



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

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Specialty section:

This article was submitted to
Child and Adolescent Psychiatry,
a section of the journal
Frontiers in Psychiatry

Received: 30 May 2021

Accepted: 01 September 2021

Published: 24 November 2021

Citation:

Song J, Li H, Wang Y and Niu C
(2021) Does Exposure to General
Anesthesia Increase Risk of ADHD for
Children Before Age of Three?
Front. Psychiatry 12:717093.
doi: 10.3389/fpsy.2021.717093

Objective: The objective of the study was to evaluate the relationship between frequency of exposure to general anesthesia before the age of 3 and subsequent risk of diagnosis for attention-deficit hyperactivity disorder (ADHD).

Method: We searched PubMed, Embase, Web of Science, and Cochrane Library database for eligible inclusion in the meta-analysis. The indicated outcomes were extracted from the included studies, and the combined effects were calculated using the RevMan software 5.3.

Results: Compared with no exposure to general anesthesia, single exposure to general anesthesia did not increase the risk of ADHD for children before the age of 3 [hazard ratio (HR): 1.14, 95% confidence intervals (CI): 0.97–1.35; $p = 0.11$; $I^2 = 0\%$], while multiple exposures to general anesthesia did increase the risk of ADHD (HR: 1.83; 95% CIs: 1.00–3.32; $p = 0.05$; $I^2 = 81\%$).

Conclusion: Multiple, but not single, exposures to general anesthesia in children before age of 3 increased the risk of ADHD.

Keywords: general anesthesia, ADHD, children, meta-analysis, single, multiple

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neuropsychological disorder, which is characterized by hyperactivity, impulsivity, inattention, lack of vigilance, and inability to adapt to the rapid changes (1). Children with ADHD typically exhibit deficits in vigilance, verbal learning, working memory, and measures of executive function (2). According to the survey, the prevalence of ADHD in children and adolescents has reached 7.2% worldwide (3). The causes of ADHD are not known well. Although ADHD is a heritable disorder, the gene–environment interaction may be important for its clinical symptoms (4). Environmental factors, such as maternal smoking, prenatal alcohol exposure, viral infections, nutritional deficiencies, low parental education level, perinatal stress, and others may be associated with ADHD (5).

Anesthesia is a state of unconsciousness and painlessness required for unpleasant invasive therapeutic or diagnostic procedures, and general anesthesia is a common anesthesia method for inhibiting the function of the central nervous system. Exposure to a neurotoxic agent, such as anesthetics, could be one of the environmental factors of ADHD. Currently, many studies have reported a relationship between anesthetic exposure and neurodevelopmental outcomes (including language and learning abilities, cognition, behavioral development, and academic performance) in children (6, 7), which implies that the exposure to general anesthesia may increase the risk of ADHD.

TABLE 1 | Summary of included studies.

References	Design type	Country	Birth year	Age of GA exposure	Number of GA exposure
Sprung et al. (11)	Retrospective cohort study	Rochester	1976–1982	Before age 2	0 (<i>n</i> = 4,156) 1 (<i>n</i> = 226) ≥2 (<i>n</i> = 43)
Ko et al. (10)	Retrospective matched-cohort study	Taiwan	2001–2005	Before age 3	0 (<i>n</i> = 13,172) 1 (<i>n</i> = 2,019) ≥2 (<i>n</i> = 1,274)
Hu et al. (9)	Retrospective cohort study	Olmsted County, Minnesota	1996–2000	Before age 3	0 (<i>n</i> = 463) 1 (<i>n</i> = 457) ≥2 (<i>n</i> = 116)
Tsai et al. (12)	Retrospective cohort study	Taiwan	1997–1999	Before age 3	0 (<i>n</i> = 3438) 1 (<i>n</i> = 804) ≥2 (<i>n</i> = 342)

GA, general anesthesia.

To our knowledge, there is no consensus on whether single or multiple exposures to general anesthesia increases subsequent risk of ADHD for young children before the age of 3. Therefore, we performed this meta-analysis to elucidate the effect of single or multiple exposure(s) to general anesthesia on subsequent diagnosis of ADHD for children before the age of 3, and then provide guidance for pediatric practitioners taking care of young children undergoing surgical procedures with general anesthesia at an early age.

