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Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis.

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ABSTRACT

Purpose: Exposure to prenatal stress has been reported to affect the risk of adverse neurodevelopmental outcomes in the offspring, however there is currently no clear consensus. The aim of this systematic review and meta-analysis was to examine the existing literature on the association between prenatal stress and autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) in the offspring.

Methods: Based on a registered protocol, we searched several electronic databases for articles in accordance with a detailed search strategy. We performed this study following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).

Results: Prenatal stress was significantly associated with an increased risk of both ASD (pooled OR=1.64, [95% CI=1.15–2.34]; I^2=90%; 15 articles) and ADHD (pooled OR=1.72, [95% CI=1.27-2.34]; I^2=85%; 12 articles).

Conclusions: This study suggests that prenatal stress may be associated with ASD and ADHD, however several limitations in the reviewed literature should be noted including significant heterogeneity and there is a need for carefully controlled future studies in this area.

Keywords: Autism spectrum disorder, attention-deficit/hyperactivity disorder, prenatal maternal stress, pregnancy, mental health.

INTRODUCTION

Prenatal maternal stress is a low or negative state of well-being in pregnancy [1]. “Stress” in this context includes negative life events, anxiety and depressive symptoms. Feelings of stress, anxiety and depression are distinct though highly correlated constructs, all belonging to the domain of negative emotions. The prevalence of depression, anxiety, and stress in pregnancy has been estimated at 12%, 28% and 31% respectively [2]. These have been suggested to influence neurobehavioral outcomes in exposed offspring [3,4].

Autism spectrum disorder (ASD) and Attention-deficit/hyperactivity disorder (ADHD) are two of the most common neurodevelopmental disorders. ASD has a prevalence of 1.7% [5] and is characterized social deficits, impaired communication, and stereotyped and repetitive behaviours [6,7]. ADHD has a prevalence of 5.3%, that is characterized by inattention, hyperactivity and impulsivity behaviour [8]. While genetics is crucial in their aetiology [9,10], a population-based Swedish study has estimated the environmental variance for ASD at 17% [11]. In addition, ADHD heritability has been reported at 70-80%, suggesting that environmental exposures may also play a role [12,13].

There is a growing literature examining the association between prenatal maternal stress and risk of ASD and ADHD in the offspring [14-16]. For example, large population-based studies have reported significant associations between prenatal exposure to bereavement and increased risk of ASD [15,17] and ADHD [18]. Others have reported that antenatal depressive symptoms were related to an increased risk of ADHD [19]. Moreover some studies have also attempted to understand the influence of gestational age of exposure [20,21]. For example, two population-based Danish studies reported an increased risk of ASD and ADHD in children following maternal exposure to bereavement in the third trimester [15,18]. Therefore, evaluating the timing of the prenatal stressor is important, because trimester-specific associations may increase the probability of a causal association [22]. However, there are inconsistencies in the literature, with some studies finding no association between prenatal maternal stress and ASD and ADHD risk [23,24]. Moreover for those studies that have reported an association, there is no clear consensus on the critical gestational period [17,25,26].

Therefore the aim of this systematic review and meta-analysis was to examine the association between prenatal maternal stress and ASD or ADHD risk in the offspring using available data from the published literature.

METHODS

Protocol and search strategy

The study protocol was registered on PROSPERO (CDR42018084222) and subsequently published [27]. The prenatal stress exposure was defined as a psychological or environmental stress such as stressful life events, maternal bereavement, anxiety or depressive symptoms, traumatic events and natural disasters. The outcome measures are ASD or ADHD that could be, for example, based on medical records or parent reporting. In accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) [28], a systematic literature search in PubMed, PsycINFO, Web of Science, EMBASE and SCOPUS was conducted by the first author (NM) from inception until March 24th, 2018.

Observational studies (cohort studies and case-control studies) evaluating the association between prenatal maternal stress and the risk of ASD or ADHD at any time before or during pregnancy or in any particular trimester were considered for inclusion. Cross-sectional study design was included in the search strategy for completeness and to ensure all relevant cohort studies are identified. The principles of the Boolean logic (AND, OR, or NOT) were used to combine search terms related to the exposure (prenatal stress) and the outcomes (ASD and ADHD) and using Medical Subject Headings as follows: (Prenatal OR Antenatal OR Pregnant) AND (Stress) OR (Distress) OR (Anxiety) OR (Bereavement) AND (Offspring OR Child) AND (Autism spectrum disorder) OR (Attention deficit/hyperactivity disorder). The detailed search strategy is presented in the supplementary Appendix 1. The literature search was not limited to humans although only human studies were included in the review and there was no language restriction. The authors hand-checked the bibliographies of included studies for further potentially eligible studies.

Study selection

Two investigators (NM and GWOK) independently screened the titles and abstracts for all articles, in order to identify potentially eligible studies. Titles and abstracts obtained from each database were stored and managed in Endnote Reference Manager X8© and duplicates were excluded using the Endnote function “remove duplicates”. The two investigators independently examined the full texts of potentially relevant articles.

Data extraction

Two investigators (NM and FB) extracted data using a standardised data extraction form. Extracted data included author, year of publication, study design, study outcome, exposure (exposure type, timing and duration), offspring gender, data sources, sample size, definition of the outcome used,

exclusion criteria, crude and adjusted estimates (if reported, including the RR, OR, HR and 95% CI). Authors of 3 studies [29-31] were contacted for further data, with a reply obtained only from one [31].

Bias and quality assessment

Included studies were critically appraised by two investigators independently (NM and KMS) using the Cochrane collaboration's tool for observational studies [32], which considers six domains: selection bias, exposure, outcome measurement, statistical analysis, study attrition and confounding. Each study was classified as having a high, moderate, low, minimal or not reported risk of bias for each domain. Then, each study was rated as having high, moderate or low risk of bias, according to the total of the six domains. For example, those with all six domains rated as minimal or low were classified as low-risk bias studies.

Disagreements regarding study eligibility, data extraction or risk of bias assessment were resolved by discussion with another investigator (ASK).

Statistical analysis

All statistical analyses were performed using Review Manager software (Cochrane Collaboration Software, RevMan 5.3). Random-effects models using the generic inverse variance method were performed to calculate the pooled odds ratio (OR) estimates and 95% CIs of the association between prenatal stress and the risk of ASD and ADHD. The analyses were performed for ASD and ADHD separately including all the eligible studies identified in the systematic review. The crude and adjusted pooled estimates were displayed using forest plots. The adjusted pooled estimates were based on the adjusted estimates as defined in each included study. Furthermore, a sensitivity analysis was performed including studies that reported both crude and adjusted estimates. Statistical heterogeneity was assessed using the I^2 statistic and the alpha of 0.05 for statistical significance, according to the Cochrane Handbook for Systematic Reviews threshold recommendations [32].

The following *a priori* subgroup analyses were performed when relevant data were available: 1) for timing of stress exposure (e.g. first trimester vs second trimester vs. third trimester); 2) according to gender (male vs female); 3) according to different type of stress (objective vs subjective stress); 4) according to study design (cohort vs case-control); and 5) according to study quality (minimal/low vs moderate/high).

Another subgroup analysis considering only the studies that investigated the association between antenatal depressive or anxiety feelings and the risk of ASD and ADHD was performed as post-hoc analysis.

The likelihood of publication bias was examined using a funnel plot of the pooled OR and standard error (SE). The Egger test was performed in order to obtain the p-value of the asymmetry of the funnel plot using the Comprehensive Meta-Analysis. Publication bias was examined when 10 or more studies were included in the meta-analysis. Moreover, the trim and fill method, with the aim of identifying potentially missing studies and correct for funnel plot asymmetry arising from publication bias was performed as a post-hoc analysis.

Ethical considerations

This systematic review and meta-analysis does not contain any studies with human participants or animals performed by any of the authors and as such ethical approval was not required.

RESULTS

Search results and study characteristics

The systematic literature search produced 511 unique results on prenatal stress and ASD after removing the duplicates, of which 22 studies were considered potentially relevant and the full text was obtained (Figure 1A). Following reviewing the full text of the 22 articles, nine were excluded because they did not meet the inclusion criteria (reasons for exclusion are reported in Figure 1A), resulting in 13 eligible studies. After reviewing the reference lists of eligible studies, we obtained two further studies [33,34], therefore a total of 15 studies were included (Figure 1A). A similar approach resulted in 12 eligible articles on ADHD (Figure 1B). Were unable to obtain the full text of a Chinese study although we sent the corresponding author two emails [35]. The hand-search of the reference lists of eligible studies did not yield additional studies. The characteristics of the included studies for ASD and ADHD are reported in Table S1 and Table S2 in the supplementary file. The oldest study was published in 1990 [36] and the most recent studies in 2016 [37,33,19]. For ASD we found eleven case-control studies and four cohort studies, while for ADHD we found seven case-control studies and five cohort studies.

