Pediatric Anesthesia and Neurodevelopmental Impairments: A Bayesian Meta-Analysis

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Abstract

Experimental evidence of anesthesia-induced neurotoxicity has caused serious concern about the long-term effect of commonly used volatile anesthetic agents on young children. Several observational studies based on existing data have been conducted to address this concern with inconsistent results. We conducted a meta-analysis to synthesize the epidemiologic evidence on the association of anesthesia/surgery with neurodevelopmental outcomes in children. Using Bayesian meta-analytic approaches, we estimated the synthesized odds ratios (OR) and 95% credible interval (CrI) as well as the predictive distribution of a future study given the synthesized evidence. Data on 7 unadjusted and 6 adjusted measures of association were abstracted from 7 studies. The synthesized OR based on the 7 unadjusted measures for the association of anesthesia/surgery with an adverse behavioral or developmental outcome was 1.9 (95% CrI 1.2, 3.0). The most likely unadjusted OR from a future study was estimated to be 2.2 (95% CrI 0.6, 6.1). The synthesized OR based on the 6 adjusted measures for the association of anesthesia/surgery with an adverse behavioral or developmental outcome was 1.4 (95% CrI 0.9, 2.2). The most likely adjusted OR from a future study was estimated to be 1.5 (95% Cr I 0.5, 4.0). We conclude that the existent epidemiologic evidence suggests a modestly elevated risk of adverse behavioral or developmental outcomes in children who were exposed to anesthesia/surgery during early childhood. The uncertainty with the existent epidemiologic evidence, however, is considerable,

implying that the value of additional research using existent data sources to enhance the evidence base is diminishing.

Introduction

Repeated laboratory demonstrations of anesthesia-induced neurotoxicity, resulting in cell death *in vitro* and impaired neurobehavioral functions *in vivo* under varying experimental conditions [1–4] have sparked increasing concern on the part of clinicians and policy makers. [5–7]. At least two prospective studies are underway to investigate the relevance and implications of the laboratory findings for children undergoing anesthesia in the setting of surgery [5, 6]. In the meantime, several observational studies based on existing data have been conducted to help determine if the animal studies have implications for humans.

Among the initial clinical investigations, a population-based retrospective cohort study found a 60% increased risk of learning disorders following more than one anesthetic exposure. [8]. A retrospective cohort analysis of Medicaid data found a two-fold increased risk for being subsequently diagnosed with developmental or behavioral disorder following inguinal hernia repair surgery under 3 years of age [9]. Both studies controlled for pre-existing medical conditions, age, gender and socio-economic status. A more tightly controlled study based on Dutch twin-registry data did not find conclusive evidence for a causal relationship between exposure to anesthesia and subsequent cognitive deficit [10]. These divergent results were reaffirmed by a sibling-controlled analysis of Medicaid data [11].

In this paper, we summarize the current clinical evidence by synthesizing the results of recent clinical studies using standardized effect measures with Bayesian meta-analytic techniques. In the process, we determine how widely study results varied, calculate the direct probability of the overall mean effect size, and estimate how likely it is that future studies would demonstrate an association similar to that found in this meta-analysis. Our goal is to present a

broad overview of the issue, provide context, and suggest future directions for researchers.

Methods

The conduct and reporting of this study followed the PRISMA statement and MOOSE guidelines for reporting systematic reviews and meta-analyses of observational studies in epidemiology [12, 13]. We searched for clinical studies of learning or behavioral effects of pediatric surgical exposure to anesthesia. Data were eligible for inclusion if they were in English, were conducted after 2000 (to better reflect current clinical practice), and presented results of comparisons of outcomes for exposed and unexposed children. We excluded obstetrical exposures, outpatient dental sedation and where possible, exposures beyond the first 5 years of life. We further excluded studies of immediate post-operative agitation, anxiety and emergence behavior. Studies were eligible for analysis if they presented results in terms of odds ratios and their standard errors, or counts, proportions or prevalence measures that could be converted to odds ratios. Where possible, analyses were based on extraction of raw data from tables and charts. We contacted corresponding authors for additional explanatory data, and for information about unpublished reports.

