J Anesth (2015) 29:749–757
DOI 10.1007/s00540-015-2030-z

ORIGINAL ARTICLE

Association between childhood exposure to single general anesthesia and neurodevelopment: a systematic review and meta-analysis of cohort study

Haifeng Zhang[1] · Lili Du[2] · Zijing Du[1] · Hao Jiang[1] · Dong Han[1] · Qingfeng Li[1]

Received: 17 March 2015 / Accepted: 4 May 2015 / Published online: 23 May 2015

Abstract
Objective Many studies have been done to seek the relationship between general anesthesia and neurodevelopment in pediatrics. However, there is no unified conclusion, especially single anesthesia affecting a child before 3 and 4 years. The association between anesthesia and neurodevelopment is studied using a meta-analysis.
Methods We summarized the currently available evidence by searching PubMed, EMBASE, and the Cochrane library over the past 10 years. An evaluation of neurodevelopment including learning disability, behavioral disorders, and cognitive problems was conducted. We estimated the synthesized hazard ratios (HR) and 95 % confidence interval (CI) according to inter-study heterogeneity and analyzed the factors for this association using meta-regression method.
Results Thirteen eligible studies met the inclusion criteria. The neurodevelopment damage was associated with single general anesthesia before age of 4 (adjusted HR 1.28 95 % CI 1.10–1.45). The pooled adjusted HR was 1.17 (95 % CI 1.07–1.28, $p = 0.001$) before 4 years old after the influence analysis and the adjusted HR was 1.18 (95 % CI 1.07–1.30, $p = 0.001$) before 3 years old. There was no significant difference between 3 and 4 years exposed to single general anesthesia ($HR_3/HR_4 = 1.008$, $p = 0.9$). Due to limitations of retrospective studies, prospective investigations are needed to determine whether anesthesia is causative.
Conclusions The current evidence suggests a modestly elevated risk of neurodevelopmental disorders exists in children near 3 years of age. A single general anesthesia is relatively safe after 3 years, as the outcome is very close before 3 and 4 years old.

Keywords Cohort studies · Pediatrics · Anesthesia, general anesthetics · Newborn · Neurodevelopmental · Infant

H. Zhang and L. Du contributed equally to this work.

✉ Dong Han
handong12000@163.com

1 Department of Plastic and Reconstructive Surgery, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, No. 639, Zhizaoju Road, Huangpu District, Shanghai 200011, China

2 Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, Xuzhou Medical College, Xuzhou, China

Introduction

The question whether there is damage to neurodevelopment after receiving a single anesthesia has frequently been queried from the family of children, while surgeons and anesthesiologists also do not answer it properly. Sometimes, the doctor would say it is an uncertain conclusion in children. However, preclinical studies have established that anesthesia is toxic to the brain in neonatal animals [1]. In addition, animals exposed early in development have documented abnormal attention, learning and memory, and behavior changes [2]. Although the answer to the question is clear on animal studies, the evidence lack of human trials, have made conclusions regarding human brain development after exposure highly tentative. Until now, the results of currently available clinical and epidemiological studies remain inconclusive to guide clinical decision-making [3, 4]. To our knowledge, clinical research investigating the neurodevelopmental outcome of children after single general exposure to anesthesia within age of four and three has not been well established. Therefore, we performed a meta-analysis and meta-regression of cohort study with accumulating evidence to discuss the topic of outcome measurement after a single anesthesia administered before 3 and 4 years.

Methods

Ethical approval and patient consent are not required since this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis were conducted and reported in adherence to preferred reporting items for systematic reviews and meta-analyses (PRISMA) [5].

Study identification and data extraction

We used PubMed, EMBASE, and The Cochrane Library database to search relevant studies over the last 10 years by using the following search terms: ([including a keyword search using the words 'anesthesia' or a MeSH search using exp 'General anesthetics'] and [including keyword search using 'pediatric' or 'child*' or 'newborns 'or 'neonate' or 'young'] and [including a MeSH search 'cohort study' or a keyword search using 'cohort analysis']). 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. The study ladder chart is shown in Fig. 1. By this search strategy, 6052 papers were identified, including 2854 papers in PubMed, 737 papers in Embase, and 2461 papers in the Cochrane Library database.