Results of the Meta-analyses

ASD: Primary Analysis

Fifteen studies [38,15,39,40,37,41,26,17,23,25,19,33,42,36,34] reported the OR, HR or RR with 95% CI or the raw data that enabled the calculation of the OR. One study [23] used two cohorts from Sweden and England and we considered them as two separate studies for the purposes of the meta-analysis. Moreover, for another study [26] we included two estimates: we used the less exposed group as a reference group, comparing it with the higher exposed (Kinney, 2008a) and moderate exposed (Kinney, 2008b) groups. The overall meta-analysis was based on 17 estimates suggesting a significant association between prenatal stress and ASD (crude OR=1.65, [95% CI: 1.31-2.09]; I^2=86%). The meta-analysis including the studies that reported adjusted estimates [15,40,41,39,17,23,25,34] (nine estimates) showed a similar result (OR=1.64, [95% CI:1.15-2.34]; I^2=90%). When the meta-analysis was restricted to adjusted estimates, a statistically significant OR (OR=3.59, [95% CI:2.02-6.38], I^2=65%) was returned for case-control studies [40,41,39,34], but there was no evidence of an association in the cohort studies (OR=1.06, [95% CI:0.91-1.24], I^2=43%) [15,17,23,25]. The test for subgroup differences between cohort and case-control studies was statistically significant (p=0.001; I^2=93.7%).

In an analysis that included the nine studies which reported both the crude and the adjusted estimates, the results were largely unchanged (Figure S1 in the supplementary). However, three studies [41,39,34] made an adjustment for unclear or limited number of potential confounders (socioeconomic factors, such as family income[39]; living close to an industry, age and sex of the child, previous childhood infection [41]; paternal age at delivery, gender and birth year [34], and the exclusion of those studies from the adjusted model resulted in a lower OR (OR= 1.12, [95% CI: 0.93-1.34]).

ADHD: Primary Analysis

Twelve studies [43,30,44,16,19,45-47,33,29,15,18] evaluating the association between prenatal stress and the risk of ADHD were included in the meta-analysis. One study [44] reported two separate estimates for the inattentive (ADHD-I) and the combined (ADHD-C) ADHD subtypes, that are reported separately in the meta-analysis. The crude meta-analysis was based on twelve estimates and indicated that prenatal stress was significantly associated with ADHD (OR=2.69, [95% CI= 1.85-3.91]; I^2=80%). The meta-analysis including the adjusted estimates [45,29,30,46,44,15,18] (eight estimates) showed lower but still statistically significant association (OR=1.72, [95% CI= 1.27-2.34]; Figure 3). The results were similar for case-control studies [43,46,33,44,47,19] (OR=2.70, [95% CI (2.04 – 3.58], I^2=17%) and cohort studies [15,45,30,16,18] (OR=2.47, [95% CI: 1.33–4.60], I^2=84%).

The adjusted results from four cohort studies [15,45,30,18] (OR=2.00, [95% CI: 1.12–3.59], I^2=82%) and four case-control studies [29,46,44] (OR=1.96, [95% CI (0.95 – 4.04], I^2=84%) were similar. When considering only the studies which reported both the crude and the adjusted estimates, the results were similar (Figure S2). Although several studies reported adjusted estimates on prenatal stress and ADHD, the majority adjusted for 1-3 potential confounders such as child gender [46], child age, sex and socio-economic status [45], anxiety before birth [30], preterm delivery and intensive care [44]. After excluding these studies [45,30,46,44,29] only two studies [15,18] remained in the adjusted meta-analysis (OR= 1.37 [95% CI: 0.99-1.91], I^2=54%).

Additional pre-specified subgroup analyses on ASD

Subgroup analyses were conducted on adjusted estimates and are presented in Table 1.

The type of stress subgroup analysis resulted in a significant association for the subjective stress subgroup [40,41,39,34] but not for objective stress subgroup [15,17,23,25] . It should be noted, however, that all the studies which used subjective measures of stress were case-control studies.
Moreover, a post-hoc meta-analysis of three case-control studies [41,39,34] which investigated the association between prenatal depressive symptoms and ASD, found an almost five-fold increased odds of ASD. We found a significant association between prenatal stress and ASD in studies where ASD was based on ICD or DSM codes [15,41,17,23,34], studies using rating scales [40,39,25] resulted in a larger but statistically non-significant association. Only two studies [17,15] performed separate analyses for each trimester of pregnancy resulting in a significant association between stress in the third trimester and ASD. Five studies [15,17,23,25,34] (six estimates) were considered having low risk of bias showed no association between prenatal stress and ASD while three studies [41,40,39] were considered having moderate risk of bias resulting in a three-fold increased odds of ASD. Only two studies [15,17] assessed the effect of stress in boys and girls separately, and reported no evidence for sex-specific associations. Subgroup analysis was not performed because only one study reported the data.

Additional pre-specified subgroup analyses on ADHD

Subgroup analyses were performed on adjusted estimates and are presented in Table 2.
The subgroup analyses based on type of stressor showed a statistically significant association for subjective stress measures and an increased but not statistically significant odds of ADHD in relation to objective stress. Three studies assessed the odds of ADHD based on maternal report [45,30,46] (i.e. structured interview) and resulted in a statistically significant association, while studies using a clinical record [15,29,18,44] based on the Diagnostic and Statistical Manual of mental disorders (DSM) or the International Classification of Diseases (ICD) showed a non-significant association. Only two studies performed separate analyses for each trimester of pregnancy [15,18]. The two studies revealed a non-significant association between stress and ADHD in all the periods considered, without differences between the four periods. Two studies [15,18] were considered as having low risk of bias resulted in a non-significant association between prenatal stress and ADHD and five studies [45,29,30,46,44] (six estimates) were considered as having moderate risk of bias resulted in more than two-fold increased odds of ADHD. Only two studies [15,18] assessed the effect of stress in boys and girls separately but subgroup analysis on gender differences was not performed because one of them did not report the data.

Publication bias

The presence of asymmetry in the funnel plot of the adjusted results (figure S3A and S3B) was established with the Egger's test for both ASD and ADHD (p for publication bias = 0.046 and p=0.0003 respectively). We used the 'trim and fill' method to correct for funnel plot asymmetry arising from publication bias. In the ADHD meta-analysis four missing studies were suggested (Figure S4), leading to a significantly lower pooled OR (from 1.72 (1.27, 2.34) to 1.22 (0.91–1.62)). In ASD meta-analysis the trim and fill method did not suggest missing studies.

Heterogeneity and quality assessment

High heterogeneity for both ASD (I^2=90%) and ADHD (I^2=85%) was found in the adjusted estimates. The high heterogeneity was not explained in the subgroup analyses. All studies were evaluated using a bias classification tool suitable for observational studies. Based on this tool, most studies were considered high in overall bias (Appendix 2) due mostly to inadequate adjustment for confounding, small sample size or inadequate assessment of exposure (for example, retrospective studies up to five to twelve years after pregnancy).

DISCUSSION

The overall findings of the meta-analysis showed an association between prenatal stress exposure and an increased risk of both ASD and ADHD, however, it is important to interpret this result with caution. Specifically, the adjusted pooled results show a 64% increased odds of ASD in children exposed to prenatal stress. However, it is important to note the results of the subgroup analyses which revealed that the association was significant only in case-control studies, studies using subjective measures of stress and studies that were rated low to moderate quality. Importantly, for cohort studies using objective measures of stress and which were rated as high quality, pooled estimates did not support an association between prenatal stress and risk of ASD. Moreover, studies that were rated high quality, and studies using ICD or DSM ADHD diagnosis did not support an association between prenatal stress exposure and increased risk of ADHD. The significant heterogeneity for both ASD and ADHD meta-analyses adds further doubt about the likelihood of a causal association. It is however worth noting that the pooled results from the two largest cohort studies to date on prenatal stress and ASD (studies of high quality) [17,15] suggested an association between bereavement in the third trimester and 48% increased risk of ASD. Similarly, there was an indication of an increased risk of ADHD in relation to prenatal stress in the third trimester, although not statistically significant.

