RISK OF ADHD DEVELOPMENT FOLLOWING MULTIPLE EXPOSURES TO GENERAL ANESTHESIA IN THE PEDIATRIC POPULATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

Megan Skakum, PA-S2, B.Sc.(Maj.)

7786532
skakumm@myumanitoba.ca

Mentors: Dr. Kelly Russell, Dr. Florencia Ricci

A capstone project submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements for the degree of MASTER OF PHYSICIAN ASSISTANT STUDIES

PAEP7350 Capstone Project
Master of Physician Assistant Studies
University of Manitoba, Winnipeg

Table of Contents. Page

Abstract:
Introduction: The risk of attention deficit hyperactivity disorder (ADHD) following multiple exposures to anesthesia has been debated in recent literature. Our study aims to settle the conflict among currently published literature.
Methods: A systematic search of EMBASE, PubMed, SCOPUS, and clinicaltrials.gov was performed using the key search terms "anesthesia", "general anesthesia", "attention deficit disorder with hyperactivity", and "attention deficit disorder". Following two stages of screening effect estimates including hazard ratios (HR) and associated 95% confidence intervals (CI), percentage, and relative risk and associated 95% CI were extracted. Studies which did not report HR and 95% CI as their effect estimate were quantitatively analyzed separately. Studies which reported HR and 95% CI were pooled and a meta-analysis was performed. Hazard Ratio and 95% CI were calculated to determine if a relationship exists between multiple exposures to general anesthesia and ADHD diagnosis.
Results: Eight studies addressing ADHD diagnosis following multiple exposures to anesthesia met inclusion criteria. Five of the included studies reported HR and 95% CI so were pooled for meta-analysis. Three studies did not report HR and 95% CI so were quantitatively analyzed separately. Multiple exposures to anesthesia were found to be associated with diagnosis of ADHD before the 19th year of life (HR = 1.74 [95% CI = 1.62-1.87]).
Conclusion: This systematic review and meta-analysis demonstrates an association between multiple early exposures to general anesthesia and later diagnosis of ADHD.

Introduction:
Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by a persistent pattern of inattention accompanied by hyperactivity and/or impulsivity which significantly interfere with daily functioning or development.[1] ADHD has an estimated prevalence of 5% in children and adolescents; prevalence however has been increasing over the past decade in part due to increased awareness of the disorder and increased pediatric assessment.[1, 2, 3, 4, 5] Current research suggests the etiology of ADHD is multifactorial, stemming from genetic, epigenetic and environmental factors.[6, 7, 8, 9] Recent research has suggested anesthesia exposure at a young age may contribute to later development of ADHD.[4, 10, 11]

To our knowledge, there has not been a systematic review which has synthesized the current available literature as of February 2022 reporting on the risk of ADHD diagnosis in the previously healthy pediatric population following multiple exposures to general anesthesia. Therefore, this systematic review will evaluate the current primary research studies to determine the overall risk of diagnosis of ADHD by the end of the 18th year of life following multiple exposures to general anesthesia before the age of 5.

Background:
[ADHD]
The prevalence of ADHD in children and adolescents is roughly 5%.[1] ADHD is diagnosed as predominantly inattentive type, hyperactive-impulsive type, or combined type.[1] Recent research has found that up to 75% of individuals who receive a diagnosis of ADHD also receive a diagnosis of another comorbid psychiatric disorder such as conduct disorder, antisocial personality disorder, or substance use disorder, further exacerbating their challenges.[1,2] When untreated, ADHD alone is associated with functional impairment that often leads to a decreased

overall quality of life, with patients often struggling with interpersonal skills resulting in decreased social relationships throughout life.[2] As a result of the behavioural consequences of ADHD children often struggle in school, and are four times less likely to complete a post-secondary degree.[2] The prevalence of ADHD in adulthood decreases to about 2.5%.[1] Persistence to adulthood often results in major occupational and social influence. Occupation effects such as decreased job performance, job instability lead to increased prevalence of unemployment.[1] While impacts on social functioning and quality relationships present due to impulsive decision making in social and financial areas of life.[1] Therefore, ADHD can have detrimental effects on socioeconomic status of these individuals, and a lifelong struggle with adequate functioning in society.[1, 2]

The risk for developing various neurodevelopmental disorders, including ADHD, is multifactorial; this includes many genetic, epigenetic and environmental components.[6, 7, 8, 9] As the genetic and epigenetic factors are thought to be relatively unmodifiable, focusing on avoidable environmental and exposure risk factors may significantly decrease the risk of developing ADHD. Of particular interest in the last decade is the contribution of medical interventions, including general anesthesia, to the environmental risk of ADHD development.

[Neurodevelopment and Anesthesia]
Anesthesia is a commonly induced state of unconsciousness required when it is anticipated that painful, unpleasant or invasive procedures are required.[4,6] It is estimated that approximately 1 million pediatric surgeries and procedures under general anesthesia occur worldwide on an annual basis.[4, 12]

The most common anesthetic agents used in surgery and pediatric surgery are Gamma-aminobutyric acid (GABA) agonists such as propofol and most volatile or inhalational anesthetics agents (halothane, isoflurane, sevoflurane) and N-methyl- D -aspartate receptor (NMDA) antagonists such as ketamine and nitrous oxide.[13, 14] Both of which have been shown in animal studies to cause an increase in neuroapoptosis.[13,14]

Apoptosis is an important component of normal neurodevelopment which is responsible for the pruning of neurons which fail to develop properly or fail to develop over the appropriate time course [13, 14, 15] Many potential factors have been proposed as contributory to the enhancement of aberrant apoptosis including adverse clinical outcomes, pain (which is known to be neurotoxic to the developing brain), exposure to various toxins in utero and after birth, and exposure to general anesthetics in the first few years of life.[13] However, it has been postulated in recent literature that exposure to general anesthesia during this period of increased vulnerability can cause an increase in aberrant apoptosis during the critical period of neurodevelopment in animal models and humans.[13]

