Journal of Language and Health
Volume 5 No 1, April 2024
e-ISSN 2722-3965; p-ISSN 2722-0311
http://jurnal.globalhealthsciencegroup.com/index.php/JLH

THE EFFECTS OF GENERAL ANESTHESIA ON INFANTS AND CHILDREN'S LATER DEVELOPMENT: A COMPREHENSIVE SYSTEMATIC REVIEW

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ABSTRACT

The relationship between pediatric neurodevelopment and general anesthesia has been the subject of numerous investigations, yet consensus remains elusive. Objective: This review aims to explore the connection between anesthesia and child development. We conducted a thorough search of Google Scholar, PubMed, and ProQuest databases from January 2000 until March 2024, using relevant search terms such as "Adolescent," "Anesthesia, General/ adverse effects," "Child," "Child Development / drug effects," and "Preschool" resulted in 40 out of 1572 studies for reviewed. The review focused on assessing the impact of general anesthesia on children's development, excluding studies involving children with significant comorbidities or lacking unexposed controls. Two coders independently evaluated the studies, adhering to Preferred Reporting Items for Systematic Reviews criteria. Our analysis of 40 primary studies unveiled a broad spectrum of outcomes regarding the impact of general anesthesia on infants and children's subsequent development. Across cognitive domains, anesthesia altered academic achievements, IQ, and language proficiency. Sensory responses were diverse, with anesthesia affecting manual dexterity, balance, and sensory performance uniquely. Psychosocially, it influenced behavior, social skills, and neuropsychological disorders, while neurodevelopmental concerns were also identified. In summary, the effects of general anesthesia on various developmental domains underscore the need for cautious consideration in medical practice. This review revealed cognitive decline, diverse sensory impacts, and increased behavioral issues, anxiety, and neurodevelopmental disorders associated with general anesthesia. Understanding these effects is crucial for implementing effective prevention and management strategies to mitigate long-term complications.

Keywords: child; development; general anesthesia

INTRODUCTION

Each year, millions of children undergo anesthesia while undergoing surgical and diagnostic procedures, yet research has unveiled a concerning reality. While it is clear that general anesthesia is necessary for sedation and pain minimization during surgical procedures, the possibility of neurotoxic impairments from its exposure is of concern (Wong-Kee-You et al., 2023). Early exposure to anesthesia may lead to brain damage and learning deficits. Despite this, it's intriguing that sensory impairments haven't been consistently identified in infants or animals exposed to anesthesia, despite evidence of significant brain tissue damage in various animal studies (Aksenov et al., 2020).

Evidence suggests that ingredients in anesthetic medications can adversely affect brain cell survival and cognitive performance in animals, fueling ongoing concerns about the safety of anesthesia in young children. While some trials have shown positive therapeutic outcomes without changes in cognitive function, others have revealed adverse clinical effects such as physical alterations and decreased performance on cognitive tests (Rosenblatt et al., 2019). According to a review by Ing and Bellinger (2022), children who were exposed to surgery and anesthesia at a young age showed little to no variations in IQ from their unexposed counterparts. Nonetheless, a number of researches have observed an increase in behavioral issues in kids under general anesthesia. Children subjected to anesthesia have also been found to have a higher frequency of attention-deficit hyperactivity disorder, especially after repeated exposures.

Given the potential risks associated with pediatric anesthesia, concerns have escalated among families, pediatric physicians, and healthcare regulators, highlighting a potential public health hazard (O'Leary & Warner, 2017). Retrospective investigations have sought to understand the link between early anesthesia exposure and neurobehavioral issues in childhood, particularly with extended or recurrent exposures. This concern extends to fetal interventions requiring sedation and analgesia, raising questions about potential neurotoxic effects on the developing fetus and the consequences of maternal anesthesia. Ultimately, the paramount concern in pediatric anesthesiology remains the possibility of anesthetic neurotoxicity (Andropoulos, 2018). The purpose of this investigation is to assess how general anesthesia affects child development.