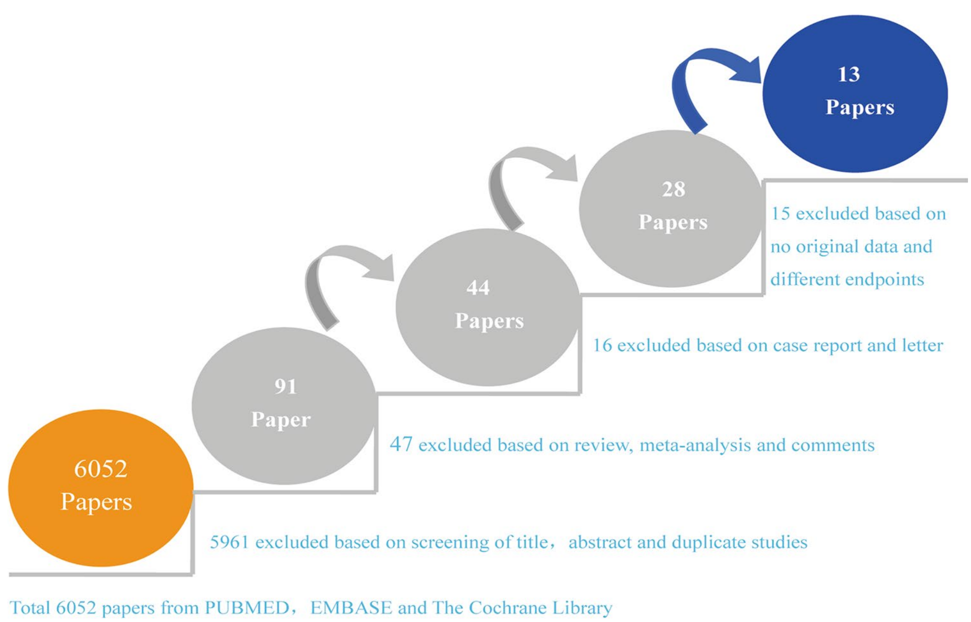
The following inclusive selection criteria were applied: (1) compare the effect of general anesthesia on later neurodevelopment. The evaluation of neurodevelopment includes language and learning disabilities, cognition, behavioral development, academic performance, and autistic disorder as well as attention deficit; (2) independent retrospective or prospective study (3) with available data to estimate hazard ratio (HR) with 95 % confidence interval (CI). Whenever available, we extracted the adjusted HR for other confounding factors, since the adjusted estimates might reflect the true odds of effect, and we select the studies that should have a single anesthesia outcome before 4 years old.

After reviewing all papers, 13 eligible studies were selected for the present meta-analysis [6–18] and one of them originates from conference data [18]. The following variables were extracted from each study if available: first author's surname, publication year, total number of cases, number of cases in exposure, adjusted HR with 95 % CI of outcomes, timing at exposure, evaluation time, evaluation standard, and evaluation items for neurodevelopment. The information was collected independently by two investigators (HFZ and LLD), and any discrepancy was resolved by discussion. The study quality was assessed using the 9-star Newcastle-Ottawa Scale (NOS). (The NOS for assessing the quality of cohort studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm).

Meta-analysis and statistical methods

The meta-analysis was planned, conducted, and reported in adherence to the standards of quality for reporting meta-analysis [19]. For each study, an adjusted HR with 95 % CI was retrieved to estimate the association between anesthesia and neurodevelopmental outcomes. The heterogeneity

Fig. 1 The ladder chart of the literature search and selection



among studies was assessed by Cochran Chi-square Q statistics and I^2 statistics, which determined the appropriate use of either fixed-effects (Mantel–Haenszel method) or random-effects (DerSimonian and Laird method) models. Heterogeneity was considered as either a p value <0.05 or $I^2 > 25$ % [20, 21]. Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity. Influence analysis (sensitivity analysis) was conducted by omitting each study to find potential outliers. The potential publication bias was assessed graphically in the Begg funnel plot of log HRs against their standard error (SE), and the degree of asymmetry was tested using Egger's test and Begg's test.

We also computed the trend from the correlated log HRs estimates across categories of exposure levels by meta-regression as previously described [22, 23]. We made calculations assuming a log-linear relationship between HR and early time exposure before 3 and 4 years old. Results were considered as statistically significant for $p < 0.05$. All of the statistical analyses were performed using Stata/SE version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

A detailed outcome of the search and selection result is shown in Table 1. A total of 85,014 children were included and 12,220 of them had experienced general anesthesia due to surgery procedures. The minimum age at exposure was at birth to 108 days and the maximum age was at the age of 48 months, with a mean age of 30.5 months, and 84.6 % papers study the relationship between the single general anesthesia and neurodevelopmental outcomes before age of 3 among 13 studies. Year of birth ranged from 1976 to 2010. Children after exposure were followed up from 1 year to 16 years. Of the 13 included studies, six were conducted in the USA [9, 12–14, 16, 18], two in the Netherlands [15, 17], two in Australia [7, 10], one in China [6], one in Denmark [11], and one in Singapore [8]. The number of ICD-9 evaluation standard accounts for 46 % in all 13 studies.

Of 13 study findings, only one (Bartels et al. [17]) used the unadjusted HR of exposure to anesthetic agents with neurodevelopmental outcome for the original paper did not report the HR and 95 % CI. However, DiMaggio et al. [24] had calculated them in their previous meta-analysis. The findings from the other 12 papers had adjusted HR for association between exposure to single anesthesia and neurodevelopmental outcomes. Two of the 13 studies reported in the subgroup analyses were in accordance with the exposed age [6, 15]. Eleven of 13 studies were utilized to analyze the association between exposure to anesthesia and neurodevelopmental outcomes before age 3. The quality of studies evaluated by the NOS is shown in Table 1.