We electronically searched PubMed for the Boolean term '(anesthe* or or anaesthe*) and (neuro* or learning or academ* or dis*) not (dental)' restricted to English language human studies of children up to age 12. The studies were downloaded in text format and entered into a reference bibliography software system [14] Duplicates were removed and the titles of the remaining studies were reviewed to exclude entries not related to learning or behavioral outcomes in children exposed to anesthesia. Abstracts of the remaining articles were reviewed to further exclude studies that did not meet entry criteria.

Full-text versions of articles were reviewed by the first author (CD) and coded for the following variables: whether the study was based on a clinical or population-based sample, the

underlying population size and sample size, the geographic region from which the population came, whether the anesthetic exposure occurred in an inpatient or outpatient setting, the age range during which exposure occurred, the earliest and latest calendar years during which exposure occurred, whether the investigators looked at primarily a behavioral or learning outcome, whether the outcome was measured on a continuous or categorical scale, the instrument on which the outcome was measured and, if continuous, the cutoff value for clinically important outcomes.

Results were assigned a unique identification number based on the investigative team, the population studied, the journal or report, and the discrete result within that report. Results of additional or repeated analyses of previously published data were excluded to maintain the independence of studies entered into the analysis.

To compare effect measures across studies, we converted results to log odds ratios (logits) and their associated standard errors, using abstracted count data for unadjusted results. We also abstracted adjusted results and and converted them to logits. For continuous outcomes, we chose cut-off values for exposed and unexposed children based on differences in standard deviation from mean values. We generally based the cut off on 2 standard deviations from the mean, but lowered this to 1.5 standard deviations if necessary to avoid division by zero. Independent results were grouped under two categories: unadjusted results based on any anesthetic exposure, and adjusted results based on any anesthetic exposure.

We used Bayesian analytic methods to synthesize the effect measures within the two categories of results. The methods were described in detail elsewhere [15]. Briefly, the prior distribution, θ, reflects our expectation or belief about the association of anesthesia with pediatric neurotoxicity and how we think it might vary if we had no data upon which to base our judgments. The likelihood informs about θ via the data itself. In this case, our abstracted logits and their standardized errors. When we have a lot of data, the likelihood predominates, and our results will essentially be the maximum likelihood or traditional es-

timate. When we have less data, the prior has greater influence. We chose as a prior probability, an odds ratio that is normally distributed with a mean of 0 on the log scale (no association, or an $OR = 1$), and a wide variance of 10^5 on the log scale. This reflects *a priori* that we believe there is a 95% probability that the true logit lies between $-1.96x316$ and $1.96X316$.

We assessed heterogeneity in the effect estimates with a Q statistic and assessed the proportion of variance due to study-to-study heterogeneity with the I^2 statistic and associated 95% confidence interval. Based on this assessment, we chose a random effects model to synthesize the logits. We placed a Uniform (0,10) prior probability on the standard deviation of the distribution describing the variation *between* studies, i.e. that random effects component of the meta-analytic model. Because there were relatively few studies in the synthesis, we tested the sensitivity of our synthesized result to the assumption of this prior distribution by comparing the results to an analysis with a gamma(0.001, 0.001) prior distribution for the variance for the random effects term. The syntax for the two models are available in the appendix Publication bias was assessed graphically with the symmetry of funnel plots.

In addition to describing the mean and spread of the posterior distribution of the synthesized effect estimate, we calculated a posterior predictive distribution of possible data values given our synthesized knowledge about θ. This is termed the posterior predictive distribution. It is invariably less precise than the posterior distribution on which it is based because it incorporates both the uncertainty of the parameter estimate and a data value based on the distribution of that gave rise to that data.