METHOD

This study was a systematic review. The research process involves searching and screening data from primary research conducted across various ethnicities, races, and global locations. The study period encompasses primary research conducted up to the year 2024. Data retrieval is conducted from several online journal databases, including Google Scholar, PubMed, and ProQuest, utilizing search keywords such as "Adolescent," "Anesthesia, General/ adverse effects," "Child," "Child Development / drug effects," and "Preschool". The dependent variable in this study is child development including cognitive, academic, behavioral, social, and neurological aspects. The independent variable is the administration of general anesthesia. The inclusion criteria for primary study were: a). Articles written in English; b). Articles describing the effects of general anesthesia in child on later development; and c). Studies utilizing primary data with observational research design or clinical trials. The exclusion criteria were: a) non-primary studies such as review or case studies; b) subjects have preexisting comorbidities or congenital anomalies or was born preterm; c) the control group were not unexposed of general anesthesia**.** The researcher collects articles examining the effects of general anesthesia on child development. Characteristics of the articles are identified, conclusions are gathered, and new conclusions are drawn based on the analysis and review of the selected articles.

RESULT

The initial search process yielded 1572 articles. After removing duplicate publications, 177 articles remained, with 99 of them meeting the criteria for further full-text review. Finally, a total of 40 articles that met the quality assessment were included in the qualitative synthesis using systematic review (figure 1).

Table 1 presents a comprehensive overview of key aspects extracted from the chosen studies. Our examination encompassed 40 research papers, all of which adopted a cohort study design. This scrutiny involved a total of 2,647,648 children as participants across various age groups. The studies were conducted across multiple geographical locations, including the Egypt(Bakri et al., 2015), Japan(Kobayashi et al., 2020), United States(Backeljauw et al., 2015; Bartels et al., 2009; DiMaggio et al., 2011; Flick et al., 2011; Hu et al., 2017; Nestor et al., 2017; Sprung et al., 2012; Stratmann et al., 2014; Sun et al., 2012, 2016; Warner et al., 2018, 2021; Wilder et al., 2009; Zaccariello et al., 2019)(Bartels et al., 2009; DiMaggio et al., 2011; Hu et al., 2017; Sun et al., 2012, 2016; Warner et al., 2018), Singapore(Bong et al., 2013), the Netherlands(de Heer et al., 2017), Taiwan(Feng et al., 2020; Ko et al., 2014, 2015; Tsai et al., 2018; Yang et al., 2021), Sweden(Arana Håkanson et al., 2020; Castellheim et al., 2018; Glatz et al., 2017; Pikwer et al., 2023), Australia(DiMaggio et al., 2009; C. Ing et al., 2012; C. Ing, Sun, et al., 2017; C. Ing, Wall, et al., 2017; C. H. Ing, DiMaggio, Malacova, et al., 2014; C. H. Ing, DiMaggio, Whitehouse, et al., 2014), Canada(Graham et al., 2016; O'Leary et al., 2016, 2019), Germany(Schüttler et al., 2021), China(J. S. Wang et al., 2023), and the United

Kingdom(Walkden et al., 2020). Notably, all participants in the intervention group were subjected to general anesthesia.

