Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias?

Short running title: confounding in acetaminophen ADHD link

Reem Masarwa[1, 2], Robert W. Platt[1, 2, 3, 4], and Kristian B. Filion[1, 2, 5]

[1] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada

[2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

[3]Research Institute of the McGill University Health Centre, McGill University, Montreal, Quebec, Canada

[4]Department of Pediatrics, McGill University, Montreal, Quebec, Canada

[5]Department of Medicine, McGill University, Montreal, Quebec, Canada

Corresponding author:

Kristian B. Filion, Centre for Clinical Epidemiology, Lady Davis Institute, Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada, Kristian.Filion@mcgill.ca

SOCIAL MEDIA QUOTE

The reported association between exposure to acetaminophen during pregnancy and the risk of ADHD in the offspring may be explained by unmeasured confounding and by characteristics such as parental ADHD and maternal migraine.

SYNOPSIS

STUDY QUESTION

Is the consistently reported association between acetaminophen use during pregnancy and the risk of ADHD in the offspring is due to unmeasured confounding?

WHAT'S ALREADY KNOWN

ADHD is a multifactorial syndrome, and its development cannot be attributed to a single risk factor. Published studies and subsequent meta-analyses of this association are likely to suffer from unmeasured confounding. Parental ADHD,and maternal migraine were not adjusted for in some published studies, and these variables may play a crucial role in the observed association.

WHAT THIS STUDY ADDS

Unmeasured confounding may explain the previously-reported association between acetaminophen use during pregnancy and risk of ADHD in the offspring. Bias analysis suggests that the association found in these previous studies is likely confounded

ABSTRACT

Background: Previous studies have suggested an association between acetaminophen use during pregnancy and the development of attention deficit hyperactivity disorder (ADHD) in the offspring. These findings may be due to bias.

Objectives: Our primary objective was to assess the role of potential unmeasured confounding in the estimation of the association between acetaminophen use during pregnancy and the risk of ADHD in the offspring through bias analysis. Our secondary objective was to assess the roles of selection bias and exposure misclassification in the estimation of this association.

Methods: We conducted a systematic literature search and meta-analyzed data across studies, using random-effects model. We conducted a bias analysis to studies that did not adjust for important confounders, to explore systematic errors related to unmeasured confounding, selection bias, and exposure misclassification.

Results: The systematic search resulted in seven studies included in our meta-analysis. When adjusted estimates were pooled across all studies, the risk ratio (RR) for ADHD was 1.35 (95% CI 1.25, 1.46, I2=48%). Sensitivity analysis for unmeasured confounding in this meta-analysis showed that a confounder of 1.69 with the exposure and outcome on the RR scale would reduce to 10% the proportion of studies with a true effect size of RR>1.10. Unmeasured confounding bias analysis decreased the point estimate in five of the seven studies and increased in two studies, suggesting that the observed association could be confounded by parental ADHD. Unadjusted and bias corrected risk ratios (bcRRs) were: RR=1.34, bcRR=1.13;

RR= 1.51, bcRR=1.17; RR=1.63, bcRR=1.38; RR=1.44, bcRR=1.17, RR=1.16, bcRR=1.18, RR=1.25, bcRR=1.05 and RR=0.99, bcRR=1.18.

Conclusions: Bias analysis suggests that the previously-reported association between acetaminophen use during pregnancy and an increased risk of ADHD in the offspring may be due to unmeasured confounding. Our ability to conclude a causal association between acetaminophen use during pregnancy and childhood ADHD is limited.

KEYWORDS acetaminophen; pregnancy; ADHD; confounding; bias

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BACKGROUND

An estimated 50-70% of women use analgesic and anti-pyretic drugs during pregnancy, with acetaminophen (e.g. Paracetamol, Tylenol) the most commonly used during this period.(1-3) Although acetaminophen crosses the placenta, it has been assigned a "Pregnancy Category B" status by the US Food and Drug Administration and is considered safe for use during all stages of pregnancy.(1, 4) However, in recent years, the use of acetaminophen in pregnancy has been associated with an increased risk of asthma and wheezing,(5) congenital malformations,(2) and neurodevelopmental disorders in the offspring.(6-8) Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in childhood. The etiology of ADHD is not fully known; (9) it is a multifactorial syndrome with a strong genetic link.(10) Other risk factors for ADHD include maternal age,(11) maternal socio-economic status,(12) maternal migraine,(13) and air pollution.(14) Although some of these risk factors, have been considered by previous studies in this area others have not been considered in the design or analysis and may confound the observed association.

In a recent meta-analysis of this association conducted by the lead author of the present study, ever use of acetaminophen during pregnancy was associated with an increased risk of ADHD in the offspring (relative risk [RR] 1.34, 95% confidence interval [CI] 1.21, 1.47, I^2=72%).(15) The meta-analysis included six cohort studies of ever use of acetaminophen during pregnancy.(15) Despite the observed association and its consistency with previous reports of this purposed association, there remains a need to better understand the potential role of bias in this

observed association given the multi-etiological nature of ADHD and the multiplicity of risk factors for ADHD.(16)

Quantitative bias analysis (QBA) is an epidemiological tool that provides a quantitative estimate of the direction, magnitude, and uncertainty arising from systematic error, under assumptions made about the bias parameters (e.g. prevalence of confounder). It models non-random errors that may distort the results of studies.(17, 18) Exploring potential biases may assist us to quantify the magnitude and direction of bias and identify factors that may influence the association between acetaminophen use during pregnancy and the risk of ADHD.

This study explored the potential role of bias in the previously-reported association between acetaminophen use during pregnancy and the risk of ADHD in the offspring. To achieve this, we updated the previous published meta-analysis and conducted a sensitivity analysis for unmeasured confounding for the meta-analytic estimate.(15) We then explored the magnitude and direction of unmeasured and uncontrolled confounding, selection, and exposure misclassification bias in original published studies.

METHODS

No institutional review board approval was required for this study, as it is a methodological paper that only uses previously published data.

Bias analysis

We performed a bias analysis to assess the potential role of unmeasured confounding, selection and exposure misclassification bias in studies that explored the association between acetaminophen and ADHD. We performed a bias analysis, by using a fixed set of assumptions for each analysis for unmeasured confounding and selection bias. For exposure misclassification bias analysis, we assumed a range of sensitivities and specificities to calculate bias corrected measures. In addition, we performed a systematic review of the literature and conducted a meta-analysis and a sensitivity analysis for unmeasured confounding of the meta-analyzed effect estimate.

Literature search

The details of our systematic literature search have been reported previously.(15) Briefly, we searched MEDLINE, EMBASE, and the Cochrane library from inception until December 2018 for all observational studies examining the association ever acetaminophen use during pregnancy and the risk of ADHD in the offspring. As part of the present study, we updated this literature search from January 2017 to January 2019 to identify newly published studies assessing the association of interest.

Studies included in bias analysis

Selection and exposure misclassification bias analyses require the total number of exposed (acetaminophen) and unexposed women by outcome (ADHD) status (i.e., the four cells of the 2 x 2 table) to estimate the unadjusted risk and perform the bias-corrected analyses. The unmeasured confounding analysis can be performed using either the 2x2 table or formula A by Lash et al.(17) For studies that did not report the required data, we contacted the authors to request these data

Formula A: $RR_{adj} = RR_{obs} *(RR_{CD}p_0(1-p_0)/RR_{CD}p_1(1-p_1))$

Bias analysis

Unmeasured confounding

We performed two separate analyses to assess bias due to unmeasured confounding. The first was a sensitivity analysis for unmeasured confounders that was applied to our meta-analysis. In this analysis, we assessed the impact of unmeasured confounding on the pooled estimate of the meta-analysis while assuming a minimum clinically important difference in meta-analysis (RR>1.10), and although the true causal effect may be heterogeneous across studies, there is evidence that overall, many of these effects are strong enough to merit scientific interest.(19) The second examined the potential impact of unmeasured confounding in each of the individual included studies that did not measure and/or adjust for a given potential confounder by assuming a different prevalence for each confounder in the exposed and unexposed groups. Parental ADHD (genetic link),(10) maternal fever,(20-22) maternal migraine,(13) maternal smoking and alcohol consumption,(23) and air-pollutants,(14) are risk factors for ADHD that

were considered as potential confounders in bias analysis.(24-26) Some of these potential confounders were measured and adjusted for in the original studies and some were not. Parental ADHD and exposure to air-pollutants were not measured in the studies,(6-8, 27-30) fever was not measured in two studies,(7, 29) smoking in two studies,(27, 28) alcohol consumption in two studies,(27, 28), and maternal migraine in five studies.(6, 27-30) We calculated bias-corrected RRs (bcRRs) for each of these potential confounders. Reported strengths of associations between the potential confounders and ADHD, the prevalence of each unmeasured confounder in the exposed and unexposed,(2, 31-33) and the R code including the calculation steps are provided in Table 1. and Appendix A, respectively.

Selection bias

Selection bias is a potential threat to the validity of any epidemiologic study. Mothers with comorbidities resulting in pain and fever medication use may be more or less likely to participate in a study examining the association between acetaminophen and ADHD. This may result in a biased observed effect. In our analysis of potential selection bias, we generated two scenarios, one resulting in a higher participation probability among the mothers-child pairs exposed to acetaminophen and the second assuming the opposite. We assumed non-differential selection. Participation probabilities were a: exposed-with outcome 0.85, unexposed-without outcome 0.45, exposed-no outcome 0.85, unexposed-no outcome 0.45 and vice versa. We calculated bcRRs and their subsequent 95% CIs. To illustrate the opening of a bias path for selection bias between the exposure (E) and the outcome (D), we present a directed acyclic graph (DAG) in **Figure 1**. Let us consider the situation at cohort entry, where

acetaminophen (E) is our exposure of interest and maternal characteristics/risk factors (U) of the outcome (D) may affect the participation probability, where S=1 indicates those who agreed to participate.

Exposure misclassification

Exposure misclassification is possible since exposure was determined by self-report, and acetaminophen is an over the counter (OTC) medication. This may lead to either under or over reporting of acetaminophen use among pregnant women. We assume a non-differential misclassification, since the probability of acetaminophen exposure misclassification is likely not related to the outcome. We performed probabilistic exposure misclassification bias analysis based on probability density functions for sensitivity and specificity for reported acetaminophen use during pregnancy.(34, 35) For exposure misclassification, we assumed a sensitivity between 0.55 and 0.80, and a specificity between 0.9 and 0.99; these estimates were based on the reporting of analgesic and antipyretic use in previous studies of pregnant women.(34, 35) We then calculated bcRRs and their subsequent 95% CIs.

E-value

The E-value is the minimum strength of association on the RR scale that an unmeasured confounder would need to have with both the exposure and the outcome to fully explain an exposure-outcome association.(36, 37) We estimated the E-values for the pooled estimate from the updated meta-analysis and for each of the four studies included in bias analysis.