METHODS

Data Sources and Search Strategy

We conducted the meta-analysis according to MOOSE (Meta-Analysis Of Observational Studies in Epidemiology: a proposal for reporting) guidelines. We have searched the following databases (inception to April 2021): PubMed, Embase, Web of Science, and the Cochrane Register of Controlled Trials. The search strategy was specific for each database by using the following search terms: [(including the keyword “anesthesia” or a MeSH search using “General anesthetics”) and (including keyword “pediatric” or “child” or “children” or “newborns” or “neonate” or “young”) and (including a MeSH search “attention-deficit/hyperactivity disorder”)]. A manual search was also performed for relevant references from the selected articles and published reviews.

Study Selection

Related studies were included on the basis of the following criteria: (1) focused on the relationship between frequency of exposure to procedures requiring general anesthesia for children before the age of 3 and the subsequent risk of ADHD; (2) with sufficient available data to estimate the hazard ratio (HR) with 95% confidence intervals (CI). Only those studies published in the English language were included; we did not define the

minimum number of cases in studies to be included for meta-analysis.

Data Extraction

We obtained data about the general characteristics (study design, country) and patient characteristics (birth, the age of exposure to general anesthesia) from studies. Times of exposure to general anesthesia and the risk of ADHD for children was also extracted as a major outcome (Table 1). All articles were examined independently for eligibility by two reviewers (SJJ, LHF). Disagreements were resolved by consultation with a third reviewer (NCG).

Statistical Analysis

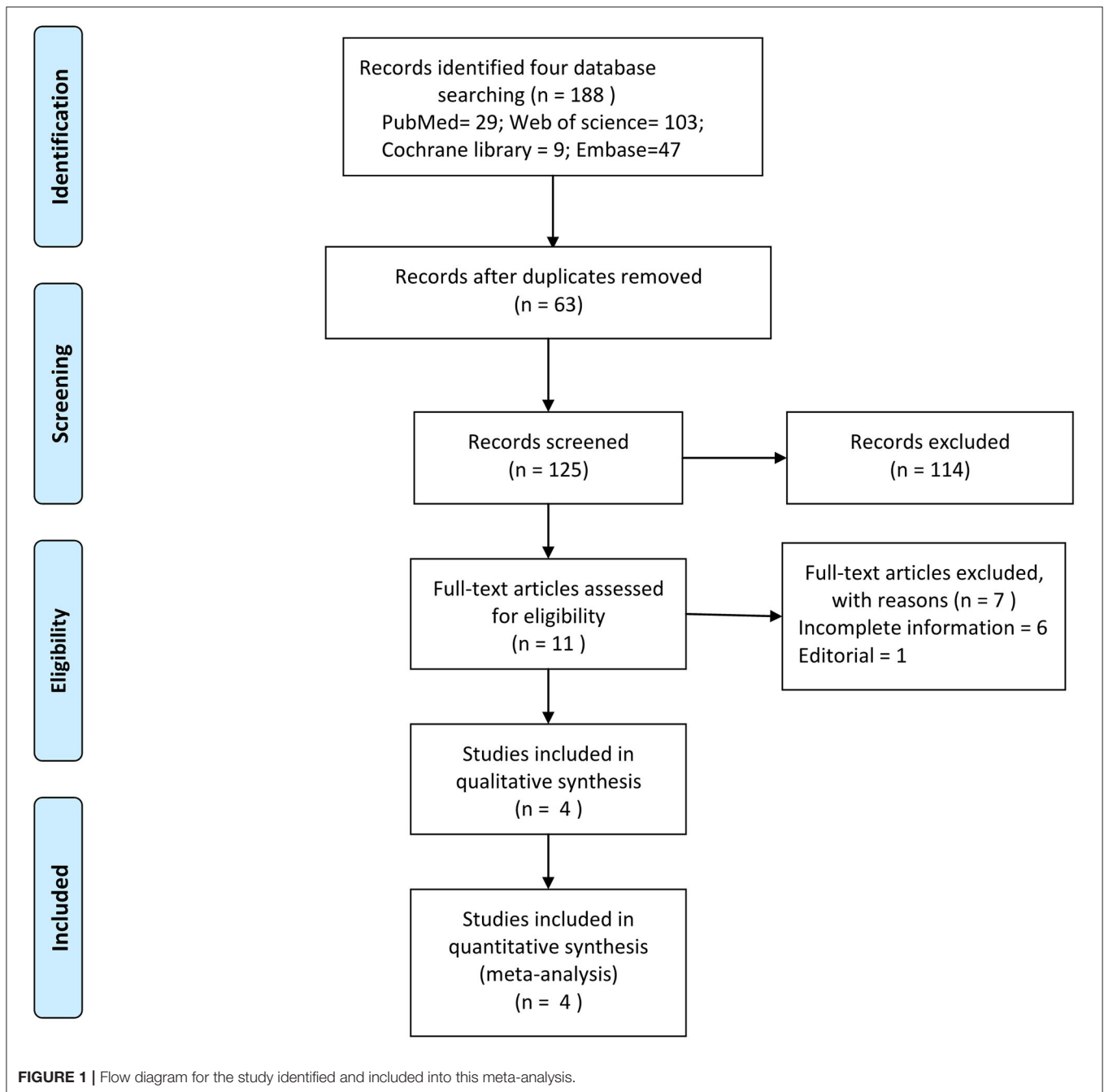
We performed statistical analyses with Review Manager (RevMan 5.3, Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark). For each study, HR was retrieved to estimate the association between the times of anesthesia exposure and the risk of ADHD. The combined HRs and their 95% CI were considered as the effect sizes for calculating the merged results. Using Cochrane-based I^2 -test (8), heterogeneity test was performed for the studies. When there was a significant heterogeneity among the studies ($I^2 > 50\%$), the random effects model was applied. On the contrary, the fixed effects model was used when homogeneous outcomes were obtained ($I^2 < 50\%$). Results were considered as statistically significant for $p < 0.05$.

