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Prenatal maternal psychosocial stress and offspring's asthma and allergic disease: a systematic review and meta-analysis

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Running head: Prenatal stress and offspring asthma and allergy disease

ABSTRACT

Background: Prenatal maternal stress may influence offspring's atopic risk through sustained cortisol secretion resulting from activation of the hypothalamic-pituitary-axis (HPA), leading to Th2-biased cell differentiation in the fetus. We undertook a systematic review and meta-analysis investigating the relationship between prenatal maternal psychosocial stress and risk of asthma and allergy in the offspring.

Design:

Methods: We searched 11 electronic databases from 1960 to 2016, search the grey literature, and contacted experts in the field. Type of stress indicator included mood disorders, anxiety, exposure to violence, bereavement and socio-economic problems occurring during pregnancy, both objectively or subjectively measured. We included all possible asthma and IgE-mediated allergy outcomes. We conducted random-effects meta-analyses to synthesize the data.

Results: We identified 9,779 papers of which 30 studies (enrolling >6 million participants) satisfied inclusion criteria. The quality of 25 studies was moderate, four were strong, and one was weak. Maternal exposure to any type of stressors was associated with an increased risk of offspring atopic eczema/dermatitis (OR 1.34, 95%CI 1.22-1.47), allergic rhinitis (OR 1.30, 95%CI 1.04-1.62), wheeze (OR 1.34, 95%CI 1.16-1.54) and asthma (OR 1.15, 95%CI 1.04-1.27). Exposure to anxiety and depression had strongest effect compared to other stressors. Exposure during the third trimester had the greatest impact compared to first and second trimesters. The increased risk was stronger for early-onset and persistent than for late-onset wheeze. Bereavement of a child (HR 1.28, 95%CI 1.10-1.48) or a spouse (HR 1.40, 95%CI 1.03-1.90) increased the risk of offspring asthma.

Conclusions: Exposure to prenatal maternal psychosocial stress was associated with increased risk, albeit modestly, of asthma and allergy in the offspring. The pronounced risk during the third trimester may represent cumulative stress exposure throughout pregnancy rather than trimester-specific effect. Our findings may represent a causal effect or a result of inherent biases in studies, particularly residual confounding.

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INTRODUCTION

The susceptibility to develop asthma and allergy may be established already in utero.[1-4] The concept of fetal programming has provided important insights on the influence of the intrauterine environment on the development of the fetus and subsequent[5] risk of chronic conditions later in life.[6] As adaptive immunity develops prenatally, allergen specific immune responses are demonstrable in newborns[2,3,7] with umbilical cord blood shown to contain fetally derived immunoglobulin E (IgE).[1,3]

One suggested pathway through which prenatal maternal stress may influence the risk of asthma and allergy in the offspring is through the activation of the hypothalamic-pituitary-axis (HPA) in response to external stress.[8,9] This then causes secretion of hormones by the hypothalamus and pituitary gland in the brain and subsequent stimulation of the release of glucocorticoids, adrenaline and noradrenaline.[8-10] The release of glucocorticoids leads to increases in cortisol levels.[8,9] The activities of the HPA and the resultant chemical reactions can be transmitted to the fetus and thus influences development.[6,11] High levels of cortisol increase airway responsiveness in the offspring and potentiated cell differentiation from T helper cell type 1 (Th1) to T helper cell type 2 (Th2) phenotypes.[12] Maternal stress can also lead to a decrease in the glutathione/glutathione disulfide (GSSG) ratio, leading to oxidative stress and subsequent risk of asthma in the offspring.[8,9]

Several epidemiologic studies investigating indicators of prenatal maternal psychosocial stress on the risk of asthma and allergy in the offspring show that maternal exposure to stress may increase the risk of asthma and allergy in the offspring. Although two recent systematic reviews summarized existing studies,[13,14] a comprehensive synthesis of the underlying evidence is lacking. In the first review, only wheeze and asthma outcomes were considered.[13] Although the second review included the full spectrum of allergy outcomes, the searches were confined to a limited number of databases and only a narrative synthesis was perfomed.[14] Since the publication of these reviews, there have been a number of additional studies published. To provide a clearer and comprehensive picture of the underlying evidence, we undertook a systematic review with meta-analysis of studies that have investigated the association between prenatal maternal exposure to psychosocial stress and the risk of asthma and allergy in the offspring. We included the full spectrum of asthma and allergy outcomes and were also interested in understanding whether the type of indicator of prenatal psychosocial stress and timing (trimester) of exposure were important.

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METHODS

We published[15] and registered in PROSPERO (registration number: 2016:CRD42016036456) the protocol for the review prior to commencement of the systematic review, which outlined the approaches to undertaking the review.

Study types

Experimental studies (i.e. randomized-controlled trials, quasi-randomized controlled trials, controlled-clinical trials, controlled before-and-after studies, interrupted time-series designs) and analytical epidemiological studies (cohort, case-control, and cross-sectional studies) were eligible for inclusion. We excluded reviews, case-studies, case-series, and animal studies.

Participants

Pregnant women and their offspring of any age.

Exposure

We included all indicators of psychosocial stress, mood states, and acute or chronic stressors or negative life events (NLEs), including: anxiety and depression, issues with existing children, exposure to violence, discrimination or prejudice, financial problems, residential move or housing issues, daily stressors or generalized psychological distress, bereavement, natural disasters, separation, divorce or marital problems, involuntary job loss for mother or partner, and homelessness. We included studies with either objectively-measured or subjectively-reported measures of the stress events.

Outcomes

Primary outcomes were: asthma, atopic dermatitis/eczema, atopic sensitization, food allergy, allergic rhinitis, urticaria and anaphylaxis. All primary outcomes, with the exception of atopic sensitization, were defined either by physician assessment or by the self-report. Additionally, asthma diagnosis through use of airway function tests including peak expiratory flow [PEF], forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], forced expiratory flow rate or alternative age appropriate pulmonary function tests [oscillometry or exhaled nitric oxide analysis] were also accepted methods of assessment. Secondary outcomes included: asthma exacerbations, use of asthma medications, hospitalization for asthma, wheeze as defined by self-report or physician diagnosis, and measures of Health Related Quality of Life (HRQoL).

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Study identification

We searched the following databases from 1960 to the end of 2016: MEDLINE, EMBASE, Cochrane Library, Web of Science, Scopus, Global Health and Cab International; WHO Global Library; Psych INFO, CINAHL, AHMED, National Health Service (NHS) Evidence Health Information Resources, and Google Scholar. The following databases for international conference proceedings were also searched: Conference Proceedings Citation Index via Web of Knowledge and Zetoc via British Library. Reference lists of eligible articles were hand checked for additional citations. International experts in the field were contacted to ask for any relevant studies not captured through our database searches. We also searched the grey literature through Open Grey and The Grey Literature Report. Finally, the following registers were searched to locate ongoing studies: The Cochrane Central Register of Controlled Trials, International Standardized Randomized Control Trial Number Registry, WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, Australian and New Zealand Clinic Trials Registry, and Current Controlled Trials. There was no language restriction. The search strategies were published in our systematic review protocol.[15]

Study selection

Records retrieved from the databases were exported to Endnote for study screening, de-duplication, and overall management of the retrieved records. Study titles and abstracts were independently screened by two reviewers (CF and BN); any discrepancies were resolved by discussion. The same process was employed for full-text screening. Multiple reports based on the same study were reported as one study. Where data or information was missing from any study, we contacted authors requesting additional information.

Data extraction and management

A standardized form was developed and used to extract relevant data from each study. The data extraction form was piloted and revised prior to use in the review and was published alongside the protocol for this study.[15] Data extraction was completed independently by two reviewers (CF and BN) and discrepancies were resolved by discussion.

Quality assessment

All included studies were assessed for quality and risk of bias by two independent reviewers (CF and BN) using the Effective Public Health Practice Project (EPHPP) tool (http://www.ephpp.ca/tools.html). In addition to a global rating for each study, the EPHPP tool provides individual ratings for six domains of study quality, including appropriateness of study design for the research question, selection bias, exposure assessment, outcome assessment, data analysis, and generalizability of findings. The two reviewers graded the

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quality of each study with regards to each of these domains. The quality grading derived from each of the domains informed an overall grading for each study. For each study, the grading for the domains individually and the global study rating were assigned one of the three categories of risk of bias: weak, moderate, or strong. Concerning the domain on confounder adjustment, we considered the number and type of potential confounders adjusted in the studies, with close attention to the confounding factors listed in our own causal diagram (see Figure S1).