Meta Analyses

We conducted three meta-analyses using DerSimonian and Laird random-effects models with inverse variance weighting to estimate pooled RRs and corresponding 95% CIs. In the first, we updated the previous meta-analysis (n=7) according to the findings from the literature search. The remaining two meta-analyses (n=4) pooled selection, and exposure misclassification bcRRs and corresponding 95% CIs among studies. For each analysis, the amount of heterogeneity that was present was estimated using the I^2 statistics.(38) For the updated meta-analysis, we conducted a sensitivity analysis for unmeasured confounding, with the results presented graphically. The plot illustrates the proportion of studies with a true effect size (assumption RR≥1.10) in relation to the magnitude of a bias factor on the RR scale (lower x-axis) and it corresponding equivalent, the minimum confounding strength that would be associated with both the exposure and the outcome (upper x-axis).(19) All analyses were conducted using R version 3.5.3 and Package "episensr" 0.9.3,(39)Package "metafor" 2.0-0,(40) Package "forestplot" 1.7.2,(41), Package "metaviz",(42) and Package "EValue" 2.0.0.(43)

RESULTS:

Search results

Literature search yielded 57 new citations. The removal of duplicates and title and abstract review led to the exclusion of 50 citations. Further review resulted in two new studies included in the updated meta-analysis. The selection process is illustrated in **e-Figure 1**. We excluded the study by Brandilstuen et al. (44), which had been included in the previous meta-analysis since it was the only sibling-matched cohort and included data from the same Norwegian cohort as the recently published study by Ystrom et al.(30) Consequently, seven studies were included in updated meta-analysis. The characteristics of these studies are listed in **e-Table 1.**

Characteristics of studies included in selection and exposure misclassification bias

The four studies included in selection and exposure misclassification bias analysis and their characteristics are listed in **e-Table 2**.(6, 7, 27, 29) In all studies, the exposure was measured prior to the occurrence of the outcome.(6, 7, 27, 29) Exposure to acetaminophen was assessed by telephone interviews during pregnancy in two studies,(7, 27) during and after delivery in one study(6), and after delivery in one study.(29)

Updated meta-analysis

The updated meta-analysis produced results (RR 1.31, 95% CI 1.23, 1.39, I^2=48%; **Figure 2)** that were consistent with those of the previous meta-analysis(15). When restricting the analysis to the four studies included in the bias analysis, the pooled RR was 1.34 (95% CI 1.09, 1.59, I^2=63%; **e-Figure 2.**).

Sensitivity analysis for unmeasured confounding in meta-analysis and E-value for meta-analysis

The sensitivity analysis plot for updated meta-analysis is shown in **Figure 3.** A bias factor of 1.50 (equivalent to a confounder, associated with both the exposure and outcome with a strength of RR=1.69) was required to reduce the proportion of studies with a true RR>1.10 to <10%. An E-value of 2.03 was required to explain away the significant association found in this updated meta-analysis.

Unmeasured confounding in individual studies

The bcRRs for unmeasured confounders are detailed in **Table 2**. Parental ADHD and maternal migraine were the unmeasured confounders that resulted in the greatest reductions in the point estimates (**e-Figures 2 and 3)**. In the studies by Stergiakouli et al.,(7) and Tovo Rodrigues et al.,(29) the point estimates increased for all unmeasured confounders. For the remaining studies,(6, 8, 27, 28, 30) the point estimates decreased for all unmeasured confounders. The study by Avella-Garcia et al (27) had the most substantial reduction in the unadjusted RR (RR=1.44) after correcting for parental ADHD (bcRR=1.17), maternal smoking (bcRR=1.05), maternal migraine (bcRR=1.03) and exposure to air pollutants (bcRR=1.30).

Selection bias and exposure misclassification corrected meta-analysis

Selection and exposure misclassification bcRRs are described in **Table 3**. Meta-analysis of bias corrected estimates resulted in a bcRR of 1.31 (95% CI 0.91, 1.71, I^2=0%; **e-Figure 4**) when correcting for selection bias and 1.91 (95% CI 0.04, 3.77, I^2=0%; **e-Figure 5**) when correcting for

exposure misclassification. The forest plots of the unadjusted meta-analysis and bias corrected meta-analysis are presented in **e-Figures 4** and **5,** respectively.

E-value for individual studies

The E-values for each individual study included in bias analysis are described in **e-Table 3**. An E-value as small as 1.60 was sufficient to explain the association in the study by Stergiakouli et al.(7) and an E-value of 2.64 was required to explain the association in the study by Thompson et al.(8)

COMMENT

Principal findings

The objective of this study was to explore the role of potential unmeasured confounding in the previously reported association between acetaminophen use during pregnancy and the risk of ADHD. Although previous reports have suggested (45, 46) the presence of bias, we were able to quantify the impact of this bias and determine its direction. Under the assumptions of our bias analysis, we showed that unmeasured confounding and exposure misclassification bias play a role in this literature. Our QBA suggested that the results of the meta-analysis (RR 1.35, 95% CI 1.25, 1.46, I^2=48%) are relatively sensitive to unmeasured confounding, with a confounding factor as small as RR=1.69, in each study is able to reduce the proportion of studies with true RRs greater than 1.10 to less than 10%. Adjusting for parental ADHD shifted the point estimate towards the null, with the RR decreasing in five of the studies and increasing in two studies. Similar results were observed for maternal migraine. The E-value for individual studies suggested that the observed association may be explained by an unmeasured confounder as small as 1.60 in the study by Stergiakouli et al.(7) These findings suggest the presence of moderate residual confounding in the original studies and support the results of sensitivity analysis for unmeasured confounding of the meta-analysis.

In the bias analysis of unmeasured confounders, we corrected for several confounders identified from the literature.(10, 14, 21, 47-49) The largest shifts in point estimates were for parental ADHD and maternal migraine. We estimated the prevalences of the confounders from the literature.(2, 31-33) These assumed prevalences are likely to drive the change in bcRRs. The

E-values for each individual study suggested that an unmeasured confounder as small as 1.61 in the study by Stergiakouli et al. (7) and 2.38 in the study by Liew et al. (6) would be required to explain the observed association. These results are compatible with reported strengths of the confounding associations for parental ADHD (OR=1.68),(10) and maternal migraine (OR=1.81).(13)

Selection bias did not explain the observed association. Exposure misclassification bias appeared to have a larger impact on the reported measure of association. In our QBA for selection bias, the bias-corrected meta-analytic result (bcRR 1.31, 95% CI 0.91, 1.71, I^2=0%) was similar to that obtained in the updated meta-analysis (RR 1.35, 95% CI 1.25, 1.46, I^2=48%). These results demonstrate that, under the assumptions made, selection bias resulting in a higher participation rate among a less or more healthy population does not explain the observed association. Exposure misclassification QBA increased the strength of the estimated association (bcRR 1.91, 95% CI 0.04, 3.77, I^2=0%) compared to that estimated in the updated meta-analysis. Although the observed association became non-significant, it strengthened, after assuming a range for sensitivity and specificity values for the reported use of analgesic medications during pregnancy.(34, 35) This may indicate under reporting of OTC medications during pregnancy and that the observed association may be underestimated. Exposure misclassification bias likely represents a more important source of bias than selection bias in this literature. Data regarding acetaminophen use was assessed by telephone interview in the studies.(6, 7, 27, 29) However, a healthy mother who experienced an uneventful pregnancy will be less likely to report medication use during and after pregnancy than a mother with comorbidities and an eventful pregnancy. This misclassification will likely result in over

reporting of acetaminophen use. In addition, the exposure definition was binary, with women classified as ever-users versus non-users, (6, 7, 27, 29) potentially resulting in substantial exposure misclassification. Although use of acetaminophen is usually for short periods and sporadic (rather than continuous), this approach considers women to be exposed throughout the entire pregnancy. This can also potentially lead to immortal time bias due to the time-fixed exposure definition and the improper classification of unexposed person-time as exposed person-time. Consequently, this bias adjustment may not be representative of the true effect of exposure misclassification bias. An additional point to consider is that bias in observational studies may be also introduced due to outcome misclassification. However, exposure misclassification is expected to have a larger impact in cohort studies, since exposure status is more difficult to assess and categorize. In addition, most outcomes that are studied are relatively uncommon; even when an association does exist, the majority of exposed and unexposed individuals do not experience the outcome.(50)

Our QBA revealed that uncertainty remains regarding the potential association between acetaminophen use during pregnancy and the risk of ADHD development in the offspring. Are these results clinically significant and with which level of certainty can we assume a causal association? A definitive answer to this question may be only achievable through a randomized controlled trial. The ideal scenario would be a trial that randomizes pregnant women to acetaminophen or an active comparator indicated for the treatment of pain and fever in pregnancy that is safe with respect to the risk of ADHD development in the offspring. Unfortunately, such a trial would be impossible to conduct due to practical considerations (e.g.,

sample size, follow-up duration, and ethical concerns). Therefore, we must rely on the available observational data to address this drug safety issue.

Strengths of the study

This bias analysis has several strengths. First, we conducted a systematic search of the literature and updated the meta-analysis. Although the results of the updated meta-analysis were consistent to the previous report, we were able to show that the pooled estimate may be biased, by conducting a sensitivity analysis. Second, we explored the role of unmeasured confounding in both the individual studies and their meta-analysis. This analysis showed that bias analysis for unmeasured confounding has an important role when conducting meta-analysis. Indeed, although the meta-analysis results showed a decrease in random error and corresponding narrowing of the CIs, bias analysis still suggested the presence of bias. Finally, our study showed that bias analysis for is especially of grave importance when assessing an association without an established biological mechanism and an outcome with multifactorial etiology and a broad definition.

Limitations of the data

Our study has several potential limitations. First, we estimated prevalence values for the bias analysis from the literature, but some were based on expert clinical opinion. Second, only four of the seven studies identified in our systematic literature search reported the data required for selection and exposure misclassification bias analysis. For this reason, we conducted sensitivity analyses restricting our meta-analysis to these four studies, facilitating comparisons across

analyses. Third, although we were unable to calculate 95% CIs when adjusting for unmeasured confounding, under the assumptions made in our analysis, we confirmed that if unmeasured confounding existed it could have biased the observed association. Fourth, the E-value is not an observed effect estimate; rather, it represents a hypothetical effect assessed in a sensitivity analysis.(51) The same RR will always generate the same E-value, regardless of the study question. Therefore, in addition to estimating E-values, we also conducted a sensitivity analysis for the meta-analysis to assess the magnitude of a bias factor and the minimum confounding strength for both the exposure and the outcome that would be required to explain the association. Fifth, although unmeasured confounding may partially explain the observed association, it may also be explained by uncontrolled or poorly measured confounders. For example, fever during pregnancy may be reported by the mother and categorized as the presence or absence of fever without reporting the temperature measured or timing of the fever. Sixth, all studies included in our analysis were cohort studies designed to assess a broad range of hyperkinetic disorders in children as an outcome and not only ADHD. Seventh, there was substantial heterogeneity in meta-analyses, which may be due to differences in the populations and different outcome assessment strategies in the studies. With only seven included studies, there were insufficient data to explore the potential sources of this heterogeneity. Finally, as is true for all systematic reviews, our study may be affected by publication bias.