Effect measure synthesis: primary outcome

The Q statistic for the 13 estimates for single exposure was 21.09 ($p = 0.049$) with heterogeneity among the studies ($I^2 = 43.1$ %). Therefore, the random-effects model was used to analyze the data and an association between anesthesia with neurodevelopmental impairment was observed with a pooled HR of 1.27 (95 % CI 1.10–1.45, $p = 0.001$). Moreover, either graphical inspection for funnel plots or quantitative evaluation from Egger's test and Begg's test indicated a presence of publication bias ($p = 0.014$ and $p = 0.012$, respectively).

Sensitivity analysis

Influence analysis was conducted to ascertain the reason of publication bias. The studies conducted by Bong et al. [8] and DiMaggio et al. [16] showed results that were completely out of range of the others and probably contributed to the heterogeneity. When deleted the Bong et al. [8], the Q statistic was 16.19 ($p = 0.134$) with an I^2 of 32.1 % and quantitative evaluation from Egger's test and Begg's test indicated the presence of publication bias ($p = 0.051$ and $p = 0.047$, respectively). Similarly, the Q statistic was 16.02 ($p = 0.140$) with an I^2 of 31.3 % and publication bias is exist from Egger's test and Begg's test ($p = 0.032$ and $p = 0.034$, respectively) after omitting DiMaggio et al. [16]. After excluding both of these, no evidence of heterogeneity and publication bias was observed among the remaining studies ($I^2 = 9.2$ %), and the relationship between anesthesia with neurodevelopmental impairment was observed with a pooled HR of 1.17 (95 % CI 1.07–1.28, $p = 0.001$; Fig. 2). Either graphical inspection for funnel plots or quantitative evaluation from Egger's test and Begg's test indicated the absence of publication bias ($p = 0.121$ and $p = 0.161$, respectively). No individual study in the 11 studies affected the overall HR dominantly, because omission of any single study made no substantial difference.

Effect measure synthesis: second outcome

On the basis of the above study, we explored further the association between childhood exposure to single general anesthesia and neurodevelopment before 3 years old. Considering heterogeneity, similarly, we used the fixed-effects model to analyze nine studies. Using the homologous method, we could obtain the results exposed to single

Table 1 Outcome of selected studies included in the meta-analysis

References	Country	Exposed/total (*n*)	Adjusted HR	95 % CI	Birth (years)	Time at expose (months)	Evaluation time (years)	Evaluation items	Evaluation standard	Study quality (NOS)
Bartels et al. [17]	Netherlands	1078/2286	1.7	0.6–5	1986–1995	<36	12	Educational achievement and cognitive problems	Dutch CITO elementary test	7
Bong et al. [8]	Singapore	257/579	4.38	1.39–13.9	1998–1999	<12	12	Learning disability	PSLE	8
DiMaggio et al. [18]	USA	625/5625	1.9	1.1–3.1	1999–2000	<48	8	Development and behavioral disorders	ICD-9	8
DiMaggio et al. [16]	USA	383/5433	2.3	1.3–4.1	1992–2002	<36	Before age 4	Development and behavioral disorders	ICD-9	8
DiMaggio et al. [13]	USA	304/10,450	1.1	0.8–1.4	1999–2005	<36	Before age 6	Development and behavioral disorders	ICD-9	8
Flick et al. [12]	USA	286/700	1.09	0.80–1.48	1976–1982	<24	19	Learning disability	Wechsler Intelligence Scale	9
Hansen et al. [11]	Denmark	2689/17,263	1.13	0.98–1.31	1986–1990	<12	15–16	Academic performance	Standardized, nationwide general test	9
Ing et al. [10]	Australia	321/2868	1.73	1.04–2.88	1989–1992	<36	10	Language and cognition	CPM	8
Ing et al. [7]	Australia	112/2868	1.35	1.05–1.75	1989–1992	<36	10	Cognitive function and behavioral disorders	ICD-9	8
Kalkman et al. [15]	Netherlands	178/243	1.27	0.74–2.16	1987–1995	<24	Median age 14.5	Cognitive problems	CBCL	6
			1.38	0.59–3.22		0–6				
			1.19	0.45–3.18		6–12				
			1.20	0.45–3.20		12–24				
Ko et al. [6]	China	5197/25,985	0.93	0.57–1.53	2001–2010	<24	6	Autistic disorder	ICD-9	8
			1.08	0.51–2.30		0–3.6				
			0.81	0.37–1.75		3.6–9				
			1.04	0.49–2.19		9–17				
			0.82	0.37–1.83		17–24				
Sprung et al. [9]	USA	341/5357	1.35	0.90–2.02	1976–1982	<24	19	Attention deficit/hyperactivity disorder	ICD-9	9
Wilder et al. [14]	USA	449/5357	1.0	0.79–1.27	1976–1982	<48	19	Learning disability	IQ and Academic achievement test	8

NOS the 9-star Newcastle-Ottawa Quality Assessment Scale, *PSLE* Primary School Leaving Examination, *ICD-9* International Classification of Diseases, 9th edition/revision, *CPM* Raven's Colored Progressive Matrices, *CBCL* Child Behavior Checklist