Xu et al. have demonstrated a connection between anesthesia exposure and aberrant neuroapoptosis in the prefrontal cortex, the brain region responsible for attention, impulse control and hyperactivity, leading to later functional deficiency in neurotransmission.[16] Adults with ADHD have been found to have abnormal growth and differentiation of dopaminergic neurons and altered neurotransmission of dopamine, NMDA, and brain derived neurotrophic factor.[16, 17, 18] These changes can be partially corrected through use of the common therapeutics methylphenidate and amphetamines.[16, 19] It has been shown that exposure to anesthetic agents such as ketamine which act on NMDA receptors in the prefrontal cortex disrupts the maturation of glutaminergic systems resulting in murine ADHD.[16, 20, 21, 22] These changes cause a shift in the relationship between excitatory and inhibitory neurological pathways in the mature brain, causing an increase in the excitatory pathways from baseline levels in adulthood.[16] Due to the multifactorial impacts of anesthetic agents on neurodevelopment, Xu proposed that general anesthetics have the potential to alter dopaminergic pathways if exposure occurs during the critical period of development, thus inducing ADHD.[16] The critical period for synaptogenesis in humans is thought to begin during the third trimester and peak at age 3, decreasing thereafter.[16, 23] Therefore, exposure to anesthetics during the period starting from the third trimester through age three may result in permanent neurostructural changes. While a proportion of these surgeries are life and limb saving, such as trauma surgeries, cardiac surgeries, and oncologic procedures, many could be delayed past the critical period of neurodevelopment, thought to start in the third trimester and taper off between the first 3-5 years of life.[13, 16, 23, 24]

[Previous research]

Given the proposed pathophysiological mechanisms of anaesthesia in early childhood and the potential to develop ADHD, several researchers have examined the effects of single exposures to general anesthetics.[10, 11, 14] Their findings have been discordant. Castellheim et al. conducted a twin cohort study in Sweden which studied twins discordant for anesthesia exposure and found that twins exposed to general anesthesia had higher scores of ADHD, even after adjusting for congenital abnormalities.[6]

More recent literature has focused on prolonged and multiple exposures to general anesthesia and the risk of subsequent diagnosis with ADHD. Sun et al.'s recent meta-analysis found a dose and duration dependent effect of anesthesia on the risk of ADHD diagnoses before age 19 in cohort study literature published before October 2020.[4] They did not include studies that were not cohort studies, including case-control studies. They conducted a secondary analysis for duration of anesthesia and number of doses of anesthesia but did not specifically look at the risk of only previously healthy children who underwent surgery and risk of ADHD diagnosis. They presented their pooled estimate as a relative risk, which does not incorporate time to diagnosis. Since this meta-analysis there has been additional literature published in the field. We will address the limitations of Sun's systematic review and meta-analysis by summarizing all of the literature available as of February 26 2022. Therefore, the aim of this study is to determine if multiple exposures as compared to no exposure to general anesthetic agents increase the risk of ADHD diagnosis.

Methods:

[Literature review and Set Up]

A systematic protocol was created before commencing the systematic review. A comprehensive literature for the history of research on this topic was conducted. A preliminary literature review was conducted reviewing literature available on MEDLINE, Embase, and PubMed. Search terms for the preliminary literature review were: "anesthesia," "general anesthesia," "attention deficit disorder with hyperactivity," and "attention deficit disorder." A formal systematic search was then done of PubMed, EMBASE, SCOPUS, and grey literature including clinicaltrials.gov. The search period was October 2021-February 2022, and study period was October 2021-May 2022. The search terms that were used for the formal systematic literature search were: "anesthetics," "anesthesia," "attention deficit disorder," "attention deficit disorder," "attention deficit disorder with hyperactivity," and "ADHD." Reference lists of included articles were screened for potential articles to include.

[Inclusion and Exclusion Criteria]
Inclusion and exclusion criteria were created (Table 1). Studies published from 1980 until February 2022 were eligible for inclusion, based on the publication of the DSM-IV which first included ADD/ADHD as an official diagnosis. Articles published in English which analyzed participants with two or more exposures to anesthesia before their 5th year of life and analyzed ADHD diagnoses before their 19th year of life were eligible for inclusion.

Table 1. Inclusion and Exclusion Criteria

	Inclusion	**Exclusion**
Date	Published between 1980 and 2022 (present)	Published before 1980
Exposure of Interest	Two or more exposures to GA before age 5 (birth-4 years and 11 months)	Less than 2 exposures (1 or none), exposure to anesthesia that is not classified as GA
Geographic	Worldwide	None
Peer Review	Peer reviewed articles	Non-peer reviewed
Study designs	Case control studies, cohort studies, longitudinal/prospective/retrospective (all forms of primary research)	Secondary research/non primary research
Language	English	Any language that is not English
Participant Characteristics	Human, Exposure under age 5, otherwise healthy children, diagnosis with ADHD after exposure of interest and before age 18 (inclusive of the 18th year)	Non-human, Not otherwise healthy children, exposure after age 5, exposures before birth, diagnosis of ADHD before exposure, diagnosis after age 18
Reported outcome of interest	Diagnosis of ADHD by professional	Self-diagnosis of ADHD, questionnaire, parental opinion

[Screening: Title and abstract, full text screening]
Articles from the search were imported into Mendeley desktop reference management system for deduplication. Following deduplication in Mendeley desktop, articles were imported into COVIDENCE, where deduplication was automatically performed again, and assigned a numerical code number. COVIDENCE was used to screen articles for inclusion by two independent reviewers. Articles were first screened by two reviewers applying the inclusion and exclusion criteria to the title and abstract the when available. Articles which did not meet exclusion criteria from title and abstract screening were entered into full text screening. Two reviewers performed full text screening using inclusion and exclusion criteria. Articles were

excluded if they failed to meet all of the inclusion criteria. Disagreements were settled by communication between two reviewers based on inclusion criteria.