Interpretation

The results of our bias analysis emphasize two major points. The first is that further studies are required to confirm our findings, which suggests that there may be a need for careful examination of current guidelines for the treatment of pain and fever during pregnancy. The second is that bias analysis may be a practical and productive tool in pharmacoepidemiology, especially in situations where the etiology and the risk factors are not fully known or when there is no established biological mechanism for the observed association.

Conclusions

The observed association between acetaminophen use during pregnancy and the increased risk for ADHD in the offspring is likely the result of bias. This systematic error appears to be predominantly driven by unmeasured confounding and exposure misclassification. We recommend the use of bias analysis when conducting observational studies, particularly for studies of associations of more modest magnitudes, when other possible explanations of the association exist, and the findings are likely to affect clinical practice and public health.

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FIGURE LEGENDS

Figure 1. Directed acyclic graph of path opening for selection bias. E and D are the exposure (acetaminophen) and the outcome of interest (ADHD), respectively. U represents a potential unmeasured confounder that may explain the observed association between E and D. S=1 represents the selection probability to participate in the cohort. The directed acyclic graph is drawn under the assumption that the selection probability is different among participants exposed and not exposed to acetaminophen.

Figure 2. Risk ratios and confidence intervals from a random effects meta-analysis of seven cohort studies on the risk for attention deficit hyperactivity disorder after acetaminophen use during pregnancy.

Figure 3. Sensitivity analysis for random-effects meta-analysis of observational studies plot. The upper x-axis represents the magnitude of a bias factor on the risk ratio scale, the upper x-axis the minimum confounding association with both the exposure and outcome. The y-axis represents the proportion of studies with a true relative risk above scientific significance, risk ratio>1.10.

Figure 4. Risk ratios and confidence intervals from a random effects meta-analysis of seven cohort studies on the risk for attention deficit hyperactivity disorder after acetaminophen use during pregnancy.

Table 1. Reported association between confounders and ADHD and confounder prevalences for bias analysis		
Potential Unmeasured confounder	**Effect size (95% CI)**	**Confounder Prevalence**
Parental ADHD (52)	OR 1.68 (1.17, 2.41)	p_1=0.5, p_0=0.2
Maternal fever (21)	OR 2.50 (1.20, 5.20)	p_1=0.75, p_0=0.25
Maternal smoking (53)	OR 2.1 (1.10, 4.10)	p_1=0.10, p_0=0.05
Maternal alcohol consumption (53)	OR 2.5 (1.10, 5.50)	p_1=0.08, p_0=0.06
Prematurity (54)	OR 3.04 (2.19, 4.21)	p_1=0.25, p_0=0.1
Maternal migraine (47)	OR 1.81 (1.53, 2.12)	p_1=0.3, p_0=0.14
Exposure to air pollutants (55)	RR 5.06 (1.43, 17.93)	p_1=0.6, p_0=0.4

Abbreviation: CI, confidence interval, p_1, confounder prevalence in the exposed, p_0, confounder prevalence in the non-exposed

Table 2. Unmeasured confounding bcRRs for individual studies examining the association between acetaminophen use during pregnancy and the risk of ADHD in the offspring.		
Confounder	**Unadjusted RR/OR, (95% CI)**	**bcRR**
Parental ADHD		
Streissguth et al. 1987 (28)	1.34 (0.93, 1.93)	1.13
Liew et al. 2014 (6)	1.51, (1.31, 1.74)	1.17
Thompson et al. 2014 (8)	1.63 (1.28, 2.08)	1.38
Avella-Garcia et al. 2016 (27)	1.44, (0.75, 2.75)	1.17
Stergiakouli et al. 2016 (7)	1.16, (0.96, 1.39)	1.18
Ystrom et al. 2017 (30)	1.25 (1.14, 1.37)	1.05
Tovo Rodrigues et al. 2018 (29)	0.99, (0.80-1.23)	1.18
Fever		
Stergiakouli et al. 2016 (7)	1.16, (0.96, 1.39)	1.40
Tovo Rodrigues et al. 2018 (29)	0.99, (0.80, 1.23)	1.42
Maternal smoking		
Streissguth et al. 1987 (28)	1.34 (0.93, 1.93)	1.27
Avella-Garcia et al. 2016 (27)	1.44, (0.75, 2.75)	1.05
Maternal alcohol consumption		
Streissguth et al. 1987 (28)	1.34 (0.93, 1.93)	1.30
Avella-Garcia et al. 2016 (27)	1.44, (0.75, 2.75)	1.02
Maternal migraine		
Streissguth et al. 1987	1.34 (0.93, 1.93)	1.20
Liew et al. 2014 (6)	1.51, (1.31, 1.74)	1.11
Avella-Garcia et al. 2016 (27)	1.44, (0.75, 2.75)	1.03
Ystrom et al. 2017	1.25 (1.14, 1.37)	1.11
Tovo Rodrigues et al. 2018 (29)	0.99, (0.80, 1.23)	1.02
Exposure to air pollutants		
Streissguth et al. 1987 (28)	1.34 (0.93, 1.93)	1.02
Liew et al. 2014 (6)	1.51, (1.31, 1.74)	1.30

Thompson et al. 2014 (8)	1.63 (1.28, 2.08)	1.24
Avella-Garcia et al. 2016 (27)	1.41, (1.01, 1.98)	1.30
Stergiakouli et al. 2016 (7)	1.16, (0.96, 1.39)	1.30
Ystrom et al. 2017 (30)	1.25 (1.14, 1.37)	0.95
Tovo Rodrigues et al. 2018 (29)	0.99, (0.80, 1.23)	1.30

Abbreviation: RR, risk ratio; OR, odds ratio; CI, confidence interval; bcRR, bias corrected risk ratio

Table 3. Selection and exposure misclassification bcRRs and 95% CIs for studies of the association between acetaminophen use during pregnancy and the risk of ADHD in the offspring.

Selection Bias	**Unadjusted RR, (95% CI)**	**bcRR, (95% CI)** **high participation rate**	**bcRR, (95% CI)** **low participation rate**
Liew et al. 2014 (6)	1.51, (1.31, 1.74)	1.51, (1.31, 1.74)	1.50, (1.30, 1.73)
Avella-Garcia et al. 2016 (27)	1.44, (0.75, 2.75)	1.44, (0.72, 2.84)	1.43, (0.72, 2.77)
Stergiakouli et al. 2016 (7)	1.16, (0.96, 1.39)	1.16, (0.96, 1.41)	1.15, (0.96, 1.37)
Tovo Rodrigues et al. 2018 (29)	0.99, (0.80-1.23)	0.99, (0.78, 1.25)	0.99, (0.81, 1.21)
Exposure Misclassification	**Unadjusted RR, (95% CI)**	**bcRR, (95% CI)**	**Direction of change**
Liew et al. 2014 (6)	1.51	1.99	↑
Avella-Garcia et al. 2016 (27)	1.44	1.66)	↑
Stergiakouli et al. 2016 (7)	1.16	1.27	↑
Tovo Rodrigues et al. 2018 (29)	0.99	1.78	↑

Abbreviation: CI, confidence interval; RR, risk ratio; bcRR, bias corrected risk ratio. *CIs are presented only for selection bias analysis.

TABLES LEGENDS

Tables are stand-alone

FIGURES

Figure 1.

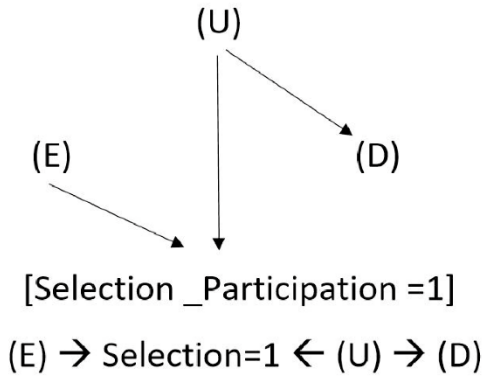


Figure 2.