RESULTS

Description of Included Studies

The flow diagram of study selection is shown in Figure 1. By the search strategy, 188 records were obtained, including 29 articles in PubMed, 103 articles in Web of Science, 47 articles in Embase, and 9 articles in the Cochrane Library database (from 1950 to April 2021). After removing 63 repeated records, 125 records remained. Then 114 records were excluded after browsing the title and reading the abstract. Furthermore, 11 records were screened out following the full-text reading. After reviewing the full-text of all possibly eligible articles, four eligible studies were

Abbreviations: ADHD, attention-deficit hyperactivity disorder; HR, hazard ratio; CI, confidence intervals.



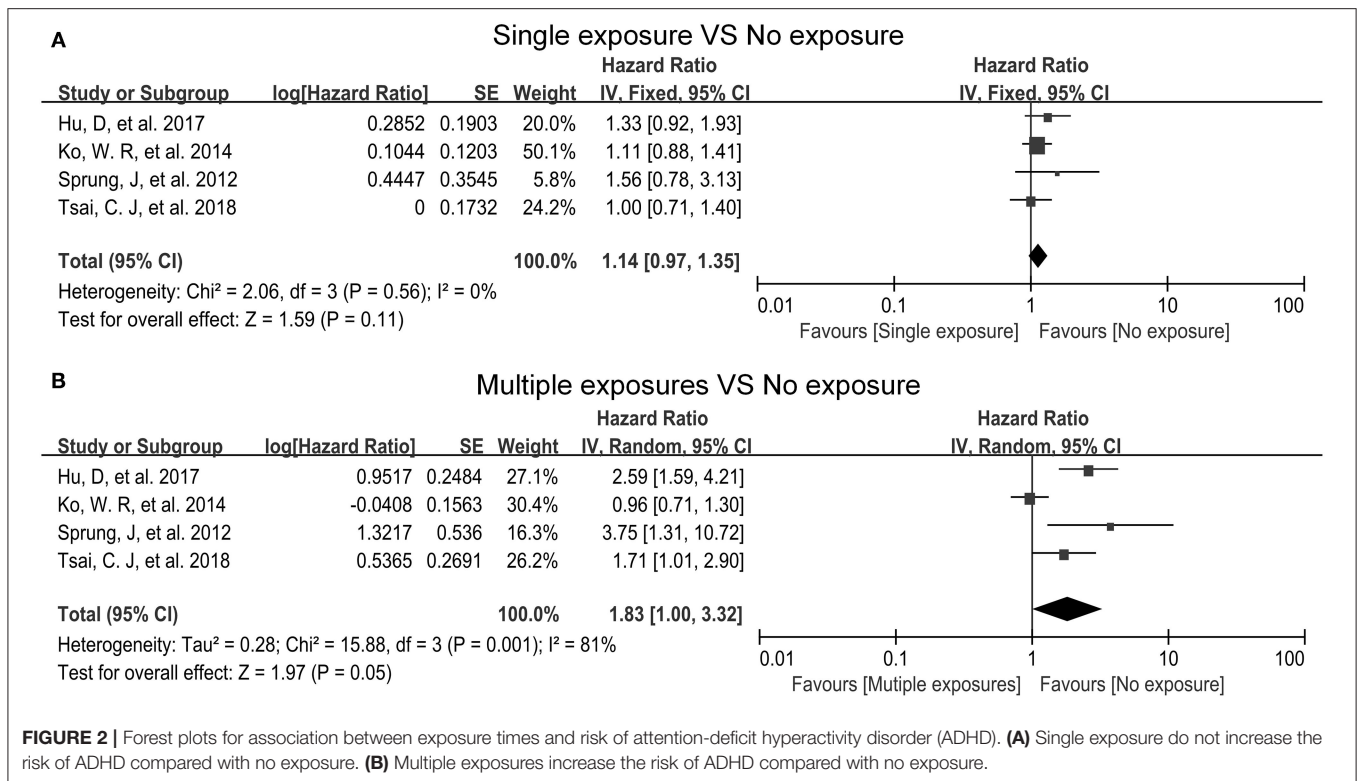
selected for the present meta-analysis (9–12). A detailed flow for the study inclusion is shown in **Figure 1**.

A total of 26,510 children were included, among which, 3,506 children had experienced single anesthesia, and 1,775 children had experienced multiple exposure to anesthesia due to surgery procedures before the age of 3. Of the four included studies, one was conducted in Olmsted County, Minnesota, USA (9), two in Taiwan, China (10, 12), and one in Rochester, MN, USA (11). Three studies reported the time length of the total duration of anesthesia exposure (9, 11). One study excluded children with learning disabilities (11). One study relied on the documentation

