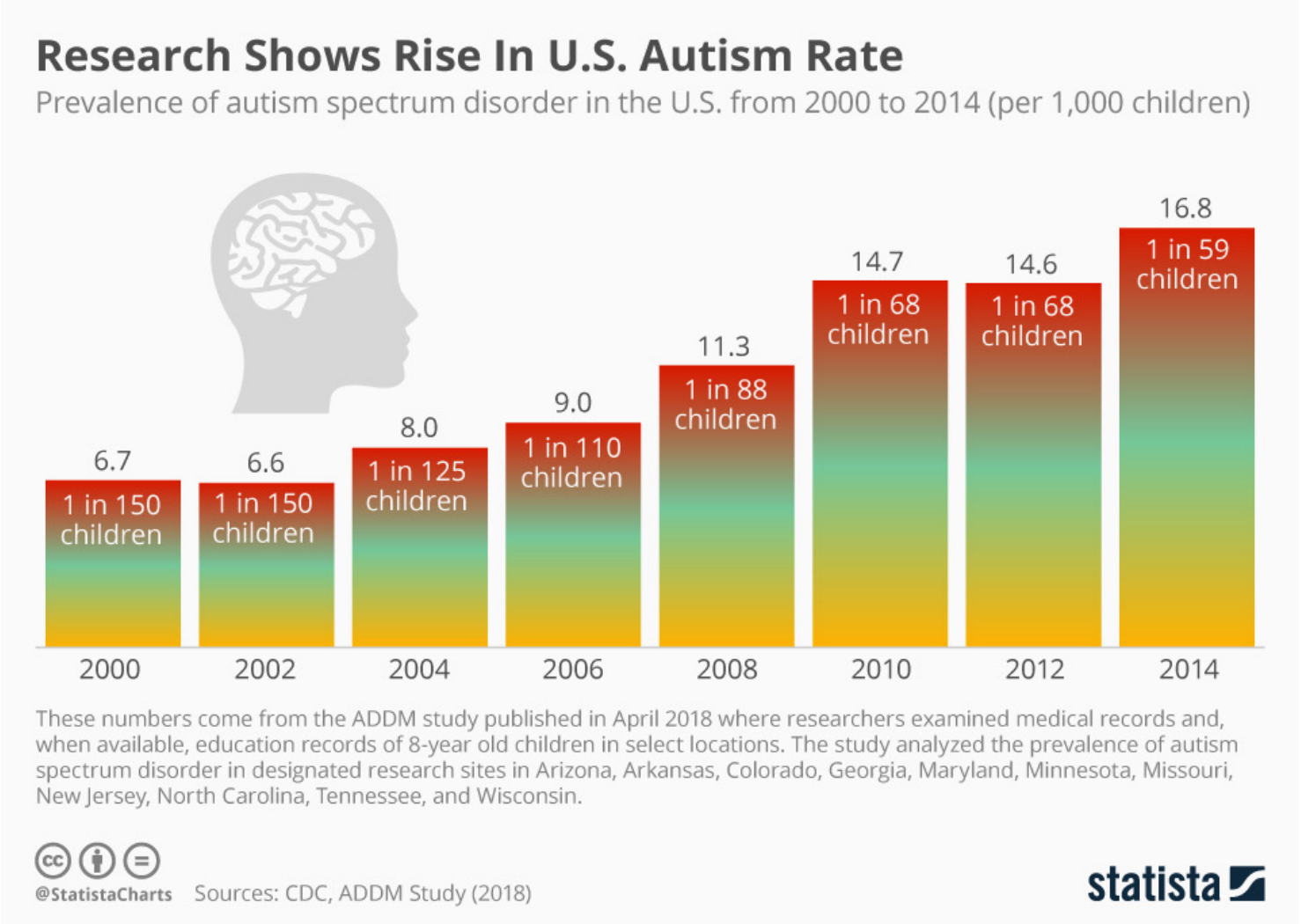


USA Prevalence Trend of ADHD



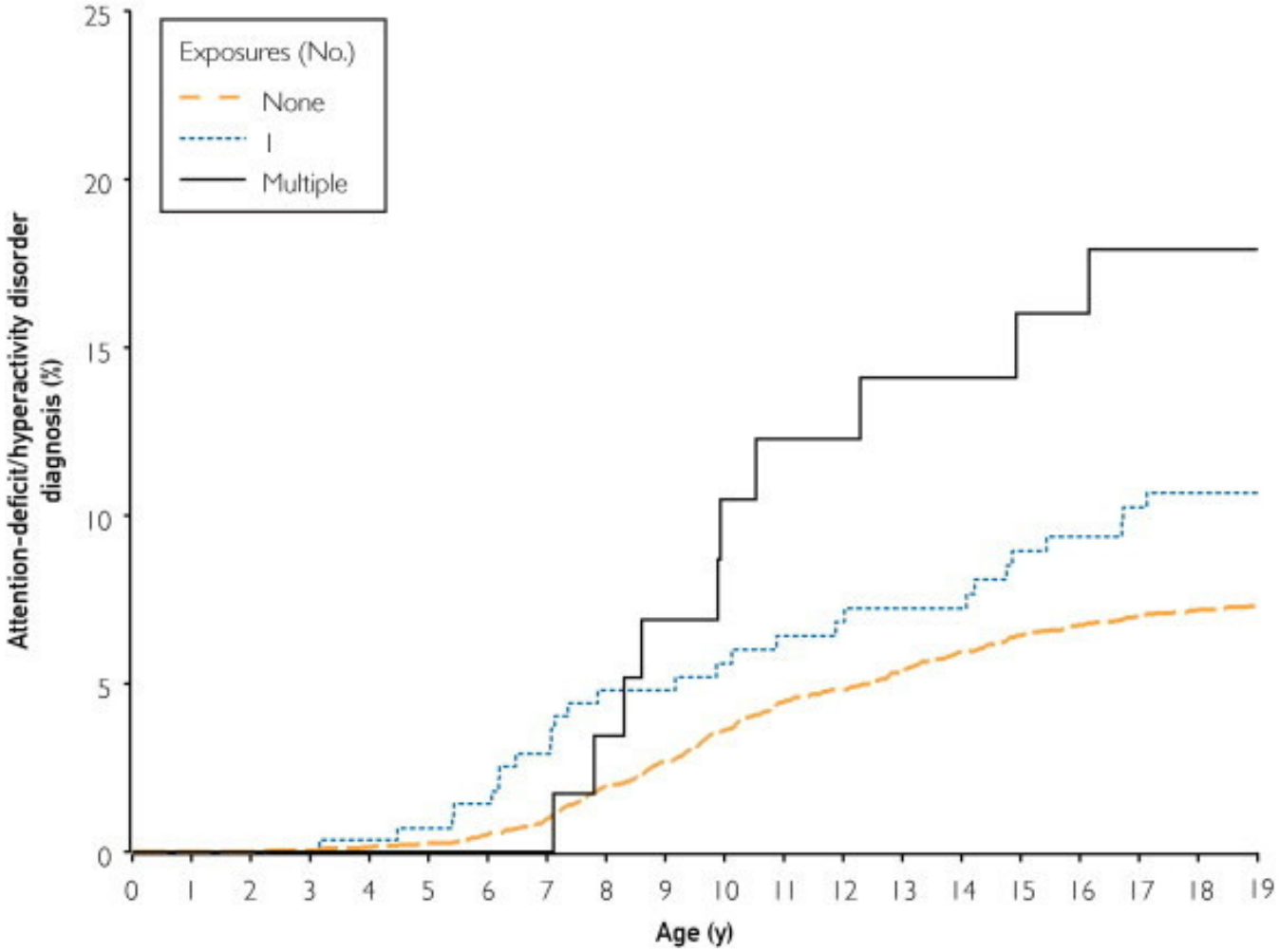
Extrapolated from: Pastor PN. QuickStats: Percentage of Children and Adolescents Aged 5–17 Years with Diagnosed Attention-Deficit/Hyperactivity Disorder (ADHD), by Race and Hispanic Ethnicity — National Health Interview Survey, United States, 1997–2014,Morbidity and Mortality Weekly Report (MMWR) 64(33):925–925.