Mechanisms

Our third trimester association is interesting given other findings showing exposure to third trimester prenatal maternal psychosocial stress was associated with the greatest increased risk of asthma and allergy in the offspring [48]. Similarly, third trimester exposure to prenatal stress has been linked with a range of other adverse outcomes in exposed offspring [49,50]. Recent data has shown that maternal immune activation in women at risk of high stress and inflammation is associated with neonatal functional brain connectivity and offspring behavior [51], suggesting a potential inflammatory involvement. However there is a need for further study to identify the biological basis of this association and whether the third trimester effect reflects a trimester-specific effect or cumulative stress exposure throughout pregnancy.

Strengths and limitations

The strengths of the current study included the use of a pre-prepared, registered and published protocol following the PRISMA guidelines throughout the systematic review stages and the meta-analysis [28]. The review process involved comprehensive searching of five databases with no language restriction, supplemented by hand searching the bibliographies of the eligible studies. We

also contacted authors for additional information when necessary. The comprehensive search strategy was evidenced in the fact that hand searching the reference lists resulted in only two more studies being found.

This review revealed serious limitations in the literature on prenatal stress and ASD and ADHD. Half the studies reporting adjusted results were case-control studies, which may be subject to recall bias therefore exaggerating the association between prenatal stress and ASD and ADHD. The majority of the studies did not adjust for key potential confounders such as family history of mental illness, maternal and paternal age, and socio-economic status. Even though several studies reported adjusted estimates, in most cases the adjustment was inadequate and limited to few potential confounders. The association between prenatal stress and neurodevelopmental outcomes may be sex-specific and we were not able to explore this hypothesis due to lack of available data [52,53]. Five studies on ASD and six on ADHD included less than 100 cases, which may have led to exaggerated associations. Several studies were case-control, with a small sample size, using subjective measures of stress likely leading to recall bias and exaggerated associations [54]. Only two studies examined the trimester-specific association, and this did not allow us to make robust conclusions on the trimester-specific hypothesis in relation to prenatal stress and neurodevelopmental outcomes.

In addition, the methods used to assess neurodevelopmental outcome may have influenced the pooled estimates. A comprehensive assessment conducted by an experienced clinician is the diagnostic gold-standard [55,56]. However, while diagnostic criteria for ASD are based on extensive empirical research and have good validity and reliability, the data on ADHD validity are far less clear. Problematic aspects, include lack of physical or psychological markers, high comorbidity rates or inconsistent clustering of symptoms, and particularly, difficulty in differentiating normal symptoms from pathological ones [57]. Moreover, children who have not formed strong attachments with their primary caregiver(s) may exhibit coercive behaviour that functions in a self-protective manner when faced with disoriented/disorienting parental behaviours [58,59]. In these instances, parental self-reports of child hyperactivity may pathologise a behaviour that would not manifest in more secure and/or predictable parent-child relationships.

The assessment of prenatal maternal stress in the reviewed studies is an additional limitation. The definition of stress used in the introduction of this article (as “stress, anxiety and depression”) is unavoidably wide and generic, but is in line with the majority of the studies examined. In effect,

stress is a complex but not well-defined concept [60] that can be assessed in different ways: detecting somatic responses, assessing life events, or assessing participant-perceived stress. Despite this it has been noted that focusing on a single psychological construct, such as stress, anxiety or depression during pregnancy overestimates its importance within what can be considered a spectrum of prenatal maternal distress [60]. Thus a broader, multi-component approach, which can include different measurements, is appropriate in this context. While some pregnancy-specific tools have been associated with better obstetric outcomes [61,62] several reviewed studies assessed stress exposure using unspecific self-report questionnaires, asking simple and generic questions on prenatal risk factors. Only nine studies [38,15,43,17,18,23,25,16,19] used validated psychometric tools, or considered bereavement or natural disasters, which have been established as stressors in the existing literature [63,64]. Variability in conceptualisation and measurement of stress introduces uncertainty about the observed effects on ASD and ADHD. Furthermore, there is often incongruence between self-report measures and biomarkers of stress, thus limiting inferences that can be made about potential psychobiological mechanisms of effect in those studies which only included maternal self-report; self-report is also subject to recall bias, potentially exaggerating the association between prenatal stress and ASD and ADHD. Finally, most of the data were derived from mother's answers to self-reports questionnaires, and only in two studies [45,29] were fathers included as sources of information.

Considering these limitations we cannot yet draw definitive conclusions about whether exposure to prenatal stress increases the risk of ASD or ADHD in the offspring based on the available evidence. However if well-designed future studies confirm any such association, the results would be of crucial importance in order to design specific psychological interventions during pregnancy, aimed at reducing stress, anxiety and depression with the view to ultimately reducing the risks of adverse neurodevelopmental outcomes in children.

Conclusion

This systematic review and meta-analysis suggests that prenatal stress exposure may be related to an increased risk of ASD and ADHD in the offspring, especially in the third trimester of pregnancy, however, we identified substantial limitations in the literature that makes difficult to draw robust conclusions. The focus of future research should be on conducting robust and well-designed longitudinal epidemiological studies addressing the limitations in the current literature.

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Conflict of Interest statement

On behalf of all authors, the corresponding authors state that there is no conflict of interest.

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Figure 1: Flow chart of the included studies for ASD (Figure 1A) and ADHD (Figure 1B)