[Data Extraction]
Articles which met all the inclusion criteria were extracted by one reviewer using a predetermined excel spreadsheet table. Data extracted was based on the population, intervention, control, outcomes (PICO) framework for this systematic review. These included author(s), date published, date of study conduction, location of study, report type, population (number eligible, number recruited, number excluded, number analyzed in both experimental and control groups, age of participants, sex of participants), reason for surgery, intervention (if available: anesthetic agents used, duration of general anesthetic, control intervention), outcomes (primary outcomes, secondary outcomes if any, and method of ADHD diagnosis), funding type (if reported), statistical analysis (available effect estimate, variance). If any data was not available in published manuscript, supplemental information documents were used to obtain desired data.

[Quality of Included Papers]
The National Institute of Health quality assessment tools for observational cohort studies and cross-sectional studies were used to determine the methodological quality of the included studies.[25] These tools use the following parameters to determine quality of cohort studies: research question or objective, population (definition and selection, eligibility and inclusion, location of individuals, time period of recruitment, sample size justification), analysis and exposures (time of measurement of exposures, sufficient time between exposure and analysis, different categories of exposure duration, defined and consistently applied exposures), outcomes (defined, valid, reliable, consistent measurement and assessment), binding of assessors, loss to

follow up, and assessment of confounding variables. Quality of included studies was assessed by one reviewer only.

[Data and Statistical Analysis]
As initial inclusion and exclusion criteria did not specify method of statistical analysis, comparison between the articles selected for inclusion was done for ability to combine into a meta-analysis. Articles which used a hazard ratio and the associated 95% confidence interval were pooled for the meta-analysis. Articles which did not report a hazard ratio with associated 95% confidence interval were unable to be combined in meta-analysis were analyzed separately in a quantitative comparison to the results of the meta-analysis.

Data was analyzed using Review Manager (RevMan) software.[26] Individual hazard ratios and 95% confidence intervals were pooled using an inverse-variance method with fixed effect meta-analysis. A test of statistical heterogeneity was calculated using an I^2 value. Assessment of heterogeneity within the study pool based on I^2 values is as follow: 75-100% represents considerable amounts of heterogeneity; 50-90% represents substantial heterogeneity; 30-60% represents moderate heterogeneity; 0-40% represents possible heterogeneity that may not be important to the quality of the results.[27] Outlier assessment was performed using sensitivity and heterogeneity assessments. A sensitivity analysis was performed excluding one study at a time from the pooled data to monitor heterogeneity. As per the Cochrane training manual the fixed-effects model is acceptable for use in meta-analyses in which all effect estimates from included studies are estimating the same intervention effect.[27] The inverse-variance method is ideal for minimizing the lack of precision of smaller studies when pooling the effect estimate by using a weighted approach.[27] A P-value of <0.05 was considered statistically significant.

Results
[Literature search]
A total of 394 articles were found for inclusion after the initial search. After deduplication 277 articles remained to be screened for inclusion. Figure 1 displays the number of articles included and excluded at each stage. Forty-nine articles were selected for full text screening, 8 articles met the inclusion criteria for the systematic review. Subsequently 5 articles were included in the meta-analysis.