USA Prevalence Trend of ASD



2016: 1 in 54 children (18.5 per 1000 children)
2018: 1 in 44 children (23.0 per 1000 children)

Early life anesthesia and ADHD



- Aim: to investigate the association between surgical procedures performed under GA prior to age of 2 and ADHD development
- Study included children born between 1976 and 1982 in Rochester, MN.
  - 348 children with previous anesthesia history
  - 4944 children with no history of anesthesia
- Even after adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to **multiple (two or more), but not single,** procedures requiring general anesthesia was associated with an increased risk for the later development of ADHD.

Sprung et al. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc. 2012 Feb;87(2):120-9.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 24 November 2021
doi: 10.3389/fpsyt.2021.717093

Check for updates

Does Exposure to General Anesthesia Increase Risk of ADHD for Children Before Age of Three?

Junjie Song[1†], *Huifang Li*[1†], *Ying Wang*[2*] *and Chenguang Niu*[1,3*]

[1] Department of Anesthesiology, The First Affiliated Hospital of Henan University, Kaifeng, China, [2] Department of Medical Hospital, Henan University, Henan Medical Hospital, Henan University, Kaifeng, China, [3] The Key Laboratory of Clinical Resources Translation, Henan University, Kaifeng, China

- Meta-analysis published in 2021. Four retrospective cohort studies were included for the analysis.
- Aim: to elucidate the effect of single or multiple exposures to general anesthesia prior to age of 3 on subsequent diagnosis of ADHD.
- The study included:
  - 3506 children with single exposure to anesthesia
  - 1775 children with multiple (two or more) exposures to anesthesia
  - 21229 children with no history of anesthesia exposure
- **Conclusion: multiple, but not single, exposures to general anesthesia in children before age of 3 significantly increased the risk of ADHD development.**

Journal of Autism and Developmental Disorders (2019) 49:3127–3135
https://doi.org/10.1007/s10803-019-04034-9

ORIGINAL PAPER

Exposure to General Anesthesia May Contribute to the Association between Cesarean Delivery and Autism Spectrum Disorder

Maayan Huberman Samuel[1] · Gal Meiri[2] · Ilan Dinstein[3,4] · Hagit Flusser[5] · Analiya Michaelovski[5] · Asher Bashiri[6] · Idan Menashe[1,4]

- The aim of the study was to examine the association of cesarean section (CS) performed under general and/or regional anesthesia and the susceptibility to developing ASD and DD (developmental disorder).
- Study included children born at the Soroka University Medical Center (Israel), between years 2009 and 2016:
  - 347 children with ASD
  - 117 children with DD
  - 2226 healthy age, sex and ethnicity matched controls
- Conclusions: CS performed **under general anesthesia, but not under regional anesthesia**, was associated with:
  - Higher susceptibility to ASD development
  - Development of more severe form of ASD
  - The risk was greater in females compared to males
- This study suggests positive correlation of general anesthesia and severe form of ASD, and resonates well with the recent FDA warning regarding the use of GA among young children or pregnant women due to its adverse effects on brain development

What Can We Take Away From This?

- Repeated, lengthy or cumulative exposure to commonly-used anesthetics has negative impacts on young and developing brain;
- An increase in the incidence of general anesthesia exposure appears to mimic an increase in the incidence of reported ASD and ADHD;
- Learning and behavioral impairments are complex and life-long;
- Great care should be taken to avoid use of anesthetics and sedatives whenever possible or **to develop new line of general anesthetics and sedatives.**

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Thank you!


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