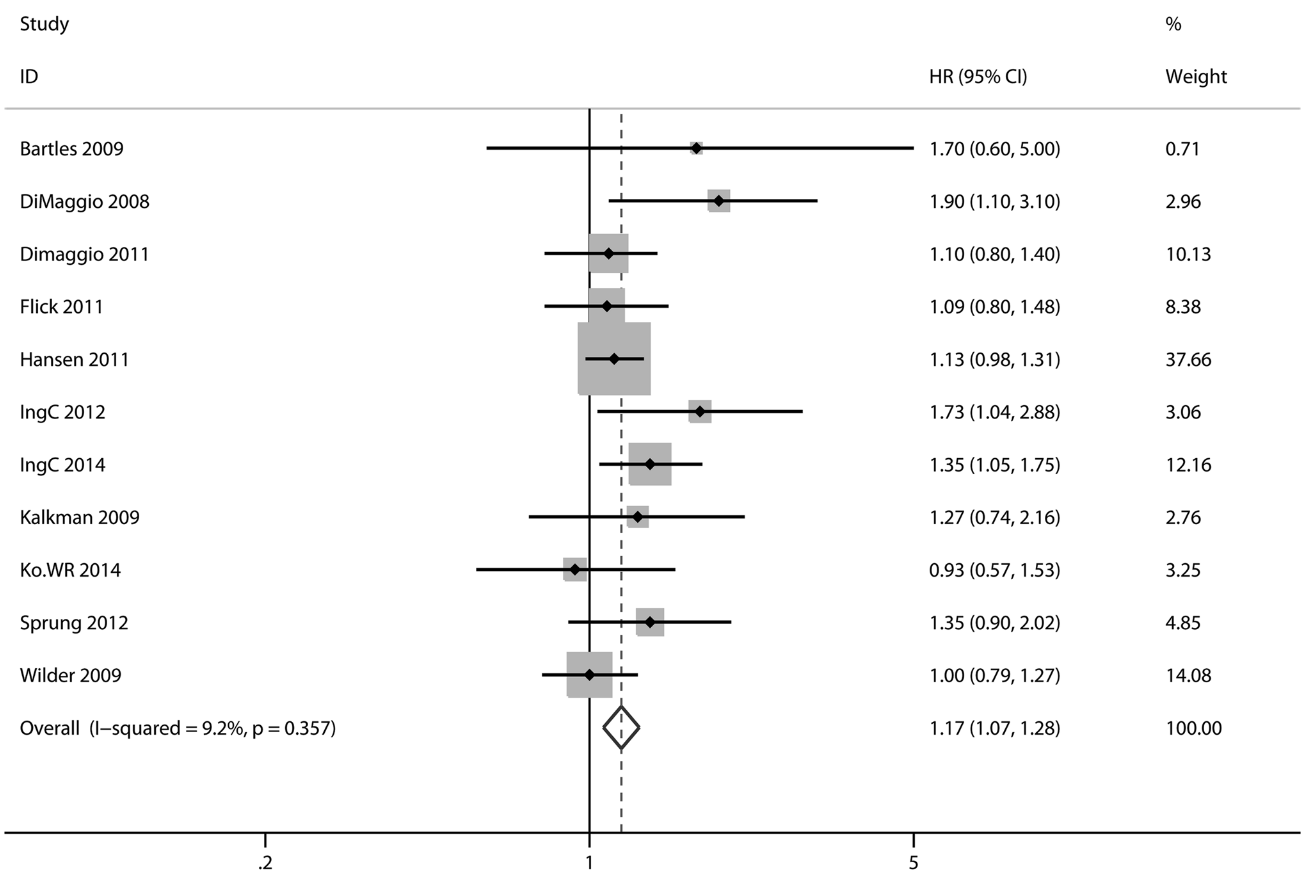


Fig. 2 Forest plot showing the association of single general anesthesia with the risk of neurodevelopment before age 4 in 11 studies after omitting Bong et al. [8] and DiMaggio et al. [16]

general anesthesia before age of 3. The Q statistic for the nine estimates for single exposure was 5.92 ($p = 0.656$) with an I^2 of 0 %, and the relationship between anesthesia with neurodevelopmental impairment was observed with a pooled HR of 1.18 (95 % CI 1.07–1.30, $p = 0.001$; Fig. 3).

The relationships between primary and second outcome

Meanwhile, we have compared the difference between before age of 4 and before age of 3 exposed to single general anesthesia in the neurodevelopmental impairment. The outcome shows that there is no significance difference, with the p value of 0.9 (Fig. 4).