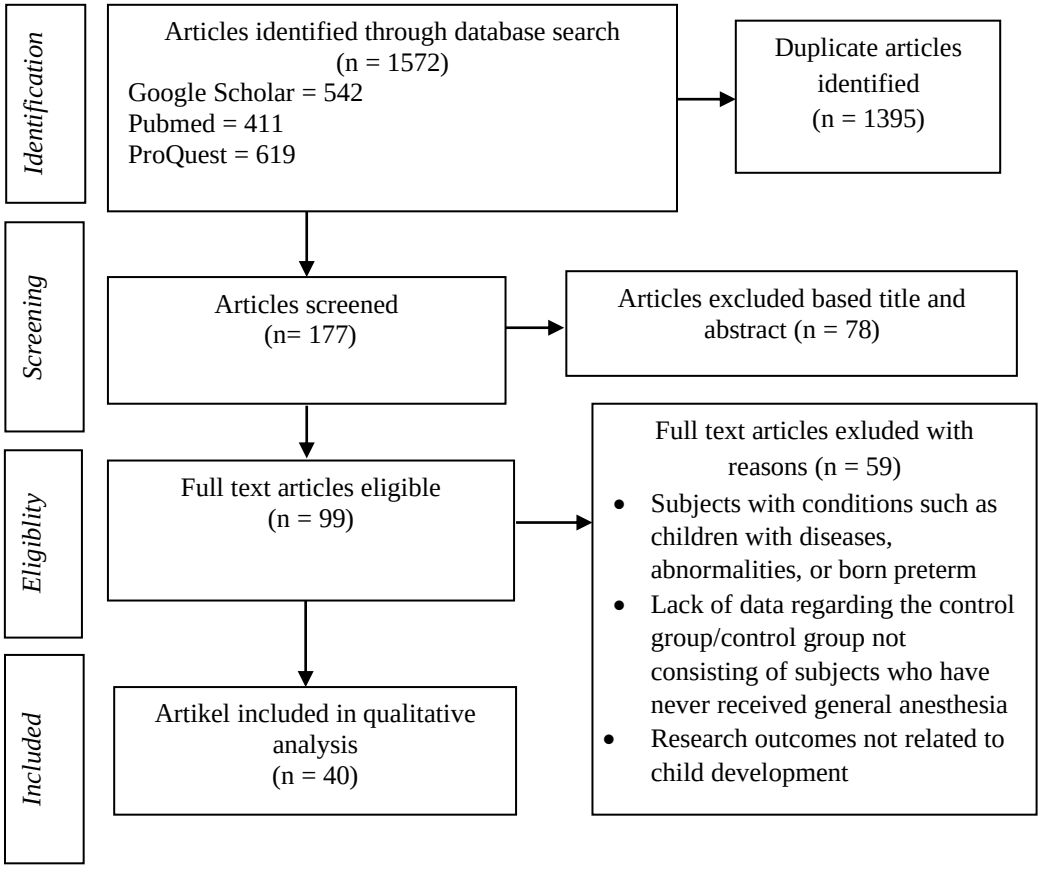

Figure 1. PRISMA Flow Diagram of the Study on the Effects of General Anesthesia Administration on Child Development

Table 1
Characteristics of included studies

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
1	Backeljauw et al., (2015)	Retrospective matched-cohort study	United States	106	Children aged 5-18 years old	Administration of anesthesia before age 4	Never received general anesthesia	Language ability, IQ (-)
2	Bakri et al., (2015)	Matched-Cohort study	Egypt	70	Children aged 1½ to 5 years old	Repeated administration of anesthesia	Never received general anesthesia	Emotionally reactive, somatic complaints, withdrawn problems, aggressive behavior, internalizing or externalizing problems, affective, pervasive developmental and oppositional defiant problems (≠) Anxiety, ADHD, Deppresive, Sleep, Attention (+)

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
3	Bartels *et al*., (2009)	Register based national cohort study	United States	1143	Children aged 12 years old	Surgical procedures and anesthesia before the age of 3, 5, 7, and 10 years	Never received general anesthesia	Educational achievement (≠) Cognitive issues (≠)
4	Bong *et al*., (2013)	Retrospective observational cohort study	Singapore	206	Children aged 12 years old	Surgical procedures and anesthesia before the age of 1 year	Never hospitalized and never received general anesthesia	Risk of learning disability diagnosis (+4.5 times)
5	Castellheim *et al*., (2018)	Register based national cohort study	Sweden	68 twin pairs	Children born born between 1997 and 2004	Administration of anesthesia before age 12	Never received general anesthesia	Neurodevelopmental disorders, ADHD (+)
6	De Heer *et al*., (2017)	Retrospective cohort study	Netherlands	3441	Children born between April 2002 and January 2006	Surgical procedures and anesthesia before the age of 5 years	Never received general anesthesia	IQ (-)
7	DiMaggio *et al*., (2011)	Retrospective sibling-matched birth cohort study	United States	10,450 pairs	Children with siblings born between 1999 and 2005 enrolled in the Medicaid program, New York	Surgical procedures and anesthesia before the age of 3 years	Children who did not undergo any surgical procedures	Risk of developmental and behavioral disorder diagnosis (+60%)
8	Feng *et al*., (2020)	Retrospective cohort study	Taiwan	34,371	Patients enrolled in the government-run Taiwan National Health Insurance (NHI)	Anesthesia procedure before the age of 2 years	Never received general anesthesia	Risk of developmental delay (+)
9	Flick *et al*., (2012)	Retrospective matched-cohort study	United States	1050	Children born between January 1, 1976, and December 31, 1982, in Rochester, Minnesota	Administration of anesthesia and surgical procedures multiple times or single before age 2	Never received general anesthesia	Multi exposures Learning disabilities (+)
10	Glatz *et al*., (2017)	Retrospective cohort study	Sweden	193,133	All children born in Sweden between January 1973 and December 1993	Surgical procedures and anesthesia at least once before the age of 4 years	Never hospitalized and never received general anesthesia	Academic achievement Cognitive performance (weak relationship)
11	Graham *et al*., (2016)	Retrospective matched-cohort study	Canada	18,056	All children who had continuous	Administration of anesthesia and surgical	Never received general	Deficit communication/ general knowledge