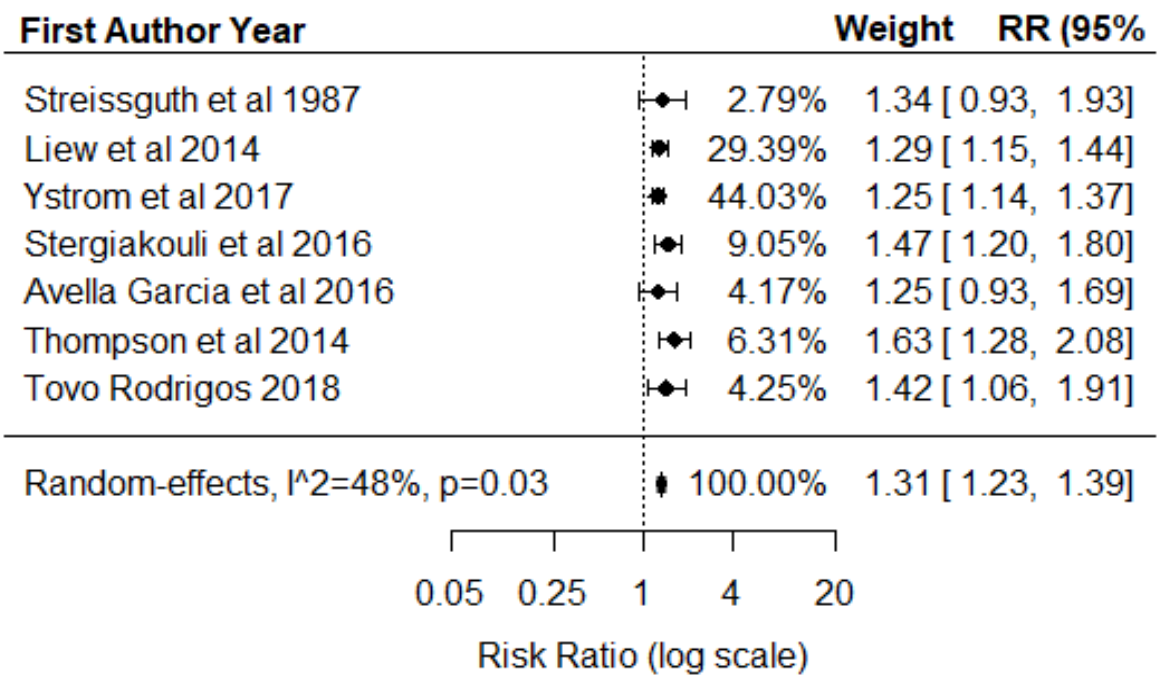
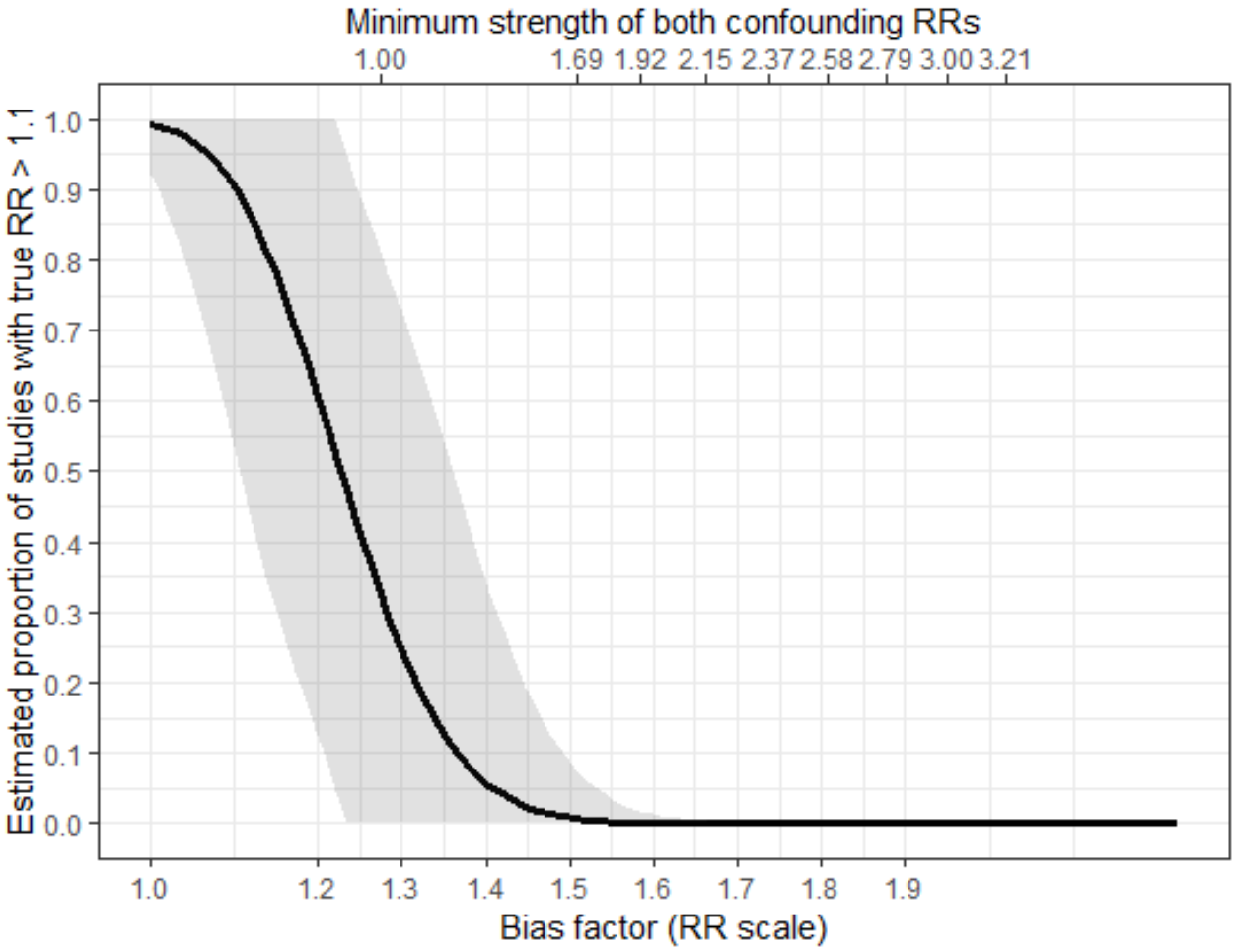

First Author Year
Weight
RR (95%
Streissguth et al 1987
2.79%
1.34 [0.93, 1.93]
Liew et al 2014
29.39%
1.29 [1.15, 1.44]
Ystrom et al 2017
44.03%
1.25 [1.14, 1.37]
Stergiakouli et al 2016
9.05%
1.47 [1.20, 1.80]
Avella Garcia et al 2016
4.17%
1.25 [0.93, 1.69]
Thompson et al 2014
6.31%
1.63 [1.28, 2.08]
Tovo Rodrigos 2018
4.25%
1.42 [1.06, 1.91]
Random-effects, I^2=48%, p=0.03
100.00%
1.31 [1.23, 1.39]
0.05
0.25
1
4
20
Risk Ratio (log scale)

Figure 3.


Minimum strength of both confounding RRs
1.00
1.69
1.92
2.15
2.37
2.58
2.79
3.00
3.21
Estimated proportion of studies with true RR > 1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
1.0
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
Bias factor (RR scale)

SUPPLEMENTAL TABLES

e-Table 1. Characteristics of studies included in updated meta-analysis

Study, Year	Exposure measurement	Prevalence of acetaminophen use	Main outcome measurement	Child age at follow up, years (range)	Trimester exposure and pregnancy weeks of exposure	Exposure assessment
Streissguth et al. 1987 (28)	Prior to the occurrence of the outcome	41%	Attention score Child IQ score	4 (4, 4.3)	Trimester(S)- 1+2 Gestational weeks- ≤ week 20	Interview during the fifth month of pregnancy
Liew et al. 2014 (6)	Prior to the occurrence of the outcome	56%	SDQ	12.7 (10.4, 15.6)	Trimester(S)- All Exposure Gestational weeks- All	Telephone interview at weeks 12 and 30 of pregnancy and 6 months after delivery
Thompson et al. 2014 (8)	Prior to the occurrence of the outcome	50%	SDQ	11 (3.5, 11)	Trimester(S)- All Gestational weeks- ≤ NA	Telephone interview immediately soon after delivery
Avella Garcia et al. 2016 (27)	Prior to the occurrence of the outcome	41%	ADHD-DSMIV	4.8 (1.2, 5)	Trimester(S)- All Exposure Gestational weeks- ≤ week	Telephone interview weeks 12 and 32 of pregnancy

					32	
Stergiakouli et al. 2016 (7)	Prior to the occurrence of the outcome	50%	SDQ	7 (4, 16)	Trimester(S)- All Exposure Gestational weeks- ≤ week 32	Interviews at weeks 18 and 32
Ystrom et al. 2018 (30)	Prior to the occurrence of the outcome	47%	DSMIV	NA (3, 15)	Trimester(S)- All Exposure Gestational weeks- All	interview at weeks 12 and 30 of pregnancy and 6 months after delivery
Tovo Rodrigues et al. 2018 (29)	Prior to the occurrence of the outcome	28%	SDQ	6 (3 ,11)	Trimester(S)- All Exposure Gestational weeks- All	Telephone interview soon after delivery Ever user

Abbreviation: IQ, intelligence quotient; SDQ, strengths and difficulties questionnaire; ADHD, attention deficit hyperactivity disorder; DSM IV, diagnostic and statistical manual of mental disorders IV.

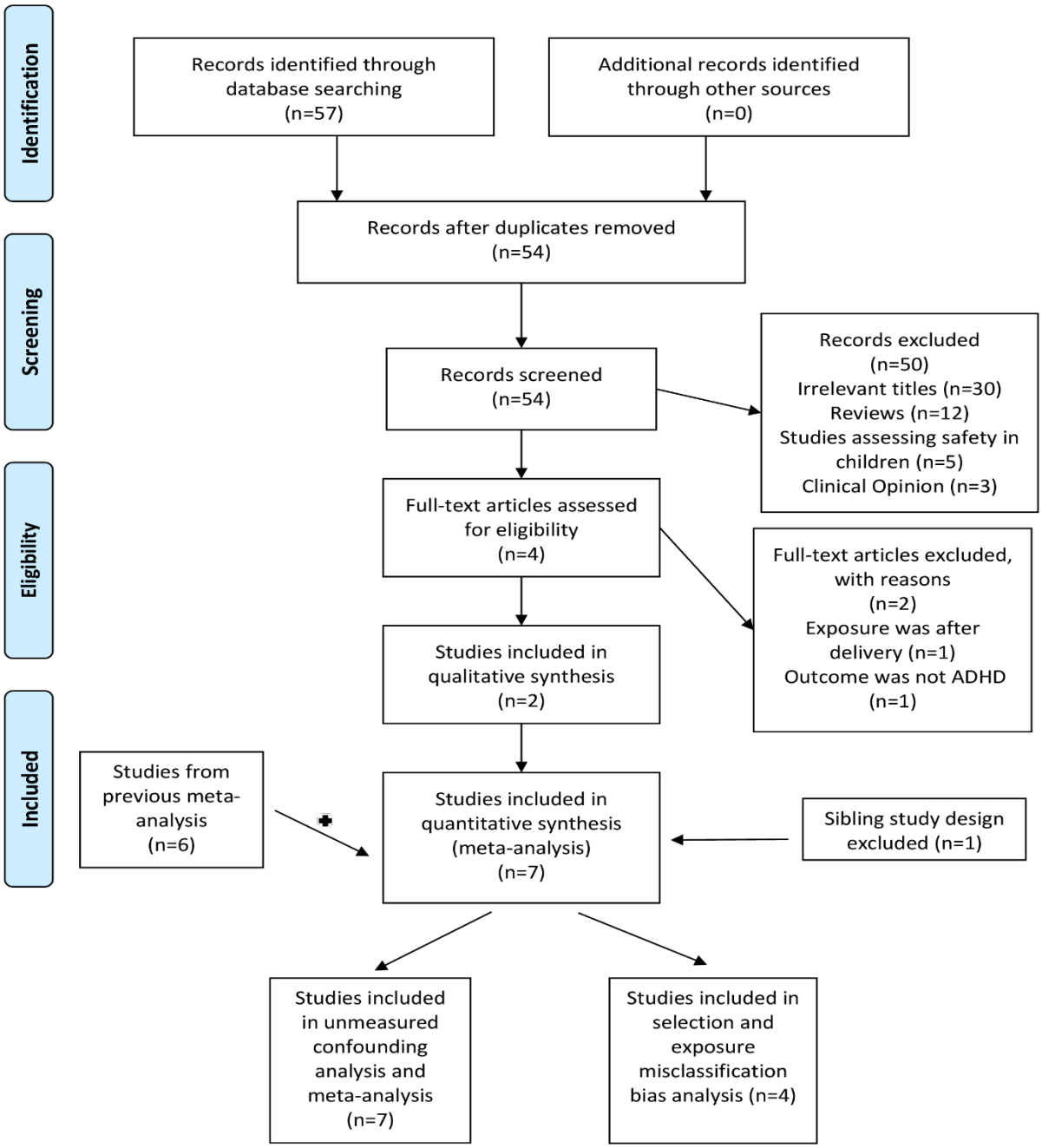
e-Table 2. Characteristics of studies included in selection and exposure misclassification bias analysis of association between acetaminophen use during pregnancy and the risk of ADHD in the offspring.