Meta-regression analysis

We have already demonstrated an association between anesthesia and neurodevelopmental impairment, and a meta-regression was further performed to explore whether the risk of neurodevelopmental impairment could be predicted according to one parameter, which is the time at exposure. The adjusted HR results of individual eligible studies listed in Table 1 are plotted in Fig. 5a, b, including 11 studies in age of four and nine studies except Bong et al. [8] and DiMaggio et al. [16]. For the time at exposure, the slope of the black bold line (by log converted HR) in Fig. 5a, b represented the risk of neurodevelopmental impairment due to per 1-year early exposure to anesthesia. Regression analysis showed that the risk of neurodevelopment disorders for anesthesia decreases as the age of the child increases. The HR of effect of early exposure per year is 0.85, with 95 % CI of 0.49–1.46 and a non-significant p value of 0.518, indicating time at exposure (before age of 4 years in 13 studies) may have no effect on neurodevelopmental impairment. However, when heterogeneity and publication bias is considered in the above studies, the HR of effect of early exposure per year in age of 4 is 1.08, with 95 % CI of 0.89–1.33 and a non-significant p value of 0.374 and the HR of effect of early exposure per year in age of 3 in nine studies is 1.09, with 95 % CI of 0.94–1.27 and a non-significant p value of 0.205; indicating time at exposure (before age of 4 or 3 years) might have a limited effect on neurodevelopmental impairment.

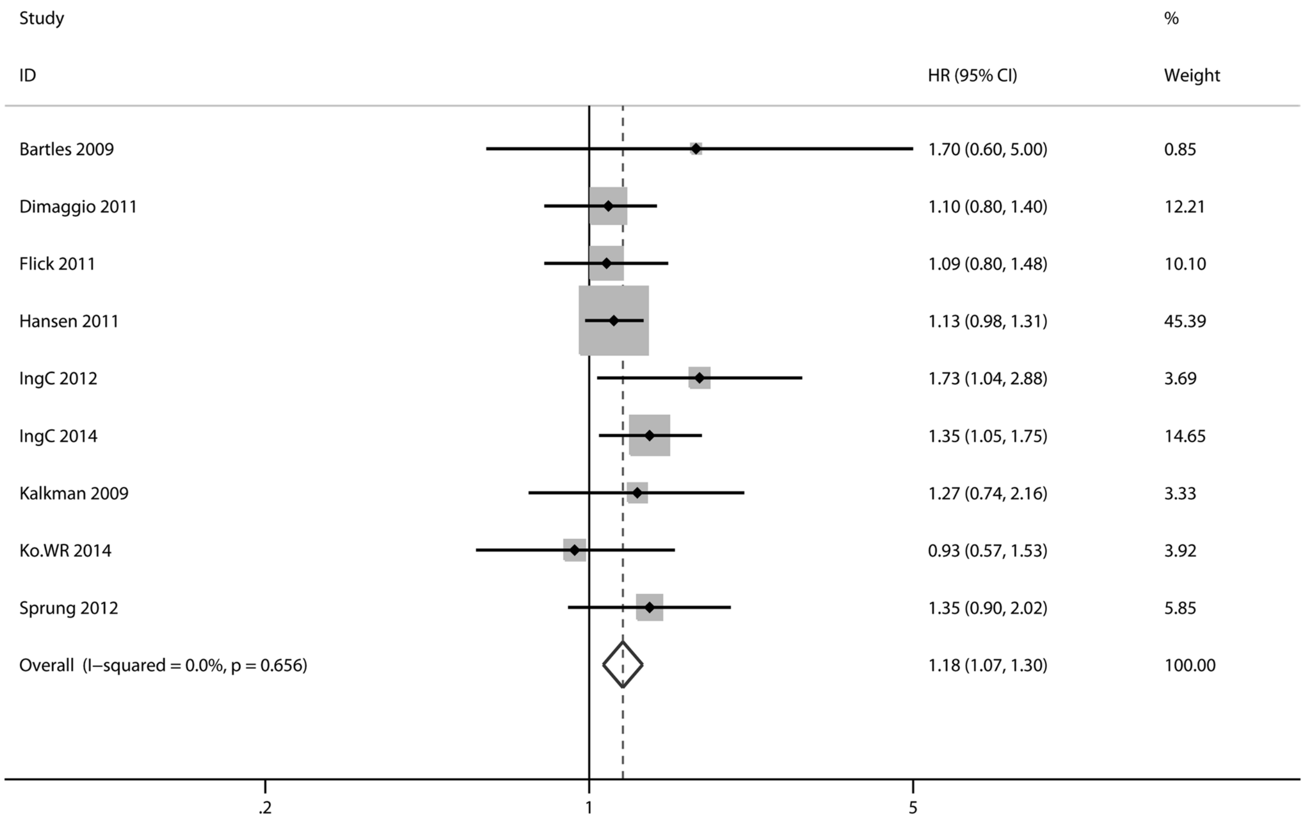


Fig. 3 Forest plot showing the association of single general anesthesia with the risk of neurodevelopment before age 3 in 9 studies