The data were initially abstracted and entered into a spreadsheet, then read into the R statistical computing system [16] for descriptive analysis. The Bayesian evidence synthesis was conducted using the R2jags package to interface with the JAGS program [17] of 'BUGS' (Bayesian Analysis Using Gibb's Sampling) for a Monte Carol Markov Chain simulation approach to parameter estimates. The program chooses samples using either Gibbs (for

which its named) or Metropolis Hasting algorithms. Because this is a simulation-based approach, we repeat many draws or iterations and evaluate whether the chain of sample values converges to a stable distribution that is assumed be the posterior distribution in which we are interested.

We entered our models into JAGS and ran two 20,000 Markov Chain Monte Carlo iterations each starting with different and dispersed initial values for the model. We based our results on the final 10,000 iterations, and assessed whether the chain of values had converged to a stable posterior distribution by monitoring and assessing a graph of the chain as well as by calculating the Brooks Gellman and Rubin statistic, a tool within the CODA package of R program for this purpose.

The results are presented as mean values of the posterior distributions and their 95% credible intervals (Cr I). Where appropriate, we exponentiated the logits which were used in the meta-analyses to present results in their original scale. Plots and graphs were created within the R statistical computing package. The study protocol was approved by the (removed for peer review) Institutional Review Board and complies with the Public Health Code of Ethics.

Results

Sample Description

A search of PubMed using the pre-specified search terms returned 442 results. After removing duplicates and non-relevant studies, 13 papers and reports addressed the issue of the association of anesthesia / surgery and neurodevelopmental outcomes [8–11,18–26]. One study was based on conference proceedings and was removed after correspondence with the authors clarified that it did not include an unexposed comparison group [26].

We conducted preliminary descriptive analyses of the remaining 12 studies. They presented

a total of 43 discrete findings. The departments of anesthesia at Columbia University in New York City, and the Mayo Clinic in Rochester, Minnesota accounted for nearly two thirds of all results (13 each). The results were about evenly split between those arising from clinical or hospital-based samples and those arising from population-based samples. Twenty-eight (65.1%) of the findings came from North America, 11 (25.6%) from Europe. Results were about evenly split between those arising from inpatient surgical anesthesia administration (22/43 or 51.2%), and those arising from either inpatient or outpatient anesthesia (21/43 or 48.8%). About half the outcomes studies were primarily behavioral (20/43 or 46.5%), and the other half primarily involving learning or mental capacity (23/43 or 53.5%). The majority of outcomes were measured with continuous scales (35/43 or 81.4%). Of the 43 results abstracted 24 (55.8%) were not statistically adjusted.

The 43 findings came from 9 independently-sampled populations. The study populations were split about evenly between clinical (5) and population-based (4) samples.The majority of samples (8) were based in North America and Europe. Taken together, a total of 40,685 children, drawn from a population of 467,505 children were studied. The minimum exposure age was birth to 1 month and the maximum exposure age ranged from 2 months (2 populations) to 48 months (one population), with a mean of 24 months and a median of 36 months. Year of birth ranged from 1976 (1 population) to 2003 (1 population), with a mean of 1990 and a median of 1988 (2 populations). Children were followed for a mean of 5 years, with one population followed for 14 years [8].

A total of 13 independent effect measures from 7 studies were entered into analysis [8–10, 20–22, 25]. Of the 13 study findings 7 were the *unadjusted* associations of *any* exposure to anesthetic agents and neurodevelopmental outcomes. Six of the 13 findings were the *adjusted* associations of *any* exposure to anesthetic agents and neurodevelopmental outcomes. Variables for which these results were adjusted varied and included, gender, race, parental education and socioeconomic status, gestational age, birth weight, malformations, Clinical

Risk Index for Babies score, antenatal corticosteroids, multiple pregnancies, complications of pregnancy, place of birth, and a number of neonatal conditions and interventions such as duration of ventilation, patent ductus arteriosus, hypoxemia, and hemodynamic failure.

The Q statistic for the 7 unadjusted estimates for any exposure was 18.8 (p=0.0045) with an I^2 of 68.1% (95% CI 29.5%, 85.6%). For the 6 adjusted estimates for any exposure the Q statistic was 11.5 (p=0.04) with an I^2 of 56.4% (95% CI 0%, 82.4%). Funnel plots for the two sets of data were subjectively symmetric (Figure 1).