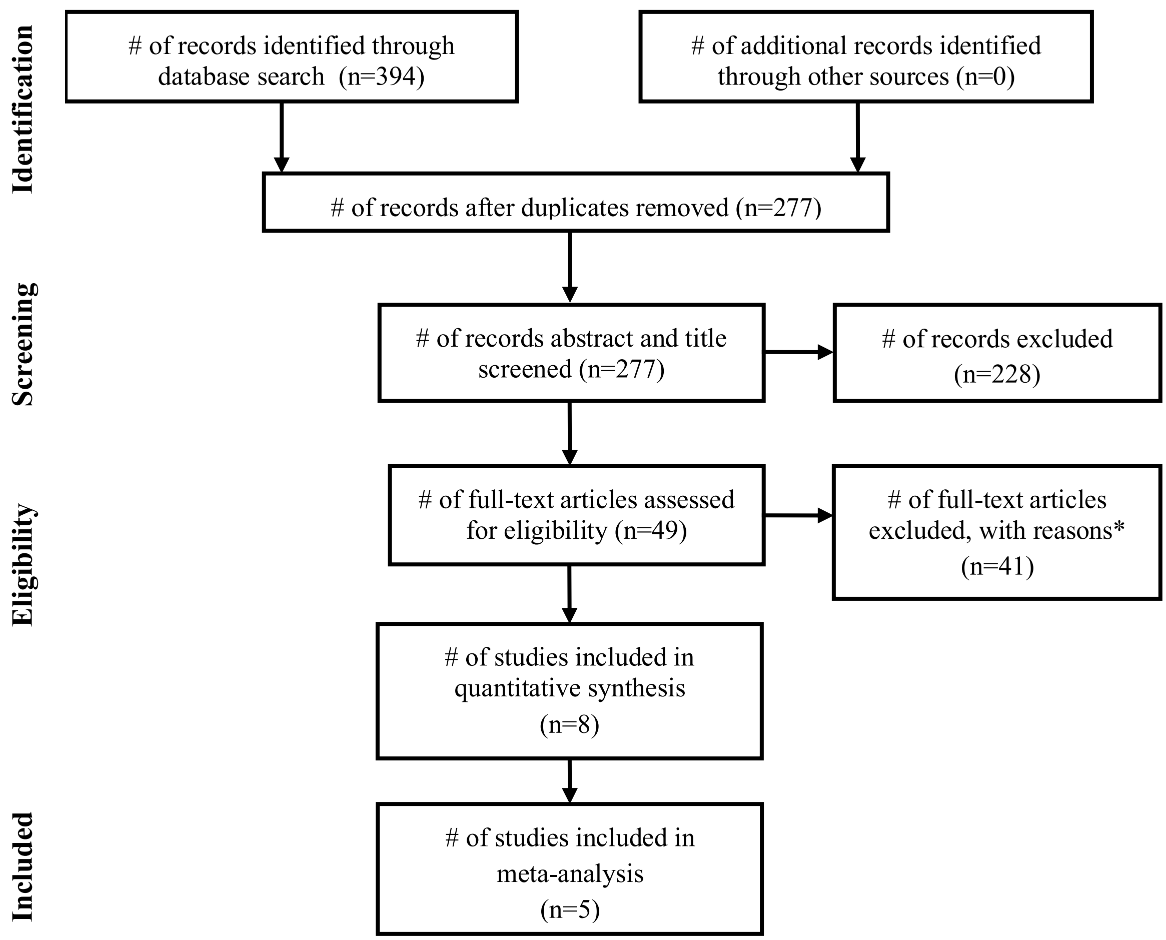

Figure 1. PRISMA flow diagram of articles included and excluded for meta-analysis.
*Reasons for exclusion include unavailable full text, wrong population, wrong intervention, wrong outcomes, and wrong study design.

[Description of included studies]
The earliest study included was published in 2012 and the most recent in 2021. Three studies were conducted in the United States, two were conducted in Taiwan, one each conducted in Iran, Korea, and Egypt. The earliest birth cohort was born 1976-1982 and the most recent was born 2006-2012. The age of exposure spanned from birth to 2 years of age to birth to 5 years of age. The sample size analyzing multiply exposed participants and their control groups spanned from 1020 to 154,751 participants. All studies analyzed multiple exposures defined as 2 or more procedures or surgeries requiring general anesthesia exposures. Types of surgeries reported were orthopedic procedures, abdominal and general surgical procedures (hernias and bowel procedures), plastic surgeries (cleft lip and palate, polydactyly, syndactyly, burn grafts), urologic procedures (circumcision, penile hypospadias), otorhinolaryngolic procedures, dental and oral procedures and surgeries, diagnostic procedures (Computed topography scans and magnetic resonance imaging scans). Number of general anesthesia exposures was determined via medical record ICD codes for general anesthesia occurring two or more times in the medical record of the participant. The most common anesthetic agents reported were opiates, midazolam, sevoflurane, halothane, isoflurane, and nitrous oxide. Diagnosis of ADHD was identified by medical record of diagnosis including written diagnosis or ICD-9 code inclusion in medical or insurance records. Method of ADHD diagnosis was via health professional (neurologist, psychiatrist, pediatrician) application of DSM-IV criteria for ADHD. In all included studies, participants were excluded if they obtained an ADHD diagnosis before anesthesia exposure. Table 2 displays the characteristics of the studies included in meta-analysis. Characteristics on the 3 studies not included in meta-analysis is reported in table 3.

[Methodological quality of included studies]

The NIH quality assessment tool revealed that all papers included in meta-analysis were of at least fair quality, with 4 of 5 selected papers achieving good quality (Table 2). The NIH quality assessment tool revealed that the remaining 3 papers included in non-meta-analysis quantitative analysis were at least of fair quality (Table 3). Notably, data pertaining to the previously healthy population from Hu et al., 2017 was obtained from supplemental information documents.[28] All other studies presented their primary data on previously healthy participants in their full manuscript.

Table 2. Articles included in meta-analysis.

Author(s), year	**Location of study**	**Study design**	**Study period**	**Birth year range**	**Age at exposure**	****Participants**	**Nature of ADHD assessment**	**Reported Effect Estimate**	**Quality rating (NIH)**
***Hu et al., 2017[28]**	United States	Cohort	1996-2014	1996-2000	<3 years	Exposed:106 Unexposed:914	DSM-IV criteria, school and ***medical records	HR, 95% CI	good
Ko et al., 2014[29]	Taiwan	Cohort	2001-2010	2001-2005	<3 years	Exposed: 1274 Unexposed:13172	Child Psychiatrist, neurologist, pediatrician diagnosis	HR, 95% CI	fair
Shi et al., 2021[30]	United States	Cohort	2006-2018	2006-2012	<5 years	Exposed: 16228 Unexposed:138523	Medical records	HR, 95% CI	good
Sprung et al., 2012[31]	United States	Cohort	1976-2012	1976-1982	<2 years	Exposed: 64 Unexposed: 5007	DSM-IV criteria	HR, 95% CI	good
Tsai et al., 2018[32]	Taiwan	Cohort	2000-2009	1997-1999	<4 years	Exposed: 342 Unexposed: 3438	Medical records	HR, 95% CI	good

*raw data for Hu et al., excluding participants with neurological or cardiovascular surgeries; **exposed = multiple exposures, unexposed = no exposures

***medical records = ICD-9 codes

DSM-IV, Diagnostics and Statistical Manual of Mental Disorders 5th edition

HR = hazard ratio, 95% CI = 95% confidence interval

Table 3. Articles included in narrative review

Author	**Location**	**Study Design**	**Study Period**	**Age at exposure**	***Participants**	**Nature of ADHD assessment**	**Reported Effect Estimate**	**Quality**
Sedighnejad et al, 2020[33]	Iran	Case-Control	February-July 2019	NR	Exposed = 3.8% unexposed = 96.2%	Pediatric psychiatrist, pediatrician, pediatric neurologist	NR	Good
Ahn et al., 2020[34]	Korea	Cohort	2008-2020	<3 years	Exposed = 265 unexposed=17136	ICD-9 code F90 for ADHD diagnosis	Percentage	Fair
Bakri et al., 2015[35]	Egypt	Case-Control	April-June 2015	1.5-5 years	Exposed = 35 unexposed = 35	DSM-IV criteria applied by resident physicians for ADHD diagnosis	RR, 95% CI	Fair