Analysis

We tabulated the features and key findings of the studies in order to provide a descriptive summary of the literature. We employed both narrative and quantitative synthesis of the underlying evidence. The quantitative synthesis (meta-analysis) was undertaken for studies judged to be reasonably homogenous with regards to similarity in the clinical, methodological, and statistical aspects. We used the random-effects meta-analysis approach for this purpose and included the adjusted risk estimates from each study. We included only cohort studies in the meta-analyses and not cross-sectional and case-control studies. Studies reporting odds ratios as effect measures were first converted to risk ratios before combining in meta-analyses with studies reporting risk ratios. Conversion of odds ratios to risk ratios was undertaken using the formulae by Grant, which given as follows: RR = OR/(1-p0+(p0 x OR)); where p0 is the baseline risk.[16] We quantified heterogeneity between studies using the I^2 test. We performed the following stratified analyses for each outcome: by type of stress indicator and timing (trimester) of exposure during pregnancy. To enhance comparability between studies that categorized any of the exposures as binary, we collapsed estimates from exposure categories in studies that used multiple exposure categories by using the Mantel-Haenszel approach,[17] thus in all analyses we estimated the risk of maternal stress versus no stress: we estimated the role of maternal exposure to any type of stress indicator (i.e. any of the studied stressors – anxiety, depression, bereavement, work-related stress, or NLEs), specific stress indicators, and trimester of exposure in relation to the outcomes. We used funnel plots to evaluate the potential for publication bias and small study effects and calculated the Begg and Egger's test for this purpose.[18] Meta-analysis was undertaken using Stata 14 statistical software.

RESULTS

In total, we identified 9779 articles, of which 7110 were included for screening by title and/or abstract after de-duplication. Of these, 7001 were excluded for not meeting the inclusion criteria and 109 articles were assessed for full text screening. A further 77 articles were excluded, leaving 32 articles (based on 30 studies) that met our inclusion criteria for

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narrative synthesis; 24 papers (based on 22 studies) were included in at least one meta-analysis (Figure 1).[19-50]

Study characteristics

The key characteristics of the studies are presented in Table E1. No experimental studies were found; therefore only analytical epidemiological studies were included, which comprised of 27 cohort studies, two case-control studies, and one cross-sectional study. The type of psychosocial stress indicators investigated in the studies included anxiety,[21-24,27,30,35,36,48,49] depression,[22-24,30,35,37,41,42] bereavemet,[29,32,38] work-related stress,[33,36,47,48] and NLEs,[19,20,25,26,28,31,34,39,40,43-46,49,50] which were usually comprised of a composite of different indicators of stressors. Most studies assessed maternal stress using self-completed validated questionnaire; in a few studies maternal stress was assessed from population registers, particularly stress resulting from bereavement of a family member. Twelve studies assessed the impact of maternal stress on asthma,[20,27-32,34,37,38,42,46] eight studies on atopic eczema/dermatitis,[22-24,28,31,44,47,48] ten studies on wheeze,[20,24-28,30,35,42,43,46] three studies on allergic rhinitis,[24,28,31] three on atopic sensitization,[27,31,42] and six studies on cord blood IgE or cytokines[19,21,36,39,45,50] (Table S1).

Risk of bias within studies

Table S2 provides details of the quality grading for the studies. Of the 30 studies graded for quality, four were strong, 25 were moderate, and one study was weak. Whilst all studies scored moderate or strong on exposure and outcome assessment, only one study scored weak on study design as it was based on a cross-sectional data. Six studies were graded weak for selection bias, whereas two studies were graded weak for confounding adjustment; no study was graded strong for selection bias and confounding adjustment.

Prenatal stress and offspring asthma

Prenatal maternal exposure to any type of stress indicator was associated with an increased risk of asthma onset (hazard ratio (HR) 1.13, 95%CI 0.98-1.32; I^2=91.5%) and current or ever asthma (RR 1.13, 95%CI 1.03-1.24; I^2=83.5%) in the offspring, although result for asthma onset was not statistically significant (Figure 2, Panel A). Concerning the type of stress indicators, only anxiety was significantly associated with an increased risk of asthma (RR 1.28, 95%CI 1.16-1.41; I^2=0%) (Figure 2, Panel B). Concerning the timing of prenatal maternal stress, only exposure during the third trimester was significantly associated with an increased risk of asthma (OR 1.45, 95%CI 1.08-1.94; I^2=78%) for the studies that measured current and ever asthma (Figure 3, Panel B). Bereavement of the death of a child (HR 1.28,

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95%CI 1.10-1.48; I^2=0%) or of a spouse (HR 1.40, 95%CI 1.03-1.90; I^2=1.3%), but not of a parent or sibling, increased the risk of asthma onset in the offspring (Figure 4).

Prenatal stress and offspring atopic eczema/dermatitis

Prenatal maternal exposure to anxiety (RR1.29, 95%CI 0.95-1.76; I^2=29.2%), depression (RR 1.45, 95%CI 1.12-1.89; I^2=0%), NLEs (OR 1.18, 95%CI 0.92-1.51; I^2=0%), and work stress (OR 1.32, 95%CI 1.16-1.50) was associated with increased risk of atopic eczema/dermatitis in the offspring, but only depression and work stress were statistically significant (Figure 5, Panel A). Maternal exposure to stress during the third and any trimester, but not during the second trimester, increased the risk of offspring atopic eczema/dermatitis (Figure 5, Panel B).

Prenatal stress and offspring wheeze

Prenatal maternal exposure to anxiety (RR 1.19, 95%CI 1.01-1.39; I^2=52%), depression (OR 1.74, 95%CI 1.42-2.13; I^2=0%), and NLEs (RR 1.23, 95%CI 1.00-1.52; I^2=88.3%) (Figure 6, Panel A) was associated with an increased risk of wheeze in the offspring. The increased risk was greater for maternal exposure to stress during the second and third than any trimester (Figure 6, Panel B). When we investigated the impact on different wheezing phenotypes, maternal stress increased the risk of early-onset, late-onset, and persistent wheeze, although the impact on late-onset wheeze was not statistically significant (Figure 7).

Prenatal stress and offspring allergic rhinitis

Prenatal maternal exposure to any type of stress indicator was associated with an increased risk of subsequent allergic rhinitis in the offspring (OR 1.36, 95%CI 1.08-1.71; I^2=43.7%) (Figure S2). These results were similar when the study by Hartwig et al was analyzed separately for allergic rhinitis at six and 14 years.[31]

Prenatal stress and offspring atopic sensitization

Prenatal maternal exposure to any stress indicator was associated with a decreased risk of atopic sensitization in the offspring (OR 0.92, 95%CI 0.86-0.98; I^2=0%) (Figure 8). These results were similar when the study by Hartwig et al was analyzed separately for atopic sensitization at six and 14 years.[31] The measurement and definition of atopic sensitization differed between the studies: whilst Cookson[27] defined it as ≥2 mm weal skin prick test to aeroallergens, Hartwig[31] and Reyes[42] were based on IgE measurements of a combination of both food and inhalant allergens.

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Prenatal stress and cord blood IgE and cytokines

Studies reporting the impact of maternal prenatal stress on cord blood IgE and cytokines were heterogeneous, particularly with regards to the type of outcomes investigated, hence a meta-analysis was not undertaken to pool the results of these studies together. However, across studies, maternal exposure to stress during pregnancy was associated with raised cord blood specific and total IgE.[36,39,45,50] One study reported an alteration of cord blood cytokine profiles (IL-12, IL-1β, IL-4, IL-5, IL6, IL-8, and TNF-α) in offspring of mothers exposed to stress during pregnancy.[19]

Assessment of publication bias

Figure S3 shows the funnel plot evaluating possible publication bias and small study effect: by interpretation, a symmetric funnel plot indicates less likelihood of publication bias influencing the estimates of effect. Indeed, the funnel plot in Figure S3 is modestly symmetric. The associated p-values for Egger's test (where Egger's test of with $P<0.05$ indicating presence of publication bias) were as follows: atopic eczema/dermatitis studies $p=0.949$; atopic sensitization studies $p=0.855$; wheeze studies $p<0.001$; asthma studies $p=0.828$; and allergic rhinitis studies $p=0.493$.