Effect Measure Synthesis

Unadjusted Results, Any Exposure

The synthesized effect estimate based on the unadjusted results for the association of any anesthesia/surgery with a behavioral or developmental outcome was OR=1.9 (95% CrI 1.2, 3.0). The mean of the predictive distribution, or the most likely odds ratio for a *future* study, based on the existing studies was OR = 2.2 with a credible interval of 0.6 to 6.1, reflecting considerable uncertainty (Figure 2).

Despite the uncertainty in the point estimate, based on the evidence, the probability that a child's exposure to anesthesia/surgery was associated with a learning or behavioral problem was nearly certain (99%), and the probability that a *future* study of this association will return an odds ratio greater than one was 87%.

In a sensitivity analysis under a gamma(0.001, 0.001) prior for the random effects term, the synthesized estimate remained OR=1.9 with a slightly tighter credible interval (95%CrI 1.3, 2.6) and the predictive result dropped to OR=2.0 with a credible interval of 0.7 to 4.7.

Adjusted Results, Any Exposure

The synthesized effect estimate for the 6 adjusted results for any exposure was OR = 1.4 with a 95% Credible Interval of 0.9 to 2.2. The estimate for a future study was an odds ratio of 1.5 (95% Cr I 0.5, 4.0) (Figure 3). The probability of a study demonstrating harm (an odds ratio greater than 1) was 95%. The probability of a future study demonstrating harm was 81%. These estimates were similarly robust to a gamma prior on the variance for the random effects heterogeneity.

Discussion

Pediatric anesthetic neurotoxicity is a complicated and complex issue. There are many variables at play in addition to the potentially toxic effects of anesthesia including maternal health, the use of antecedent medications and other exposures during pregnancy, labor and delivery, as well as confounding factors due to indications for surgery, pre-existing medical conditions in the child, and environmental or ecological characteristics.

Although there is an increasing acceptance of the basic laboratory evidence, and a movement toward investigations of potential interventions to mitigate against these effects [27–29], there remain distinct challenges in translating the bench science to bedside practice. Infant rats have relatively short vulnerable synaptogenic period in contrast to humans, and relatively high doses of anesthetic agents and long duration of anesthetic exposure have been employed to trigger apoptosis in published reports, any extrapolation to humans may require frequent, repeated or lengthy exposures. The difficulty in monitoring neonatal rodents compared to human infants also raises the possibility that the effects in rodents might be due to hypoxia or other physiologic or metabolic disturbances rather than the anesthetic agents [30]. Notably, most studies were not performed in animals undergoing surgery, although in one instance in which animals received anesthesia in the presence of painful stimulation, ketamine attenuated

pain-induced cell death and impaired neurocognitive behaviors induced by neonatal exposure to inflammatory pain [31].

Given this complexity, observational studies are hard put to demonstrate unequivocal associations or risk. The results of this meta-analysis must be taken cautiously within the context of the data upon which it is based. No statistical approach, even one as robust as Bayesian meta-analysis, is a panacea for potentially biased or confounded data.

Our main conclusion is that concern over the effects of anesthesia on the developing brain remains well placed, but what can reasonably be learned from continuing to analyze existing data sources is increasingly limited. The probability that a future such study will demonstrate a risk, even adjusted for multiple potentially confounding factors, is approximately 80%.