within medical and school records of ADHD diagnoses and questionnaires to identify the ADHD (9), and the other two papers utilized ICD-9-CM (10, 12) and DSM-IV (11).

Outcome Analysis

All articles reported the adjusted HR for the association between the times of exposure to general anesthesia and the risk of ADHD. Data in the study of Hu were adjusted for sex, birth weight, gestational age, mother's education, and socioeconomic status (9). Data in the study of Ko were adjusted for place of residence, parental occupation, perinatal conditions, and



congenital anomalies (10). Data in the study of Sprung were adjusted for sex, birth weight, and gestational age (11). Data in the study of Tsai were adjusted for gestation age, sex, living area, parental economic status, parental occupation, and comorbid health condition (12).

Because there was no significant heterogeneity ($I^2 = 0.0\%$), a fixed-effects model was used to combine adjusted HRs of single exposure vs. no exposure. As shown in **Figure 2A**, single exposure was not significantly associated with an increased risk of ADHD [HR = 1.14, 95% = (0.97–1.35), $p = 0.11$].

Because there was significant heterogeneity ($I^2 = 81\%$), a random-effects model was used to combine adjusted HRs of multiple exposures vs. no exposure. As shown in **Figure 2B**, multiple exposures did associate with an increased risk of ADHD [HR = 1.83, 95% CI = (1.00–3.32), $P = 0.05$].