DISCUSSION

This study provides the most comprehensive and robust synthesis of the evidence to date on the association between prenatal maternal exposure to psychosocial stress and the risk of allergy and asthma in the offspring. The majority of included studies were at moderate risk of bias. Overall, prenatal maternal exposure to any psychosocial stress was associated, albeit modestly, with an increased risk of asthma, atopic eczema/dermatitis, wheeze and its phenotypes, and allergic rhinitis. A decreased risk was seen for atopic sensitization. Although these results were similar for specific indicators of stress, exposure to anxiety and depression had the strongest effects. The third trimester appeared to be more vulnerable period of exposure compared to first and second trimesters. Specific to asthma, maternal bereavement of a child or a spouse, but not of a parent or sibling, increased the risk of asthma in the offspring.

We undertook an exhaustive search of the literature, covering the major medical and public health databases, which was supplemented through search of grey literature and through contacting experts in the field. The search strategies were implemented and published in order to enhance reproducibility. It is therefore unlikely that we missed any relevant literature, this being confirmed by somewhat symmetric funnel plot on publication bias and small study effect. Two reviewers independently performed each stage of the review,

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including literature screening, data extraction, and quality appraisal of included studies. We developed, published and registered a detailed protocol[15] prior to undertaking the review, which enhanced the transparency of the review process.

At the same time of publishing our review protocol, two related systematic reviews were published.[13,14] By the time we were planning the current review, no protocol was published for those reviews, neither were they registered in PROSPERO; hence our preliminary search did not identify them. Nevertheless, in the first review only asthma and wheeze were outcomes, which limits its scope.[13] The second review considered all possible asthma and allergic outcomes, but only provided narrative synthesis of the existing literature.[14] We aimed for a comprehensive and exhaustive approach by including the full spectrum of allergy and asthma outcomes and considering whether the type of stressor and trimester of exposure were important. We identified 30 unique studies as against 16 studies in the second review[14] and 18 studies as against 10 studies in the first review with regards to asthma/wheeze outcomes.[13] Whilst the second study[14] performed only narrative synthesis, with careful consideration, we judged several of these studies to be reasonably homogenous to be combined in meta-analyses with respect to exposure and outcome definitions, study design, and statistical analyses. Regardless of the differences in methodological rigor and comprehensiveness, the conclusions from the two previous systematic reviews align with our findings, indicating that prenatal maternal exposure to psychosocial stress was associated with increased risk of asthma and allergic disease in the offspring.

The majority of studies included in our review were graded as at moderate risk of bias, with only four being graded as strong studies, an indication of the potential for biases across studies, particularly within the domains of selection bias and confounding adjustment. In particular, most studies assessed maternal prenatal stress using self-report questionnaires, usually for recall of previous exposure to stress across several months. No study used both self-report and objective measures at regular intervals, which would provide a more robust and informative understanding of unique and combined contribution of environmental and mechanistic factors involved in the developmental pathway of atopic conditions. Several studies also assessed allergy outcomes using maternal subjective questionnaires and the age of onset of the outcomes was not consistent across all studies. Objective assessment of both maternal prenatal stress and offspring outcomes and within the same time-point will improve the underlying evidence and provide a stronger basis to evaluate whether these findings are causal.[14] The test for heterogeneity was significant for a number of associations, an indication of the variations in methods and measures between studies; however as we did not have sufficient number of studies for each of these associations, we were unable to

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further investigate the possible reasons for these significant heterogeneity tests. Furthermore, as it was not feasible to perform a formal test between subgroups, it is possible that the associations found within subgroups may be a result of chance.

Although some studies have examined the role of maternal stress during the postpartum period and the child's exposure during infancy on subsequent risk of allergy and asthma in the child,[26,51] *a priori*,[15] the underpinning objective of our review was to assess the impact of prenatal stress on offspring's asthma and allergy. This objective aligns within the framework of the fetal programming hypothesis. Within this framework, we assumed that the pathway of prenatal stress influencing offspring asthma and allergy risk may be independent of the effects of postnatal and early life stress, hence we excluded all studies not investigating maternal prenatal stress. However, we cannot rule out the possibility that these findings may also be partly explained by postnatal or early life stress exposures.[52] Furthermore, whilst the timing of exposure was based on the trimester of assessment of prenatal stress, this single time-point assessment may fail to reflect specific trimester effect, as stressful events may be acute or may chronologically be present throughout pregnancy or may even be an extension of stressful events prior to pregnancy.[52]

Regardless of the type of stress indicator, timing of exposure, and the type of allergy and asthma outcomes, by bringing together all the available evidence, the current evidence synthesis shows that prenatal maternal psychosocial stress is associated with an increased, albeit modest, risk of asthma and allergy in the offspring. The findings were particularly more evident for depression and anxiety than for other indicators of prenatal stress. This could reflect that anxiety and depression scores were based on self-assessment and questionnaires. However, it should also be noted that the largest study had a strongly positive result.[32] This study also had a strong design due to using a 'natural experiment' design and an objective measure of hospitalized asthma, thereby avoiding the risks of reporting bias and reverse causation.[32] In addition, although depression and anxiety reflect mood states, they are robust correlates of psychosocial stress and strongly predispose to stress-related conditions, such as smoking, poor diet, poor sleeping habits, and poor quality of life which may also lead to asthma and allergy in offspring.[53]

Whilst our observations may represent causal relationships, they may also be a consequence of over-reporting of offspring disease status by distressed mothers[22,54]or due to residual confounding in the original studies. The number and type of confounders adjusted varied across included studies. In particular, the omission of key confounders in several studies, including maternal allergic history, pregnancy complications, acid reflux conditions,

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medication use during pregnancy (e.g. antibiotics and acetaminophen), and pregnancy weight gain indicates sub-optimal confounding adjustment and therefore may impact on the observed risk. One way to test for residual confounding in fetal programming studies is to use family design studies such as sibling studies[54,55] or to use a paternal negative control. A positive association for paternal exposure to stress during the mother's pregnancy and subsequent offspring asthma or allergy may indicate residual confounding is affecting the prenatal maternal stress and offspring asthma association. A recent study using fathers as a negative control in this way, found that after adjusting for measured confounders there was no evidence for residual confounding.[56]

One hypothesized pathway through which stress may influence risk of asthma and allergy is that high levels of cortisol resulting from external stress may potentiate cell differentiation from Th1 to Th2 phenotype.[12] Prenatal stress-generated cortisol has been linked to increased airway responsiveness in the offspring in animal models.[12] This indicates that prenatal maternal stress may increase risk of atopic sensitization in the offspring and subsequent allergic disease and asthma. However, our findings did not support this line of reasoning, but showed a decreased risk of atopic sensitization and increased risk of clinical allergic outcomes and asthma. The reason for these differential findings between atopic sensitization and other clinical outcomes is unclear. Other suggested mechanism indicate that prenatal maternal stress may cause epigenetic effects with deoxyribonucleic acid (DNA) methylation and altered gene expression in the placenta,[57] but this proposal and its implication for the development of allergy and asthma in the offspring has yet to be determined.[51] There is some evidence that prenatal stress exposure can influence the composition of the offspring's intestinal microbiota and may also result in increased susceptibility to asthma.[58,59]

CONCLUSION

Prenatal maternal psychosocial stress – particularly anxiety and depression - was associated with a modest increased risk of asthma and allergy in the offspring. Whilst exposure during the third trimester had the greatest impact compared to the first and second trimesters, this may represent cumulative stress exposure throughout pregnancy rather than a trimester-specific effect. These findings may represent a causal association; they may also result from inherent biases in the included studies, particularly residual confounding. Further studies with objective measures of prenatal stress and optimal adjustment of confounding are required, as well as studies elucidating the likely mechanisms for these associations.

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CONFLICTS OF INTEREST

The authors declare no competing interest related to this work.

AUTHORS' CONTRIBUTIONS

BN conceived the idea for this work. It was drafted by CF and BN and was then revised after several rounds of critical comments from AS, ADG, BKB, and CA.