A useful epidemiological approach to interpreting these results is through population attributable risk. In this approach, the overall risk of learning or behavioral disorders in children in a community that one may attribute to anesthetic exposure will depend on the point estimate for that risk, and the prevalence of anesthetic exposure in the population. [1] Assume that 4 million children, out of a population of 75 million, are exposed to anesthesia in a given year. [32] The attributable risk for learning or behavioral disorders in the United States due to anesthesia would be 2.6% $((.053 * .5)/(1 + (.053 * .5)) = .0258)$ using the results of our synthesis of adjusted results. Similar calculations return an attributable risk of 4.6% for the unadjusted results for any exposure. As a point of reference, the population attributable risk for cardiovascular disease due to smoking has been estimated at 10.9%. [33]

In general, combining studies through meta-analysis increases the power to find significant results and imposes a useful discipline on data synthesis by making the process of combining studies more organized and systematic than in traditional reviews. A Bayesian approach ad-

[1] The attributable risk (AR), is calculated using the formula: $PAR = \frac{p(OR-1)}{1+p(OR-1)}$, where p is the prevalence of the risk factor and OR is the adds ratio associated with the risk factor

ditionally allows us to make explicit what we often do implicitly, i.e. evaluate evidence given our expectations, and permits us to make (cautious) predictions by combining information about the probability distribution of a parameter or effect size with the likelihood of seeing a specific value given the observed data.

This must be balanced against the recognized weaknesses of a meta-analytic approach. It is limited to close-ended quantitative formats and outcomes. Missing or unpublished studies may differ systematically from what is found in the literature. The studies that are combined may differ appreciably and in many important aspects related to type and conduct.

The statistical summaries should not overshadow the more important aspects of appreciating the entire landscape of the extant research. In this study, that there were few studies to combine, particular caution is warranted.

Despite these cautions, the current evidence demonstrates an association between pediatric anesthetic in the setting of surgery, and later learning or behavioral problems in children. To be informative, future studies should address populations or outcomes not represented in these results. By pooling the available evidence, these results may help establish evidence against which to measure the results of ongoing prospective trials.