NR = not reported; RR = relative risk; 95% CI = 95% confidence interval

*exposed = multiple exposures, unexposed = no exposures

[Meta-analysis]

Meta-analysis of these five articles deemed appropriate for the meta-analysis showed that multiple exposures before age 5 in previously healthy pediatric patients was associated with a statistically significant increased risk of ADHD diagnoses before the end of the 18th year of life (HR = 1.74; [95% CI:1.01, 2.98]; $p < 0.05$). The outlier assessment showed that the HR varied from 1.65 [95% CI: 1.35,2.02] to 1.78 [95% CI: 1.65,1.92]. Pooled data showed significant heterogeneity (I^2=62%; Figure 2); excluding Ko et al., 2014 after individual study exclusion assessment yielded the greatest decrease in heterogeneity (I^2=36%; Figure 3). While Ko et al., 2014 shows the most deviation in heterogeneity when excluded, the pooled HR with inclusion and exclusion both remain statistically significant (HR with inclusion = 1.74 [95% CI:1.62,1.87], HR with exclusion = 1.78 [95% CI:1.65,1.92]).

A

Study or Subgroup	log[Hazard Ratio]	SE	Exposed Total	Non-Exposed Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Hu, 2017	0.9858	0.2322	106	463	2.5%	2.68 [1.70, 4.22]
Ko, 2014	0.2311	0.1387	1274	13174	7.0%	1.26 [0.96, 1.65]
Shi, 2021	0.5596	0.0394	16228	138523	87.3%	1.75 [1.62, 1.89]
Sprung, 2012	0.9517	0.3212	64	5007	1.3%	2.59 [1.38, 4.86]
Tsai, 2018	0.5365	0.2686	342	3438	1.9%	1.71 [1.01, 2.89]
Total (95% CI)			**18014**	**160605**	**100.0%**	**1.74 [1.62, 1.87]**

Heterogeneity: $Chi^2 = 10.43$, df = 4 (P = 0.03); $I^2 = 62\%$
Test for overall effect: Z = 15.00 (P < 0.00001)

B

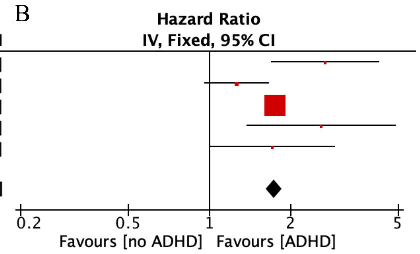

Figure 2. Results of meta-analysis. A. Tabulated results including hazard ratio, 95% confidence interval, and heterogeneity. B. Forest plot.

A

Study or Subgroup	log[Hazard Ratio]	SE	Exposed Total	Non-Exposed Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Hu, 2017	0.9858	0.2322	106	463	2.7%	2.68 [1.70, 4.22]
Ko, 2014	0.2311	0.1387	1274	13174	0.0%	1.26 [0.96, 1.65]
Shi, 2021	0.5596	0.0394	16228	138523	93.9%	1.75 [1.62, 1.89]
Sprung, 2012	0.9517	0.3212	64	5007	1.4%	2.59 [1.38, 4.86]
Tsai, 2018	0.5365	0.2686	342	3438	2.0%	1.71 [1.01, 2.89]
Total (95% CI)			**16740**	**147431**	**100.0%**	**1.78 [1.65, 1.92]**

Heterogeneity: $Chi^2 = 4.68$, df = 3 (P = 0.20); $I^2 = 36\%$
Test for overall effect: Z = 15.09 (P < 0.00001)

B

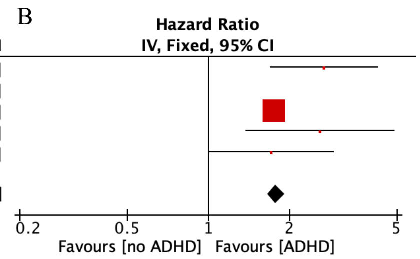

Figure 3. Results of meta-analysis excluding Ko et al., 2014. A. tabulated results including hazard ratio, 95% confidence interval, and heterogeneity. B. Forest plot.

[Results of studies not included in the meta-analysis]
The case-control study of 210 children by Sedighnejad et al. reported a significant association between multiple exposures to general anesthesia and diagnosis of ADHD (p=0.001).[33] They failed to report an effect estimate and variance for this outcome. The cohort study by Ahn et al. reported no significant association between two or more exposures to general anesthesia and diagnosis of ADHD before school age (p=0.59).[34] They found that 2.00% of children with multiple exposures were diagnosed with ADHD, while only 1.03% of participants with no exposure to general anesthesia were diagnosed with ADHD. The case-control study by Bakri et al. found that repeated general anesthesia in children aged 1.5-5 years demonstrated associated increased risk of ADHD diagnosis (RR=3.00 [95% CI: 1.1-8.4]).[35]