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
					provincial health insurance coverage from birth to the end of their fifth year in the Province of Manitoba, Canada	procedures multiple times or single before age 4	anesthesia	and language/ cognition (=)
12	Håkanson*et al*., (2020)	Retrospective cohort study	Sweden	5320	Children born between 1976 to 2002	Administration of anesthesia and surgical procedures before age 1	Never received general anesthesia	Cognitive dysfunction, ADHD (≠)
13	Hu *et al*., (2017)	Retrospective cohort study	United States	920	Children born between 1996 and 2000	Surgical procedures and anesthesia before the age of 3 years	Never received general anesthesia	Learning disability, Attention deficit/hyperactivity disorder (ADHD) (+) Cognitive ability, Academic achievement (-) Single exposure: Reading and language performance (-) Cognitive ability (≠)
14	Ing *et al*., (2017)-a	Retrospective cohort study	Australia	1444	Children born in Perth, Western Australia, between 1989 and 1992	Surgical procedures and anesthesia before the age of 3 years	Never received general anesthesia	Language and cognitive deficits (=) Severe behavioral deficit (≠)
15	Ing *et al*., (2017)-b	Retrospective cohort study	Australia	1622	Children registered in birth cohort in Perth, Western Australia, born from 1989 to 1992	Administration of anesthesia before age 3 with the duration of ≤25, >25 to ≤35, >35 to ≤60 and >60 min	Never received general anesthesia	≤35 min Language scores (≠) >35 min Language scores (-)
16	Ing *et al*., (2017)-c	Retrospective cohort study	Australia	230,958	Children enrolled in Texas and New York Medicaid from 1999 to 2010 were	Administration of anesthesia at ≤28 days old, >28 days and ≤6 months, >6 months and ≤1 year, and 6 month age intervals between >1 year old and ≤5 years old	Never received general anesthesia	Mental disorder, Development Delays and ADHD diagnoses (+)
17	Ing *et al*., (2014)-1	Retrospective cohort study	Australia	2868	Children aged 10 years old	Administration of early anesthesia	Never received general	Risk of motor deficits (+)

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
						between 3 and 5 years and between 5 and 10 years	anesthesia	
18	Ing *et al*., (2014)-2	Retrospective cohort study	Australia	781	Children aged 10 years old	Administration of anesthesia under 3 years	Never received general anesthesia	Risk of neuropsychological language assessment deficits (+) Academic performance scores (≠)
19	Ing *et al*., (2012)	Retrospective cohort study	Australia	2868	Children born between 1989 and 1992	Administration of anesthesia under 3 years	Never received general anesthesia	Risk of language disability (+)
20	Ko *et al*., (2015)	Retrospective cohort study	Taiwan	114,435	Pediatric patients enrolled in the NHI Research Database of Taiwan from 2001 to 2010	Administration of anesthesia under 2 years	Never received general anesthesia	Autistic disorder (≠)
21	Ko *et al*., (2014)	Retrospective cohort study	Taiwan	16,465	Children born between January 1, 2001, and December 31, 2005	Administration of anesthesia under 3 years	Never received general anesthesia	ADHD (≠)
22	Kobayashi *et al.*, (2020)	Prospective cohort study	Japan	64,141	Children from pregnant women were recruited between January 2011 and March 2014 from 15 regions throughout Japan	Administration of anesthesia and surgical procedures multiple times or single	Never received general anesthesia	Developmental delays (+)
23	Nestor *et al.*, (2017)	Retrospective cohort study	United States	457	Children were selected from the 2010–2011	Administration of anesthesia and surgical procedures multiple times or single	Never received general anesthesia	Developmental delay (=)
24	O'Leary *et al*., (2019)	Retrospective cohort study	Canada	10,897 pairs	Children aged 5-6 years old	Surgical procedures and general anesthesia from birth to completion of Early Development Instrument	Never received general anesthesia	Early developmental vulnerability, child's readiness to learn in 5 major domains (physical health and well-being, knowledge and social competence, emotional health and maturity, language and cognitive development, and

