Association between prenatal maternal anxiety and/or stress and offspring's cognitive functioning: a systematic review and meta-analysis

Garance Delagneau
Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University

Renee Testa
Murdoch Children's Research Institute

Sarit Van Veen
Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University

Peter Anderson (peter.j.anderson@monash.edu)
Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University

Research Article

Keywords: prenatal stress, prenatal anxiety, child cognitive development, meta-analysis

Posted Date: May 13th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-516746/v1

Abstract

The relationship between prenatal maternal stress and/or anxiety and children's cognitive development is inconclusive. This systematic review and meta-analysis aims to examine the relationship between the different domains of stress, anxiety and children's cognitive outcomes during the first 18 years of life.

Five databases were searched for all observational studies investigating the association between symptoms of prenatal maternal anxiety and/or stress and children's cognitive outcomes. Of 7,004 articles identified, 21 met the inclusion criteria and 11 provided usable data that were further analysed quantitatively. A weak negative association was found between prenatal stress and/or anxiety exposure and the offspring's language development. Associations varied based on the type of prenatal psychological exposure (i.e., trait anxiety, state anxiety, perceived stress, stress response). Specifically, maternal prenatal exposure to stress but not anxiety was found to correlate with children's general intellectual skills. Moreover, trait anxiety but not the combined exposure to trait and state anxiety was correlated with attention in the offspring. While exposure to stress and/or anxiety at any stage of pregnancy was found to be associated with adverse cognitive outcomes in the offspring, there was a trend that timing of exposure may be associated with distinct cognitive outcomes.

Findings support the need for screening and interventions to prevent or minimise mental health problems in pregnant women in order to optimise child development. Findings also have implications for conceptualising prenatal stress and anxiety in future research, as well as investigating timing and cumulative effects of prenatal stress and/anxiety exposure.

Introduction

Many women do not receive appropriate mental health checks during pregnancy, despite the high rate of maternal stress and anxiety in the prenatal period which affects up to 78% and 18-22% of pregnant women worldwide respectively [1, 2, 3, 4, 5]. Studies have reported that stress and anxiety are associated with negative health and neurobehavioural outcomes in the offspring [6, 7, 8, 9], while systematic reviews have found prenatal maternal stress/anxiety to be related to infant (0-2 years) cognitive development [10,11,12,13]. Studies examining prenatal stress and anxiety typically pooled these exposure factors, which is a limitation if the nature of the association with cognition varies across these different maternal psychological constructs. Thus, future research should 1) separates the concepts of prenatal anxiety and prenatal stress, and 2) examines a range of cognitive outcomes beyond infancy.

Stress can be operationalised and measured as perceived stress or a stress response [14]. Perceived stress is an emotional reaction characterised by feelings or thoughts that arise from individuals' appraisal of life stressors and vary based on several factors, including one's social support, personality traits and coping behaviours [14,15,16]. A stress response is most commonly characterised as biological changes in cortisol levels triggered by a perceived stressful event. It is mediated by factors such as personality traits and cognitive appraisal processes [17,18].

Anxiety is also a multi-dimensional construct, comprising state and trait anxiety. State anxiety refers to situation-specific and transient negative emotion characterised by psychological and physiological reactions, such as irritability, difficulties concentrating, palpitations and a reduction in serotonin release[19,20,21]. Trait anxiety refers to an innate and enduring characteristic of a person which predisposes them to experience more intense degrees of fear and worry across many situations that most people would not find threatening [22]. Pregnancy-related anxiety has also been described, which refers to worries specifically related to pregnancy, such as giving birth or bearing a handicapped child[23].

While related, perceived stress, stress response, trait anxiety, state anxiety and pregnancy-related anxiety constitute unique psychological constructs with distinct neurobiological underpinnings, causes and outcomes [14,22,24,25]. Accordingly, these different psychological constructs are assessed using different methods [16,26,27]. Studies have shown a lack of correlation between 1) the different aspects of stress, types of anxiety, and 2) these constructs and health and birth outcomes [14,22,28,29]. As such, exposure to these different constructs may have a differential impact on the cognitive development of the child. For instance, research has shown that prenatal exposure to stress but not anxiety has a negative impact on attentional control in childhood, whilst prenatal exposure to trait but not state anxiety has been associated with poorer speech-language development [30,31].

This review aimed to examine the relationship between prenatal maternal stress and anxiety and a range of key cognitive domains (i.e., general intellectual skills, attention, language, learning, memory, executive functions) in infancy, childhood, and adolescence (birth until 18 years of age). Unlike previous reviews, we will also separately examine the influence of the different aspects of stress and anxiety. We hypothesised that there would be an association between maternal prenatal stress and anxiety and offspring's cognitive domains, but expected the association with cognition would differ for the different psychological constructs of perceived stress, stress response, trait anxiety, state anxiety and pregnancy-related anxiety.

Methods

Protocol and search strategy

The study protocol was registered on PROSPERO (CRD42020185906). A search strategy was conducted for papers published before the date of the search (May 2020) on PsycINFO, MEDLINE, Web of Science Core Collection, CINAHL and EMBASE databases. The search strategy included key-terms related to the prenatal period, maternal anxiety, maternal stress, childhood and cognitive development (see supplement materials). The literature search was limited to humans and studies published in English. There were no criteria for years of publication. Additional articles were identified using reference list from previous meta-analyses and review articles.

Inclusion and exclusion criteria

Prospective and retrospective observational studies investigating the association between symptoms of prenatal maternal anxiety and/or stress and children's cognitive outcomes were considered for inclusion. Measures of prenatal maternal anxiety and/or stress included validated physiological measures and self-

report questionnaires. The outcome measures were validated age-standardised measures of general intelligence, learning, memory (long-term free recall, long-term recognition), language (receptive, expressive), speed of information processing, attention (span, divided, switching, sustained, selective), executive functions (working memory, inhibition, planning, organisation, self-monitoring, decision making, cognitive flexibility, word generation) and academic skills (reading, maths, writing). Both direct assessment and parent and teacher-rated questionnaires were included if relevant.

Studies were excluded for the following reasons: (i) the study was a treatment or clinical trial, case-control study, review, comment, letter, thesis or book, (ii) individual cognitive skills were not assessed separately, (iii) the offspring were older than 18 years old or specifically selected based on a previous diagnosis (e.g. autism and ADHD), (iv) anxiety and/or stress was examined in the postnatal period, (v) a measure of anxiety and/or stress was not included, (vi) measures of anxiety and stress were combined in the analyses, (vii) children's cognitive function was assessed using experimental measures only, and (iix) the study involved non-human participants.