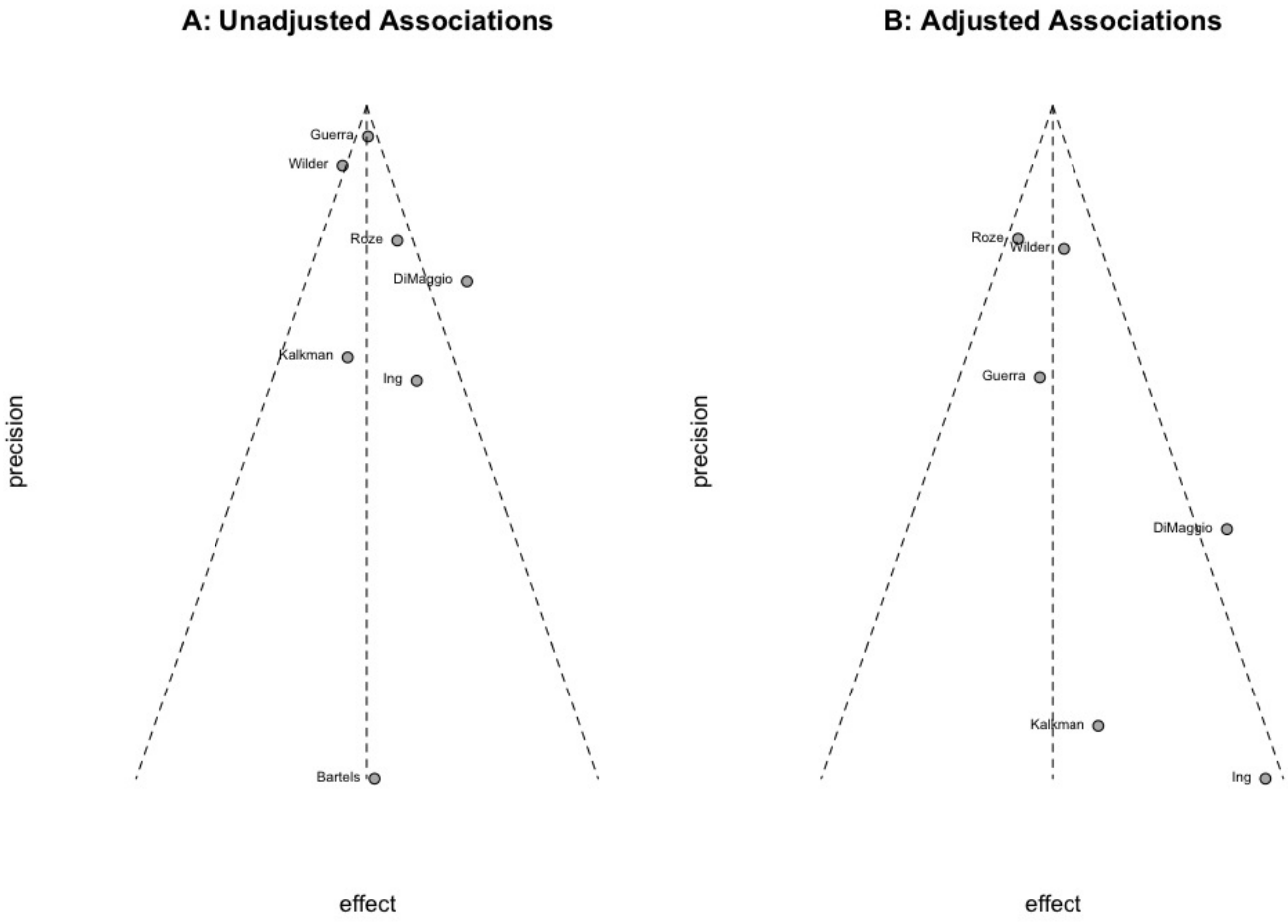

Figure 1: Funnel Plots, meta-analysis of clinical studies of the association of pediatric anesthesia/surgery with neurodevelopmental pathology (A) unadjusted odds ratios for association of *any* exposure, (B) *adjusted* odds ratios for association of *any* exposure.

Study	Sample Type	Sample Size	Location	Setting	Outcome	Scale	Cut Off	Exp (Mos)	Birth (Yrs)
Bartels 2009 [10]	Population	8284	Europe	All	Behavior	Continuous	NA	0 - 36	1986 - 1995
Wilder 2009 [8]	Population	5357	N America	All	Learning	Continuous	15 - 23 pts	0 - 48	1976 - 1982
Kalkman 2009 [20]	Clinical	243	Europe	Inpatient	Behavior	Continuous	95th percentile	0 - 6	1981 - 1995
DiMaggio 2009 [9]	Clinical	5433	N America	Inpatient	Behavior	Categorical	NA	0 - 36	1999 - 2001
Roze 2008 [21]	Clinical	1345	Europe	Inpatient	Behavior	Continuous	LT 70	0 - 1	1997 - 1997
Guerra 2011 [22]	Clinical	95	N America	Inpatient	Learning	Continuous	2 SD below	0 - 1.5	2003 - 2006
Ing 2012 [25]	Population	2608	Australia	all	Learning	Continuous	1.5 SD Below	1 - 36	1989 - 1992

Table 1: Studies entered into meta-analysis association of pediatric anesthesia/surgery with neurodevelopmental pathology.