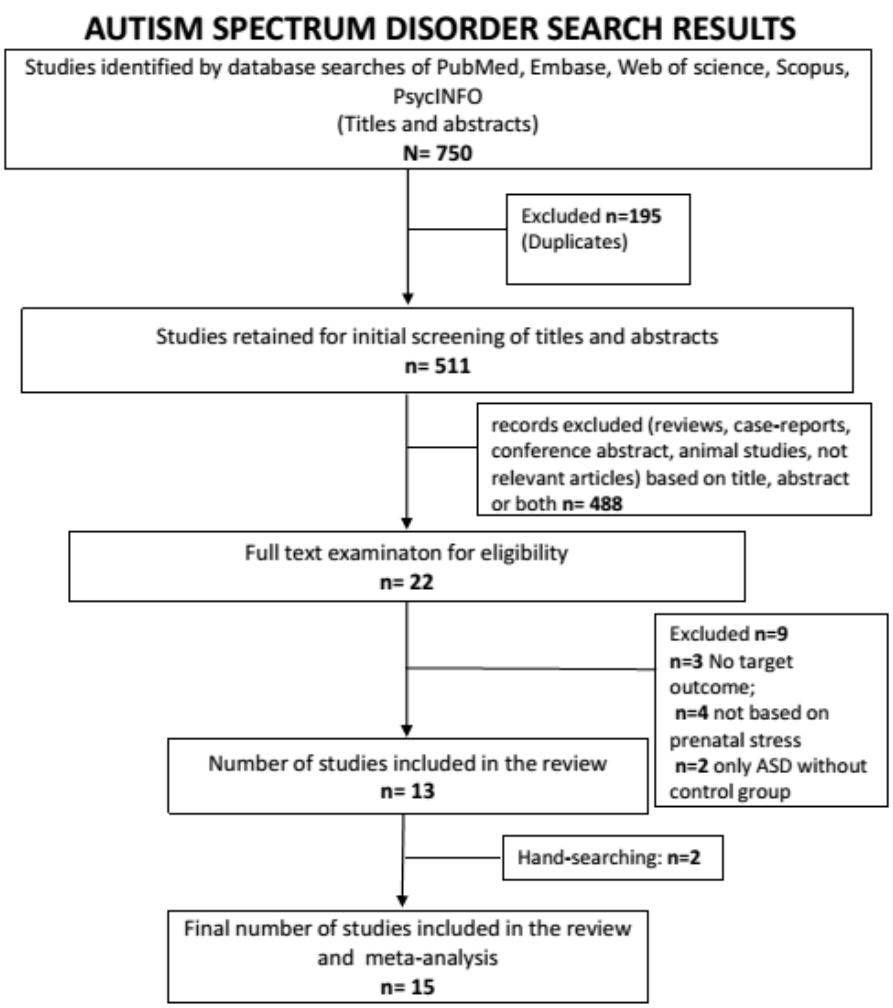


Figure 1a: Flow chart of the search process for ASD studies

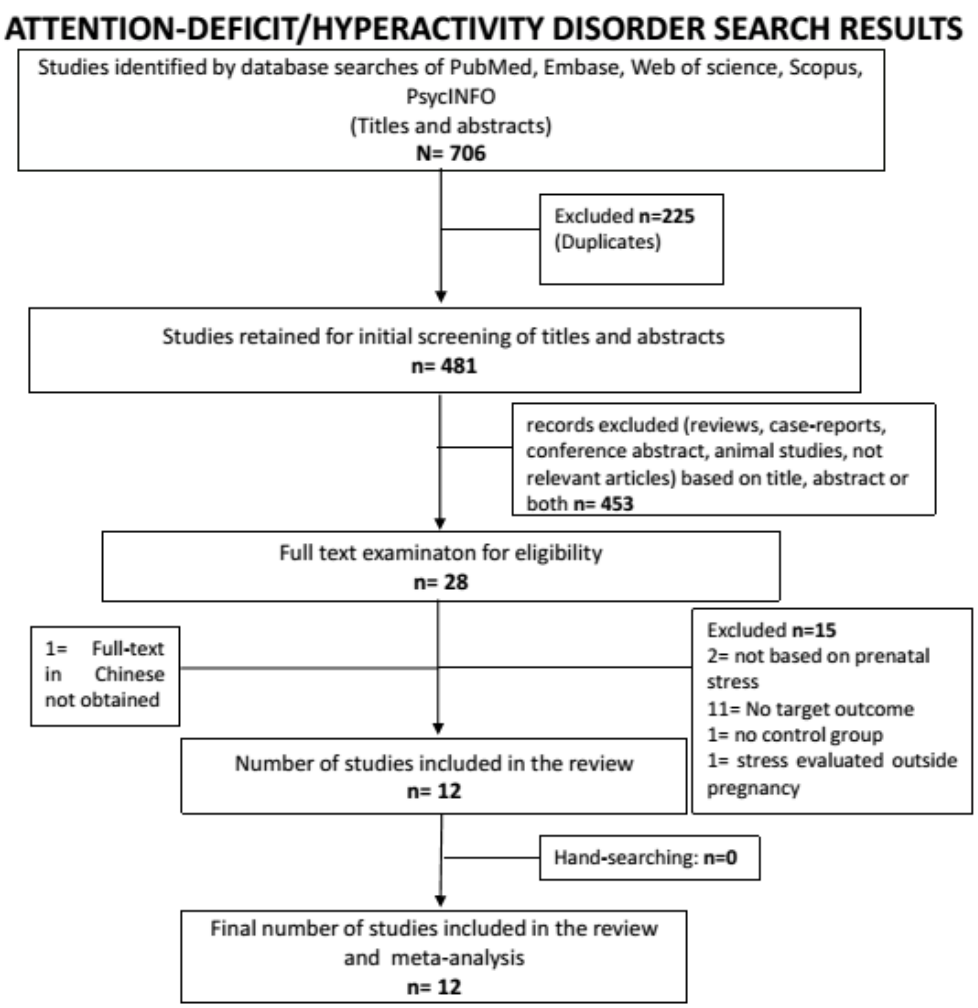


Figure 1b: Flow chart of the search process for ADHD studies

Table 1: Subgroup analyses of the impact of prenatal stress on ASD

Study characteristics	*Number of estimates (articles)*	*Sample size (exposed)*	*Outcomes*	*Pooled OR (95% CI)*	*I^2 %*	*Test for subgroup differences – p value*
Overall unadjusted **Overall adjusted**	n=17 (15) n=9 (8)	2,668,609 (150,964) 2,346,200 (45,884)	15130 14266	1.65 (1.31–2.09)* 1.64 (1.15–2.34)*	86% 90%	/ /
Design						p=0.0001
Cohort	n=5 (4)	23,44483 (45,424)	13,763	1.06 (0.91 – 1.24)	43%	
Case-control	n=4 (4)	1717 (336)	460	3.59 (2.02 – 6.38)*	65%	
Type of Stress						p=0.0001
Objective	n=5 (4)	23,44483 (45,424)	13,763	1.06 (0.91 – 1.24)	43%	
Subjective	n=4 (4)	1717 (336)	460	3.59 (2.02 – 6.38)*	65%	
ASD definition						p=0.58
Rating scale	n=3 (3)	56,039 (1512)	787	1.85 (0.63 – 5.41)	89%	
DSM or ICD	n=6 (5)	2,290161 (44372)	13479	1.34 (1.01 – 1.80)*	85%	
Time of exposure						p=0.49
Before pregnancy	n=4 (4)	2,333,329 (21510)	451	1.12 (0.85 – 1.48)	53%	
1st trimester	n=2 (2)	2,230,853 (10823)	30	1.18 (0.82-1.70)	0%	
2nd trimester	n=2 (2)	2,230,853 (11972)	31	1.08 (0.76-1.54)	0%	
3rd trimester	n=2 (2)	2,230,853 (11488)	49	1.48 (1.12-1.97)*	0%	
Study quality						p=0.002
High quality	n=6 (5)	2,344,673 (45812)	14180	1.15 (0.91 – 1.46)	76%	
Moderate quality	n=3 (3)	1527 (241)	422	3.22 (1.77 – 5.87)*	74%	

* = $p<0.05$

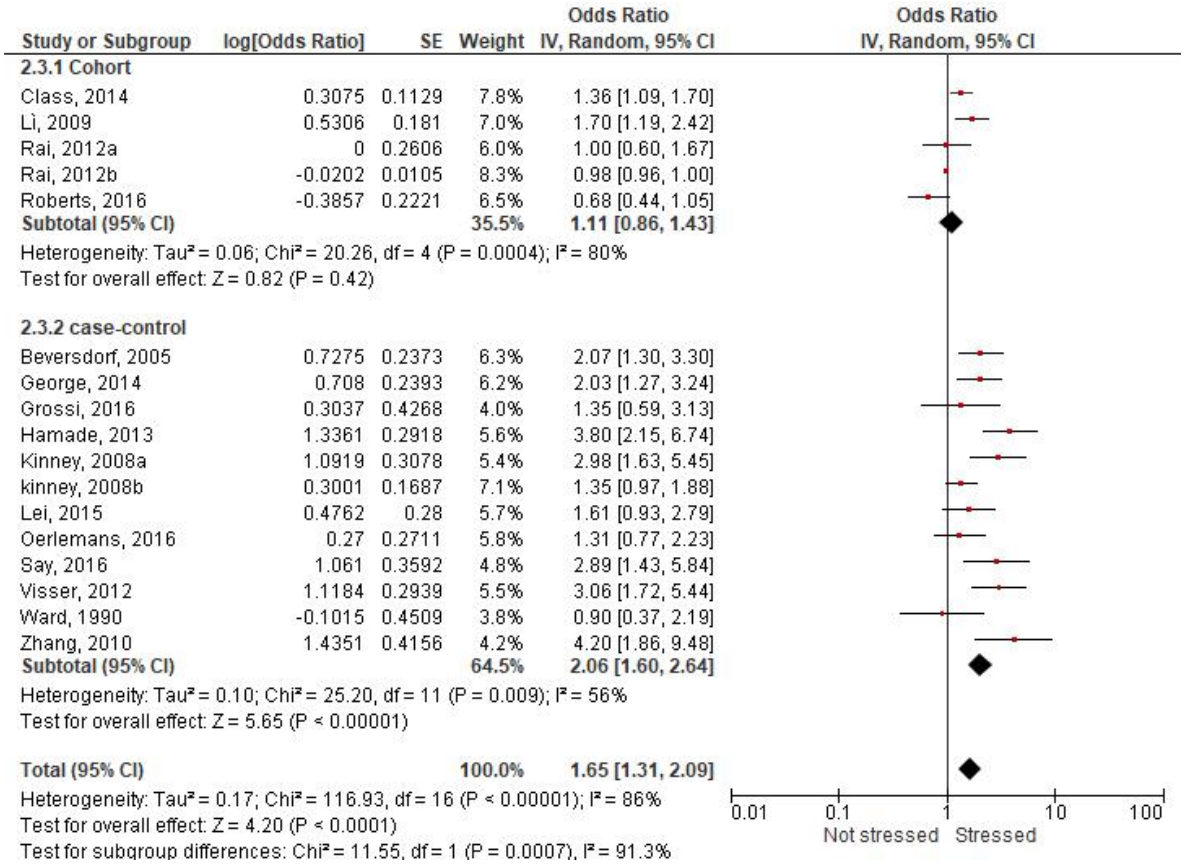
Table 2: Subgroup analyses of the impact of prenatal stress on ADHD