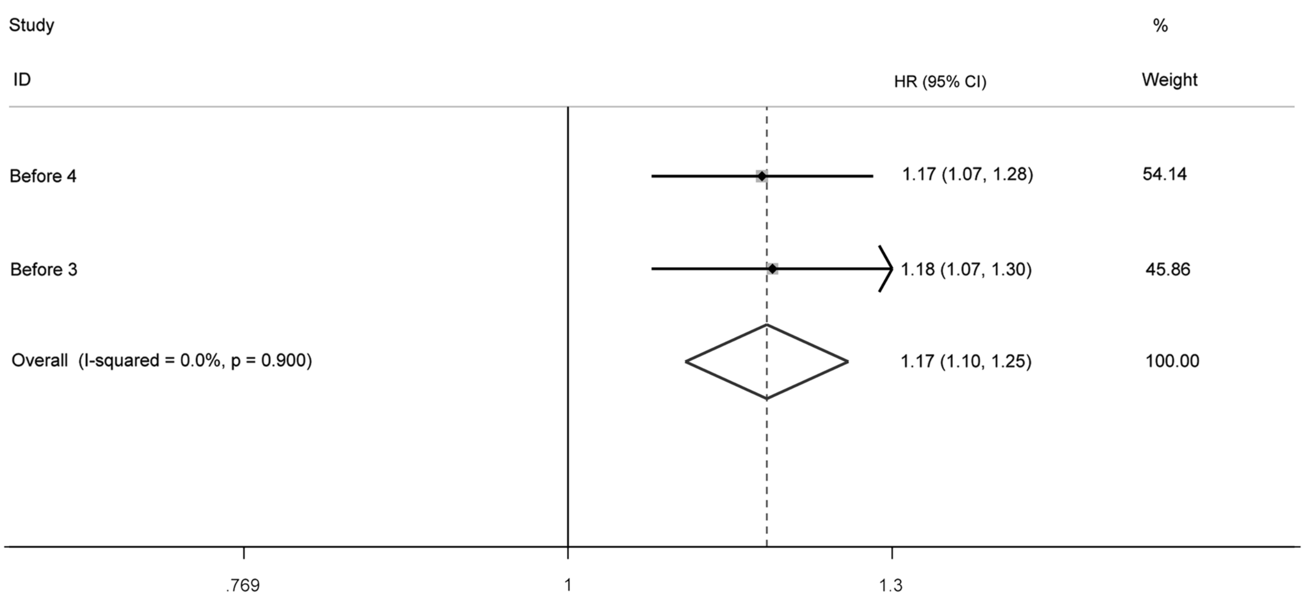


Fig. 4 The relationships between within age 4 and age 3 exposed to single general anesthesia

Therefore, surgeons should take note that children with early single exposure may have a higher risk of neurodevelopmental impairment compared to those with later exposure and it is better that exposures to single anesthesia before the age of 3 years be avoided in selective operation.

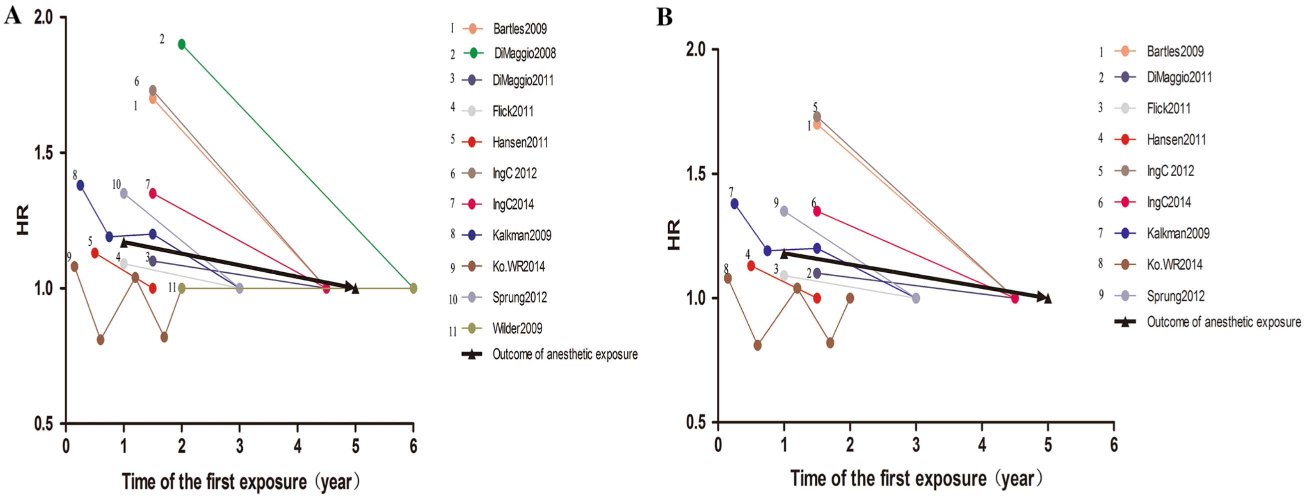


Fig. 5 **a** Meta-regression analysis: effect of time at exposure of single general anesthesia on neurodevelopment in children in 11 studies before age of 4. The *black line* indicates the effect of time at exposure on neurodevelopmental deficits. **b** Meta-regression analysis: effect of time at exposure of single general anesthesia on neurodevelopment in children in nine studies before age of 3 after influence analysis