When the same cognitive domain was measured at multiple time points in the same cohort or when different measures of a same cognitive domain were examined, preference was given to the largest sample size. When two timepoints were of similar sample size, the timepoint where children were the eldest was given preference. If the above two criteria were the same, the cognitive outcome evaluated by the most valid or widely used measure in the field was used [32,33]. For the overall analysis, when a study reported multiple stress and/or anxiety exposures, preference was given to the to the exposure that was the most comparable to those included in the analysis.

Study selection

All the references retrieved using the strategy search outlined above were downloaded and deduplicated into Endnote before being transferred, stored and managed into Covidence. Titles and abstracts were screened independently by two reviewers, GD and SV. Full texts of potentially relevant articles were obtained and independently assessed for inclusion by the two reviewers using the previously described criteria. In case of disagreement, the reviewers discussed eligibility. When disagreement could not be resolved, PJA made the final decision. Ninety-nine percent agreement was reached after the first screen of titles / abstracts, and 91% after the first screen of full texts. After discussion, 100% agreement was reached by the three reviewers.

Data extraction

A customised extraction excel sheet adapted from the Cochrane Review handbook was used to guide extraction. Reviewers (GD and SV) extracted relevant information independently and discussion was organised in case of discrepancy. When available, extracted information included:

Independent variable: Measures used to assess maternal anxiety and/or stress during pregnancy; anxiety levels during pregnancy; stress levels during pregnancy; trimester(s) of exposure.

Outcome variables: Tasks; Performance on cognitive tasks; unadjusted and adjusted effect sizes

Confounding factors: Covariates considered and adjusted for in analysis.

Methodology: Participants' demographic information; Participant attrition rate; study design; times of measurement, sample size.

Bias and quality assessment

The quality of the studies selected was assessed by GD using a modified version of the Scottish Intercollegiate Guideline Network appraisal tool (SIGN) criteria for cohort studies (https://www.sign.ac.uk/sign-50). SIGN is a widely used tool which appraises studies by examining six domains: study design, withdrawals and drop-outs, potential for selection bias, measurement of outcomes and exposure factors, confounders and report of statistical analyses, and blinding. Using a scoring algorithm adapted from the Quality Assessment Tool for Quantitative Studies (http://www.ephpp.ca/tools.html), each of these domains were rated as being of low, moderate or strong quality, and an overall study quality rating was made based on the quality of each domain. Studies encompassing four or more strong and no weak domains were rated as strong; those with less than four strong and no more than one weak domain were rated as moderate; and those with more than two weak domains were rated as weak.

Meta-analytic procedures

Using Comprehensive Meta-Analysis Version 3, a series of standard meta-analyses of correlations estimated the pooled associations between prenatal maternal anxiety and/or stress and children's cognitive function. Due to the variability in characteristics and sample sizes across studies, the more conservative random-approach was used [34]. Separate meta-analyses were performed when at least two studies provided an effect for an outcome [35]. Results were stratified by type of exposure (i.e., stress and anxiety) and cognitive domain (i.e., general intellectual function, language, attention, learning and memory and working memory). While pregnancy-related anxiety was found to constitute a valid and reliable construct [36,37], the scales used to measure this psychological construct assess the nature of their anxiety or worries rather than the type and severity of symptoms of anxiety [30,36,37,38]. As such, studies examining this construct were not included in the main analyses examining the relationship between all types of anxiety and/or stress combined and children's later cognitive outcomes to maximise consistency. When enough data was available, results were stratified by type of anxiety and stress exposure (i.e., perceived stress, stress response, trait anxiety and state anxiety) and timing of exposure (trimester 1, 2 or 3). Although the original intent was to assess associations for different developmental periods, this was not possible due to the small number of eligible studies which examined stress and/or anxiety at different timepoints during pregnancy. Consequently, analyses were performed combining children from all age groups to increase power and were also performed for the infancy period only.

A measure of effect size (coefficient of correlation r) was calculated for each study. A correlational effect size r of .05 was considered as very small, .10 as small, .30 as medium, .30 as large, and .50 or greater as large [39]. The statistical significant level used was $\alpha = 0.05$. Both I^2 statistic and Tau squared were computed to assess for heterogeneity of effect sizes [34]. I^2 reflects the percentage of variability in the correlational effect size that is attributed to heterogeneity rather than sampling error. A value of 25% or below can be interpreted as a small amount of heterogeneity, while values of 50% and 75% or above represent moderate and high heterogeneity, respectively [40]. Tau squared represents the variance of the true correlational effect size across studies.

Results

Study Selection, Characteristics, and Quality

The PRISMA flow diagram displayed in Figure 1 details the selection strategy and resulting outcomes. Our electronic search of five databases yielded 7,001 articles after duplicates were removed and three articles were further identified from the references of the retrieved articles. Of these, 21 met our eligibility criteria and 11 had sufficient data that enabled their quantitative analysis. Characteristics of studies included in the systematic reviews are reported in Tables 2a and 2b. Thirteen studies examined the association between stress and children's cognitive outcomes and 13 investigated the influence of anxiety. Sample sizes ranged from 29 to 5,768 in studies examining prenatal stress (mean = 632) and from 46 to 3,298 in those assessing prenatal anxiety (mean = 1,092). Of the eligible stress studies, the majority measured maternal prenatal perceived stress (n = 8). Of the eligible anxiety studies, n = 3 measured state anxiety, n = 5 measured trait anxiety, n = 4 measured trait and state anxiety combined, and n = 2 measured pregnancy related anxiety. Anxiety and stress were predominantly assessed during the third trimester only, while 4 studies measured maternal prenatal mental health across multiple trimesters. Children were aged 0 to 9 years old. In relation to child cognition, most studies assessed offspring cognition during infancy, i.e., 0-2 years old (75% and 58% of studies investigating stress and anxiety, respectively), with only nine studies examining child cognition past the age of 2 years. Five studies were from the USA, five from the UK, three from Canada, two from Greece, and one from the Netherlands, Poland, China, Germany, Spain and New-Zealand.

In relation to study quality, 1 study was classified as strong, 7 as moderate and 3 as weak (Table 1). Few studies reported information on whether the outcome assessment was made blind to the exposure status (n = 5), which was needed to reach an overall strong quality rating. A notable risk of bias was also identified, related to inappropriate adjustment of missing data when attrition rate was high. As attrition was found to be associated with poorer mental health status, there is a risk of selective sampling bias that should be taken into account when interpreting the results [41]. Notably, all studies addressed a specific research question, clearly defined their outcome of interest, and used reliable and valid methods of measurement.