Study characteristics	*Number of estimates (articles)*	*Sample size (exposed)*	*Outcomes*	*Pooled OR (95% CI)*	*I^2 %*	*Test for subgroup differences – p value*
Overall unadjusted Overall adjusted	n=12 (11) n=8 (7)	1,760,174 (36,843) 1,758,906 (27,172)	25,677 25,215	2.69 (1.85 – 3.92)* 1.72 (1.27 – 2.34)*	80% 85%	/ /
Design						p=0.96
Cohort	n=4 (4)	1,756,944 (26,821)	24,956	2.00 (1.12 – 3.59)*	82%	
Case-control	n=4 (3)	1242 (351)	259	1.96 (0.95 – 4.04)	84%	
Type of Stress						p=0.50
Objective	n=3 (3)	1,574,278 (26,758)	24,643	1.77 (0.94– 3,33)	81%	
Subjective	n=5 (4)	4628 (414)	572	2.44 (1.23 – 4.85)*	86%	
ADHD definition						p=0.0001
Rating scale	n=3 (3)	3830 (141)	417	4.36 (2.52 – 7.54)*	0%	
DSM or ICD	n=5 (4)	1,755,076 (27,151)	24,798	1.25 (0.99 – 1.58)	78%	
Time of exposure						p=0.34
Before pregnancy	n=2 (2)	1,754,056	117	1.11 (0.69 – 1.70)	81%	
1st trimester	n=2 (2)	1,754,056	36	0.89 (0.64 - 1.23)	0%	
2nd trimester	n=2 (2)	1,754,056	49	1.26 (0.76- 2.11)	32%	
3rd trimester **Study quality**	n=2 (2)	1,754,056	75	1.76 (0.81 - 3.083)	68%	p=0.09
High quality	n=2 (2)	1,754,056 (26,719)	24,591	1.27 (0.90 – 1.79)	57%	
Low quality	n=6 (5)	4850 (453)	624	2.47 (1.24 – 4.92)*	87%	

* = $p<0.05$

Figure 2: forest plot for crude and adjusted estimates stratified by study design - ASD

Forest plot with the crude estimates



Forest plot with the adjusted estimates

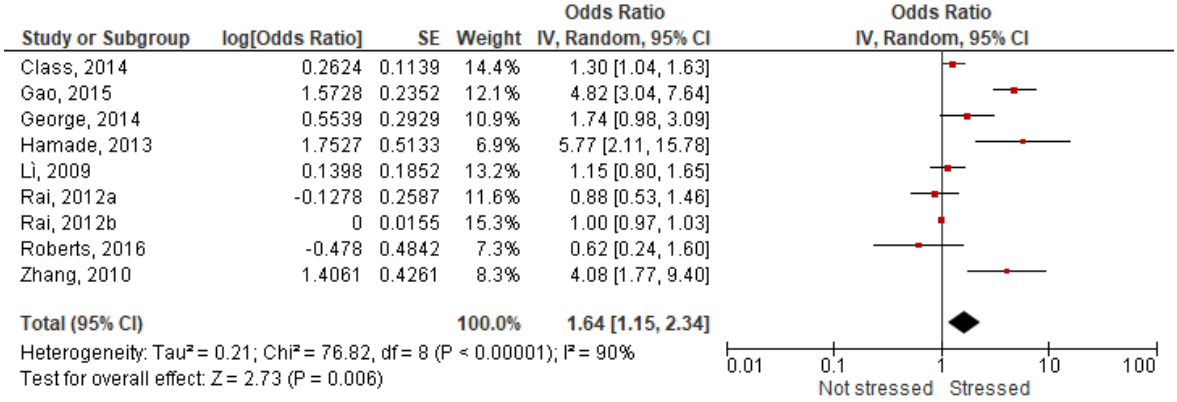
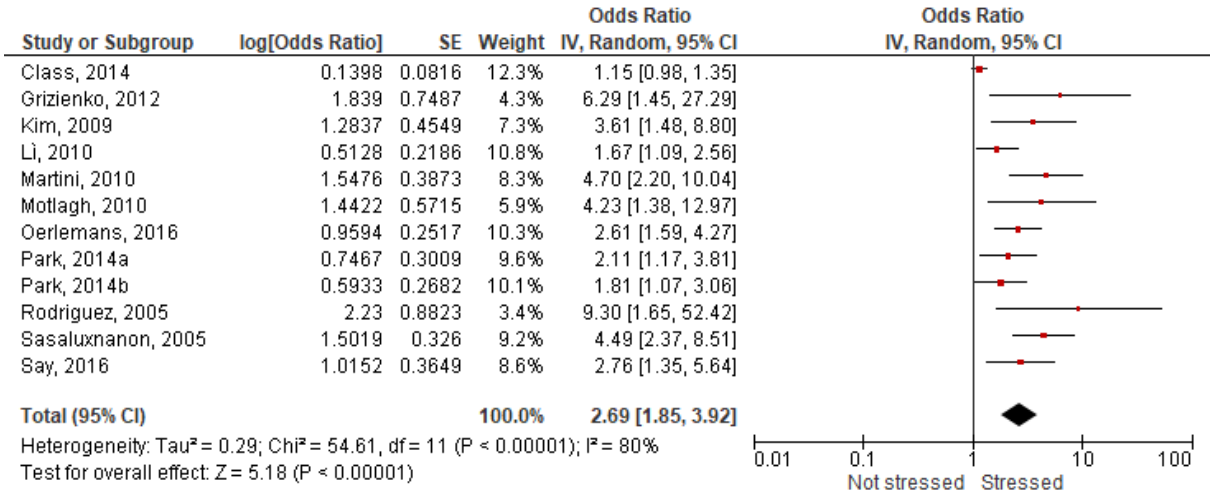


Figure 3: forest plot for crude and adjusted estimates stratified by study design - ADHD

Forest plot with the crude estimates



Forest plot with the adjusted estimates

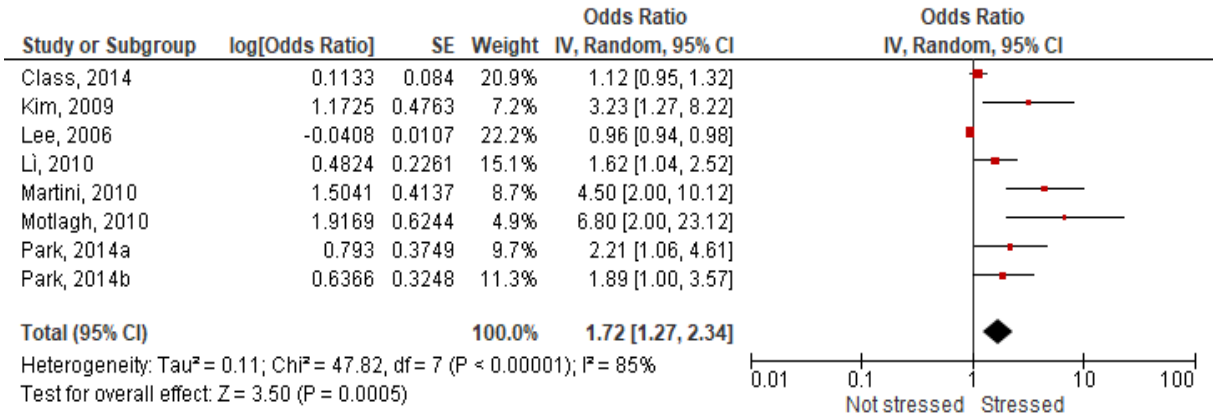


Table S1: study characteristics for ASD. n= number of subject exposed; N= total outcome number

