

Association between childhood exposure to general anesthesia and risk of ADHD: A meta-analysis of cohort studies

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Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder that occurs primarily in childhood, which is characterized by inattention, hyperactivity, and impulsivity. Children may exhibit deficits in alertness, language learning, and memory[1]. It has been suggested that ADHD may persist into adolescence as well as adulthood with concomitant attention and memory impairments and behavioral inhibition[2-4]. There may be a correlation between the onset of ADHD and early general anesthesia (GA) exposure[5-6], but there is no consensus on the findings. In this study, we conducted a meta-analysis of the association between exposure to GA and ADHD prevalence, and additionally investigated the link between the frequency of GA exposure and ADHD.

Methods: We searched PubMed/MEDLINE, Embase, CINAHL, Web of Science, and the Cochrane Library from inception to June 2023. Studies evaluating the prevalence of ADHD after general anesthesia exposure versus non-exposure were selected. The quality of the studies analyzed was evaluated using the Newcastle-Ottawa Scale (NOS). Due to the heterogeneity across the studies, we employed a random-effects model to estimate the relative risk (RR) and 95% confidence intervals (CI) to investigate the possible association between exposure to GA in children and the likelihood of developing ADHD later in life.

Results: Our meta-analysis examined ten cohort studies that evaluated the risk of ADHD associated with exposure to GA in comparison to non-exposed individuals. In addition, we conducted further subgroup analyses to assess the correlation between the frequency of GA exposure and ADHD. Out of the 427,481 children identified, 107,514 had been exposed to GA while 319,967 had not been exposed. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS), revealing ten studies of high quality (Table 1). The results of the meta-analyses indicated that children exposed to GA were at an increased risk for subsequent ADHD (RR = 1.22, 95% CI 1.06–1.41; P = 0.005; I² = 49%; Fig 1). A single exposure to general anesthesia during childhood was associated with an increased risk of developing ADHD (RR = 1.28, 95% CI 1.18-1.40; P < 0.001; I² = 4%; Fig. 2), and the risk of ADHD escalated with two or more exposures (RR = 1.61, 95% CI 1.32-1.96; P < 0.001; I² = 58%; Fig 2).

Conclusions: Exposure to GA during childhood heightens the risk of developing ADHD, particularly when subjected to multiple surgical procedures with GA. Early administration of anesthesia may impede neuronal differentiation and synaptogenesis, leading to possible neurotoxicity and resulting cognitive dysfunction. Our findings indicate the potential negative outcomes of undergoing surgeries involving GA at a young age. Further exploration is necessary to examine the effects of the duration of exposure to GA on ADHD.

Table 1 NOS for Assessment of Quality of Included Studies: Cohort

	Selection			Comparability		Outcome			
	Representativeness	Selection of the non-exposed	Ascertainment of exposure	Outcome not present at start	Comparability	Comparability	Assessment of outcome	long enough follow-up	Adequacy (completeness) of follow-up
					on most important factor	on other risk factors			
Sprung et al., 2012	*	*	*	*	*	*	*	*	*
Ko et al., 2014	*	*	*	*	*	*	*	*	*
Bakri et al., 2015		*	*	*				*	*
Ing et al., 2017	*	*	*	*	*	*	*	*	*
Hu et al., 2017	*	*	*	*	*	*	*	*	*
Tsai et al., 2018	*	*	*	*	*	*	*	*	*
Arana et al., 2020	*	*	*	*			*	*	*
Ahn, et al., 2020	*	*	*	*			*	*	*
Warner et al., 2020	*	*	*	*	*	*		*	*
Yang et al., 2021	*	*	*	*	*	*	*	*	*
Song et al., 2023	*	*	*	*	*	*	*	*	*