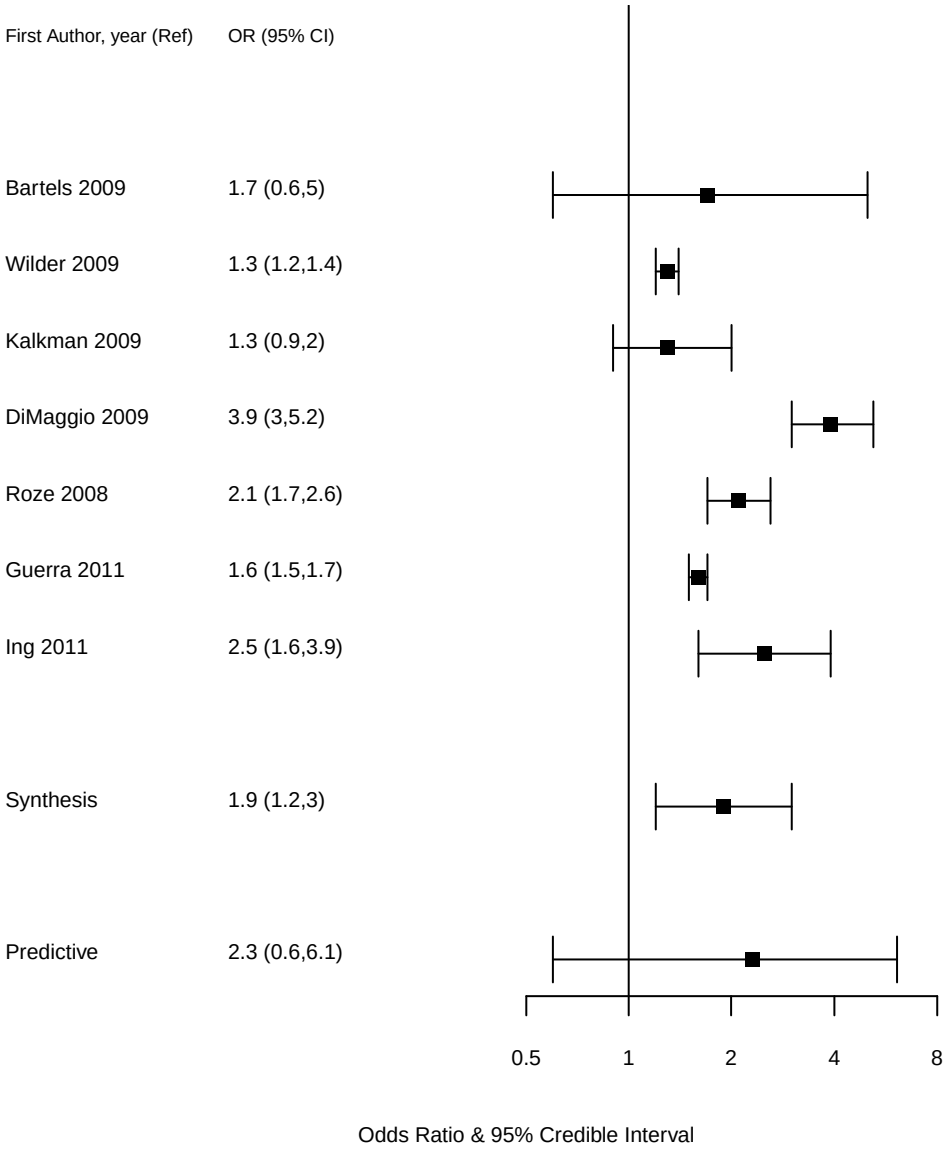

Figure 2: Forest Plot, meta-analysis unadjusted odds ratios for association of *any* exposure to anesthesia/surgery and behavioral or intellectual problems.