Meta-analytic Results

Maternal prenatal mixed anxiety and stress (Tables 3 and e1)

Exposure to prenatal maternal stress and/or anxiety was significantly associated with lower language skills (r = -0.10 [95% CI, -0.19; -0.01], I^2 = 47.02%), albeit with a small effect size (Figure 2). Nonsignificant negative associations were also observed between prenatal exposure to maternal stress and/or anxiety and the general intellectual and attentional skills of the offspring. Similar findings were found when these associations were examined during the infancy period only. Heterogeneity varied from moderate but non-significant (47.02%) to high and significant (82.27%) across studies. Results could not be stratified by timing of exposure as most studies measured prenatal maternal stress/anxiety in the 3rd trimester only.

Maternal prenatal anxiety (Tables 3 and e2)

No associations were found between maternal prenatal anxiety and offspring's general intellectual functions, sustained attention, expressive language, receptive language and working memory. Review of state anxiety and trait anxiety separately demonstrated a weak adverse association between trait anxiety and offspring's sustained attention (r = -0.15 [95% CI, -0.24; -0.05], I^2 = 0.00%; Figure 3). No significant relationships were found between state anxiety or trait anxiety and general intellectual functions (state: r = 0.03 [95% CI, (-0.21; 0.27], trait: r = -0.07 [95% CI, -0.25; 0.18]). When analysed during the infancy period only, results remained weak for the general cognitive development and attention skill domains. Notably, the samples for the above analyses were small and included only two to four studies (n = 281 to 3,382) for the primary analyses and two to three studies (n = 186 to 403) for the secondary. Heterogeneity ranged from low to high, with I^2 ranging from 0.00% to 89.01%.

Maternal prenatal stress (Tables 3 and e3)

A weak adverse relationship was found between maternal prenatal stress and offspring's general intellectual skills (r = -0.26 [95% CI, -0.41; -0.10, I^2 = 87.43%; Figure 4). In contrast, no evidence for an association was found between prenatal exposure to stress and children's attention, learning and memory abilities. For perceived stress, a weak negative association between maternal prenatal stress and children's general intellectual skills remained but was nonsignificant (r=-.25 [95%CI -.50; .04], I^2 = 76.63%). Heterogeneity varied substantially across studies, ranging from 0.00% to 87.20%. Sample sizes were generally small, with two to three studies (n = 309 to 428) for the primary analyses and two studies (n = 205) for the secondary analysis.

Covariates and Timing (Tables 4a and 4b)

Twenty studies performed regression analyses, adjusting for a range of covariates including gestational age, birthweight, parental socioeconomic status and child sex. In comparison to unadjusted analyses, some associations reduced or disappeared with adjustment [38,42,43,44, 45,46,47] while others remained [38,48,49,50,51,52,53,54,55].

With regard to timing, most studies measured maternal prenatal stress and/or anxiety during the third trimester and only one study assessed these constructs in the first trimester. Only one study examined stress and/or anxiety at different timepoints during pregnancy and reported usable data [30]. As such, associations between prenatal maternal stress and/or anxiety and children's cognitive functions for different developmental periods could not be examined.

Discussion

Two key findings emerged from this meta-analysis examining the association between maternal prenatal stress and anxiety with different aspects of offspring's cognitive development from infancy through adolescence. Firstly, there was a weak negative association between the exposure to stress and anxiety (combined) during pregnancy and the offspring's language development. Meaningful relationships did not extend to other cognitive skills, such as general intellectual abilities and attention. Previous systematic reviews and meta-analyses that focused only on developmental outcomes in infants reported adverse negative associations between prenatal stress and/or anxiety exposure and offspring's cognitive functions,

but the strength of the associations reported has varied across reviews [11,13,56]. Different factors may contribute to these disparities across reviews, including distinct selection criteria around the type of prenatal exposure and outcome measures.

The second key finding of this meta-analysis was some evidence for differential associations between the different types of exposure and children's cognitive function. Exposure to stress but not anxiety was found to weakly correlate with children's general intellectual skills. Furthermore, when only including studies which looked at trait anxiety, a significant negative correlation was found with attention skills in the offspring. However, when including studies that looked at both trait and state anxiety, this association disappeared. The present findings provide some support for perspectives suggesting that state anxiety, trait anxiety, stress response and perceived stress constitute distinct constructs that might be differentially associated with children's cognitive outcomes [14,18,22]. Based on this preliminary evidence, future research should attempt to examine these prenatal types of exposure independently.

Although the original intent was to assess associations between prenatal maternal stress and/or anxiety at different developmental periods and children's cognitive functions, this was not possible due to the small number of eligible studies which analysed these psychological constructs at different timepoints. Pregnancy involves key processes that arise in a timely manner [57,58,59,60,61]. For instance, trimester 1 involves the formation of the neural tube and early neurogenesis, while trimester 2 includes neural migration and some axonal/dendritic development and trimester 3 largely consists of synaptogenesis and early myelination [61]. Also specific brain structures have unique developmental trajectories and peak period of rapid growth and differentiation [61,62]. For example, the cerebellum's peak period of development starts around week 4 of gestation and proceeds throughout childhood, the thalamus develops from week 5 to week 10 of pregnancy, and the striatum from week 7 to week 19 of pregnancy [63]. Consequently, exposure to stress and/or anxiety at different timepoints during pregnancy is likely to differentially affect different neural networks which, in turns, may be associated with different cognitive outcomes in children. The literature on different teratogens, such as depression, nicotine, marijuana and cocaine, supports this assumption, revealing distinct cognitive outcomes in rodents and children exposed to teratogens at different timepoints during pregnancy [7,64]. Similar findings might also arise following prenatal exposure to stress and/or anxiety. For instance, Polanska and colleagues [54] revealed that exposure to perceived stress during the second semester was associated with lower general intellectual skills but not language in children, and Koutra and colleagues [46] reported that exposure to trait anxiety during the third trimester was associated with attention difficulties but not with other cognitive domains in the offspring. Accordingly, future research should aim to evaluate the influence of timing in the associations between maternal prenatal stress and/or anxiety and children's later cognitive outcomes by examining these psychological constructs at different timepoints during pregnancy.

Numerous confounders should be considered when evaluating the association between prenatal stress/anxiety and later cognitive outcome, however this was implausible in our analyses due to the extensive variability in covariates across studies. Some of the above associations between stress and/or anxiety and developmental outcomes in childhood weaken when covariates were included in the analyses. For instance, Koutra and colleagues[46] reported that the association between prenatal exposure to trait anxiety and children's lower attention skills weaken once covariates, such as maternal age at delivery, maternal education,

child's sex and prematurity, were controlled for. In another study by Polanska and colleagues[54], a negative association between perceived stress and infants' general intellectual skills persisted after adjusting for several covariates, including active/passive smoking and alcohol consumption during pregnancy, maternal education, child sex, prematurity and breastfeeding duration. Agreeing on a consistent set of confounders to include in future studies by an expert panel would help to overcome the issue.