Study, Year	Exposure measurement	Number of patients by group	Age at outcome assessment, method of assessment	Exposure assessment, exposure definition
Liew et al. 2014 (52)	Prior to the occurrence of the outcome	Exposed events: 551 Unexposed events: 283 Exposed non-events: 35,656 Unexposed non-events: 27,852	11 years, parental SDQ score	Telephone interview at weeks 12 and 30 of pregnancy and 6 months after delivery, Ever user
Stergiakouli et al. 2016 (7)	Prior to the occurrence of the outcome	Exposed events: 246 Unexposed events: 187 Exposed non-events: 4,169 Unexposed non-events: 3,715	7 years, parental SDQ score	Telephone interview weeks 18 and 32 of pregnancy, Ever user
Avella Garcia. 2016 (27)	Prior to the occurrence of the outcome	Exposed events: 18 Unexposed events: 18 Exposed non-events: 802 Unexposed non-events: 1,163	5 years, ADHD-DSMIV	Telephone interview weeks 12 and 32 of pregnancy, Ever user
Tovo Rodrigues et al. 2018 (29)	Prior to the occurrence of the outcome	Exposed events: 102 Unexposed events: 274 Exposed non-events: 852 Unexposed non-events: 2,245	6 years, parental SDQ score	Telephone interview soon after delivery, Ever user

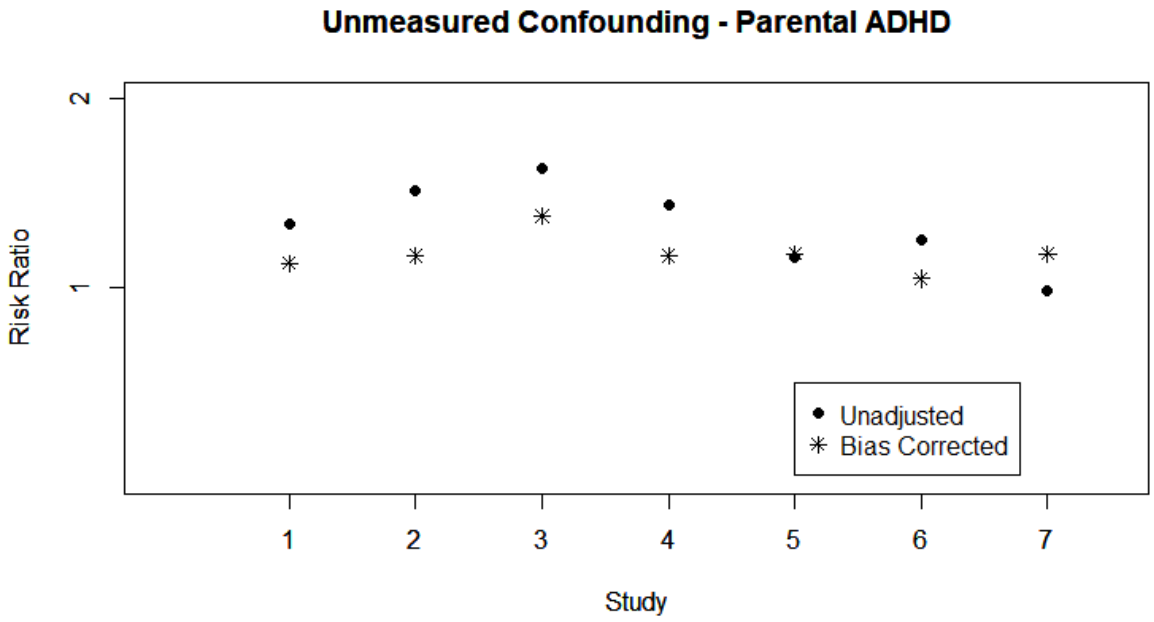
Abbreviation: ADHD, attention deficit hyperactivity disorder; SDQ, strengths and difficulties questionnaire; DSMIV, diagnostic and statistical manual of mental disorder IV

SUPPLEMENTAL FIGURES

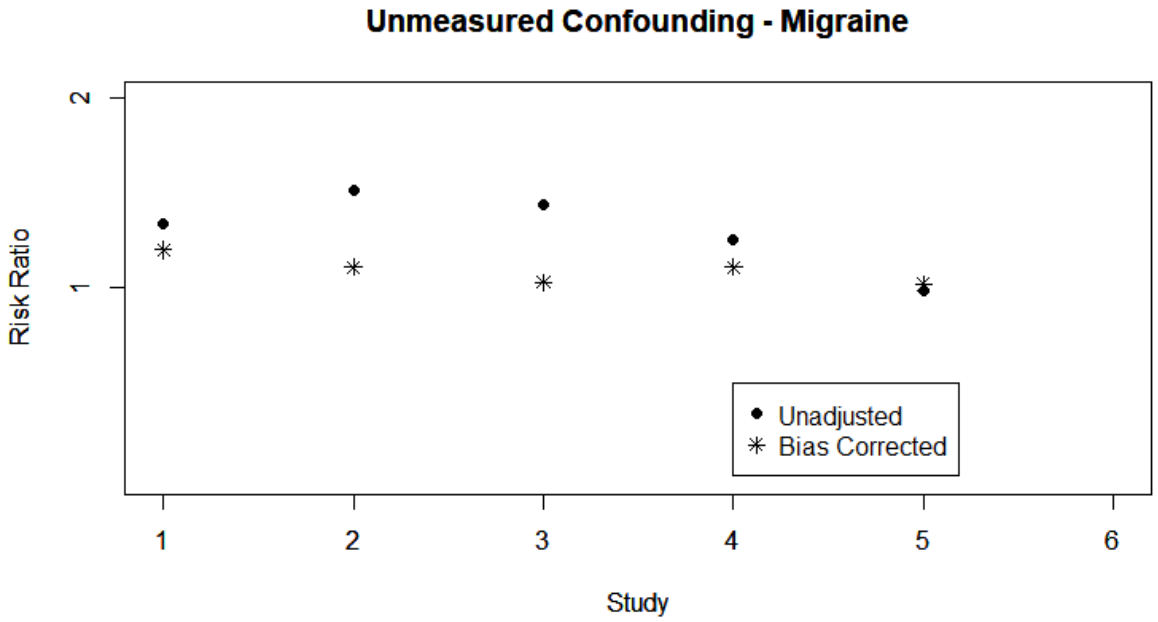
e-Figure 1. PRISMA Flow diagram describing study selection for updated systematic literature search for studies of the association between acetaminophen use during pregnancy and the risk of Attention deficit hyperactivity disorder in the offspring.



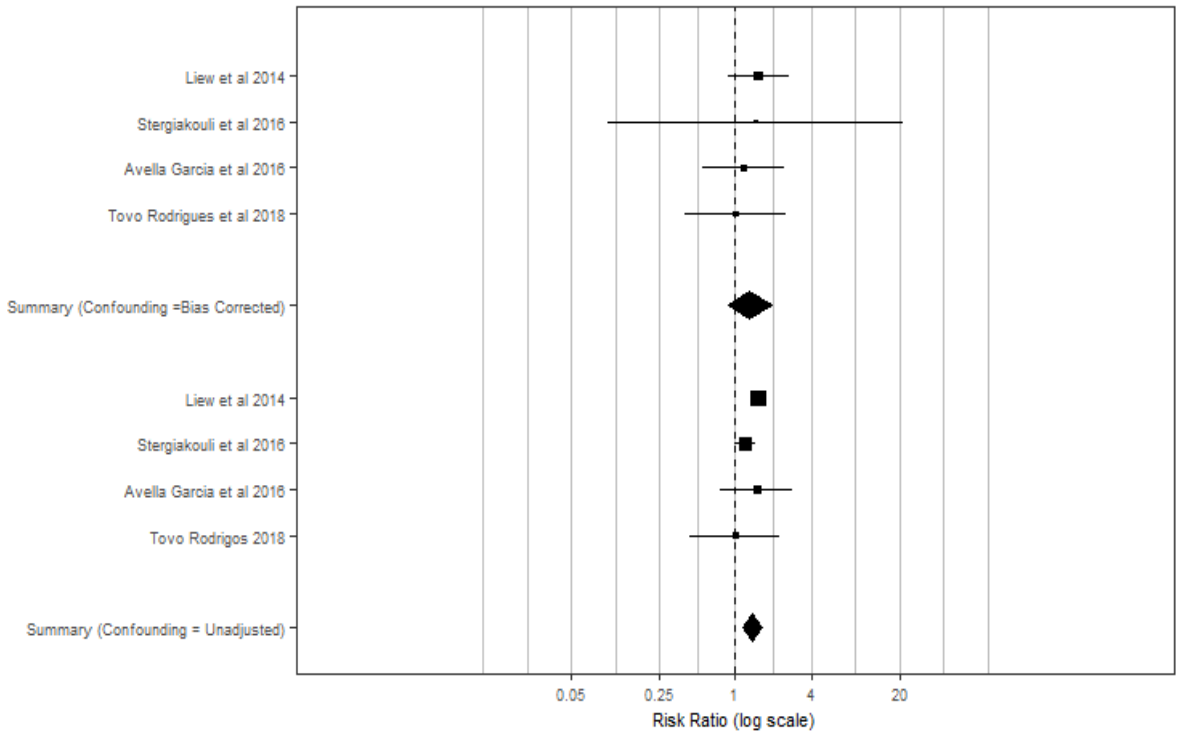
e-Figure 2. Unadjusted and bias corrected risk ratios for unmeasured confounding- parental ADHD. X-axis: study number, y-axis: RR. 1: Streissguth et al. 1987, 2: Liew et al. 2014, 3: Thompson et al. 2014, 4: Avella-Garcia et al. 2016, 5: Stergiakouli et al. 2016, 6: Ystrom et al. 2017, 7: Tovo Rodrigues et al. 2018.