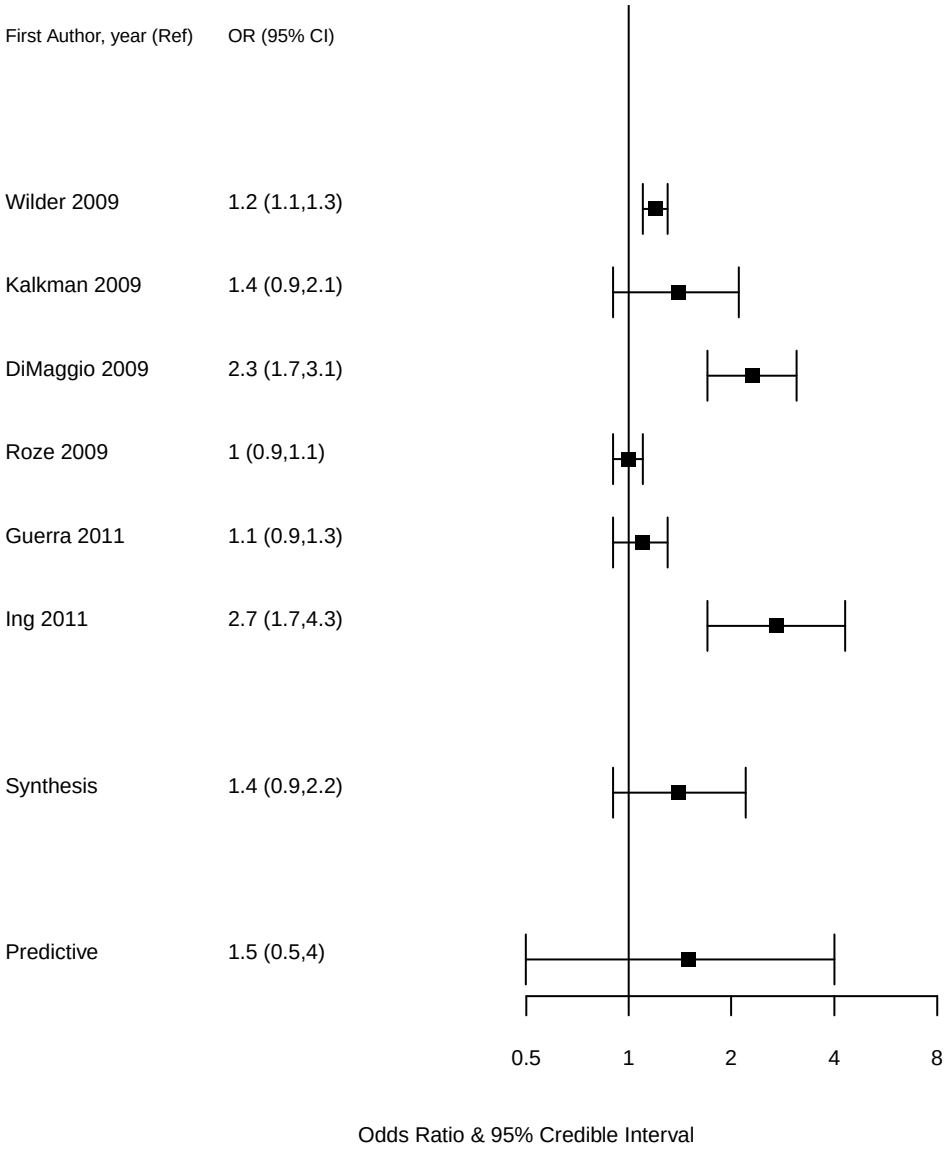

Figure 3: Forest Plot, meta-analysis *adjusted* odds ratios for association of *any* exposure to anesthesia/surgery and behavioral or intellectual problems.

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Appendix

```
# agnostic prior on studies, uniform prior on heterogeneity between
# studies (standard deviation of tau)
model
{
  for (i in 1:k)
     {
        P[i] <- 1/V[i] #define variance in terms of precisions for BUGS
   logor[i] ~ dnorm(delta[i], P[i]) #variation within studies
   delta[i] ~ dnorm(d, prec)  #variation between studies
}
d ~ dnorm(0, 1.0E-5) #summary for all studies
OR <- exp(d) #exponentiate to get back to OR scale

tau~dunif(0,10)
tau.sq<-tau*tau  #heterogeneity or between study variance
prec<-1/(tau.sq)
        p.harm<-step(d)  # probability that the OR is greater than 1

        d.new ~ dnorm(d, prec) #predictive distribution
OR.new <-exp(d.new)
        p.harm.new<-step(d.new)
}

# agnostic prior on studies, gamma prior on heterogeneity
# between studies (precision of tau)
```

```
model
{
  for (i in 1:k)
     {
        P[i] <- 1/V[i] #define variance in terms of precisions for BUGS
   logor[i] ~ dnorm(delta[i], P[i]) #variation within studies
   delta[i] ~ dnorm(d, prec)  #variation between studies
}
d ~ dnorm(0, 1.0E-5) #summary for all studies
OR <- exp(d) #exponentiate to get back to OR scale

prec~dgamma(0.001, 0.002)
        p.harm<-step(d)  # probability that the OR is greater than 1

        d.new ~ dnorm(d, prec) #predictive distribution
OR.new <-exp(d.new)
        p.harm.new<-step(d.new)}
```