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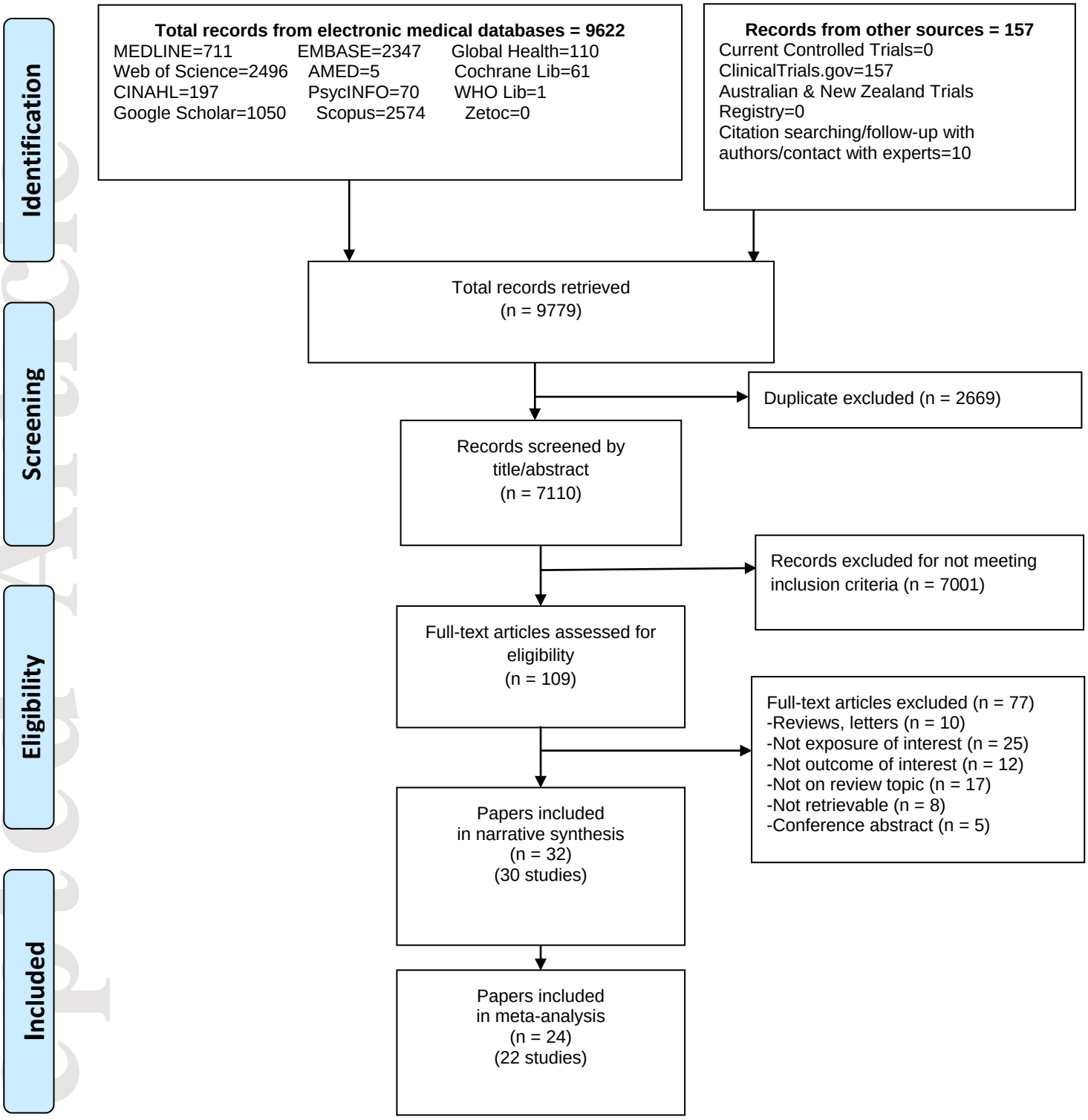

Figure 1. PRISMA flow diagram of studies on the association between maternal prenatal stress and risk of allergy and asthma in the offspring

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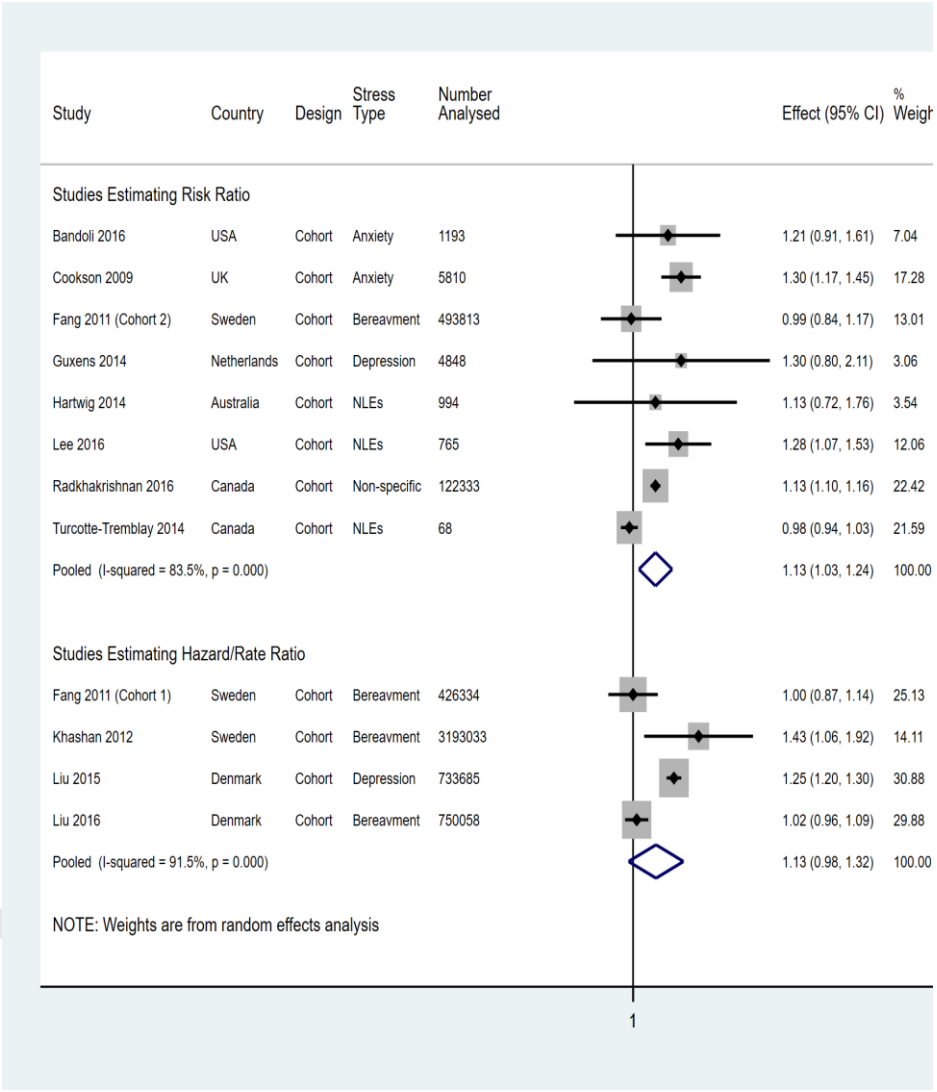
PANEL A