The present meta-analysis has several limitations that need to be taken into account when interpreting the results. One important consideration is that our analyses were correlational. As such, causality between maternal prenatal stress and/or anxiety and adverse children's cognitive outcomes cannot be established, and the role of covariates in this relationship remains unknown. It is likely that factors that were not taken into account in the meta-analysis (such as children's postnatal stress) played an important role in the relationship between prenatal maternal stress and/or anxiety and children's later cognitive functions. Another limitation of this study was the collapsing of participants across all age groups in the main analyses. We had hoped to assess the association across different developmental stages but this was not possible given the small number of eligible studies and large number of outcomes of interest. A third limitation of this body of work is that many of the studies pooled had limited samples and the pooled sample sizes were small. Accordingly, some of our analyses have lacked power, thereby potentially overestimating some of our effect sizes [65]. Fourth, low to high heterogeneity was found across studies, potentially limiting our ability to detect meaningful relationships [66]. For example, nonsignificant associations of small to medium effect sizes were sometimes found in analyses with high heterogeneity, such as between prenatal exposure to anxiety and children's working memory (r=-.24). Thus, more studies are required to increase confidence in the findings that emerged from this systematic review and meta-analysis. It would also be interesting to understand why such a high heterogeneity was observed and address contributing factors in future research. One reason might be the wide range of measures used to assess stress response. Stress response was measured using blood, saliva and hair cortisol samples collected both in the morning and evening. The reliability as well as maternal and children's outcomes associated with these distinct measurement modes and times, however, were previously found to vary [67,68,69]. Therefore, an expert panel should come out with recommendations around which measurement method best assesses stress response to increase consistency in future research and provide more comparable results. Fifth, given the small number of studies found, we could not examine regional differences, even though studies were pulled from different regions of the world. Due to the small number of studies identified, we could not examine the effect of timing of prenatal stress and/or anxiety exposure either. Lastly, the current study focused specifically on the cognitive outcomes of offspring. It is possible that the effects on offspring may be greater for other outcome domains such as emotional, behavioural and social outcomes. Therefore, future meta-analyses should also aim to separately examine the influence of stress and anxiety on these domains.

In summary, our findings support the current consensus that prenatal maternal stress and/or anxiety is negatively, albeit weakly, associated with offspring cognitive function. These findings are of public health significance and support the need for screening and interventions to prevent or minimise mental health problems in pregnant women and optimise child development. Our findings also have implications for conceptualising prenatal stress and anxiety in future research, as well as investigating the timing and cumulative effects of prenatal stress and/anxiety exposure. Finally, our findings support the need for future

studies to examine the relationship between maternal prenatal stress and/or anxiety and children's domains of cognitive function, in particular in children older than 2 years old.

Declarations

Authors contribution

GD and PA designed the search strategy

GD and SV searched the literature and extracted data

PA supervised and assisted the extraction of studies

GD and PA interpreted the results

Under the supervision of PA, GD assessed the quality of the studies, performed the analyses, wrote the main manuscript text and prepared the figures and tables.

All authors reviewed the manuscript

References

1. Darwin, Z., McGowan, L., & Edozien, L. C. Antenatal mental health referrals: review of local clinical practice and pregnant women s experiences in England. *Midwifery*, ***31***, e17-e22 (2015).
2. Dennis, C. L., Falah-Hassani, K., & Shiri, R. Prevalence of antenatal and postnatal anxiety: systematic review and meta-analysis. *The British Journal of Psychiatry*, **210**, 315-323 (2017).
3. Kelly, R. H., Danielson, B. H., Zatzick, D. F., Haan, M. N., Anders, T. F., Gilbert, W. M., & Burt, V. K. Chart-recorded psychiatric diagnoses in women giving birth in California in 1992. *American Journal of Psychiatry*, ***156***, 955-957 (1999).
4. Moss, K. M., Reilly, N., Dobson, A. J., Loxton, D., Tooth, L., & Mishra, G. D. How rates of perinatal mental health screening in Australia have changed over time and which women are missing out. *Australian and New Zealand Journal of Public Health*, ***44***, 301-306 (2020).
5. Woods, S. M., Melville, J. L., Guo, Y., Fan, M. Y., & Gavin, A. Psychosocial stress during pregnancy. *American journal of obstetrics and gynecology*, **202**, 61-e1 (2010).
6. Bussières, E. L., Tarabulsy, G. M., Pearson, J., Tessier, R., Forest, J. C., & Giguère, Y. Maternal prenatal stress and infant birth weight and gestational age: A meta-analysis of prospective studies. *Developmental Review*, **36**, 179-199 (2015).
7. Madigan, S., Oatley, H., Racine, N., Fearon, R. P., Schumacher, L., Akbari, E., ... & Tarabulsy, G. M. A meta-analysis of maternal prenatal depression and anxiety on child socioemotional development. *Journal of the American Academy of Child & Adolescent Psychiatry*, **57**, 645-657 (2018).
8. Manzari, N., Matvienko-Sikar, K., Baldoni, F., O'Keeffe, G. W., & Khashan, A. S. Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis. *Social psychiatry and psychiatric epidemiology*, **54**, 1299-1309 (2019).