Discussion
To our knowledge this is the first systematic review and meta-analysis to specifically look at the healthy pediatric population excluding cardiovascular and neurological genetic and congenital abnormalities. Our study shows an increased risk of ADHD diagnoses before the 19th year of life associated with multiple general anesthesia exposures before the 5th year of life. Pooling the effect estimates provides a larger sample size and allows an increase in the power of the results, and can settle controversies from conflicting results among available individual studies.[36] This meta-analysis allows a more precise representation of the potential risk of ADHD diagnosis following multiple exposures to general anesthesia.[36] This is a consistent finding with the majority of the available literature that suggests multiple exposures to anesthesia at a young age has a greater impact than a single exposure to general anesthesia, as explained through a 'multiple hit' phenomenon. This is a common phenomenon seen in genetic disorders such as non-alcoholic fatty liver disease, cancers, developmental disorders.[37] The multiple hit phenomenon suggests that one exposure to an environmental toxin or influence may not have

enough influence to cause long term effects while multiple exposures can have an additive effect producing non-recoverable long terms changes.[37] Current research has not shown a convincing association of a single anesthetic exposure with an increased risk of ADHD in later life.[5, 10] Flick et al., 2011 addressed exposure (single or multiple occurrences) and association with ADHD and reported multiple exposures to anesthesia and/or surgery during early life could not be excluded from having long term consequences on neurodevelopment.[38] Following Flick et al., multiple studies have found significant association between multiple anesthesia exposures and diagnosis of ADHD.[28, 30, 31, 32, 33] Therefore, it is plausible that this multiple hit phenomenon can be used to explain these findings concerning multiple exposures showing a significant correlation with increased risk of ADHD diagnosis.

This study builds on the work by Warner et al., Hakånson et al., and Flick et al. by addressing the effects of multiple exposures to general anesthesia as compared to no exposures. One study included in this systematic review, Sedighnejad et al., 2020, showed statistically significant associations between multiple exposures to general anesthesia and later diagnosis with ADHD.[33] Conversely, Ahn et al., 2020, Ko et al., 2014 and Bakri et al., 2015 did not show association between multiple exposures to GA and later diagnosis with ADHD.[29, 34, 35] In these articles potential confounding factors could have played a role in their varying results. In both Ko et al. and Ahn et al. the follow up time was significantly shorter than the other studies.[29, 34] This allowed potential for diagnosis of ADHD in participants to be missed. In Bakri et al., 2015, the sample size was considerably smaller than other studies of its kind, including only 70 participants (35 in both case and control groups).[35]

According to the National Institute of Mental Health the average age for ADHD diagnosis is 6 years old which suggests that an appropriate period to follow children for diagnosis of ADHD should exceed this time frame.[39] The follow up period used in Ko et al. would not allow for a portion of participants to reach their 6th year of life during follow up, potentially increasing the false negative rate.[29] Sensitivity analysis of the included studies showed no change to clinical significance whether Ko et al. was included or excluded from calculations. However, between-study heterogeneity could be accounted for in part by the study duration. It is plausible that the ability of anesthetic drugs to enhance apoptosis during the critical period of neurodevelopment has only a significant and long-lasting effect after multiple attacks to the process of dendritic formation.

For many years it has been postulated and studied through animal studies that exposure to general anesthetics during the critical period of neurodevelopment can increase risk of development of neurodevelopmental aberrancies, learning disorders, and errors in memory, focus and attention.[4, 40, 41, 42] Many of these studies have proven that during the critical period of brain development, the brain is susceptible to the anesthetic drugs commonly used for general anesthesia resulting in structural neurological changes such as apoptosis, pathological neurogenesis, and abnormal or lost dendritic function and formation.[6, 43, 44] Pre-clinical research has shown that while apoptosis is a key component of regular neurodevelopment, the commonly used anesthetics such as ketamine and propofol can trigger both intrinsic and extrinsic pathways of apoptosis resulting in aberrant apoptosis.[14]

[Limitations]
While the results from this meta-analysis were significant and consistent with two of the included articles not included in the meta-analysis, there are limitations to be mentioned in this study. Firstly, given the limited number of studies included in the systematic review (n=8) and meta-analysis (n=5), there is a risk of sampling bias. While this risk is small as there were two reviewers involved in creating search terms and carrying out the search, as well as two reviewers involved in each screening stage. The area of most concern for sampling bias is the language of publication as there are possible studies published only in another language. A large portion of the data included in the meta-analysis was obtained from studies completed in the United States and Taiwan. Therefore, the generalizability of these results without recognition of confounding cultural, language, and location specific factors should be approached with caution. Secondly, all studies included were retrospective cohort studies which have their own increased bias to detection, and unaccounted confounding variables. Thirdly, the anesthetic medications used in all participants of each included article were not available therefore no analysis on particular anesthetic agents could be performed. Fourthly, the nature of the studies included relies on patients being formally diagnosed with ADHD by a healthcare professional. This means that children who may have developed ADHD but were not diagnosed were not included in the risk calculation. Fifthly, limitations of this study's conduction were such that two reviewers were used for primary and secondary screening for inclusion of papers. However, only one reviewer performed data extraction, methodological quality assessment, and analysis.

[Future clinical considerations]
Given the persistent nature of an association between exposure to general anesthesia during the critical period of brain development and the later diagnosis of ADHD, other anesthetic options could be considered more strongly in future. Anesthetic options such as using non-inhalational

agents when possible, using local and spinal blocks and anesthetics could aid in reducing the systemic effects of these anesthetic agents and their associated neurodevelopmental effects. However, the occurrence of administering regional anesthetics alone in the pediatric population is low.

Additionally, if multiple surgeries are going to be required for a pediatric patient, perhaps performing the medically urgent or emergent surgeries during the critical phase of neurodevelopment and then postponing subsequent procedures until after the critical period could lessen the risk of ADHD developing.

Effects of these findings could be eased with early intervention to decrease the effects of other contributing risk factors to the development of ADHD as well as providing early access to resources for management of ADHD in these children to ease the effects of ADHD on their quality of life starting from a young age.