1st author (year)	*Sample size and exposed (n)*	*Study design*	*Measurement of stress*	*Type of exposure*	*Time of exposure*	*Gender effect*	*Covariates accounted for*	*Outcome (n/N)*	*Measurement of the outcome*	*Main effect size (Crude)*	*Main effect size (adjusted)*
Beversdorf, 2005 (USA)	400 (101)	Case-control (mean age 7.9±4.0)	Survey distribution	Severe life events (events matching the SRRS)	During pregnancy with peak at 21-32 weeks gestation	**No**	-	**ASD (61/188)**	Diagnosis according to DSM-IV	2.07 (1.30-3.28) calculated	
Class, 2014 (Sweden)	738,144 (6625)	Cohort (follow-up up to 17 years)	Nationwide register	Maternal bereavement	At any time and 3rd trimester	Yes (no difference)	Sex, birth weight, gestational age, parental age, birth country, education, criminal convinction, mental illness, death by suicide	**ASD (79/6,430)**	Inpatient and outpatient diagnoses of Autism and Asperger's syndrome	Across pregnancy:1.36 (1.09-1.70); 3rd trimester:1.67 (1.22-2.28)	Across pregnancy: 1.30 (1.04–1.62);3rd trimester:1.58 (1.15-2.17)
George, 2014 (India)	343 (100)	Case-control (child age 2-6y)	Questionnaire	Excessive mental stress	At any time during pregnancy	No	Gender, place of residence, family size, type of family education of mother and father, occupation of father, SES	**ASD (54/143)**	CARS score >30	2.03 (1.27-3.26)	1.74 (0.98-3.08)
Grossi, 2016 (Italy)	113 (Death or disease 5; Conjugal problems 6; job difficulties 10)	Case-control (mean age 12.88±3.49)	Structured interview	Stressful life events	At any time during pregnancy	No	-	**ASD (Death or disease 2 Conjugal problems 5; job difficulties 7/ 45)**	Diagnosis according to DSM-V	Death or disease of a relative: 1.01 p>0.05; conjugal problems: 8.4 p=0.056; Job difficulties: 4.0 p=0.054	-
Hamade, 2013 (Lebanon)	258 (72)	Case-control (child age 3 to 27y)	Self-administered Questionnaire	Depressive symptoms	At any time during pregnancy	No	Living close to an industry; age and sex of the child; Previous childhood infection	**ASD (40/86)**	Diagnosis according to DSM-IV	3.80 (2.15-6.73) [calculated]	5.77 (2.11-15.80)
Kinney (2008) (USA)	320.686 (high: 9,003: medium: 95651)	Case-control	NCHS census data	Natural disaster (storm)	During pregnancy and 5 gestational periods;	Yes (no difference)	-	**ASD (12 high-58 moderate exposed/ 167)**	Children with DSM-III o IV diagnosis	High: 2.98 (1.63-5.42); Medium: 1.35 (0.97-1.87);)	-

Lei, 2015 (China)	926 (69)	Case-control (mean age 9.90±4.39)	Survey questionnaire (yes/no)	Unhappy emotional state	At any time during pregnancy	No	Socioeconomic factors	**ASD (20/193)**	Children diagnosed by pediatrician according to DSM-IV and to CARS score >30	1.61 (0.93-2.79)	4.82 (3.05-7.63)
Li (2009) (Denmark)	1.492.709 (37,275)	Cohort (follow-up up to 28y)	Nationwide register	Maternal bereavement	1 year before & during pregnancy	**Yes (no difference)**	Gender, birth weight, gestational age, sibling order, paternal age, maternal age, maternal psychiatric history, maternal education, maternal income, maternal residence, and maternal cohabitation status.	**ASD (31/2367)**	Children in psychiatric hospital or in receipt of outpatient care because of autism	1.70 (1.19-2.42);	1.15 (0.80-1.65)
Oerlemans (2016 (the Netherlands)	405 (65)	Case-control (mean age 12.0±3.7)	Questionnaire (1=yes; 0=no)	Maternal stress (severe tensions)	During pregnancy	**No**	-	**ASD (31/152)**	ASQ and ADI-R	1.31 (0.77-2.27)	
Rai et al, 2012a (Sweden)	47706 (181 exp. during pregnancy)	Cohort	Nationwide register	Severe life events (death, serious accident or illnesses)	During pregnancy and 1-2-3 years after birth	**No**	Age of parents, parity, family income, education, occupational class, migration status of parents; for life events at other time points	**ASD (17/4429)**	Diagnosis by parental report, direct observation and a structured neuropsychiatric assessment	1 year before:1.28 (0.92-1.79); during pregnancy:1.00 (0.60–1.65);	1 year before 1.28(0.91-1.78); during pregnancy: 0.88 (0.53–1.46);
Rai et al, 2012b (England)	11154	Cohort	Questionnaire	Exposure to rare and common life events	Early and mid-late pregnancy; at 8, 21, 33mts postnatal; and at 3 yr 11 mts postnatal	**No**	Parent age, highest occupational class of either parent; tenure of accommodation; parity sex of child and for weighted life event scores at all other time points under study.	**ASD (86)**	Diagnosis identified through National Health Records and the Pupil Level Annual Schools Census (PLASC)	Early pregnancy 0.98(0.95-1.01; late pregnancy: 0.99(0.95-1.02);	Early pregnancy 1.00 (0.95-1.06); late pregnancy: 1.01(0.95-1.07);
Roberts, 2016 (USA)	54,770 (1,343)	Cohort	Question "were you physically hurt by your spouse during this pregnancy?	Sexual, emotional or physical abuse	1 and 2 yrs before birth; during birth yr and during pregnancy	**No**	birth weight, gestational age, smoking or alcohol, gestational diabetes, preeclampsia, or induced abortion. maternal age, birth year., child's sex, mother's childhood SES and mother's abuse in childhood	**ASD (451)**	Administration of the ADI-R in subsample of 50 randomly selected cases	Birth year: 0.68 (0.44, 1.03); 1yr before: 1.92 (1.28-2.88)	*During pregnancy: 0.62 (0.24,1.67)* Birth year: 0.64(0.41-1.00); 1yr before: 1.58 (1.04-2.40);
Say et al, 2016 (Turkey)	180 (52)	Case Control (mean age8.80±1.98)	Standardized questionnaire	Depressive mood	At any time during pregnancy	**No**	-	**ASD (38/100)**	Diagnosis according to DSM-IV	2.88 (1.43-5.84) [calculated]	-

Visser et al, 2012 (Netherlands)	507 (60)	Case control (age [months] 32.6±6.6)	Questionnaire	Questions about severe stress and depression	At any time during pregnancy	**No**	-	**ASD (40/196)**	Diagnostic protocol with medical history, observation, psychiatric evaluation, ADOS, ADI-R	3.06 (1.72-5.44)	-
Ward, 1990 (USA)	118 (93)	Case-control (child age 7to12y)	Questionnaire	Family problems	At any time during pregnancy	No	-	**ASD (46/59)**	Children hospitalized	t-test $p<0.05$ 0.90 (0.38-2-19) [calculated]	-
Zhang, 2010 (China)	190 (95)	Case Control (child age 3to21y)	Questionnaire	Unhappy emotional state	At any time during pregnancy	**No**	advanced paternal age, sex and birth year	**ASD (29/38)**	Autism diagnosis according to the World Health Organization's International Classification of Diseases, Tenth Revision (ICD-10).	4.20 (1.86-9.47)	4.08 (1.77-9.41)

Table S2: study characteristics for ADHD. n= number of subject exposed; N= total outcome number

1st author, year and (country)	*Sample size and exposed (n)*	*Study design*	*Measurement of stress*	*Type of exposure*	*Time of exposure*	*Analysis of gender effect*	*Covariates accounted for*	*Outcome exposed (n/N)*	*Measurement of the outcome*	*Main effect size (Crude)*	*Main effect size (adjusted)*
Class, 2014 (Sweden)	738,144 (6625)	Cohort (follow-up: 17 years)	Nationwide register	Maternal bereavement	At any time during pregnancy and 3rd trimester	Yes (no difference)	Child sex, birth order, birth weight, gestational age, parental age, country of birth, education, criminal history, severe mental illness, death by suicide	ADHD (79/14,313)	Inpatient and outpatient diagnosis of hyperkinetic disorder	Across pregnancy: 1.15 (0.98-1.35); 3rd trimester: 1.34 (1.06-1.70)	Across pregnancy: 1.12 (0.95-1.32); 3rd trimester 1.31 (1.04-1.66)
Grizenko 2012 (Canada)	142 (43)	Case control (child age 9 to 10)	5 point likert scale (KMGQ)	Stressful life events (separation, repeated physical or sexual abuse, imprisonment of a spouse or death of a very close relative)	At any time during pregnancy	No	-	ADHD (29/71)	(CBCL) and the Conners' Global Index for Parents (CGI-P)	6.29 (1.45-27.26)	
Kim, 2009 (Korea)	2,673	Retrospective cohort (child mean age; 9)	Structured questionnaire	Maternal stress and depression	At any time during pregnancy	No	Age, gender, SES	Full and subthreshold ADHD (119/354)	DISC-IV	3.61 (1.48-8-80)	3.23 (1.27-8.22)
Lee, 2006 (Taiwan)	120	Case-control (child mean age 8)	Questionnaires (MAS, MSS and SRSS)	Marital adaptation, marital satisfaction and life events perception	At any time during pregnancy	No	Child age and sex	ADHD (60)	patient of the hospital that fulfilled the DSM-IV criteria.	-	Marital adaptation: 0.96 (0.94-0.99)
Li 2010 (Denmark)	1.015.912 (20,094)	Cohort (follow-up: 16 years)	Nationwide register	Maternal bereavement (unexpected death)	At any time during pregnancy and 3rd trimester	Yes (only in boys)	Sex, birth year maternal age, residence, education, income, psychiatric diseases, smoking; gestational age, Apgar, SGA	ADHD (51/10,278)	Hospital diagnosis (ICD-10) and ADHD medication	1.67 (1.09-2.56) Boys: 1.77; 3rd trimester: 3.04 (1.26-7.31)	1.62 (1.04–2.52); boys 1.72 (1.09–2.73); 3rd trimester 2.98 (1.24–7.16)
Martini 2010 (Germany)	935 (102)	Cohort (follow-up 10 years)	Question "During pregnancy, how much did you feel	Self-perceived distress	At any time during pregnancy	No	Anxiety before birth	ADHD (11/N)	Composite International Diagnostic Interview (CIDI)	4.7 (2.2–10.0)	4.5 (2.0–10.12)