DISCUSSION

To our knowledge, this is the first meta-analysis to reveal the relationship between the frequency of exposure to general anesthesia and the risk of ADHD in children before age of 3. The major finding of our meta-analysis was that single exposure to general anesthesia might not be responsible for ADHD in children before the age of 3, but multiple exposures to general anesthesia could increase the risk of ADHD in children before the age of 3 (**Figure 2**).

Though this meta-analysis shows that there is no significant difference of subsequent ADHD risk between none and single anesthesia, some proximate studies display an inconsistent

statistical result. A matched study showed that children who undergo single minor surgery requiring anesthesia under the age of 5 had a small significantly increased risk of ADHD diagnoses (13). Another twin study found that ADHD was slightly associated with single anesthesia under 0–12 years (14). Superficially, it seems that the above researches challenge the result from this meta-analysis, but in truth, their data are in accordance with ours, because their HR values are similar with ours. Besides, the study design and population age in the above researches are different from the included studies, so there is conflict even if the risks of ADHD caused by anesthesia were varied.

Compared with no general anesthesia, multiple general anesthesia increased the risk of ADHD, and the HR is up to 1.83 with a statistical significance. We think one of the possible reasons for this result is the total duration of anesthesia exposure and the total usage amount of anesthesia agent. Children receiving multiple general anesthesia may suffer a long total duration of exposure and thereby take more anesthetic. Relevant studies have revealed that exposing to general anesthesia agents would duration-dependently and dosage-dependently increase the risk of neurodevelopmental deficit (15, 16). In addition, repeated use of inhalation anesthetics, such as sevoflurane, in multiple general anesthesia, may be one reason for increasing the risk of ADHD. Several experiments demonstrated that single exposure to sevoflurane could not cause significant neuronal apoptosis or long-term neurocognitive impairment (17, 18), but when sevoflurane was used again, the mitochondrial apoptotic pathways would be activated, causing significant apoptosis of

hippocampal neurons that is vital for learning and memory (17, 18). Impaired hippocampal function may then increase the risk of ADHD.

In this meta-analysis, we have chosen the children who were exposed before the age of 3 years as the study population. In general speaking, the age of 3 years was used frequently as a definition of early life (19, 20). The period of synaptogenesis has been considered to extend through the age of 3 years in humans (21), and the period from birth to the age of 2–4 years is suspected to be the period of brain vulnerability. Besides, we have noticed a warning of the U.S. Food and Drug Administration (FDA). The warning informed that repeated or lengthy use of general anesthetics during surgeries or procedures in children younger than 3 years may affect the development of the brains of children (22).

Significant heterogeneity was detected among HRs of multiple exposures to general anesthesia vs. no exposure in this meta-analysis. By sensitivity analysis, we found that heterogeneity disappeared when the study of Ko was excluded (10). In the study of Ko, the sample size was relatively big, with a total of 16,465 samples; therefore, a smaller standard error of HR was exhibited. In addition, the study is a matched cohort, and its HR was not adjusted for gender, age, and weight because it was not necessary; however, the other three studies are independent cohorts, and their HRs were adjusted for the above factors. So we speculate all these may cause its HR and standard error to be different from the others.

The major limitation of this meta-analysis is that all studies included were observational retrospective studies due to the lack of randomized controlled study. The observational cohort studies are inherently biased on selection and confounding, though these do provide real-world results. The other limitation is that children who require anesthesia might differ in healthy

status from those who do not. Beyond that, children receiving anesthesia also experienced surgery or other procedures at the same time, and it is possible that the factors associated with the surgery or procedure could be the risk factor of ADHD. Consequently, we were not able to distinguish the effect of anesthesia by itself on ADHD from the potential effect of the surgery or procedure.

In summary, multiple exposures, but not single, to general anesthesia before the age of 3 increased later risk of ADHD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

JS conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. HL carried out the initial analyses, and reviewed and revised the manuscript. YW and CN conceptualized and designed the study, coordinated and supervised the data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

FUNDING

This study was supported by the Henan Provincial Science and Technology Department (No. 142300410129), Henan Provincial Education Department (No. 19A320021), and National Natural Science Foundation of China (Nos. 81800395 and 81600940).

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