[Future research considerations]

Future research considerations include but are not limited to a larger study looking at the difference between purely inhalational versus IV administration of general anesthetics in the pediatric population (both of which are standard of care in North America) and following patients for 10 years or more for development and diagnosis of ADHD, a randomized control trial looking at the risk of ADHD diagnosis associated with regional only anesthesia, randomized control trials for use of adjunct medications to anesthesia such as melatonin, dexmedetomidine, and hypotension. Particularly looking at the diagnosis of ADHD.

There has been some research concerning use of adjunct treatments during administration of anesthesia which could potentially mitigate the association suggested by our findings. Firstly, it has been suggested that the use of reducing agents such as melatonin during surgery requiring general anesthetic.[13, 14] Melatonin has been found to play a role in stabilizing the mitochondrial membrane, which could reduce the effects of aberrant apoptosis.[13] Hypothermia has been shown to reduce the occurrence of apoptosis in rat studies, suggesting possible use in human studies for reduction in amounts of apoptosis occurring during pediatric surgeries.[13] Dexmedetomidine can have sedative and analgesic effects and has shown potential as a neuroprotective agent in conjunction with isoflurane administration.[13]These adjuncts come with side effects and implications of their own, so further research is required in these areas. For instance, melatonin has been shown to decrease apoptosis in general, but does not target aberrant apoptosis which leaves potential for impact on the normal patterns of apoptosis during the synaptic pruning phase of neurodevelopment. Hypothermia has other physiologic effects and will require more thorough research for use in this application. Dexmedetomidine, although a promising candidate due to its sedative and analgesic effects may not be desirable in the pediatric population due to its ability to induce hypotension and bradycardia which is not well tolerated.[13]

Conclusion:

This study found a significant association among currently published studies between multiple exposures to anesthesia and later diagnosis of ADHD. Further research to determine a significant correlation should be done, while accounting for possible confounding factors. Additionally, investigations into different modes of anesthesia other than general anesthesia should be investigated for their risk as an environmental factor of ADHD development.

References:

1. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition: ADHD [Internet]. Psychiatry Online. 2013 [cited 15 May 2022]. Available from: https://dsm-psychiatryonline-org.uml.idm.oclc.org/doi/book/10.1176/appi.books.9780890425596

2. Banaschewski T, Becker K, Döpfner M, Holtmann M, Rösler M, Romanos M. Attention-Deficit/Hyperactivity Disorder. Deutsches Ärzteblatt international. 2017;(114):149-159.

3. Posner J, Polanczyk G, Sonuga-Barke E. Attention-deficit hyperactivity disorder. The Lancet. 2020;395(10222):450-462.

4. Sun J, Zhu C, Jiang H. Exposure to general anaesthesia in childhood and the subsequent risk of attention-deficit hyperactivity disorder: A meta-analysis of cohort studies. Asian Journal of Psychiatry. 2021;62(102708).

5. Arana Håkanson C, Fredriksson F, Engstrand Lilja H. Attention deficit hyperactivity disorder and educational level in adolescent and adult individuals after anesthesia and abdominal surgery during infancy. PLOS ONE. 2020;15(10):e0240891.

6. Castellheim A, Lundström S, Molin M, Kuja-Halkola R, Gillberg C, Gillberg C. The role of general anesthesia on traits of neurodevelopmental disorders in a Swedish cohort of twins. Journal of Child Psychology and Psychiatry. 2018;59(9):966-972.

7. Gardener H, Spiegelman D, Buka S. Perinatal and Neonatal Risk Factors for Autism: A Comprehensive Meta-analysis. Pediatrics. 2011;128(2):344-355.

8. Millan M. An epigenetic framework for neurodevelopmental disorders: From pathogenesis to potential therapy. Neuropharmacology. 2013;68:2-82.

9. Mitchell R, Goldstein B. Inflammation in Children and Adolescents With Neuropsychiatric Disorders: A Systematic Review. Journal of the American Academy of Child & Adolescent Psychiatry. 2014;53(3):274-296.

10. Warner D, Hu D, Zaccariello M, Schroeder D, Hanson A, Wilder R et al. Association Between Behavioral and Learning Outcomes and Single Exposures to Procedures Requiring General Anesthesia Before Age 3: Secondary Analysis of Data From Olmsted County, MN. Anesthesia & Analgesia. 2020;133(1):160-167.

11. Gleich S, Shi Y, Flick R, Zaccariello M, Schroeder D, Hanson A et al. Hypotension and adverse neurodevelopmental outcomes among children with multiple exposures to general anesthesia: Subanalysis of the Mayo Anesthesia Safety in Kids (MASK) Study. Pediatric Anesthesia. 2021;31(3):282-289.

12. Sun L. Early childhood general anaesthesia exposure and neurocognitive development. British Journal of Anaesthesia. 2010;105:i61-i68.

13. McCann M, Soriano S. General anesthetics in pediatric anesthesia: Influences on the developing brain. Current Drug Targets. 2012;13(7):944-951.

14. McCann M, Soriano S. Does general anesthesia affect neurodevelopment in infants and children?. BMJ. 2019;367:l6459.

15. Hays S, Deshpande J. Newly Postulated Neurodevelopmental Risks of Pediatric Anesthesia: Theories That Could Rock Our World. Journal of Urology. 2013;189(4):1222-1228.

16. Xu L, Hu Y, Huang L, Liu Y, Wang B, Xie L et al. The association between attention deficit hyperactivity disorder and general anaesthesia - a narrative review. Anaesthesia. 2019;74(1):57-63.

17. Huang J, Zhong Z, Wang M, Chen X, Tan Y, Zhang S et al. Circadian Modulation of Dopamine Levels and Dopaminergic Neuron Development Contributes to Attention Deficiency and Hyperactive Behavior. Journal of Neuroscience. 2015;35(6):2572-2587.