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
								communication skills and general knowledge) (≠)
25	O'Leary *et al*., (2016)	Population-based cohort study	Canada	84,276	Children in all public and Catholic schools in three consecutive cycles between 2004 and 2012	Administration of anesthesia and surgical procedures multiple times or single before age 6 years	Never received general anesthesia	Early developmental vulnerability (+)
26	Pikwer *et al*., (2023)	Retrospective cohort study	Sweden	1,589,546	Children aged 0-5 years old	Administration of anesthesia before the age of 5 years	Never received general anesthesia	Risk of autism or autism spectrum disorder (+)
27	Schüttler *et al*., (2021)	Retrospective cohort study	Germany	497	Children born full-term between 2007 and 2011	Administration of anesthesia before the age of 5 years	Never received general anesthesia	Non-inferiority of intelligence and traits (-)
28	Schneuer *et al*., (2018)	Retrospective cohort study	Australia	211,978	Children born in New South Wales, Australia, entering school in 2009, 2012, or taking 3rd-grade school exams from 2008 to 2014	Administration of anesthesia before 48 months of age	Never received general anesthesia	Developmental risk (+17%) Below-national-minimum-standard scores in mathematics (+34%) and reading (+23%)
29	Stratmann *et al.*, (2014)	Retrospective matched-cohort study	United States	56	Children aged 6-11 years old	Administration of anesthesia before age 1	Never received general anesthesia	Recollection scores (lower) Recollecting associative information (impaired) IQ, Child Behavior (≠)
30	Sprung *et al*., (2012)	Retrospective cohort study	United States	5357	All children born between January 1, 1976, and December 31, 1982, in Rochester, MN	Administration of anesthesia and surgical procedures multiple times or single	Never received general anesthesia	Repeated exposures ADHD (+)
31	Sun *et al*., (2016)	Retrospective cohort study	United States	105 pairs	Children aged 8-15 years old	Administration of anesthesia before 36 months of age	Never received general anesthesia	IQ (≠)

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
32	Sun *et al*., (2012)	Retrospective cohort study	United States	28 pairs	Children aged 6-11 years old	Administration of anesthesia before 36 months of age	Never received general anesthesia	IQ (≠)
33	Tsai *et al*., (2018)	Retrospective cohort study	Taiwan	4584	Children born between 1997 and 1999	Administration of anesthesia before age 3	Never received general anesthesia	ADHD (+)
34	Wang *et al*., (2023)	Retrospective cohort study	China	307	Children aged 6-12 years old	Administration of anesthesia under 2 years	Never received general anesthesia	IQ (≠) Continuous visual and auditory performance (minor impact) Social life skills scale scores (minor impact)
35	Walkden *et al*., (2020)	Retrospective cohort study	United Kingdom	13,433	Children enrolled in the Avon Longitudinal Study of Parents born between 1991 and 1993 in southwest England	Administration of anesthesia and multiple or single surgical procedures before the age of 4 years	Never received general anesthesia	Dynamic balance score on repeated exposure, Manual dexterity performance, Social communication scores (-) Disruptions in other neural developmental steps including: general cognitive ability, attention, working memory, reading, spelling, comprehension, verbal expression, behavioral difficulties; or national assessments in English, mathematics, and science (≠)
36	Warner *et al*., (2021)	Retrospective cohort study	United States	5339	Children born between 1976 and 1982 and between 1996 and 2000	Administration of anesthesia and surgical procedures multiple times or single	Never received general anesthesia	ADHD (≠) Reading, mathematics, written language, and need for individual education programs (speech/language and emotional/behavioral) (≠)
37	Warner *et al*., (2018)	Retrospective cohort study	United States	997	Children born in Olmsted County, Minnesota, from 1994 to 2007	Administration of anesthesia and surgical procedures multiple times or single	Never received general anesthesia	Intellectual intelligence (≠) Processing speed, Social abilities (-) Issues related to executive function, behavior, and reading (+)
38	Wilder *et al*., (2009)	Retrospective birth cohort study	United States	5357	All children born to mothers residing in five	Administration of anesthesia multiple times or single before age 4	Never received general anesthesia	Multi exposures Learning disabilities (=) Single exposure Learning disabilities