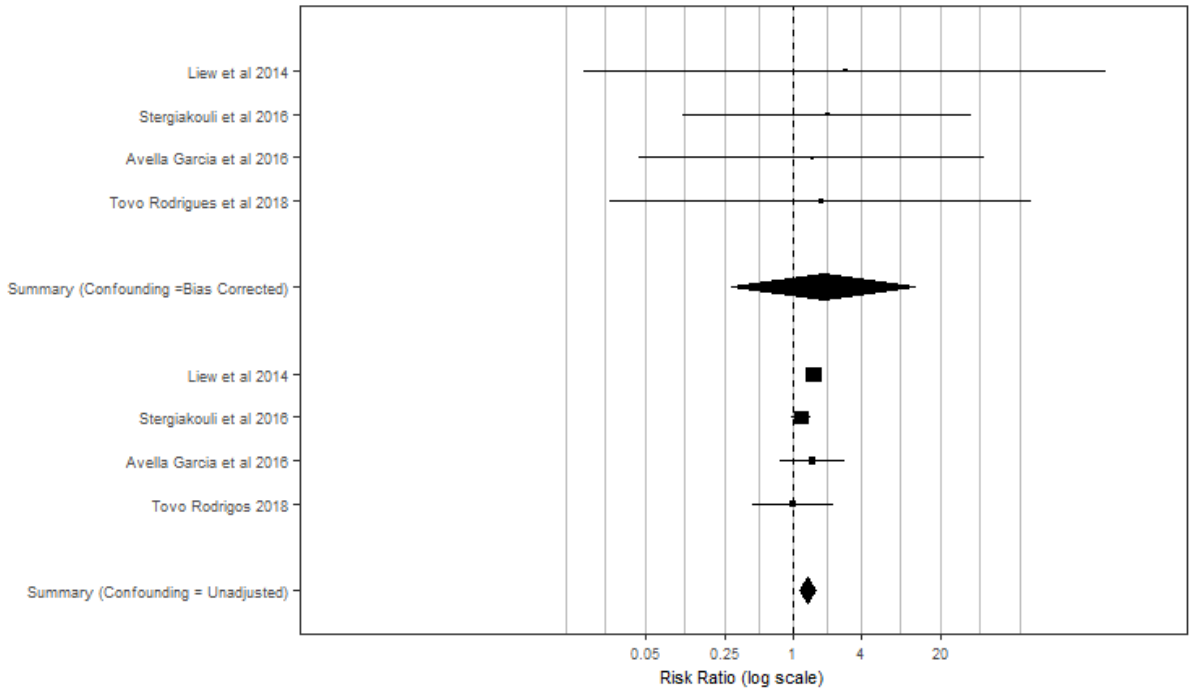
e-Figure 3. Unadjusted and bias corrected risk ratios for unmeasured confounding- maternal migraine. X-axis: study number, y-axis: RR. 1: Streissguth et al. 1987, 2: Liew et al. 2014, 3: : Avella-Garcia et al. 2016, 4: Ystrom et al. 2017, 5: Tovo Rodrigues et al. 2018.



e-Figure 4. Forest plot of unadjusted and selection bias corrected estimates. Risk ratios and confidence intervals from a random effects meta-analysis of four cohort studies corrected for selection bias, estimating the risk for attention deficit hyperactivity disorder after acetaminophen use during pregnancy.



e-Figure 5. Forest plot of unadjusted and exposure misclassification bias corrected estimates. Risk ratios and confidence intervals from a random effects meta-analysis of four cohort studies corrected for exposure misclassification bias, estimating the risk for attention deficit hyperactivity disorder after acetaminophen use during pregnancy.



APPENDIX A

R code

```
install.packages("metafor")
install.packages("compute.es")
install.packages("epiR")
install.packages ("episensr")
install.packages("meta")
install.packages('forestplot')
install.packages('EValue')
install.packages('metaviz')
library(metafor)
library(compute.es)
library(epiR)
library(episensr)
library(meta)
library(forestplot)
library(EValue)
library(metaviz)

#Bias analysis
#Selection Bias for 4 studies
#Infirmation bias for 4 studies
#Unmeasured confoundinf for 7 studies, when unmeasured inoriginal studies
# start with selection, then information then unmeasured for each study
# Meta analysis : updated, 4 studies included in selection and information ias - regualr and bias adjusted meta analysis
#sensitivity analysis for met analysis (unmeasured confounding)
# E value for individual studies
# results are valid under assumptions made

#set work directory
setwd('C:/Reem/Post Doc/quantative bias analysis/R')
setwd('C:/Users/reem.masarwa/Documents/quantative analysis/R')


#selection bias Liew 2014
#Assume different exposure prevalences in cases and controls and exposed and unexposed-paracetamol
# non differential
# exposed = sicker = more to participiate
ADHD1 <- selection (matrix(c(551, 283, 35656, 27852),
                    dimnames = list(c("ADHD+", "ADHD-"),
                                    c("P+", "P-")),
                    nrow=2, byrow=TRUE),
```

```
            bias_parms =c(0.85, 0.85, 0.45, 0.45))

ADHD1

#selection bias Liew 2014
#Assume different exposure prevalences in cases and controls and exposed and unexposed-
paracetamol
# non differential
# exposed = sicker = more likely NOT to participiate
ADHD2 <- selection (matrix(c(551, 283, 35656, 27852),
                dimnames = list(c("ADHD+", "ADHD-"),
                            c("P+", "P-")),
                nrow=2, byrow=TRUE),
            bias_parms =c(0.45, 0.45, 0.85, 0.85))

ADHD2

#bootsraping liew for selection bias
selection_boot1 <- boot.bias(ADHD1, R = 10000, ci_type = c("norm",
                                        "perc"))
selection_boot1

plot(selection_boot1, "rr")

selection_boot2 <- boot.bias(ADHD2, R = 10000, ci_type = c("norm",
                                         "perc"))
selection_boot2

#misclassification bias Liew
#Assume different exposure prevalences in cases and controls and exposed and unexposed

exposuremiss1 <- probsens(matrix(c(551, 283, 35656, 27852),
                    dimnames = list(c("ADHD+", "ADHD-"), c("P+", "P-")),
                    nrow = 2, byrow = TRUE),
                type = "exposure",
                reps = 50000,
                seca.parms = list("uniform", c(.55, .80)),
                spca.parms = list("uniform", c(.9, .99)))

exposuremiss1

str(exposuremiss)
```

```
#selection bias Avella Garcia
#Assume different exposure prevalences in cases and controls and exposed and unexposed

ADHD3<- selection (matrix(c(18, 18, 802, 1163),
                  dimnames = list(c("ADHD+", "ADHD-"),
                                  c("P+", "P-")),
                  nrow=2, byrow=TRUE),
               bias_parms =c(0.85, 0.85, 0.45, 0.45))

ADHD3

ADHD4<- selection (matrix(c(18, 18, 802, 1163),
                  dimnames = list(c("ADHD+", "ADHD-"),
                                  c("P+", "P-")),
                  nrow=2, byrow=TRUE),
               bias_parms =c(0.45, 0.45, 0.85, 0.85))

ADHD4

#bootsraping avella  for selection bias
selection3 <- boot.bias(ADHD3, R = 10000)
selection3

plot(misclass_boot, "rr")
#bootsraping avella  for selection bias
selection4 <- boot.bias(ADHD4, R = 10000)
selection4

#misclassification bias Avella
#Assume different exposure prevalences in cases and controls and exposed and unexposed

exposuremiss2 <- probsens(matrix(c(18, 18, 802, 1163),
                         dimnames = list(c("ADHD+", "ADHD-"), c("P+", "P-")),
                         nrow = 2, byrow = TRUE),
                  type = "exposure",
                  reps = 50000,
                  seca.parms = list("uniform", c(.55, .80)),
                  spca.parms = list("uniform", c(.9, .99)))

exposuremiss2


str(exposuremiss2)
```

```
#selection bias Stergiakouli
#Assume different exposure prevalences in cases and controls and exposed and unexposed


ADHD5 <- selection (matrix(c(246, 187, 4169, 3715),
                    dimnames = list(c("ADHD+", "ADHD-"),
                                    c("P+", "P-")),
                    nrow=2, byrow=TRUE),
                  bias_parms =c(0.85, 0.85, 0.45, 0.45))
ADHD5


ADHD6 <- selection (matrix(c(246, 187, 4169, 3715),
                    dimnames = list(c("ADHD+", "ADHD-"),
                                    c("P+", "P-")),
                    nrow=2, byrow=TRUE),
                  bias_parms =c(0.45, 0.45, 0.85, 0.85))
ADHD6

#bootsraping stergioukouli for selection bias
selection5 <- boot.bias(ADHD5, R = 10000)
selection5

plot(misclass_boot, "rr")
#bootsraping stergioukouli for selection bias
selection6 <- boot.bias(ADHD6, R = 10000)
selection6

#misclassification bias Stergiakouli
#Assume different exposure prevalences in cases and controls and exposed and unexposed

exposuremiss1 <- probsens(matrix(c(246, 187, 4169, 3715),
                     dimnames = list(c("ADHD+", "ADHD-"), c("P+", "P-")),
                     nrow = 2, byrow = TRUE),
                  type = "exposure",
                  reps = 50000,
                  seca.parms = list("uniform", c(.55, .80)),
                  spca.parms = list("uniform", c(.9, .99)))

exposuremiss1
```

```
#selection bias Tovo Rodriguez
#Assume different exposure prevalences in cases and controls and exposed and unexposed


ADHD7 <- selection (matrix(c(102, 271, 852, 2245),
                    dimnames = list(c("ADHD+", "ADHD-"),
                                    c("P+", "P-")),
                    nrow=2, byrow=TRUE),
                  bias_parms =c(0.85, 0.85, 0.45, 0.45))
ADHD7

ADHD8 <- selection (matrix(c(102, 271, 852, 2245),
                    dimnames = list(c("ADHD+", "ADHD-"),
                                    c("P+", "P-")),
                    nrow=2, byrow=TRUE),
                  bias_parms =c(0.45, 0.45, 0.85, 0.85))
ADHD8

#bootsraping Tovo Rodriguiez for selection bias
selection_boot7 <- boot.bias(ADHD7, R = 10000, ci_type = c("norm",
                                          "perc"))
selection_boot7

plot(selection_boot, "rr")

#bootsraping Tovo Rodriguiez for selection bias
selection_boot8 <- boot.bias(ADHD8, R = 10000, ci_type = c("norm",
                                           "perc"))
selection_boot8

#misclassification Tovo Rodriguez
#Assume different exposure prevalences in cases and controls and exposed and unexposed

exposuremiss3 <- probsens(matrix(c(102, 271, 852, 2245),
                         dimnames = list(c("ADHD+", "ADHD-"), c("P+", "P-")),
                         nrow = 2, byrow = TRUE),
                       type = "exposure",
                       reps = 50000,
                       seca.parms = list("uniform", c(.55, .80)),
                       spca.parms = list("uniform", c(.9, .99)))

exposuremiss

#Unmeasured confounding - steps and explenation
```