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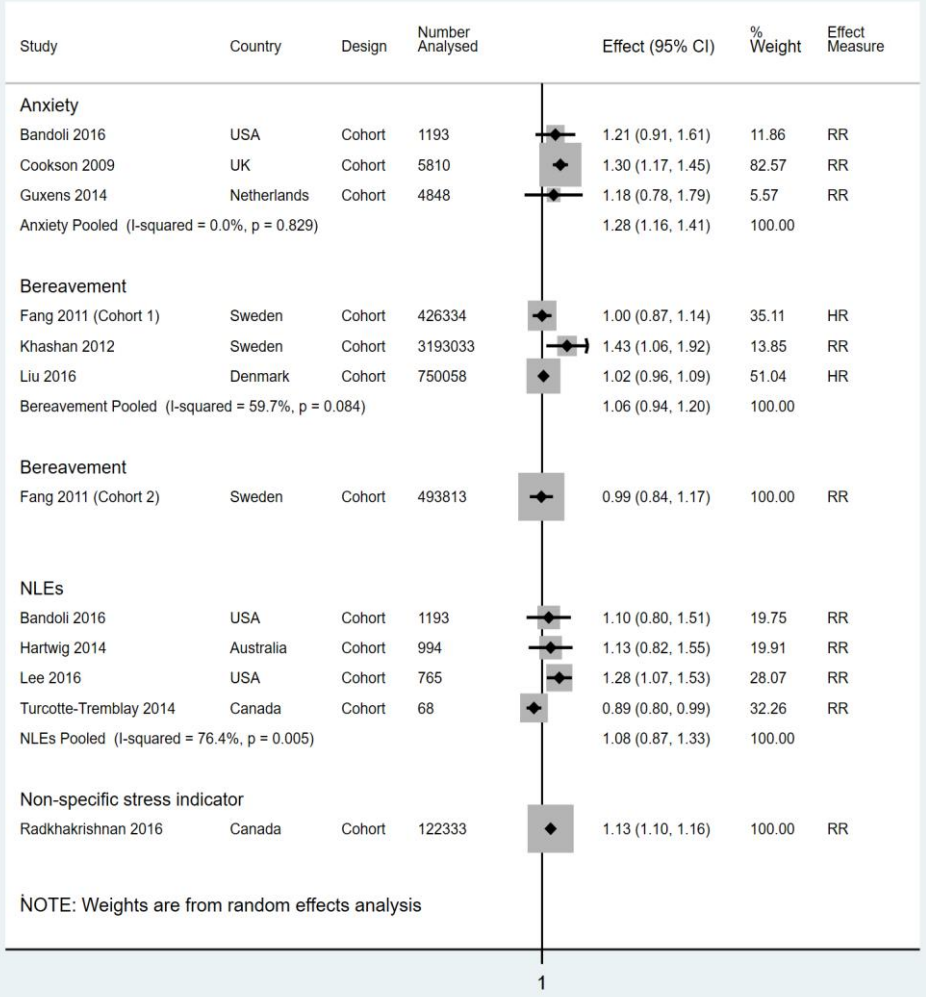

Figure 2. Association between prenatal maternal stress (**Panel A**: any type of stress and **Panel B** by type of stress) and risk of asthma in the offspring. NLEs = Negative life events. The results included Hartwig 2014 and Liu 2016 populations of 14 years and 4-15 years, respectively, as these were not substantially different from the population of 6 years and 0-3 years, respectively, also presented in the studies.

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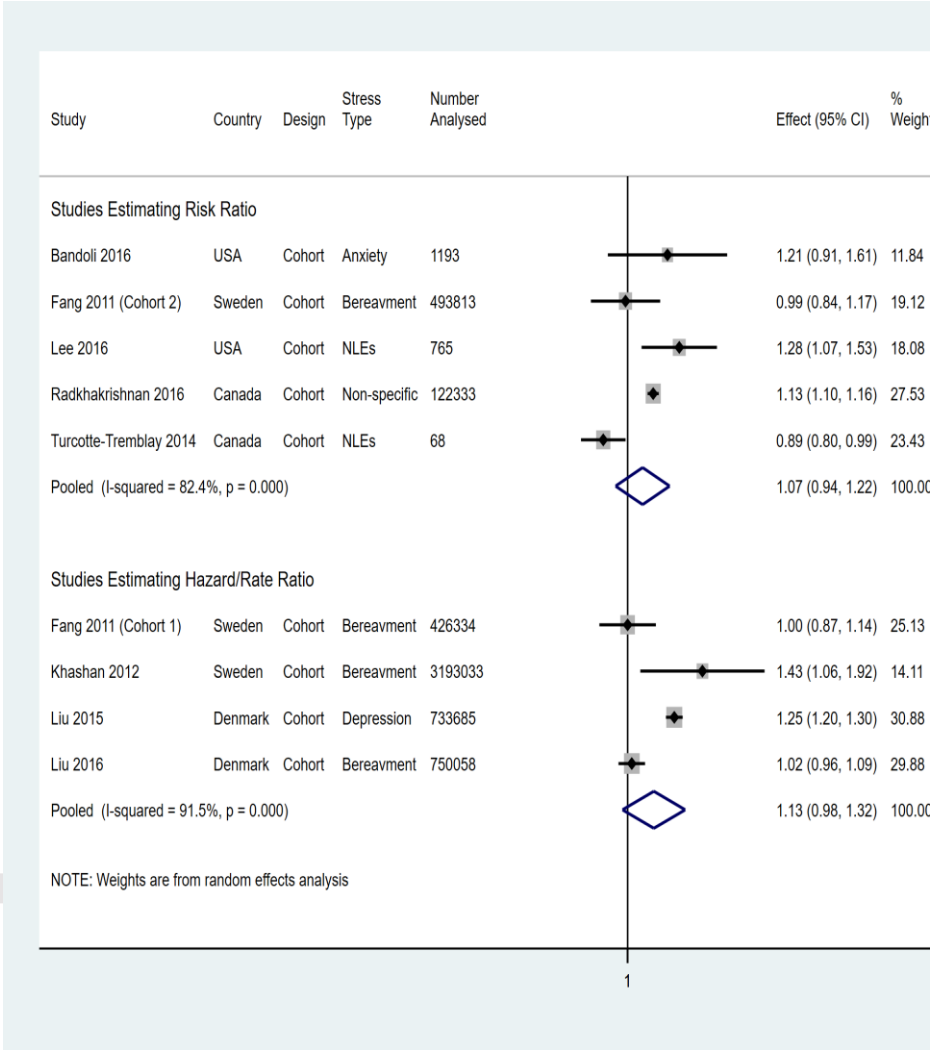

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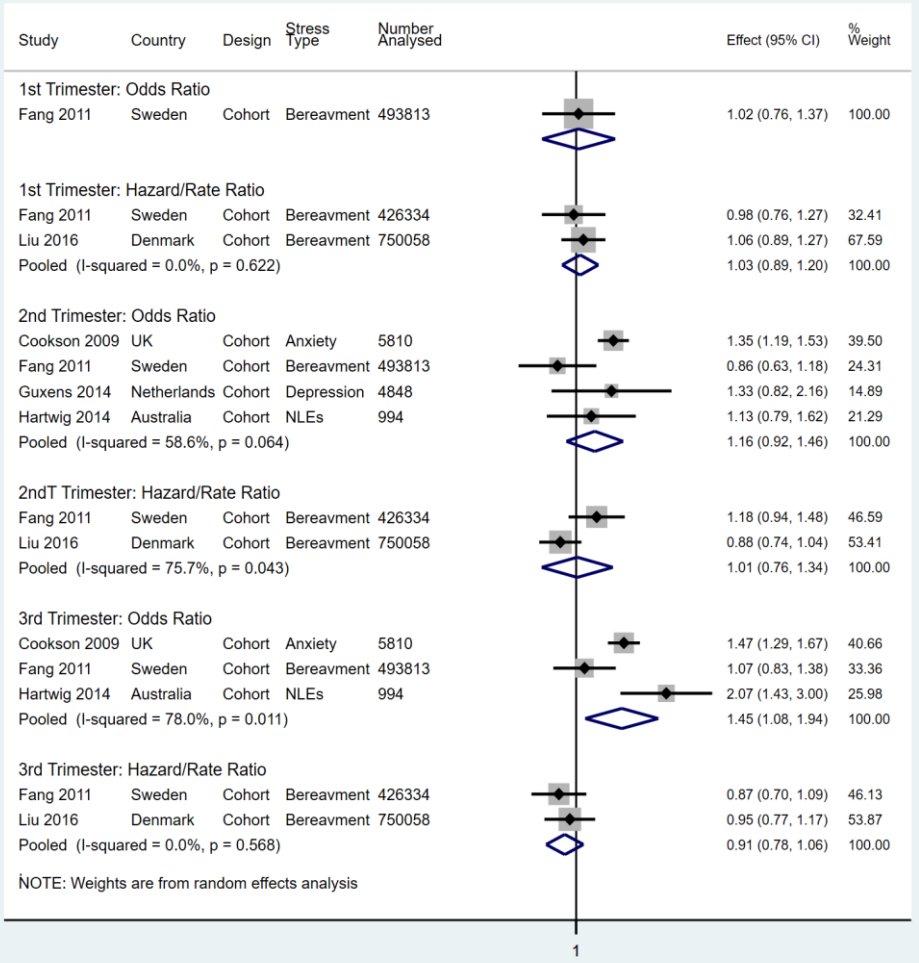

Figure 3. Association between prenatal maternal stress and risk of asthma in the offspring, by timing of exposure during pregnancy: **Panel A**: during any trimester; **Panel B**: at different trimesters. The results included Hartwig 2014 and Liu 2016 population of 14 years and 4-15 years as these were not substantially different from the population of 6 years and 0-3 years also presented in the studies.