Discussion

It is estimated that more than 6 million children (including 1.5 million infants) will receive general anesthesia for both surgical and nonsurgical procedures in the United States in 2012 [25]. Numerous preclinical and retrospective human studies have reported that the provision of anesthetic to infants and children may be associated with adverse neurodevelopmental outcomes. However, few meta-analyses have been done to enlighten both researchers and clinicians regarding any iatrogenic effects of anesthesia in a deeper lever. DiMaggio et al. [24] have performed a Bayesian meta-analysis to investigate the association between pediatric anesthesia and neurodevelopmental impairment. The synthesized HRs based on seven unadjusted and six adjusted measures for the association of anesthesia with an adverse developmental outcome were 1.9 (95 % CI 1.2–3.0) and 1.4 (95 % CI 0.9–2.2). However, they have a concentration on any exposure on anesthesia and failed to include all eligible studies available at the age of analysis. The results of the present meta-analysis suggest a potential influence of anesthesia on the later neurodevelopmental deficits, especially those before 3 years old exposed to single anesthesia. Considering the existence of heterogeneity, the results of exposed to single general anesthesia before age of 3 and age of 4 have no evident difference after deleting Bong et al. [8] and DiMaggio et al. [16]. Similarly, the results of meta-regression analysis indicate that there is no evident different trend from the viewpoint in the time at exposure. Moreover, it seems that the range between age of 4 and age of 3 is no significant risk factor for neurodevelopmental impairment, that is to say, postponing surgical procedures that require first anesthesia if possible have better performed in children after 3.

Our findings from pooled meta-analysis are consistent with most, although not all, findings only from currently available literature—cohort study. Randomized trials provide strong clinical evidence and attractive purity of its design. However, they are not without limitations and challenges, and the RCT has drawbacks particularly in pediatric anesthesia that include the ethics of randomization, choice of comparison group, choice of relevant dose in the treatment arm, and definition of suitable outcome measure as well as protocol adherence [26, 27]. Indeed, due to numerous biases in these observational cohort studies—bias related to selection of the population and the control subjects and their comparability as well as outcome measure assessment, it has become extremely important to evaluate studies [28]. We, here, select the 9-star NOS to assess all 13 studies and use adjusted HR to do a meta-analysis (except Bartels et al. [17]), which can lead to selective bias. Commonly, the method of HR extrapolation requires comment. If not reported, the HRs was calculated from the data available in the published article. However, we can not obtain the adjusted HR from the origin article. We get the value of HR in the meta-analysis from DiMaggio et al. [24].

Significant heterogeneity was detected among the studies included in the meta-analysis. Heterogeneity was still observed when we limited the scope of analysis to studies investigating Bong et al. [8]. When studies were limited to DiMaggio et al. [16], heterogeneity was still detected. Therefore, we omit both of them, and heterogeneity reduced in a significant range. For the first study from Bong et al., the heterogeneity is from the size of the sample. The sample size is relatively small, with a total of 579 samples. The existing bias in the DiMaggio et al. study comes from unmeasured confounders, measurement error, and misclassifications in their comparison groups, leading to an underestimate of the true association between anesthesia and hernia repair with outcome. Therefore, the primary outcome in this study was not standardized, and as such, it could easily be subjected to variation owing to differences in local practice patterns and misclassification from diagnostic coding.

The other limitations, as Sun et al. [25] described, should be declared. First of all, there should be other prognostic factors not controlled in the meta-analysis. Differences in surgical techniques, varying patient populations, changes in definition of recurrence, and difficulty with long-term follow-up, all hamper firm conclusions. Second, pediatric anesthetic neurotoxicity is a complicated and complex issue. There are many confounding factors at play in addition to the potentially toxic effects of anesthesia, including maternal health, drug exposures during pregnancy and delivery, preexisting medical conditions in the child, environmental characteristics, and as Servick noted [29], a lack of funding as well as ethical issues. Third, the evaluation of neurodevelopment should use standard measurement forms, and different forms would result in different outcomes of neurodevelopmental assessment.

Publication bias is a well-known problem in meta-analysis. The meta-analysis was restricted to papers published in English, and language bias might exist. However, our analysis did not suggest publication bias, so the summary statistics obtained may only approximate the actual average. After all, no statistical approach is a panacea for potentially biased or confounded data. Selective bias exists in meta-analysis for we just select all the studies in last 10 years considering the updated anesthetic agents.

Despite the limitations listed above, our study did find that single general anesthesia was possibly associated with neurodevelopment, especially exposed anesthesia before the age of 3. The outcome of the meta-analysis hints that we had better shift the focus to come the child who need operation under single general anesthesia within 3 years of age, rather than within 4 years old. To become a useful prognostic marker for individual patients and in the context of targeted therapy, these results clearly need to be confirmed by well-designed clinical experiments, for instance prospective studies, with larger, more clearly defined patient populations.