9. D O'Connor, T. G., Heron, J., Golding, J., Glover, V., & AL Spac Study Team. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *Journal of child Psychology and Psychiatry*, **44**, 1025-1036 (2003).
10. Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A. Y., & Tordjman, S. Effects of prenatal stress on fetal and child development: a critical literature review. *Neuroscience & biobehavioral reviews*, **43**, 137-162 (2014).
11. Kingston, D., McDonald, S., Austin, M. P., & Tough, S. Association between prenatal and postnatal psychological distress and toddler cognitive development: A systematic review. *PloS one*, **10**, e0126929 (2015).
12. Van den Bergh, B. R., Mulder, E. J., Mennes, M., & Glover, V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neuroscience & Biobehavioral Reviews*, **29**, 237-258 (2005).
13. Tarabulsy, G. M., Pearson, J., Vaillancourt-Morel, M. P., Bussières, E. L., Madigan, S., Lemelin, J. P., ... & Royer, F. Meta-analytic findings of the relation between maternal prenatal stress and anxiety and child cognitive outcome. *Journal of Developmental & Behavioral Pediatrics*, **35**, 38-43 (2014).
14. Epel, E. S., Crosswell, A. D., Mayer, S. E., Prather, A. A., Slavich, G. M., Puterman, E., & Mendes, W. B. More than a feeling: A unified view of stress measurement for population science. Frontiers in neuroendocrinology, **49**, 146-169 (2018).
15. Lazarus, R. S., & Folkman, S. *Stress, appraisal, and coping*. Springer publishing company (1984).
16. Nast, I., Bolten, M., MeinIschmidt, G., & Hellhammer, D. H. How to measure prenatal stress? A systematic review of psychometric instruments to assess psychosocial stress during pregnancy. *Paediatric and perinatal epidemiology*, **27**, 313-322 (2013).
17. Gaab, J., Rohleder, N., Nater, U. M., & Ehlert, U. Psychological determinants of the cortisol stress response: the role of anticipatory cognitive appraisal. Psychoneuroendocrinology, **30**, 599-610 (2005).
18. Thau, L. & Sharma, S. Physiology, Cortisol. *Physiology, cortisol*. https://www.researchgate.net/publication/331386381_Physiology_Cortisol. (2009)
19. Briley, M., & File, S. E. (Eds.). *New concepts in anxiety*. Macmillan International Higher Education (1991).
20. National Institute of Mental Health, N. I. H. *Anxiety Disorders*. National Institute of Mental Health, Transforming the Understanding and Treatment of Mental Illnesses. https://www.nimh.nih.gov/health/topics/anxiety-disorders/index.shtml (2018).
21. Vytal, K., Cornwell, B., Arkin, N., & Grillon, C. Describing the interplay between anxiety and cognition: from impaired performance under low cognitive load to reduced anxiety under high load. *Psychophysiology*, ***49***, 842-852 (2012).
22. Endler, N. S., & Kocovski, N. L. State and trait anxiety revisited. Journal of anxiety disorders, **15**, 231-245 (2001).
23. Huizink, A. C. *Prenatal stress and its effect on infant development* (2000).
24. Saviola, F., Pappaianni, E., Monti, A., Grecucci, A., Jovicich, J., & De Pisapia, N. Trait and state anxiety are mapped differently in the human brain. *Scientific Reports*, **10**, 1-11 (2020).
25. Sullivan, G. M., Kent, J. M., & Coplan, J. D. *The neurobiology of stress and anxiety* (2000).

26. Brunton, R. J., Dryer, R., Saliba, A., & Kohlhoff, J. Pregnancy anxiety: A systematic review of current scales. *Journal of Affective Disorders*, ***176***, 24-34 (2015).
27. Sinesi, A., Maxwell, M., O'Carroll, R., & Cheyne, H. Anxiety scales used in pregnancy: systematic review. *BJPsych open*, **5** (2019).
28. Schetter, C. D., & Tanner, L. Anxiety, depression and stress in pregnancy: implications for mothers, children, research, and practice. *Current opinion in psychiatry*, **25**, 141 (2012).
29. Wadhwa, P. D., Sandman, C. A., Porto, M., Dunkel-Schetter, C., & Garite, T. J. The association between prenatal stress and infant birth weight and gestational age at birth: a prospective investigation. *American journal of obstetrics and gynecology*, **169**, 858-865 (1993).
30. Gutteling, B. M., de Weerth, C., Zandbelt, N., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. Does maternal prenatal stress adversely affect the child's learning and memory at age six?. *Journal of abnormal child psychology*, ***34***, 787-796 (2006).
31. Vujović, M., Sovilj, M., Plešinac, S., Rakonjac, M., Jeličić, L., Adamović, T., & Stokić, M. Effect of antenatal maternal anxiety on the reactivity of fetal cerebral circulation to auditory stimulation, and early child development. *Srpski arhiv za celokupno lekarstvo*, **147**, 327-334 (2019).
32. Carlson, S. M. Developmentally sensitive measures of executive function in preschool children. *Developmental neuropsychology*, **28**, 595-616 (2005).
33. Fagan, J. F., Holland, C. R., & Wheeler, K. The prediction, from infancy, of adult IQ and achievement. *Intelligence*, **35**, 225-231 (2007).
34. Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. *Introduction to meta-analysis*. John Wiley & Sons (2011).
35. Valentine, J. C., Pigott, T. D., & Rothstein, H. R. How many studies do you need? A primer on statistical power for meta-analysis. *Journal of Educational and Behavioral Statistics*, **35**, 215-247 (2010).
36. Brunton, R. J., Dryer, R., Saliba, A., & Kohlhoff, J. The initial development of the Pregnancy-related Anxiety Scale. *Women and Birth*, ***32***, e118-e130 (2019).
37. Brunton, R., Gosper, K., & Dryer, R. Psychometric evaluation of the pregnancy-related anxiety scale: Acceptance of pregnancy, avoidance, and worry about self subscales. Journal of Affective Disorders, **278**, 341-349 (2021).
38. Huizink, A. C., De Medina, P. G. R., Mulder, E. J., Visser, G. H., & Buitelaar, J. K. Psychological measures of prenatal stress as predictors of infant temperament. *Journal of the American Academy of Child & Adolescent Psychiatry*, ***41***, 1078-1085 (2002).
39. Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Erlbaum (1988).
40. Higgins, J. P., & Thompson, S. G. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*, **21**, 1539-1558 (2002).
41. Molewyk Doornbos, M., Zandee, G. L., Timmermans, B., Moes, J., Heitsch, E., Quist, M., ... & VanWolde, A. Factors impacting attrition of vulnerable women from a longitudinal mental health intervention study. *Public health nursing*, **37**, 73-80 (2020).
42. Barker, E. D., Jaffee, S. R., Uher, R., & Maughan, B. The contribution of prenatal and postnatal maternal anxiety and depression to child maladjustment. *Depression and anxiety*, ***28***, 696-702 (2011).