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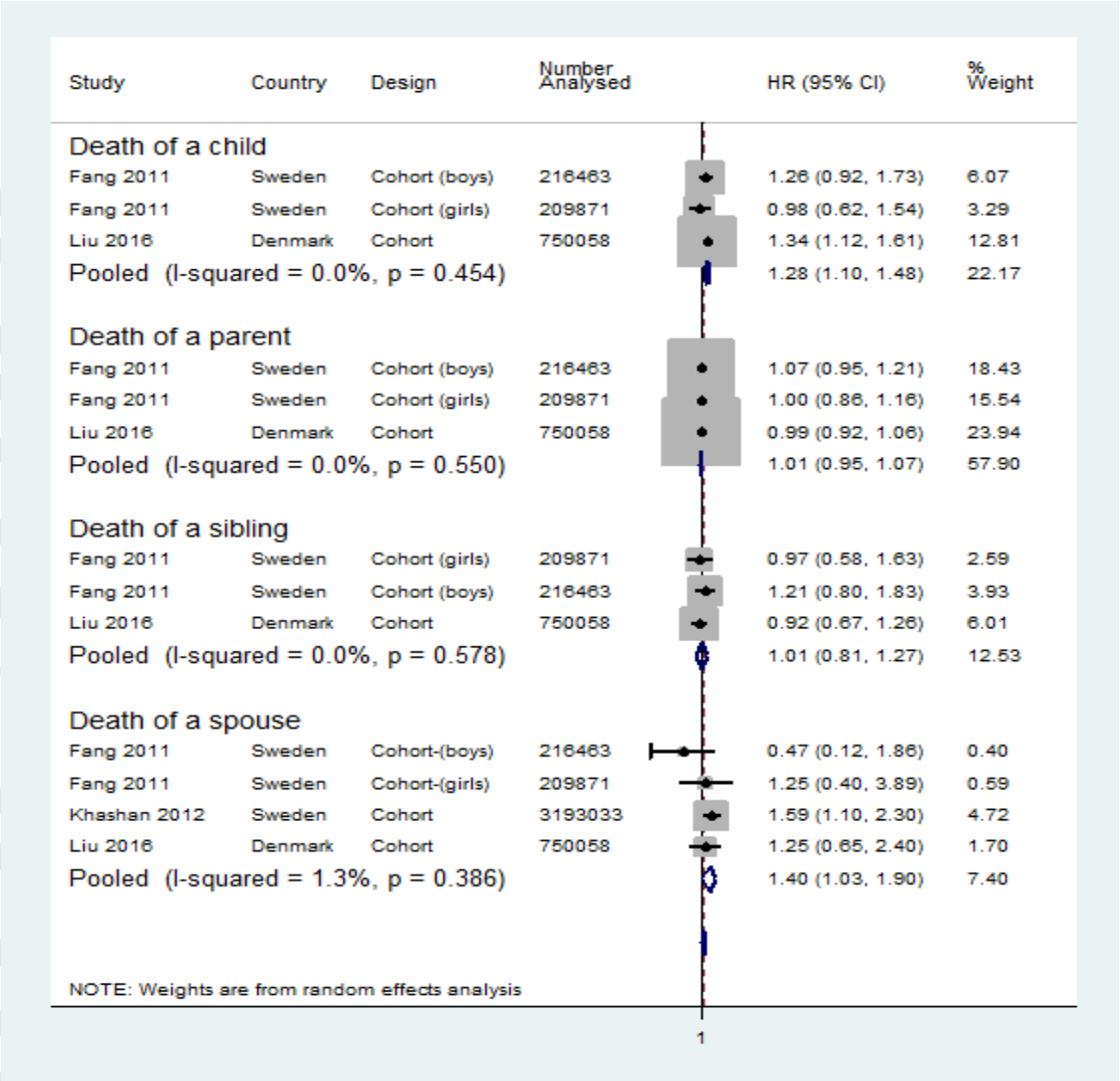

Figure 4. Association between maternal stress resulting from bereavement of a relative and risk of asthma in the offspring, by type relative. The results included Hartwig 2014 and Liu 2016 population of 14 years and 4-15 years as these were not substantially different from the population of 6 years and 0-3 years also presented in the studies.

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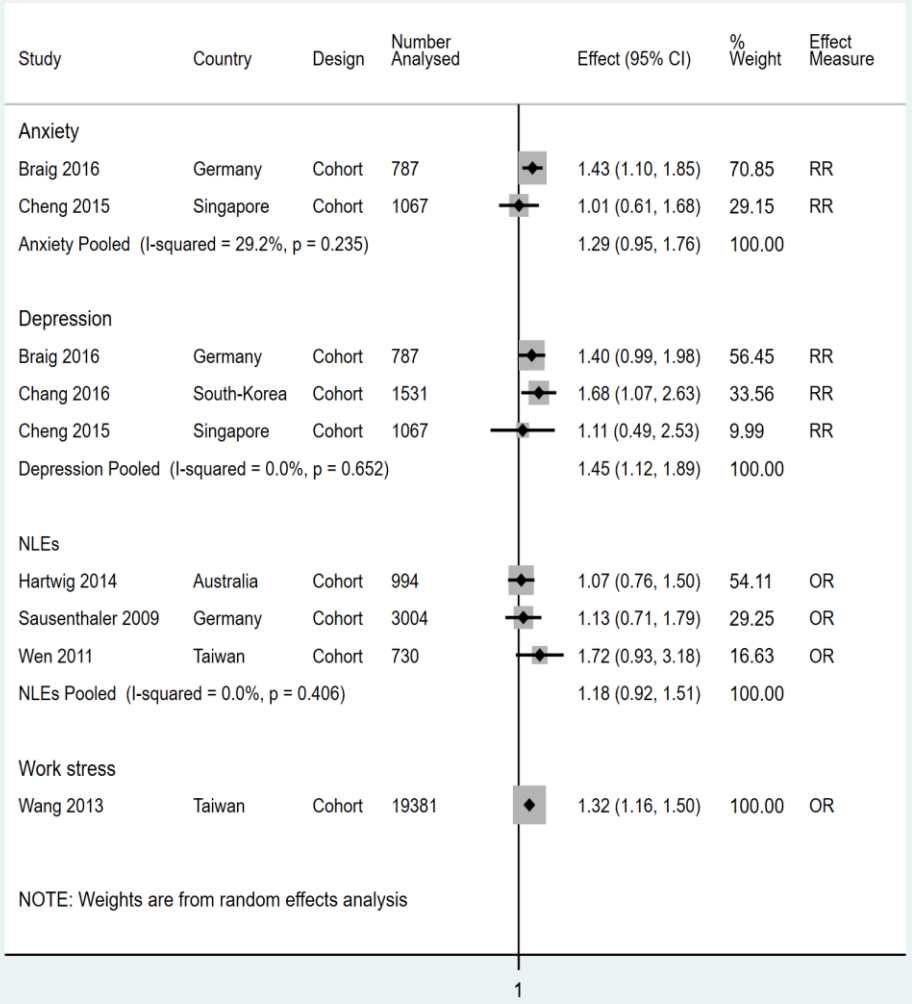
PANEL A