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. Sun L. Early childhood general anaesthesia exposure and neurocognitive development. Br J Anaesth. 2010;105:i61–8.
2. Wang C, Slikker W Jr. Strategies and experimental models for evaluating anesthetics: effects on the developing nervous system. Anesth Analg. 2008;106:1643–58.
3. Rappaport B, Mellon RD, Simone A, Woodcock J. Defining safe use of anesthesia in children. N Engl J Med. 2011;364:1387–90.
4. Glass NL, Malviya S. Anesthesia in children—limitations of the data on neurotoxicity. N Engl J Med. 2011;364:1466–7.
5. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264–9.
6. Ko W-R, Huang J-Y, Chiang Y-C, Nfor ON, Ko P-C, Jan S-R, Lung C-C, Chang H-C, Lin L-Y, Liaw Y-P. Risk of autistic disorder after exposure to general anaesthesia and surgery: a nationwide retrospective matched cohort study. Eur J Anaesthesiol. 2014;31:1–8.
7. Ing CH, DiMaggio CJ, Malacova E, Whitehouse AJ, Hegarty MK, Feng T, Brady JE, von Ungern-Sternberg BS, Davidson AJ, Wall MM. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. Anesthesiology. 2014;120:1319–32.
8. Bong CL, Allen JC, Kim JTS. The effects of exposure to general anesthesia in infancy on academic performance at age 12. Anesth Analg. 2013;117:1419–28.
9. Sprung J, Flick RP, Katusic SK, Colligan RC, Barbaresi WJ, Bojanić K, Welch TL, Olson MD, Hanson AC, Schroeder DR. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia. Mayo Clin Proc. 2012;87:120–9.
10. Ing C, DiMaggio C, Whitehouse A, Hegarty MK, Brady J, von Ungern-Sternberg BS, Davidson A, Wood AJ, Li G, Sun LS. Long-term differences in language and cognitive function after childhood exposure to anesthesia. Pediatrics. 2012;130:e476–85.
11. Hansen TG, Pedersen JK, Henneberg SW, Pedersen DA, Murray JC, Morton NS, Christensen K. Academic performance in adolescence after inguinal hernia repair in infancy: a nationwide cohort study. Anesthesiology. 2011;114:1076–85.
12. Flick RP, Katusic SK, Colligan RC, Wilder RT, Voigt RG, Olson MD, Sprung J, Weaver AL, Schroeder DR, Warner DO. Cognitive and behavioral outcomes after early exposure to anesthesia and surgery. Pediatrics. 2011;128:e1053–61.
13. DiMaggio C, Sun L, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. Anesth Analg. 2011;113:1143.
14. Wilder RT, Flick RP, Sprung J, Katusic SK, Barbaresi WJ, Mickelson C, Gleich SJ, Schroeder DR, Weaver AL, Warner DO. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. Anesthesiology. 2009;110:796.
15. Kalkman CJ, Peelen L, Moons KG, Veenhuizen M, Bruens M, Sinnema G, de Jong TP. Behavior and development in children and age at the time of first anesthetic exposure. Anesthesiology. 2009;110:805–12.
16. DiMaggio C, Sun LS, Kakavouli A, Byrne MW, Li G. A retrospective cohort study of the association of anesthesia and hernia repair surgery with behavioral and developmental disorders in young children. J Neurosurg Anesthesiol. 2009;21:286.
17. Bartels M, Althoff RR, Boomsma DI. Anesthesia and cognitive performance in children: no evidence for a causal relationship. Twin Res Hum Genet. 2009;12:246–53.
18. DiMaggio CJ, Sun L, Kakavouli A, Li G. Exposure to anesthesia and the risk of developmental and behavioral disorders in young children. Anesthesiology. 2008;109:A1415.
19. Higgins J, Green SE. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from: http://www.cochrane-handbook.org.
20. Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.

21. Higgins J, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539–58.
22. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. Epidemiology. 1993;4:218–28.
23. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemol. 1992;135:1301–9.
24. DiMaggio C, Sun LS, Ing C, Li G. Pediatric anesthesia and neurodevelopmental impairments: a Bayesian meta-analysis. J Neurosurg Anesthesiol. 2012;24:376.
25. Sun LS, Li G, DiMaggio CJ, Byrne MW, Ing C, Miller TL, Bellinger DC, Han S, McGowan FX. Feasibility and pilot study of the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) project. J Neurosurg Anesthesiol. 2012;24:382.
26. Davidson AJ, McCann ME, Morton NS, Myles PS. Anesthesia and outcome after neonatal surgery: the role for randomized trials. Anesthesiology. 2008;109:941–4.
27. Hansen TG, Henneberg SW, Morton NS, Christensen K, Davidson AJ, Lee KJ, Hardy P, Wolf A. Pro–con debate: cohort studies vs the randomized clinical trial methodology in pediatric anesthesia. Paediatr Anaesth. 2010;20:880–94.
28. Cans C. Neonatal exposure to anesthesia and adverse cognitive outcome in childhood. Insight from epidemiology. Archives de pediatrie: organe officiel de la Societe francaise de pediatrie. 2013;20:1011–5.
29. Servick K. Biomedical Research. Researchers struggle to gauge risks of childhood anesthesia. Science (New York, NY). 2014;346(6214):1161–2.