43. Bergman, K., Sarkar, P., O'Connor, T. G., Modi, N., & Glover, V. Maternal stress during pregnancy predicts cognitive ability and fearfulness in infancy. *Journal of the American Academy of Child & Adolescent Psychiatry*, ***46***, 1454-1463 (2007).
44. Coplan, R. J., O'Neil, K., & Arbeau, K. A. Maternal anxiety during and after pregnancy and infant temperament at three months of age. *Journal of Prenatal & Perinatal Psychology & Health*, ***19***, 199 (2005).
45. D'Souza, S., Crawford, C. N., Buckley, J., Underwood, L., Peterson, E. R., Bird, A., ... & Waldie, K. E. Antenatal determinants of early childhood talking delay and behavioural difficulties. *Infant Behavior and Development*, ***57***, 101388 (2019).
46. Koutra, K., Roumeliotaki, T., Kyriklaki, A., Kampouri, M., Sarri, K., Vassilaki, M., ... & Chatzi, L. Maternal depression and personality traits in association with child neuropsychological and behavioral development in preschool years: Mother-child cohort (Rhea Study) in Crete, Greece. *Journal of affective disorders*, ***217***, 89-98 (2017).
47. Pearson, R. M., Bornstein, M. H., Cordero, M., Scerif, G., Mahedy, L., Evans, J., ... & Stein, A. Maternal perinatal mental health and offspring academic achievement at age 16: the mediating role of childhood executive function. *Journal of Child Psychology and Psychiatry*, ***57***, 491-501 (2016).
48. Caparros-Gonzalez, R. A., Romero-Gonzalez, B., Gonzalez-Perez, R., Lucena-Prieto, L., Perez-Garcia, M., Cruz-Quintana, F., & Peralta-Ramirez, M. I. Maternal and neonatal hair cortisol levels are associated with infant neurodevelopment at six months of age. *Journal of clinical medicine*, **8**, 2015 (2019).
49. Davis, E. P., Head, K., Buss, C., & Sandman, C. A. Prenatal maternal cortisol concentrations predict neurodevelopment in middle childhood. *Psychoneuroendocrinology*, ***75***, 56-63 (2017).
50. DiPietro, J. A., Novak, M. F., Costigan, K. A., Atella, L. D., & Reusing, S. P. Maternal psychological distress during pregnancy in relation to child development at age two. *Child development*, ***77***, 573-587 (2006).
51. Keim, S. A., Daniels, J. L., Dole, N., Herring, A. H., Siega-Riz, A. M., & Scheidt, P. C. A prospective study of maternal anxiety, perceived stress, and depressive symptoms in relation to infant cognitive development. *Early human development*, ***87***, 373-380 (2011).
52. Koutra, K., Chatzi, L., Bagkeris, M., Vassilaki, M., Bitsios, P., & Kogevinas, M. Antenatal and postnatal maternal mental health as determinants of infant neurodevelopment at 18 months of age in a mother–child cohort (Rhea Study) in Crete, Greece. *Social psychiatry and psychiatric epidemiology*, ***48***, 1335-1345 (2013).
53. Nazzari, S., Fearon, P., Rice, F., Ciceri, F., Molteni, M., & Frigerio, A. Neuroendocrine and immune markers of maternal stress during pregnancy and infant cognitive development. *Developmental psychobiology*, ***62***, 1100-1110 (2020).
54. Polanska, K., Krol, A., Merecz-Kot, D., Jurewicz, J., Makowiec-Dabrowska, T., Chiarotti, F., ... & Hanke, W. Maternal stress during pregnancy and neurodevelopmental outcomes of children during the first 2 years of life. *Journal of paediatrics and child health*, ***53***, 263-270 (2017).
55. Savory, K., Garay, S. M., Sumption, L. A., Kelleher, J. S., Daughters, K., Janssen, A. B., ... & John, R. M. Prenatal symptoms of anxiety and depression associated with sex differences in both maternal perceptions of one year old infant temperament and researcher observed infant characteristics. *Journal of affective disorders*, ***264***, 383-392 (2020).

56. Rogers, A., Obst, S., Teague, S. J., Rossen, L., Spry, E. A., Macdonald, J. A., ... & Hutchinson, D. Association between maternal perinatal depression and anxiety and child and adolescent development: a meta-analysis. JAMA pediatrics, **174**, 1082-1092 (2020).
57. S Ackerman, S. The Development and Shaping of the Brain. *Discovering the Brain*, 86-103 (1992).
58. Department of Health & Human Services. Pregnancy - week by week. Better Health Channel. https://www.betterhealth.vic.gov.au/health/healthyliving/pregnancy-week-by-week (2012).
59. Dobbing, J., & Sands, J. Quantitative growth and development of human brain. *Archives of disease in childhood*, **48**, 757-767 (1973).
60. Dobbing, J., & Sands, J. Developmental events. *Growth (Lakeland)*, **2**, 503-5 (1979).
61. Linderkamp, O., Janus, L., Linder, R., & Skoruppa, D. B. Time table of normal foetal brain development. *International Journal of Prenatal and Perinatal Psychology and Medicine*, **21**, 4-16 (2009).
62. Stiles, J., & Jernigan, T. L. The basics of brain development. Neuropsychology review, **20**, 327-348 (2010).
63. Howdeshell, K. L. A model of the development of the brain as a construct of the thyroid system. Environmental health perspectives, **110**, 337-348 (2002).
64. Minnes, S., Lang, A., & Singer, L. Prenatal tobacco, marijuana, stimulant, and opiate exposure: outcomes and practice implications. *Addiction science & clinical practice*, **6**, 57 (2011).
65. Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. Power failure: why small sample size undermines the reliability of neuroscience. Nature reviews neuroscience, **14**, 365-376 (2013).
66. Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. Cochrane bias methods group; cochrane statistical methods group. *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ,* **343**, d5928 (2011).
67. Cieszyński, Ł., Jendrzejewski, J., Wiśniewski, P., Kłosowski, P., & Sworczak, K. Correlation analysis of cortisol concentration in hair versus concentrations in serum, saliva, and urine. *Endokrynologia Polska*, **71**, 539-544 (2020).
68. Short, S. J., Stalder, T., Marceau, K., Entringer, S., Moog, N. K., Shirtcliff, E. A., ... & Buss, C. Correspondence between hair cortisol concentrations and 30-day integrated daily salivary and weekly urinary cortisol measures. *Psychoneuroendocrinology*, **71**, 12-18 (2016).
69. Vanaelst, B., Huybrechts, I., Bammann, K., Michels, N., De Vriendt, T., Vyncke, K., ... & De Henauw, S. Intercorrelations between serum, salivary, and hair cortisol and child-reported estimates of stress in elementary school girls. *Psychophysiology*, ***49***, 1072-1081 (2012).
70. Plamondon, A., Akbari, E., Atkinson, L., Steiner, M., Meaney, M. J., Fleming, A. S., & MAVAN research team. Spatial working memory and attention skills are predicted by maternal stress during pregnancy. *Early Human Development*, ***91***, 23-29 (2015).
71. Campbell, R. K., Devick, K. L., Coull, B. A., Cowell, W., Askowitz, T., Goldson, B., ... & Wright, R. J. Prenatal cortisol modifies the association between maternal trauma history and child cognitive development in a sex-specific manner in an urban pregnancy cohort. *Stress*, ***22***, 228-235 (2019).
72. Lin, Y., Xu, J., Huang, J., Jia, Y., Zhang, J., Yan, C., & Zhang, J. Effects of prenatal and postnatal maternal emotional stress on toddlers' cognitive and temperamental development. *Journal of affective*

disorders, ***207***, 9-17 (2017).