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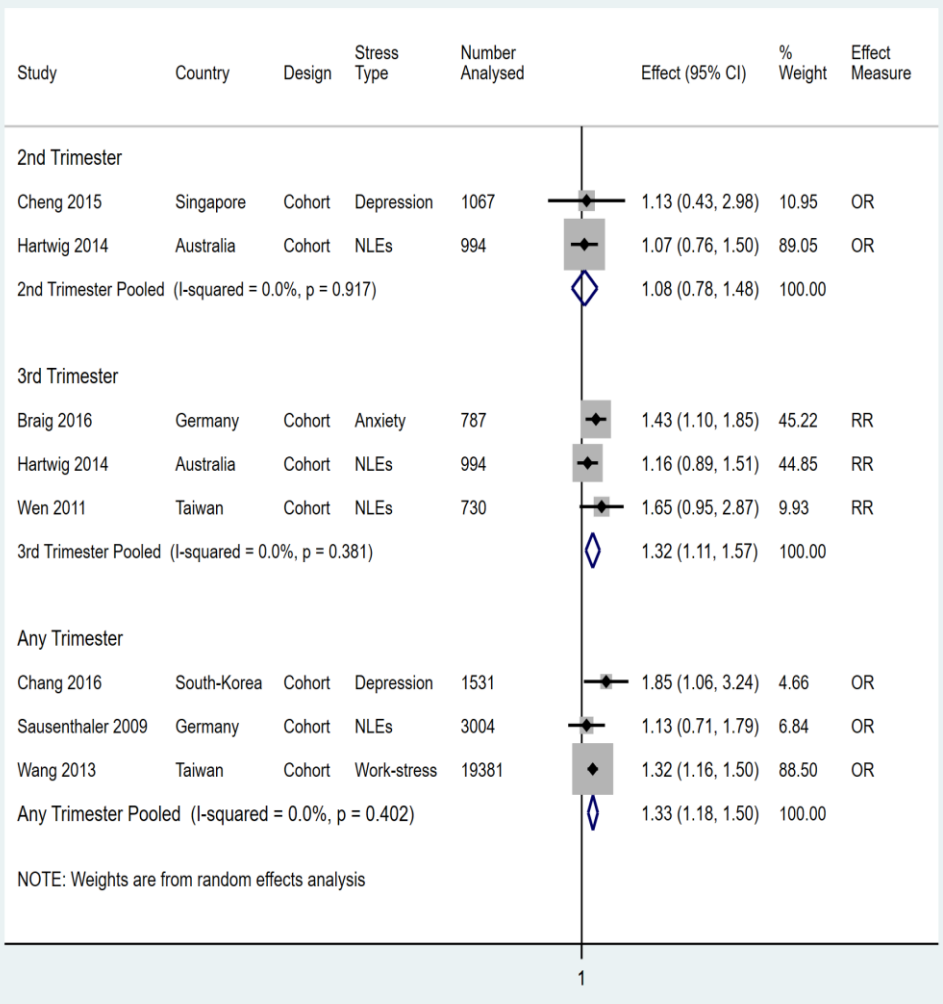

Figure 5. Association between maternal prenatal stress and risk of atopic eczema/dermatitis in the offspring, by type of stress (**Panel A**) and timing of exposure during pregnancy (**Panel B**). NLEs = negative live events. No major differences when Hartwig 2014's 6-year-olds and 14-year-olds were analysed separately, hence we presented the results for 6-year-olds

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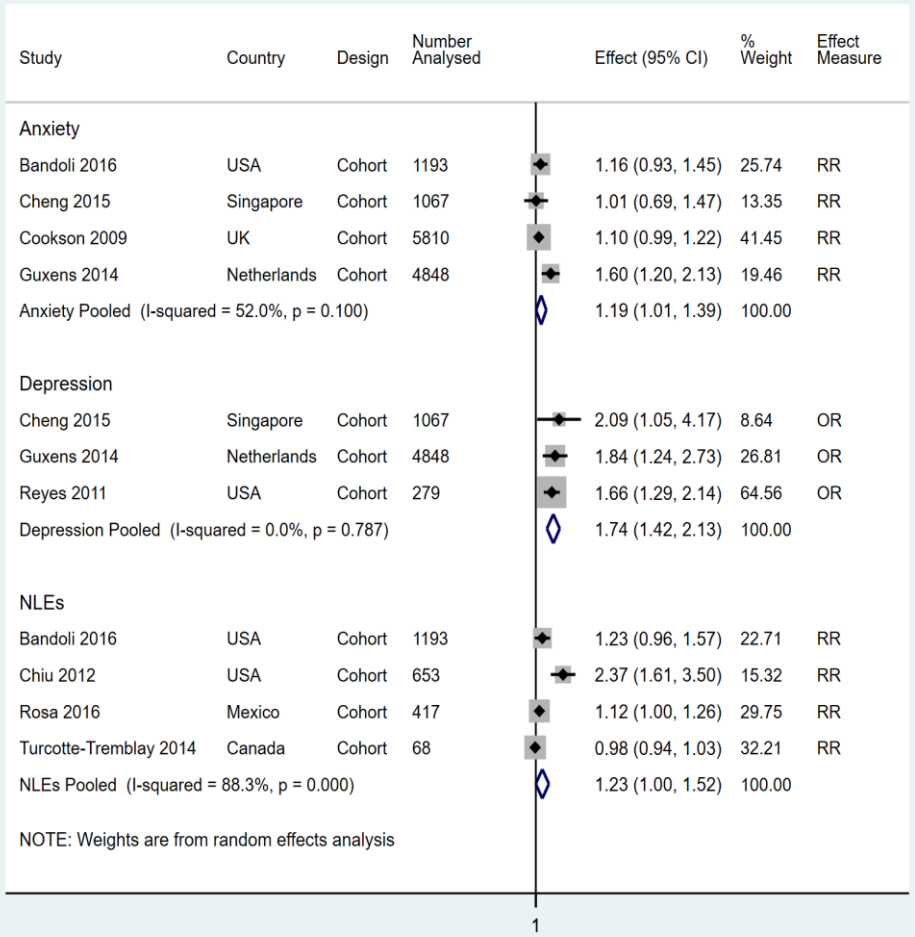
PANEL A



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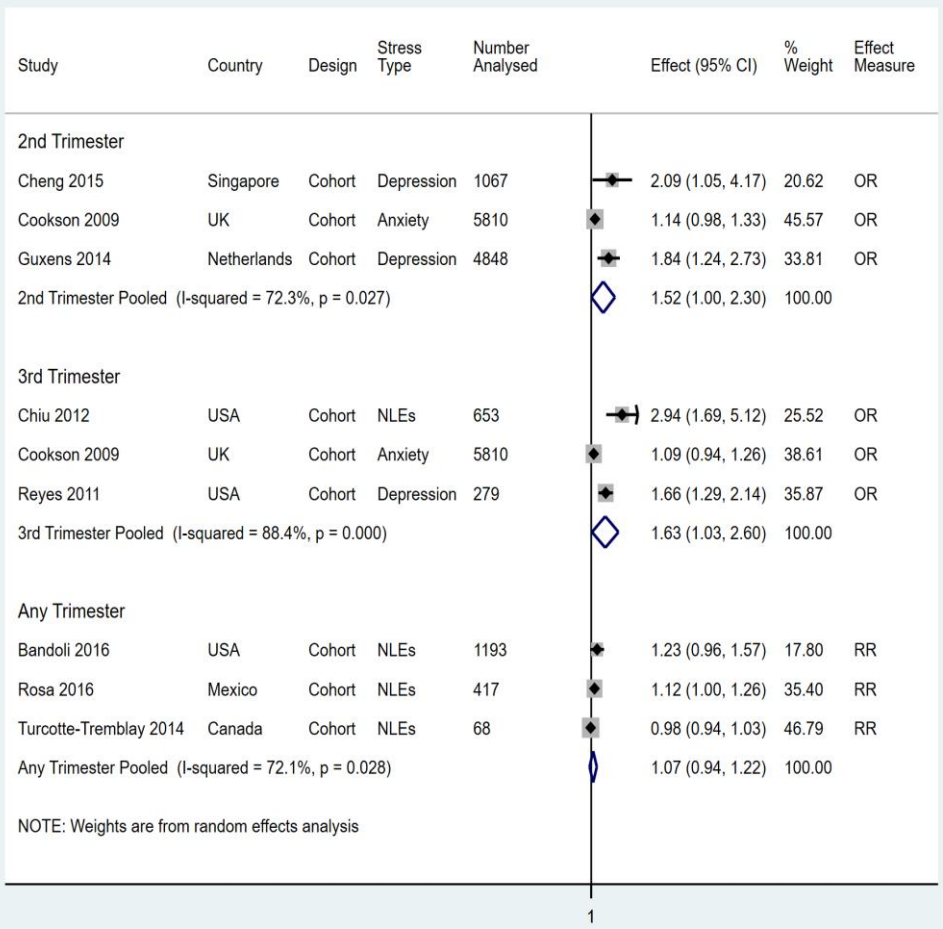