			strained?"								
Motlagh 2010 (USA)	222 (18)	Case control (mean age 11.8 ±2.7)	MSRPFED interview	Psychosocial stressors about home environment, parental relationship, emotional supports, employment, financial status, physical health, and legal issues	At any time during pregnancy	No	Gender	ADHD (13/52)	SADS-PLV	4.23 (1.38-12.97)	6.8 (2.0–23.12)
Oerlemans, 2016 Netherlands	476 (84)	Case-control (mean age 11.8 ±2.4)	Interview (1=yes; 0=no)	Maternal stress (tensions and concerns about the child)	At any time during pregnancy	No	-	ADHD (50/162)	CTRS and PACS	ADHD vs NC: 2.61 (1.52-4.48);	-
Park, 2014 (Korea)	900 (313)	Case-control (mean age 8.63 ±2.21)	Question (had you been stressed during pregnancy: yes/no)	Stressful life events	At any time during pregnancy	No	(e.g., low birth weight, preterm delivery, or intensive care)	ADHD-I (32/65) ADHD-C (38/82)	ADHD diagnosis made by an expert psychiatrist	ADHD-I: 2.11 (1.17-3.79); ADHD-C: 1.81 (1.07-3.05)	ADHD-I 2.21(1.06-4.61); ADHD-C: 1.89 (1.00-3.56)
Rodriguez & Bohlin, 2005 (Sweden)	290	Cohort (follow-up: 7 year)	Perceived Stress Scale (PSS)	Global perceived stress	At any time during pregnancy (Stronger week 10)	Yes (only in boys)	-	ADHD (n/7)	Fulfilment of ADHD criteria based on those listed in DSM.	9.30 (1.65–52.38)	
Sasaluxnanon, 2005 (Turkey)	241	Case-control (child age 6 to 12)	Self-report questionnaire	Emotional distress (anxiety, depression, stressed)	At any time during pregnancy	No	-	ADHD (n/122)	Clinical diagnosis based DSM-IV TR criteria	4.49 (2.37-8.45)	-
Say, 2016 (Turkey)	180 (40)	Case Control (mean age 8.80±1.98)	Standardized questionnaire	Depressive mood-anhedonia	At any time during pregnancy	No	-	ADHD (26/100)	Diagnosis by expert psychiatrist using the DSM-IV	2.76 (1.35-5.64;	-

Figure S1: Forest plot of ASD studies which reported both crude and adjusted estimates

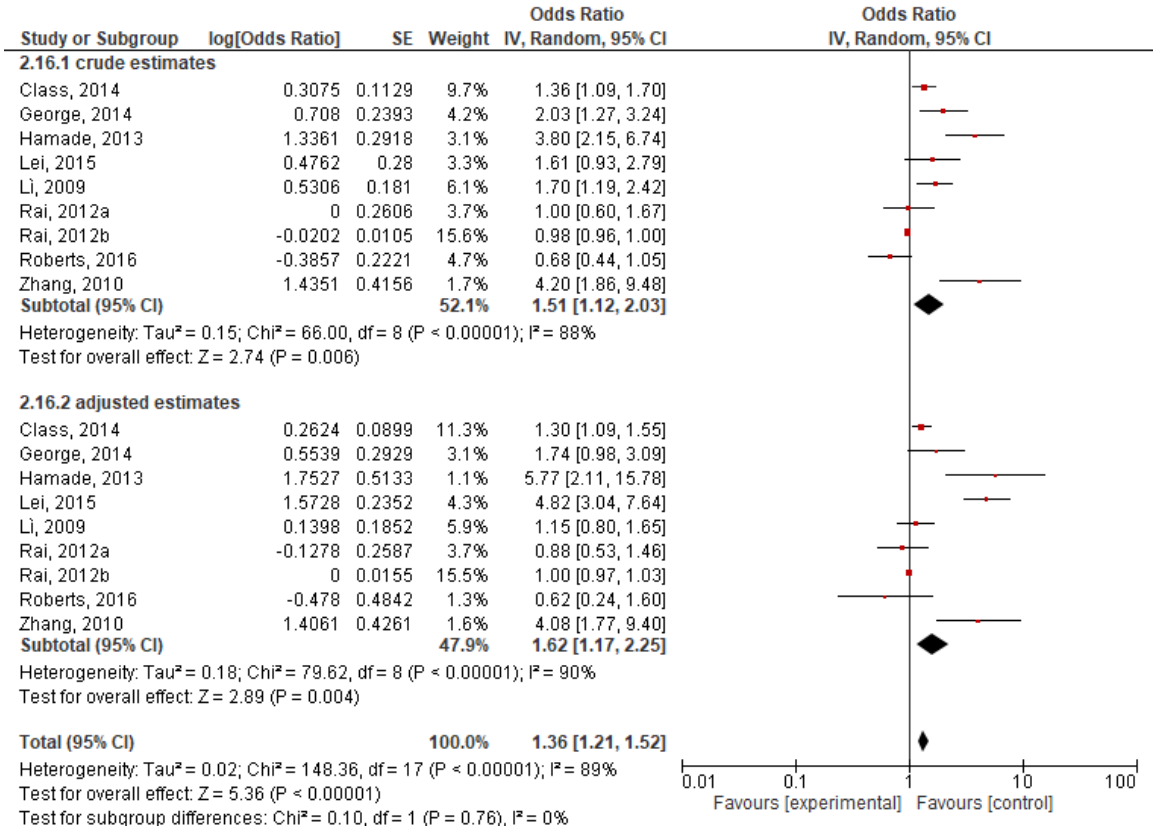


Figure S2: Forest plot of ADHD studies which reported both crude and adjusted estimates

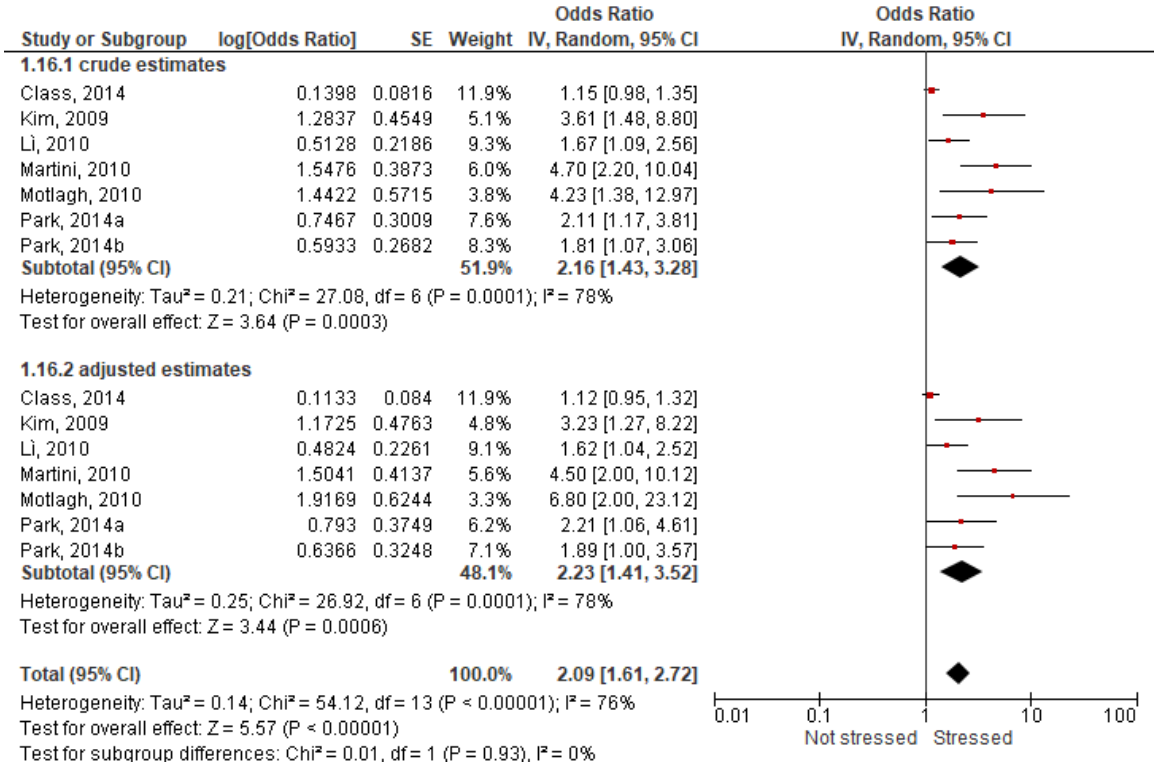


Figure S3: funnel plot with observed values for adjusted estimates for ASD (figure S3A) and ADHD (figure S3B)