73. Haselbeck, C., Niederberger, U., Kulle, A., Wache, K., Brauner, E., Gutermuth, M., ... & Siniatchkin, M. Prenatal maternal distress seems to be associated with the infant's temperament and motor development: an explorative study. *Journal of Neural Transmission*, ***124***, 881-890 (2017).
74. Davis, E. P., Glynn, L. M., Schetter, C. D., Hobel, C., Chicz-Demet, A., & Sandman, C. A. Prenatal exposure to maternal depression and cortisol influences infant temperament. *Journal of the American Academy of Child & Adolescent Psychiatry*, ***46***, 737-746 (2007).
75. O'Donnell, K. J., Glover, V., Lahti, J., Lahti, M., Edgar, R. D., Räikkönen, K., & O'Connor, T. G. Maternal prenatal anxiety and child COMT genotype predict working memory and symptoms of ADHD. *PloS one*, **12**, e0177506 (2017).

Tables

Table 1 *Summary of Quality of Studies Included in Meta-analysis*

Study	Design	Selection bias	Withdrawals	Confounder and analyses	Measurement	Blinding	Overall study quality
Savory et al., 2020 [55]	W	S	M	W	S	S	W
Plamondon et al., 2015 [70]	S	S	S	M	S	S	S
Pearson et al., 2016 [47]	S	S	S	M	S	W	M
Nazzari et al., 2020 [53]	M	M	M	M	M	S	M
Koutra et al., 2017 [46]	M	S	M	S	S	W	M
Huizink et al., 2002 [38]	M	M	M	M	S	S	M
DiPietro et al., 2006 [50]	M	M	W	M	S	S	M
Coplan et al., 2005 [44]	W	S	W	M	M	S	W
D'Souza et al., 2019 [45]	S	S	M	M	S	W	M
Campbell et al., 2019 [71]	M	W	M	S	S	W	W
Bergman et al., 2007 [43]	M	S	M	M	M	S	M

Note. S=Strong; M=Moderate; W=Weak

Table 2a *Summary of Eligible Studies Examining Prenatal Stress*

s	N	Trimester of exposure	Timing of assessment	Aspect of stress	Cognitive domain	Children's age
:a 4	219 – 337	T2, T3	T2, T3	Perceived stress	GIF, language	1 – 2 years
et 0	104	T3	T3	Stress response	GIF	3 months
l., 2	225	T2-T3	T3	Perceived stress	Attention, language	24 – 30 months
t 1	358	T2	T2	Perceived stress	GIF, language	1 year
et 2	170	T1, T2, T3	T1, T2, T3	Perceived stress	Attention regulation	3 - 8 months
ck 3	29	T1, T2, T3	T1, T2, T3	Stress response	GIF	1.4 years
ıg 0	113	T1, T2, T3	T1, T2, T3	Stress response, perceived stress	Learning and memory	6-7 years
et 6	82 – 90	T3	T3	Perceived stress	GIF, attention	2 years
t 7	91	T2, T3	T2, T3	Stress response	Visual skills, expressive language	6 – 9 years

et 9	5,768	T3	Late pregnancy	Perceived stress	Expressive language	2 years
s- ez 8	41	T1, T2, T3	T1, T2, T3	Stress response	GIF, language	6 months
ell 1	91	T3	T3	Stress response	Attention/concentration, memory	6.5 years
n 3	123	Pregnancy	14-19 months post-pregnancy	Perceived stress	GIF	14 – 19 months

Table 2b *Summary of Eligible Studies Examining Prenatal Anxiety*

Authors	N	Trimester of exposure	Timing of assessment	Type of anxiety (time of assessment)	Cognitive domain	Children's age
Savory et al., 2020 [55]	58-76	T3	T3	Trait	GIF, Sustained attention, expressive and receptive language	1 year
Plamondon et al., 2015 [70]	112-150	T3	T3	General	Focused and shifting attention, orientation, EF (spatial [2]WM)	3 months – 4 years
Pearson et al., 2016 [47]	3,270	T3	T3	General	Selective and switching attention, Processing speed, EF (Working memory)	8 years
O'Donnell et al., 2017 [75]	6,969	T3	T3	General	EF (Working memory)	8 years
Nazzari et al., 2020 [53]	104	T3	T3	State	GIF	3 months
Koutra et al., 2017 [46]	288	T3	T3	Trait	GIF, verbal, quantitative and perceptual skills, attention, memory	4 years
Koutra et al., 2013 [52]	223	T3	T3	Trait	GIF, EL, RL	18 months
Keim et al., 2011 [51]	358	T1-T2	T1-T2	Trait	Visual skills, receptive and expressive language	1 year

Huizink et al., 2002 [38]	170	T1, T2, T3	T1, T2, T3	PS	Attention regulation	8 months
Gutteling et al., 2006 [30]	113	T1, T2, T3	T1, T2, T3	PS	Learning and memory	6-7 years
DiPietro et al., 2006 [50]	82 – 90	T3	T3	State	GIF, attention regulation	2 years
Coplan et al., 2005 [44]	46	T3	T3	State, trait	Attention span	3 months
Barker et al., 2011 [42]	3,298	T3	T3	General	Verbal skills	8 years

Note. [1]GFI = General Intellectual Functions. [2]WM = Working Memory. [3]PS = Pregnancy-specific. T1 = trimester 1; T2 = Trimester 2 ; T3 = Trimester 3.

Table 3 *Association Between Prenatal Stress and/or Anxiety, Stress, Anxiety and Offspring Cognitive Outcomes Across All Ages of Development*

	Stress and anxiety			Stress			Anxiety		
	Number of studies (sample size)	Correlations r (95% CI), p-value	I^2 value, %	Number of studies (sample size)	Correlations r (95% CI), p-value	I^2 value, %	Number of studies (sample size)	Correlations r (95% CI), p-value	I^2 value, %
l	5 (n = 673)	-0.14 (-.32; 0.05), 0.16	82.27	3 (n = 309)	-0.26 (-0.41; -0.10), 0.002	87.43	4 (n = 550)	-0.02 (-0.15; 0.10), 0.70	44.71
	6 (n = 981)	-0.05 (-0.17; 0.07), 0.43	69.76	2 (n = 428)	-0.04 (-0.30; 0.23), 0.80	87.20	4 (n = 553)	-0.06 (-0.21; 0.09), 0.43	61.01
e	NA	NA	NA	NA	NA	NA	2 (n = 281)	-0.03 (-0.35; 0.29), 0.85	80.82
	NA	NA	NA	NA	NA	NA	2 (n = 281)	-0.15 (-0.41; 0.13), 0.28	73.47
e	3 (n = 6,051)	-0.10 (-0.19; -0.01), 0.03	47.02	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	NA	NA	NA
	NA	NA	NA	NA	NA	NA	2 (n = 3,382)	-0.24 (-0.49; 0.04), 0.09	89.01