Figure 6. Association between maternal prenatal stress and risk of wheeze in the offspring, by type of stress (**Panel A**) and timing of exposure during pregnancy (**Panel B**). NLEs = negative live events. No major differences when Cookson 2009's wheeze at 6-18 months and 69-81 months were analysed separately, hence we present the results for the 6-18 month age group

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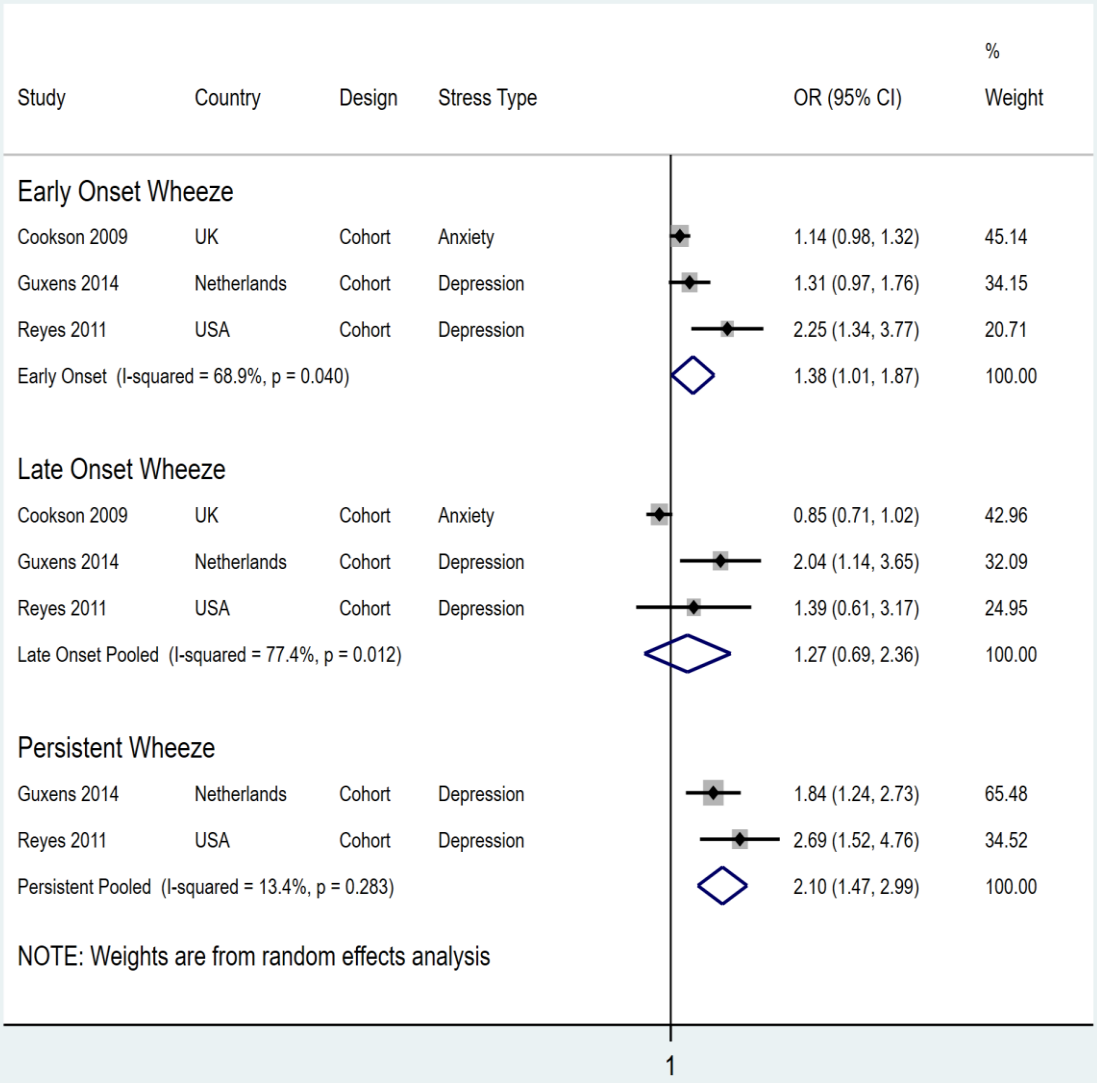

Figure 7. Association between maternal prenatal stress and risk of wheeze phenotypes in the offspring

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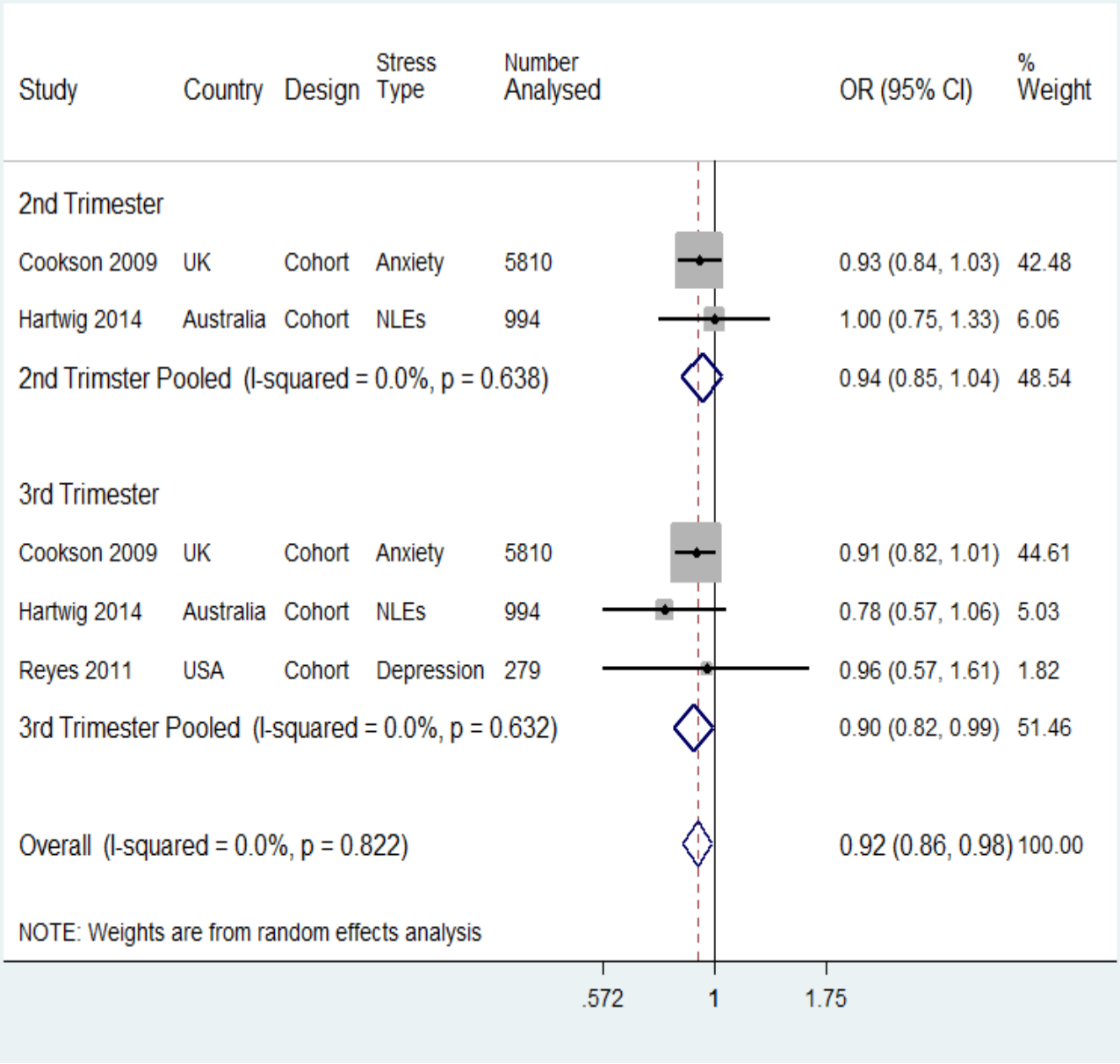

Figure 8. Association between maternal prenatal stress and atopic sensitisation in the offspring, by timing of exposure during pregnancy: No major differences when Hartwig 2014's 6-year-olds and 14-year-olds were analysed separately, hence we presented the results for 6-year-olds

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