No	Author (year)	Study Method	Study Location	Sample size	Population	Intervention	Control	Outcome
					townships of Olmsted County, Minnesota from 1976–1982 and who remained in the community at 5 years of age			(≠)
39	Yang *et al*. (2021)	Register based national cohort study	Taiwan	6783	All children registered in National Health Insurance Research Database (NHIRD) of Taiwan	Administration of anesthesia and surgical procedures multiple times or single before age 3	Never received general anesthesia	ADHD, autism and intellectual disability (≠)
40	Zaccariello *et al*., (2019)	Retrospective cohort study	United States	997	Children born in Olmsted County, MN, USA from 1994 to 2007	Administration of anesthesia and surgical procedures multiple times or single before age 3	Never received general anesthesia	Deficits in neuropsychological tests (=)

After meticulous examination, our exhaustive systematic review unveiled a spectrum of outcomes regarding the impact of general anesthesia on the subsequent development of infants and children. Within the cognitive domain, our findings encompassed academic achievements, general knowledge, intelligence quotient (IQ), language proficiency, learning aptitude, mathematical proficiency, reading skills, presence of neurodevelopmental disorders, and executive functioning. The sensory spectrum comprised assessments such as dynamic balance scores upon repeated exposure, auditory performance, manual dexterity proficiency, motor deficits, and continuous visual capabilities. Additionally, within the psychosocial domain, our analysis delved into affective responses, attentional capacities, behavioral patterns, sleep patterns, developmental milestones, emotional reactivity, presence of mental health disorders, social adeptness, and neuropsychological disorders.

The impact of general anesthesia on the subsequent development of infants and children within the sensory domain

The impact of general anesthesia on various aspects of performance varies, as indicated by different studies. According to Walkden et al. (2020), general anesthesia decreases manual dexterity performance and dynamic balance score on repeated exposure. Conversely, Ing et al. (2014)-1 reported an increase in motor deficit following general anesthesia. Wang et al. (2023) found that general anesthesia had a minor impact on continuous visual and auditory performance.

The impact of general anesthesia on the subsequent development of infants and children within the cognitive domain

Through a comprehensive examination of various studies, the impact of general anesthesia on cognitive aspects and abilities in infants and children has been thoroughly explored.

In the realm of general cognitive issues, Bartels et al. (2009) discovered no significant association. Conversely, Hu et al. (2017) noted a correlation, particularly with multiple exposures. This relationship, although weak, was also identified by Håkanson et al. (2020) and Ing et al. (2017)-a. Moreover, Graham et al. (2016) highlighted an association with overall cognitive ability. Transitioning to academic or educational achievement, Bartels et al. (2009) and Ing et al. (2014)-2 found no notable correlation, whereas Glatz et al. (2017) observed a weak relation. Hu et al. (2017) reported a decrease in academic performance, while Schneuer et al. (2018) identified an increased risk of below-national-standard math scores. Interestingly, Warner et al. (2021) found no such association with math ability. Exploring learning ability, encompassing processing speed and associative memory, Wilder et al. (2009) and Hu et al. (2017) linked repeated exposures to learning disabilities. Flick et al. (2012) echoed these findings, indicating an increased risk. Conversely, O'Leary et al. (2019) found no such association with children's readiness to learn. However, Graham et al. (2016) suggested a relationship with general knowledge.