The following steps were taken to calculate bias-corrected RRs (bcRRs) for each confounder in each study. First, the unadjusted RRs from each study were calculated using the 2x2 table or extracted from the reported estimate when raw data were not available. Second, a confounded RR was calculated based on the literature-reported strength of association of each confounder with the outcome, and the prevalences of the confounder among the exposed (p1) and unexposed (p0) were set (Table 1). Third, the unadjusted RR (observed effect) from the original studies was divided by the confounded RR to produce a bcRR. When available, the estimated prevalences of the confounders among the exposed and non-exposed were based on the literature; when these data were not available, we used clinical opinion to make assumption about the distribution of the confounders. For each analysis of unmeasured confounding, the same prevalence values were used in each of the studies.

```
#Uunmeasered Confounding
#Genetic Factors-parental ADHD
#Liew et al

con <- confounders(matrix(c(551, 283, 35656, 27852),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",
        bias_parms = c(1.68, 0.50, 0.20))
con


#Uunmeasered Confounding
#Air Polution
#Liew et al
confounders(matrix(c(551, 283, 35656, 27852),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",
        bias_parms = c(5, 0.60, 0.4))

#Uunmeasered Confounding
#Migaraine
#Liew et al
confounders(matrix(c(774, 458, 21174, 17730),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",
        bias_parms = c(1.81, 0.3, 0.14))
```

```
#Uunmeasered Confounding
#Genetic Factors-parental ADHD
#Stergiakouli et al

confounders(matrix(c(246, 187, 4169, 3715),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",
        bias_parms = c(1.68, 0.50, 0.20))

#Uunmeasered Confounding
#Maternal Migraine
#Stergiakouli et al

confounders(matrix(c(246, 187, 4169, 3715),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",
        bias_parms = c(1.8, 0.3, 0.14))


#Uunmeasered Confounding
#Air Polution
#Stergiakouli et al
# non differential in exposed and not exposed

confounders(matrix(c(246, 187, 4169, 3715),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",
        bias_parms = c(5, 0.60, 0.40))


#Uunmeasered Confounding
#Fever
#Stergiakouli et al
confounders(matrix(c(246, 187, 4169, 3715),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
```

```
        type = "RR",
        bias_parms = c(2, 0.75, 0.25))



#Uunmeasered Confounding
#Genetic Factors-parental ADHD
#Avella Garcia et al

confounders(matrix(c(18, 18, 802, 1163),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",


              bias_parms = c(1.68, 0.50, 0.20))

#Uunmeasered Confounding
#maternal smoking ADHD
#Avella Garcia et al

confounders(matrix(c(18, 18, 802, 1163),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2.1, byrow = TRUE),
        type = "RR",

        bias_parms = c(2.1, 0.10, 0.05))
#Uunmeasered Confounding
#maternal Migraine
#Avella Garcia et al
confounders(matrix(c(18, 18, 802, 1163),
            dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",


        bias_parms = c(1.81, 0.07, 0.03))

#Uunmeasered Confounding
#maternal alchol consumtion ADHD
```

```
#Avella Garcia et al

confounders(matrix(c(18, 22, 802, 1163),
            dimnames = list(c("ADHD+", "ADHD-"),
                            c("P+", "P-")),
            nrow = 2.5, byrow = TRUE),
        type = "RR",


        bias_parms = c(2.5, 0.08, 0.06))


#Uunmeasered Confounding
#Parental ADHD
#Tovo Garcia
confounders(matrix(c(102, 271, 852, 2245),
            dimnames = list(c("ADHD+", "ADHD-"),
                            c("P+", "P-")),
            nrow = 2.5, byrow = TRUE),
        type = "RR",


        bias_parms = c(1.68, 0.50, 0.20))



#Uunmeasered Confounding
#maternal Migraine
#Tovo Garcia
confounders(matrix(c(102, 271, 852, 2245),
            dimnames = list(c("ADHD+", "ADHD-"),
                            c("P+", "P-")),
            nrow = 2, byrow = TRUE),
        type = "RR",


        bias_parms = c(1.81, 0.07, 0.03))


#Uunmeasered Confounding
#Air Polution
#Tovo Garcia

confounders(matrix(c(102, 271, 852, 2245),
```

```
        dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
        nrow = 2, byrow = TRUE),
      type = "RR",
      bias_parms = c(5, 0.60, 0.40))


#Uunmeasered Confounding
#Fever
#Tovo Garcia
confounders(matrix(c(102, 271, 852, 2245),
        dimnames = list(c("ADHD+", "ADHD-"),
                        c("P+", "P-")),
        nrow = 2, byrow = TRUE),
      type = "RR",
      bias_parms = c(2, 0.75, 0.25))


#Biasplots
#my meta-analysis
bias_plot(RR=1.35, xmax=10)


#E-Value - using the reported RRs from oroginal studies
# For studies included in selection and information bias analysis

# my meta-analysis (updated)
evalues.RR(est=1.35, lo = 1.25, hi = 1.46, true = 1)
# E-value my meta = 2.03

#Liew
evalues.RR(est=1.51, lo = 1.31, hi = 1.74, true = 1)
# Liew Evalue=2.08

#Avella
evalues.RR(est=1.44, lo = 0.75, hi = 2.75, true = 1)
# Aveela E value= 2.23

#Stergiuokouli
evalues.RR(est=1.16, lo = 0.96, hi = 1.39, true = 1)
# Stergiuokouli Evalue = 1.60

#Tovo Rodriguez
evalues.OR(est=0.99, lo = 0.80, hi = 1.23, rare = 1, true = 1)
```

```
# E vaue Tovo= 1.1, upper CI = 1

#Ystrom E=1.80
evalues.RR(est=1.25, lo = 1.14, hi = 1.37, true = 1)
#1987 E=2.01
evalues.RR(est=1.34, lo = 0.93, hi = 1.93, true = 1)
#Thompson E-2.64
evalues.RR(est=1.63, lo = 1.28, hi = 2.08, true = 1)

# META ANALYSES


#MA of 4 studies no bias analysis
# RR, METHOD DL
# Use this to plot against selection and onformationbias forest plots

RAW <- read.csv("ADHD_26.4.19_RAW.csv", TRUE, ",")
RAW

MA1 <- metabin(event.e , n.e, event.c, n.c, studlab=StudyIDyear,
          data = RAW, subset = NULL, method = "MH",
          sm = "RR", comb.random = gs("comb.random"), comb.fixed = FALSE,
          incr = 0.5, allincr = FALSE, addincr = FALSE, allstudies = FALSE,
          MH.exact = FALSE, RR.cochrane = FALSE, warn = TRUE, showweights=TRUE)
MA1

forest(MA1, print.I2=TRUE, print.Q =TRUE, print.pval.Q=TRUE, showweights=TRUE)

#Same analysis use LLR ans STER
RAW1 <- read.csv("RAW_LRR.csv", TRUE, ",")
RAW1

RAWMA <- rma(yi=LRR, sei=Ster, measure="RR", method="DL",
                  data=RAW1,  slab=paste(Study.Year, comb.random = RAW1$comb.random))
RAWMA


forest(RAWMA  , annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="2" ,
showweights=TRUE,lty = "solid",
     steps=5,level=RAWMA$level, refline=log(1), digits=2L, width = 5,
     mlab="Random-effects, I^2=63%, p=0.04",
     xlab= "Risk Ratio (log scale)", efac = 2, pch=18, psize=1.2, col="Black", border="Black",
     cex=1, at=log(c(0.05,0.25,1,4,20)), xlim = c(-10,8), atransf=exp)
#add Column headings to plot
```

```
text(c(-7.5),              5.5, c("First Author Year"), font=2)
text(5.9,                  5.5, "Weight     RR (95% CI)", font =2)


#now do bias adjusted meta analysis for selection bias in studies
#particapants with sick children/comorbidities, will participate more
#RR Will increase?
# MA of bias coreected RRs and 95% CIs (Taken from selection bias analysis)

MAbiasselection <- read.csv ("ADHDAdjusted_WithSelection_29.7.19.csv", TRUE, ",")
MAbiasselection

ADHDselectionBias <- rma(yi= exp(LRR), sei=Ster, measure="RR", method="DL",
data=MAbiasselection,  slab=paste(Study.Year, comb.random =
MAbiasselection$comb.random))
ADHDselectionBias


forest(ADHDselectionBias, annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto"
     ,showweights=TRUE,lty = "solid", at= c(0.5,1,1.5,2,2.5),
    steps=3,level=ADHDselectionBias$level, refline=1, digits=2L, width = 5,
    xlab= "Risk Ratio", efac = 2, mlab="RE, I^2=85%, p=0.0001    Overall RR",pch=18,
    psize=1.2, col="Black", border="Black",
    cex=1,  rightlabs = c("RR","[95% CI]","weight"), print.I2.ci = TRUE)
#add Column headings to plot
text(c(-1.5),              5.5, c("First Author Year"), font=2)
text(4.2,                  5.5, "Weight      RR (95% CI)", font =2)


#information bias corrected meta analysis
# 4 studies
#Bias analysis results from information bias

MAbiasinformation <- read.csv ("ADHDAdjusted_WithInformation_29.7.19.csv", TRUE, ",")
MAbiasinformation

ADHDinformationBias <- rma(yi= exp(LRR), sei=Ster, measure="RR", method="DL",
data=MAbiasinformation, slab=paste(Study.Year))
ADHDinformationBias

forest(ADHDinformationBias, annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto"
, showweights=TRUE,lty = "solid", at= c(0.5,1,1.5,2,2.5),
     steps=3,level=ADHDinformationBias$level, refline=1, digits=2L, width = 5,
```

```
     xlab= "Risk Ratio", mlab="RE, I^2=38%, p=0.18   Overall RR", efac = 2, pch=18, psize=1.2,
col="Black", border="Black",
     cex=1)
#add Column headings to plot
text(c(-3.1),              5.3, c("First Author Year"), font=2)
text(6.4,                  5.3, "Weight      RR (95% CI)", font =2)


#Regular MA update
#remove siblings
#keep original adjusted LRR and STRS
#add ystrom et al and tovo rodrigues

update3 <- read.csv ("ADHDAdjusted_RegularUpdate_21.3.19.csv", TRUE, ",")
update3


ADHDall3 <- rma(yi=LRR, sei=Ster, measure="RR", method="DL", slab=paste(FirstAuthorYear),
data=update3)
ADHDall3

Figure2 <- forest(ADHDall3 , annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto" ,