18. Arnsten A. Stimulants: Therapeutic Actions in ADHD. Neuropsychopharmacology. 2006;31(11):2376-2383.

19. Mitra'no D, Pare J, Smith Y, Weinshenker D. D1-dopamine and α1-adrenergic receptors co-localize in dendrites of the rat prefrontal cortex. Neuroscience. 2014;258:90-100.

20. Chang J, Lane H, Tsai G. Attention Deficit Hyperactivity Disorder and N-methyl-D-aspartate (NMDA) Dysregulation. Current Pharmaceutical Design. 2014;20(32):5180-5185.

21. Melo A, Leite-Almeida H, Ferreira C, Sousa N, Pêgo J. Exposure to Ketamine Anesthesia Affects Rat Impulsive Behavior. Frontiers in Behavioral Neuroscience. 2016;10:226.

22. Carli M, Invernizzi R. Serotoninergic and dopaminergic modulation of cortico-striatal circuit in executive and attention deficits induced by NMDA receptor hypofunction in the 5-choice serial reaction time task. Frontiers in Neural Circuits. 2014;8:58.

23. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. Nature Reviews Neuroscience. 2016;17(11):705-717.

24. Byrne M, Ascherman J, Casale P, Cowles R, Gallin P, Maxwell L. Elective Procedures and Anesthesia in Children. Journal of Neurosurgical Anesthesiology. 2012;24(4):396-400.

25. Study Quality Assessment Tools | NHLBI, NIH [Internet]. Nhlbi.nih.gov. 2022 [cited 15 May 2022]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

26. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.

27. Chapter 10: Analysing data and undertaking meta-analyses [Internet]. Training.cochrane.org. 2022 [cited 15 May 2022]. Available from: https://training.cochrane.org/handbook/current/chapter-10

28. Hu D, Flick R, Zaccariello M, Colligan R, Katusic S, Schroeder D et al. Association between Exposure of Young Children to Procedures Requiring General Anesthesia and Learning and Behavioral Outcomes in a Population-based Birth Cohort. Anesthesiology. 2017;127(2):227-240.

29. Ko W, Liaw Y, Huang J, Zhao D, Chang H, Ko P et al. Exposure to general anesthesia in early life and the risk of attention deficit/hyperactivity disorder development: a nationwide, retrospective matched-cohort study. Pediatric Anesthesia. 2014;24(7):741-748.

30. Shi Y, Dykhoff H, Guevara L, Sangaralingham L, Schroeder D, Flick R et al. Moderators of the association between attention-deficit/hyperactivity disorder and exposure to anaesthesia and surgery in children. British Journal of Anaesthesia. 2021;127(5):722-728.

31. Sprung J, Flick R, Katusic S, Colligan R, Barbaresi W, Bojanić K et al. Attention-Deficit/Hyperactivity Disorder After Early Exposure to Procedures Requiring General Anesthesia. Mayo Clinic Proceedings. 2012;87(2):120-129.

32. Tsai C, Lee C, Liang S, Tsai P, Chen V, Gossop M. Risk of ADHD After Multiple Exposures to General Anesthesia: A Nationwide Retrospective Cohort Study. Journal of Attention Disorders. 2015;22(3):229-239.

33. Sedighnejad A, Soltanipour S, Saberi A, Kousha M, Bidabadi E, Biazar G et al. Risk of Attention Deficit Hyper Activity Disorder After Early Exposure to General Anesthesia; A Case Control Study. Iranian Journal of Pediatrics. 2020;30(3).

34. Ahn E, Bang S. Exposure to general anesthesia before 4 years of age did not affect growth and development: A nationwide retrospective cohort study using an early childhood health screening database. International Journal of Surgery Open. 2020;25:47-51.

35. Bakri M, Ismail E, Ali M, Elsedfy G, Sayed T, Ibrahim A. Behavioral and emotional effects of repeated general anesthesia in young children. Saudi Journal of Anaesthesia. 2015;9(2):161.

36. Chapter 10: Analysing data and undertaking meta-analyses [Internet]. Training.cochrane.org. 2022 [cited 15 May 2022]. Available from: https://training.cochrane.org/handbook/current/chapter-10#section-10-3

37. Buzzetti E, Pinzani M, Tsochatzis E. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016;65(8):1038-1048.

38. Flick R, Katusic S, Colligan R, Wilder R, Voigt R, Olson M et al. Cognitive and Behavioral Outcomes After Early Exposure to Anesthesia and Surgery. Pediatrics. 2011;128(5):e1053-e1061.

39. Attention-Deficit/Hyperactivity Disorder (ADHD) [Internet]. National Institute of Mental Health (NIMH). 2022 [cited 15 May 2022]. Available from: https://www.nimh.nih.gov/health/statistics/attention-deficit-hyperactivity-disorder-adhd

40. Fan X, Shi G, Zhao P. Neonatal Sevoflurane Exposure Impairs Learning and Memory by the Hypermethylation of Hippocampal Synaptic Genes. Molecular Neurobiology. 2020;58(3):895-904.

41. Sasaki Russell J, Chinn G, Maharjan D, Eichbaum Y, Sall J. Female rats are more vulnerable to lasting cognitive impairment after isoflurane exposure on postnatal day 4 than 7. British Journal of Anaesthesia. 2019;122(4):490-499.

42. Yan J, Li J, Cheng Y, Zhang Y, Zhou Z, Zhang L et al. Dusp4 Contributes to Anesthesia Neurotoxicity via Mediated Neural Differentiation in Primates. Frontiers in Cell and Developmental Biology. 2020;8.

43. O'Leary J, Orser B. Neurodevelopment after general anaesthesia in infants. The Lancet. 2019;393(10172):614-615.

44. McCann M, de Graaff J. Current thinking regarding potential neurotoxicity of general anesthesia in infants. Current Opinion in Urology. 2017;27(1):27-33.