In terms of language ability, Ing et al. (2017)-b observed decreased scores for durations exceeding 35 minutes, with Backeljauw et al. (2015) confirming this trend. Hu et al. (2017) associated single exposures with diminished language and reading abilities, while Warner et al. (2018) specifically highlighted these effects for single exposures. Additionally, Ing et al. (2012) identified an increase in language issues. Schneuer et al. (2018) reported an increased risk of below-national-standard reading scores, and Ing et al. (2014)-2 found a heightened risk of neuropsychological language assessment deficits. Graham et al. (2016) corroborated these findings, emphasizing an association with language ability. Regarding intellectual intelligence, Stratmann et al. (2014), Sun et al. (2016), Sun et al. (2012), Wang et al. (2023), and Warner et al. (2018) found no significant association. Conversely, Backeljauw et al. (2015), De Heer et al. (2017), and Schüttler et al. (2021) reported decreases. Yang et al. (2021), however, found no association with intellectual deficits. Exploring the domain of recollecting associative information, Stratmann et al. (2014) noted impairment, with Warner et al. (2018) identifying decreases in processing speed and increased issues with executive function.

In terms of ADHD, Hu et al. (2017) and Sprung et al. (2012) identified an association with multiple exposures, whereas Tsai et al. (2018), Bakri et al. (2015), Ing et al. (2017)-c, and Castellheim et al. (2018) highlighted an increased risk of ADHD following general anesthesia. Conversely, Håkanson et al. (2020), Ko et al. (2014), Warner et al. (2021), and Yang et al. (2021) found no significant association. Concerning autism, Yang et al. (2021) and Ko et al. (2015) found no notable association, whereas Pikwer et al. (2023) reported an increase in autism diagnoses..

The impact of general anesthesia on the subsequent development of infants and children within the psychosocial domain

Upon examination of various studies, the impact of general anesthesia on behavior, social skills, and neuropsychological disorders in infants and children has been extensively investigated.

In terms of behavior, Stratmann et al. (2014) found no association, whereas Warner et al. (2018) observed an increase in behavior issues. Conversely, Ing et al. (2017)-a reported no association with severe behavioral deficits. However, DiMaggio et al. (2011) noted a 60% increase in behavioral

disorder diagnosis. Graham et al. (2016) identified an association with deficit communication. Regarding social skills, Wang et al. (2023) noted a minor impact on social life skills, whereas Warner et al. (2018) observed a decrease. Walkden et al. (2020) reported a decrease in social communication scores.

In the domain of neuropsychological disorders, Bakri et al. (2015) found no association with specific disorders such as emotionally reactive, somatic complaints, withdrawn problems, and aggressive behavior. However, they observed an increase in anxiety, depressive symptoms, sleep issues, and attention problems. Ing et al. (2017)-c noted an increase in mental disorders, while Zaccariello et al. (2019) reported deficits in neuropsychological tests. Conversely, Warner et al. (2021) found no association with the need for individual education programs for emotional/behavioral issues.

Additionally, concerning general neurodevelopmental disorders, Castellheim et al. (2018), Walkden et al. (2020), and DiMaggio et al. (2011) reported an increase, while Schneuer et al. (2018) observed a 17% higher risk for developmental issues. Regarding early developmental vulnerability, O'Leary et al. (2016) noted an increase, although O'Leary et al. (2019) found no association. For the risk of developmental delay, Feng et al. (2020), Kobayashi et al. (2020), Nestor et al. (2017), and Ing et al. (2017)-c observed an increase.

DISCUSSION

Previous meta-analyses have been conducted to provide insight to both researchers and clinicians regarding any iatrogenic effects of anesthesia at a deeper level. In research conducted by Zhang et al. in 2015, they conducted a meta-regression on 13 studies and found a possible association between single general anesthesia exposure and neural development, especially if anesthesia was administered before the age of 3(Zhang et al., 2015). Walkden et al. (2019) conducted a narrative review of 76 studies and highlighted the increasing international concern that general anesthesia exposure in childhood may lead to long-term neurological developmental disorders. However, distinguishing the effects caused by general anesthesia from the effects of surgery remains a significant challenge in studies on anesthesia-induced neurotoxicity(Walkden et al., 2019). In 2014, Wang et al. presented an updated systematic review with meta-regression on 7 studies and found an increased risk of adverse neurodevelopmental outcomes in children exposed to anesthesia/surgery during childhood, especially those exposed multiple times(X. Wang et al., 2014).