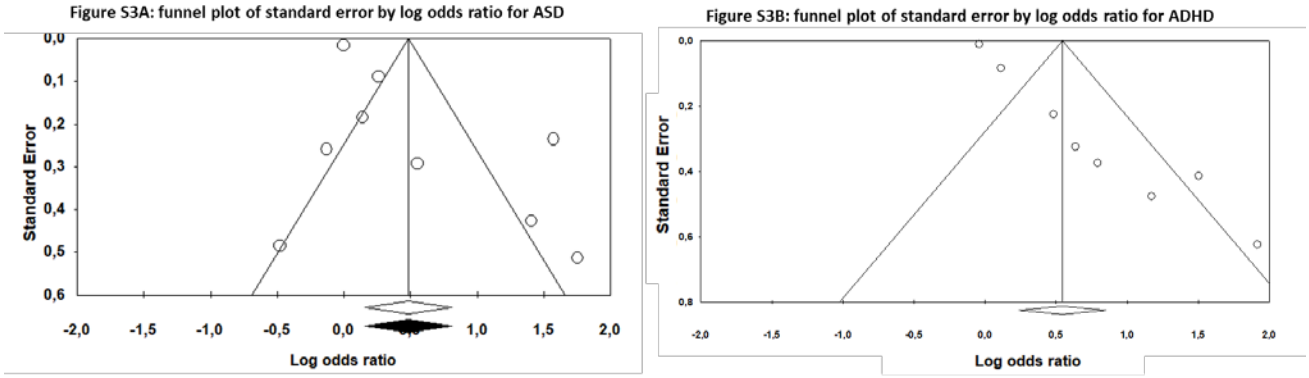
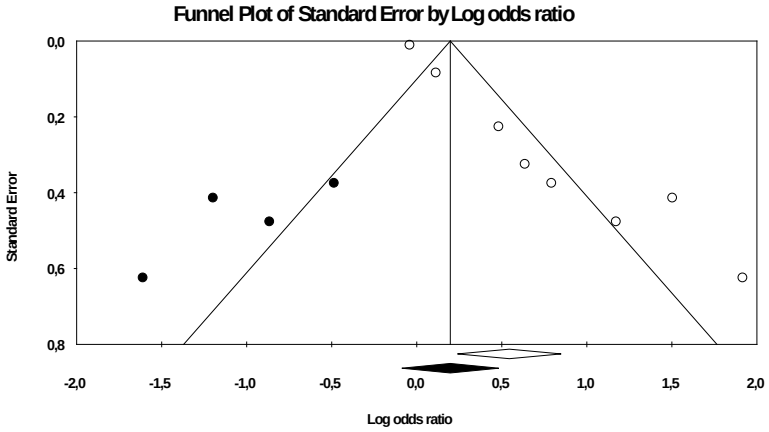


Figure S4: funnel plot with observed and imputed values for adjusted estimates of ADHD



APPENDIX 1

Strategies to search PUBMED, PsycINFO, Web of Science, EMBASE to identify cohort, cross-sectional and case–control studies to determine the association prenatal maternal stress and offspring neurodevelopmental disorders

Search terms
For PubMed (1966- March 2018)
1. ADHD
2. ASD
3. attention deficit hyperactivity disorder
4. Autism
5. autism spectrum disorder
6. Autism spectrum disorders
7. Autistic
8. Autistic spectrum
9. Autistic spectrum disorder
10. Autistic spectrum disorders
11. Case control study
12. Child
13. Cohort study
14. Cross sectional study
15. Development
16. Distress
17. Emotional Stress
18. hyperactivity disorder
19. impulsivity
20. Inattent*
21. Infant
22. Life Stress
23. Life Stresses
24. Maternal
25. Maternal Exposure
26. Maternal Exposures
27. neurodevelopment
28. Offspring
29. Outcomes
30. perinatal
31. Pregnancy
32. Pregnancy outcome
33. prenatal
34. prenatal maternal stress
35. Prospective study
36. Psychologic Stress
37. Psychological Stress
38. Psychological Stresses
39. Retrospective study
40. Trauma
41. trimester

We used a very similar approach for searching in the other databases.

APPENDIX 2

Bias classification - ADHD

Study	Selection	Exposure	Outcome	Confounding	Analytical	Attrition	Total
Class, 2014	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal (Assessed for common confounders)	Minimal	Minimal	**LOW**
Grizienko, 2012	Minimal (Rational for case and control selection explained)	Moderate (Recall >5 years after birt, but additional steps taken)	Minimal	Moderate (Not assessed for confounders)	Minimal	NR	**MODERATE**
Kim, 2009	Low (Sample selected from large population but selection criteria not defined)	High	Minimal	Low (Only certain confounders assessed)	Minimal	NR	**MODERATE**
LI, 2010	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal (Assessed for common confounders)	Minimal	Minimal	**LOW**
Lee, 2006	Moderate (Rationale for cases and controls not explained)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct confounders)	Minimal	NR	**MODERATE**
Martini, 2010	Minimal	Moderate (Extrapolating data from population)	Minimal	Moderate (Not assessed for correct confounders)	Minimal	NR	**MODERATE**
Motlagh, 2010	Minimal	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct confounders)	Low	NR	**HIGH**
Oerlemans, 2016	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct confounders)	Low	NR	**HIGH**

Park, 2014	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birt)	Minimal	Low (Only certain confounders assessed)	Low	NR	**MODERATE**
Rodriguez, 2005	Minimal	Minimal	Minimal	Moderate (Not assessed for confounders)	Low	High (>20% attrition),	**MODERATE**
Sasaluxanon, 2005	Low	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Low	NR	**MODERATE**
Say, 2016	Minimal	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Moderate	NR	**HIGH**

Bias classification - ASD

Study	Selection	Exposure	Outcome	Confounding	Analytical	Attrition	Total
Beversdorf, 2005	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Low	NR	**MODERATE**
Class, 2014	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal	Minimal	Low	**LOW**
Lei, 2015	Low	High (Recall >5 years after birt)	Low	Moderate (Not assessed for correct confounders)	Low	NR	**MODERATE**
George, 2014	Moderate (Sample selection ambiguous)	Moderate (Recall 1-5 years after birth)	Low	Moderate (Not assessed for correct confounders)	NR	NR	**MODERATE**
Grossi, 2016	Moderate (Sample selection ambiguous)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Minimal	NR	**MODERATE**
Hamade, 2013	High (A very select population studied)	High (Recall >5 years after birt)	Minimal	Low (Only certain confounders assessed)	Low	NR	**HIGH**
Kinney, 2008	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Moderate (Not assessed for confounders)	Low	NR	**LOW**
LI, 2010	Minimal	Low	Minimal	Minimal	Minimal	Minimal	**LOW**

		(Assessment of exposure from a dataset)					
Oerlemans, 2016	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct confounders)	Low	NR	**HIGH**
Rai, 2012a	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal	Minimal	Minimal	**LOW**
Rai, 2012b	Minimal	Minimal	Minimal	Minimal	Minimal	Low	**LOW**
Roberts, 2016	Minimal	Minimal (direct questioning)	Low (administration of the ADI-R)	Low (Only certain confounders assessed)	Minimal	Low	**LOW**
Say, 2016	Minimal	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Moderate	NR	**HIGH**
Visser, 2012	Minimal (Rational for case and control selection explained)	Moderate	Minimal	Moderate (Not assessed for confounders)	Minimal	NR	**MODERATE**
Ward, 1990	Moderate (Sample selection ambiguous)	Moderate	Low (Hospitalized children)	Moderate (Not assessed for confounders)	High	NR	**HIGH**
Zhang, 2010	Minimal (Rational for case and control selection explained)	Moderate	Minimal	Low (Only certain confounders assessed)	Minimal	NR	**LOW**