showweights=TRUE,lty = "solid",
     steps=5,level=ADHDall3 $level, refline=log(1), digits=2L, width = 5,
     mlab="Random-effects, I^2=48%, p=0.03",
     xlab= "Risk Ratio (log scale)", efac = 2, pch=18, psize=1.2, col="Black", border="Black",
     cex=1, at=log(c(0.05,0.25,1,4,20)), xlim = c(-10,8), atransf=exp)
#add Column headings to plot
text(c(-7.5),              8.5, c("First Author Year"), font=2)
text(5.9,                  8.5, "Weight     RR (95% CI)", font =2)

Figure2


tiff(
  filename="Figure2.tiff",
  width=480, pointsize = 12,
  height=480,  bg = "white", compression = "none",
  units="px",
  res=300)
plot(ADHDall3)
dev.off()
```

```
#  at= c(0.5,1,1.5,2,2.5) atransf=exp,
#Publication Bias - Funnel and Egger's test for updated meta analysis (N=7)
funnel(ADHDall3, ref.triangle=TRUE, comb.random=TRUE, lty.random=1)
regtest(ADHDall3)
trimfill(ADHDall3)

#Forest plot for updated meta analysis (N=7)
forest(ADHDall3 , annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto" ,
showweights=TRUE,lty = "solid", at= c(0.5,1,1.5,2,2.5),
     steps=5,level=ADHDall3 $level, refline=1, digits=2L, width = 5,
     xlab= "Risk Ratio", mlab="RE, I^2=55%, P=0.05  Overall RR", efac = 2, pch=18, psize=1.2,
col="Black", border="Black",
     cex=1)
#add Column headings to plot
text(c(0.1),              7.5, c("First Author Year"), font=1)
text(2.8,                  7.5, "RR (95% CI)", font =1)

#Ma of 4 studies included in bias analysis
# use adjusted point estimates

update4 <- read.csv ("ADHDAdjusted_4StudiesBias_29.4.19.csv", TRUE, ",")
update4


bias4 <- rma(yi= exp(LRR), sei=Ster, measure="RR", method="DL", slab=paste(FirstAuthorYear),
data=update4)
bias4

forest(bias4 , annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto" ,
showweights=TRUE,lty = "solid", at= c(0.5,1,1.5,2,2.5),
     steps=5,level=ADHDall3 $level, refline=1, digits=2L, width = 5, mlab="random-effects,
I^2=50%, p=0.09  Overall RR",
     xlab= "Risk Ratio", efac = 2, pch=18, psize=1.2, col="Black", border="Black",
     cex=1)
#add Column headings to plot
text(c(-0.5),              6.5, c("First Author Year"), font=2)
text(3.1,                  6.5, "Weight   RR (95% CI)", font =2)


#Calculate Yr and Vr foe sensitivity analysis for unmeasured confounding for pooled estimate of
meta analysis
yr = as.numeric(ADHDall3$b)
yr
```

```
vyr = as.numeric(ADHDall3$vb)
vyr
t2 = ADHDall3$tau2
t2
vt2 = ADHDall3$se.tau2^2
vt2
#confounding in META ANALYSIS

confounded_meta(q=log(1.10), r = 0.2, muB = log(1.2), sigB = 0, yr=log(1.35), vyr = 0.0026,
t2=0.007,
            vt2 = 0.00010, CI.level = 0.95, tail = NA)

#figure 3 - sensitivity analysis for meta analysis (N=7)
 Figure3 <- sens_plot(type="line", q=log(1.10),sigB = 0, yr=log(1.35), vyr = 0.0026, t2=0.007, vt2
= 0.00010, Bmin=0, Bmax=0.8,
        breaks.x1 = c(1,1.2,1.3,1.4,1.5,1.6,1.7,1.8,1.9), breaks.x2 = NA, CI.level = 0.95)

Figure3

 Tiff(
  filename="Figure.jpeg",
  res=300)
dev.off()



sens_table("prop", q=1.10, r = seq(0.1, 0.9, 0.1), muB = log(2), sigB = 0.0001, yr=log(1.35),
         t2=0.0075)

#NOT FOR PAPAER
#incorperating biased RRs in previous MA
#selection bias
#remove siblong study since it's sibling and same cohort
#using adjusted data from rest of studies

update1 <- read.csv ("ADHDAdjusted_WithSelection_21.3.19.csv", TRUE, ",")
update1


ADHDall <- rma(yi= exp(LRR), sei=Ster, measure="RR",
method="DL",slab=paste(FirstAuthorYear), data=update1)
ADHDall
```

```
forest(ADHDall , annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto" ,
showweights=FALSE,lty = "solid", at= c(0.5,1,1.5,2,2.5),
     steps=5,level=ADHDall $level, refline=1, digits=2L, width = 5,
     xlab= "Risk Ratio", mlab="RE, I^2=70%, P=0.05  Overall RR", efac = 2, pch=18, psize=1.2,
col="Black", border="Black",
     cex=1)
#add Column headings to plot
text(c(-0.4),              7.5, c("First Author Year"), font=1)
text(3.5,                  7.5, "RR (95% CI)", font =1)

#incorperating biased RRs in previous MA
#information bias
#remove siblong study since it's sibling and same cohort
#using adjusted data from rest of studies

update2 <- read.csv ("ADHDAdjusted_WithInformation_21.3.19.csv", TRUE, ",")
update2


ADHDall2 <- rma(yi= exp(LRR), sei=Ster, measure="RR",
method="DL",slab=paste(FirstAuthorYear), data=update2)
ADHDall2

forest(ADHDall2 , annotate=TRUE, addfit=TRUE, addcred=TRUE,graphwidth="auto" ,
showweights=FALSE,lty = "solid", at= c(0.5,1,1.5,2,2.5),
     steps=5,level=ADHDall2 $level, refline=1, digits=2L, width = 5,
     xlab= "Risk Ratio", mlab="RE, I^2=54%, P=0.05  Overall RR", efac = 2, pch=18, psize=1.2,
col="Black", border="Black",
     cex=1)
#add Column headings to plot
text(c(-0.6),              7.5, c("First Author Year"), font=1)
text(4,                  7.5, "RR (95% CI)", font =1)



#calulate E value to explain strength of association of confounder with outcome and exposure
#E-value express the magnitude of the confounder associations that can produce confounding
bias
#equal to the observed exposure-outcome association.
# E value for my MA

confounders.evalue(est = 1.34, lower_ci = 1.21, upper_ci = 1.47, type = "RR")
```

```
# Results : E value = 2.01 CI closest to H0=1.71, meaning of results, an unmeasred confounder
needs to have a risk ratio
# of at least 2.01 with both the exposure and the outcome to explain the observed RR

#now lets try to calculate the magnidute of a confounder to bring the RR
#towards the null, menaing RR=1

confounders.evalue(est = 1.34, lower_ci = 1.21, upper_ci = 1.47,
                   type = "RR", true_est = 1.0)


twoXtwoRR(n11, n10, n01, n00, alpha = 0.05)

#Arguments
#n11 Number exposed (X=1) and diseased (D=1)
#n10 Number exposed (X=1) and not diseased (D=0)
#n01 Number unexposed (X=0) and diseased (D=1)
#n00 Number unexposed (X=0) and not diseased (D=0)
#alpha Alpha level associated with confidence interval


#Plot meta analysis data from N=4 studies included in bias -RAW
# Against : 1- Selection corrected meta analysis, 2-Information corrected meta analysis


#selection bias
pink <- read.csv("Selection_dual_25.7.19.csv", TRUE, ",")
pink

viz_forest(x = pink[1:8, c("LRR", "Ster")],
           group = pink[1:8, "Confounding"],
           study_labels = pink[1:8, "FirstAuthorYear"],
           summary_label = c("Summary (Confounding =Bias Corrected)", "Summary (Confounding =
Unadjusted)"),
           xlab = "Risk Ratio (log scale)",
           col = "Greys",x_limit = c(-8,8),x_breaks=log(c(0.05,0.25,1,4,20)),
           x_trans_function = exp, method="DL",  confidence_level = 0.95,
           variant="classic")

#Misclassification

red <-  read.csv("Information_dual_25.7.19.csv", TRUE, ",")
red
```

```
viz_forest(x = red[1:8, c("LRR", "Ster")],
        group = red[1:8, "Confounding"],
        study_labels = red[1:8, "FirstAuthorYear"],
        summary_label = c("Summary (Confounding =Bias Corrected)", "Summary (Confounding =
Unadjusted)"),
        xlab = "Risk Ratio (log scale)",
        col = "Greys",
        x_trans_function = exp, method="DL", confidence_level = 0.95, x_limit = c(-10,8),
        variant="classic", x_breaks=log(c(0.05,0.25,1,4,20)))


#CALCULATE LRR AND STER FOR RAW DATA TO CREATE DUAL FUNNEL PLOT IN ORDER TO USE
RMA FUNCTION

#Liew, LRR=0.45, ster=
propes(p1=0.014, p2=0.009, n.ab=36207, n.cd=28135,
     level = 95, cer = 0.2, dig = 2, verbose = TRUE, id=NULL, data=NULL)

#Avella LRR=0.39, ster=  0.336
propes(p1=0.022, p2=0.015, n.ab=820, n.cd=1181,
     level = 95, cer = 0.2, dig = 2, verbose = TRUE, id=NULL, data=NULL)

#Stergiakouli LRR=0.17, ster=    0.099
propes(p1=0.0585, p2=0.050, n.ab=4415, n.cd=3902,
     level = 95, cer = 0.2, dig = 2, verbose = TRUE, id=NULL, data=NULL)

#Tovo LRR= -1.24, ster= 0.42
propes(p1=0.119, p2=0.318, n.ab=954, n.cd=2516,
     level = 95, cer = 0.2, dig = 2, verbose = TRUE, id=NULL, data=NULL)


#unmeasured confounding Parental ADHD
black <-  read.csv("Unmeasured_29.7.19.csv", TRUE, ",")
black

x <- black$Study
y1 <- black$Unadjusted.RR
Y2 <- black$Bias.Corrected.RR

plot(x, y1, main = "Unmeasured Confounding - Parental ADHD",
    xlab = "Study", ylab = "Risk Ratio",
    pch = 16, frame = TRUE, xlim= c(0,7.5), at=c(1,2,3,4,5,6,7), ylim=c(0,2), col='black')

par(new=TRUE)
```

```
plot(x, Y2, main = "Unmeasured Confounding - Parental ADHD",
    xlab = "Study", ylab = "Risk Ratio",
    pch = 8, frame = TRUE, xlim= c(0,7.5), at=c(1,2,3,4,5,6,7), ylim=c(0,2), col='black')
legend(x=5, y=0.5, legend=c('Unadjusted', 'Bias Corrected'),
      col=c('black', 'black'), pch=c(16,8))

#unmeasured confounding Maternal Migraine
peach <- read.csv("Unmeasured_Migraine.csv", TRUE, ",")
peach

x <- peach$Study
y1 <- peach$Unadjusted.RR
Y2 <- peach$Bias.Corrected.RR

plot(x, y1, main = "Unmeasured Confounding - Migraine",
    xlab = "Study", ylab = "Risk Ratio",
    pch = 16, frame = TRUE, xlim= c(1,6), at=c(1,2,3,4,5,6), ylim=c(0,2), col='black')

par(new=TRUE)
plot(x, Y2, main = "Unmeasured Confounding - Migraine",
    xlab = "Study", ylab = "Risk Ratio",
    pch = 8, frame = TRUE, xlim= c(1,6), at=c(1,2,3,4,5,6), ylim=c(0,2),  col='black')
legend(x=4, y=0.5, legend=c('Unadjusted', 'Bias Corrected'),
      col=c('black', 'black'), pch=c(16,8))
```