Research conducted by Reighard et al. in 2022 combined data from 31 studies in a systematic review and meta-analysis. They found that the relationship between anesthesia exposure during childhood and subsequent neurodevelopmental deficits varied depending on specific neurodevelopmental domains(Reighard et al., 2022). In 2022, Xiao et al. conducted a systematic review of 72 studies and found that a higher frequency of general anesthesia exposure, longer duration, and major surgeries may indicate a higher risk of negative outcomes(Xiao et al., 2022). According to Levy et al., exploring populations already predisposed to neurocognitive challenges, such as premature infants, children with congenital heart disease, or those with mitochondrial cytopathies, holds promise. This approach leverages the potential "two-hit" phenomenon, where these individuals might exhibit a more pronounced response to anesthesia exposure, thus offering a clearer indication of susceptibility to its

neurotoxic effects. However, this strategy faces significant hurdles. The high prevalence of confounding variables within these patient groups complicates efforts to establish a direct causal relationship. Moreover, it's important to acknowledge that findings from studies involving these vulnerable cohorts may not necessarily translate to the broader population. While animal studies provide compelling and extensive data, the absence of a distinct injury phenotype in infants and children poses a challenge. This absence could undermine the assertion that anesthetic-related neurotoxicity represents a significant clinical issue and poses a substantial risk to public health. Consequently, the justification for allocating resources and effort towards further research on this topic may be questioned (Levy et al., 2016).

In this recent review, there are several significant differences compared to previous research. Firstly, there is the addition of new studies that were not included previously, expanding the scope of the evaluated literature. Secondly, some studies have been removed due to potential biases, such as subjects born prematurely or with congenital abnormalities, thereby enhancing the validity of the results. Thirdly, the focus of the independent variables is not only on the administration of anesthesia but also on specific types of surgeries, allowing for a deeper investigation into the specific effects of these surgical procedures on neurodevelopment. Fourthly, there is no clear control group that is not exposed to general anesthesia, or the control group may have received other interventions before anesthesia administration, enabling more accurate research on the direct effects of general anesthesia on neurodevelopmental outcomes**.**

We categorize the findings of the effects of general anesthesia administration in children into three domains: sensory domain, cognitive domain, and psychological domain, although there is overlap in cognitive and psychological aspects such as findings regarding the influence on neurodevelopmental disorders, autism, and ADHD. Variations in findings indicate a range from no association to increased disabilities in each domain. According to previous study by Aksenov et al., Anesthesia has the potential to trigger alterations in the structure, function, and adaptive mechanisms of both sensory and cognitive systems. Notably, exposure to anesthesia has been associated with changes in myelination and neurodegeneration in the gray matter across various brain regions. Anesthesia-induced cell death, particularly affecting the balance between excitatory and inhibitory cells, can result in a lasting imbalance in neural activity, impacting both learning-related networks and sensory processing. Furthermore, anesthesia may directly influence synaptic plasticity, a fundamental process crucial for acquiring new knowledge. However, it's intriguing to note that while anesthesia can cause damage, sensory systems seem to possess a greater capacity for compensation compared to specialized learning networks(Aksenov et al., 2020).

CONCLUSION

The comprehensive systematic review on the effects of general anesthesia on the subsequent development of infants and children revealed diverse outcomes. In the cognitive domain, significant impacts were noted on academic achievement, language proficiency, and learning abilities, with findings indicating declines in some cognitive areas following exposure to general anesthesia. Conversely, in the sensory domain, the impacts varied, with some studies reporting decreases in motor performance and sensory abilities after general anesthesia exposure, while others found minor impacts.

Meanwhile, in the psychosocial domain, the effects of general anesthesia influenced behavior, social skills, and neuropsychological disorders. The results highlighted an increased risk of behavioral issues, anxiety, depression, and sleep problems following general anesthesia exposure. Additionally, some studies associated general anesthesia with increased risks of neurodevelopmental disorders and early developmental delays. In conclusion, the impact of general anesthesia on the development of infants and children warrants deeper understanding and specific attention, necessitating the development of effective prevention and management strategies to reduce the risk of long-term complications.

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