Table 4a *Overview of Association Between Prenatal Stress and Children's Cognitive Outcomes*

e	Sample size	Age points	Weeks of gestation	Covariates	Cognitive domain	Results
et [54]	337 at 1 years old 219 at 2 years old	1 and 2 years old	20-24 weeks	parental age and education; marital status, place of residence, socioeconomic status (SES) and their changes over the study period; child gender; major pregnancy complications which appeared after inclusion into the study; type of delivery; gestational age and birth outcomes; breastfeeding; number of siblings; day care attendance; active/passive smoking and alcohol consumption during pregnancy; child environmental tobacco smoke (ETS) exposure after birth; child health status and hospitalisations.	GIF, language	**1-year-old** Unadjusted: GIF: b=-.09, p>.05 Language: b=-.03, p>.05 Adjusted: GIF: b=-.02, p>.05 Language: -.02, p>.05 **2-year-old** Unadjusted: GIF: b=-0.02 [95%CI -1.2; -.2] Language: b=-.2, p>.05 Adjusted: GIF: b=-.08 [95%CI -1.3;-.2] Language: b=-.3, p>.05
et [53]	104	3 months	30-33 weeks	Maternal age, education, socio–economic status, parity, infants' age, mode of delivery, length of labor, gestational age, birth weight, head circumference, actual weight, postnatal smoke exposure, breastfeeding	GIF	Unadjusted: r=-0.26, p<.01 Adjusted: b= -.37, -<.001

				vs. formula-feeding, maternal emotional availability and IQ, and gestational age at birth		
,	225	24-30 months	28-36 weeks	Maternal age at the time of study enrolment, maternal educational levels, maternal IQ, family monthly income, maternal blood lead levels during pregnancy, gestational weeks, and the infant's sex and age	Language, attention	Adjusted: Language: b=-12.40, p=.06 Attention: ns
al.,	358	1 year	17-22 weeks	income, pre-pregnancy body mass index (BMI), education, social support, self-esteem, maternal age, infant sex, gestational age, presence of a spouse/partner, depressive symptoms and perceived stress	GIF, EL, visual skills	Adjusted: Visual: b=0.0, p>.05 EL: b=.2, p<.05 RL: Wald x=4.09, p<.05 GIF: b=.03, p<.05
et [38]	170	3 and 8 months	15-17, 27-28 and 37-38 weeks	Educational level and professional level of the pregnant woman and her partner, pregnancy complications, use of medication during pregnancy, medication that poses risks for the fetus, fertility problems, high blood pressure, in vitro fertilisation, gestational	Attention	**3 months** Unadjusted: r=-.12, p>.05 **8 months** Unadjusted: r=-.18, p<.05

				diabetes mellitus, gynecological risk, pre-existing disease, smoking during pregnancy, alcohol use during pregnancy, birth weight, gestational age at birth, complications during delivery, gender, breast-feeding, psychological well-being, and perceived stress of the mother at 3 and 8 months after childbirth and postnatal depression scores of the mother		
ck et [73]	29	16 months	12-14, 22-24 and 32-34 weeks	n/a	GIF	Unadjusted: Ns
g et [30]	113	6-7 years	15–17, 27–28 and 37–38 weeks	child's gender, gestational age, and birthweight, maternal age, maternal educational level, prenatal smoking, alcohol use, and postnatal maternal stress	Learning and memory	Unadjusted: Perceived stress: r=.11, p>.05 Stress response T1: .12, p>.05 Stress response T2: -.14, p>.05 Stress response T3 : .10, p>.05 Adjusted : b=-.01, p>.05
et [50]	82-90	2 years old	28 weeks	Maternal education, fetal sex, prenatal depression and anxiety, postnatal depression and anxiety	Attention	Unadjusted: Attention: .00, p>.05
al.,	91	6-9 years	19 and 31 weeks	Gestational age at delivery, maternal depressive	Visual skills, EL	**19 weeks:** Adjusted:

				symptoms and household income Also considered but not significantly associated with variables: race/ethnicity, maternal marital status, maternal education, and household income, concurrent depressive symptoms, gestational age at birth, birth order		Visual skills: r=.0, p>.05 EL: r=.05, p>.05 **31 weeks:** Adjusted: Visual skills: r=0.22, p<.05 EL: r=.24, p<.05
et [45]	5,768	2 years old	Pregnancy	Mother's ethnicity and education, mother's age when pregnant, area-level deprivation, child's gender, gestational age, birthweight and age at assessment	EL	Unadjusted: b=-0.096, p<.05 Adjusted: b=-0.01, [95%CI 0.98; 1.01]
;- : et [48]	41	6 months	12, 24 and 34 weeks	Maternal level of education, salary, and infant birth weight	GIF, EL, RL	Unadjusted: GIF: -.16, p<.05 RL: -.06, p>.05 EL: -.14, p>.05 Adjusted: GIF: b=.30, p=.04 RL: .01, p>.05 EL: -.21, p>.05
l et [71]	91	6.5 years old	29 weeks	Adjusted for: maternal age, race, education, pre-pregnancy BMI, gestational age at cortisol assessment and for child age at cognitive testing Considered: Maternal age,	Attention/concentration, memory	Unadjusted: Memory: r=.08, p>.05 Attention: r=.10, p>.05 Adjusted: Memory: b=1.14, p>.05 Concentration: b= 5.63, p>.05

				race/ethnicity, education completed, self-reported pre-pregnancy weight and height; child sex, date of birth, and gestational age at birth; gestational age at cortisol assessment		
ı et [43]	123	14-19 months	14-19 months post-pregnancy	maternal age, parity, ethnicity, smoking, alcohol and prescribed drugs during pregnancy; birth weight, gestational age at birth, method of delivery, and child sex; maternal postnatal anxiety and depression and maternal social support postnatally	GIF	Unadjusted: r= -.38, p < .05

Note. GIF = general intellectual skills; RL=Receptive language; EL=Expressive language; T1, T2, T3=Trimesters 1, 2, 3

Table 4b *Overview of Association Between Prenatal Anxiety and Children's Cognitive Outcomes*

:e	Sample size	Age points	Weeks of gestation	Covariates	Cognitive domain	Results
t	76	1 year old	At birth	Infant age at questionnaire completion, parity	GIF, attention, EL, RL	<u>Unadjusted results:</u> GIF: r=-.19, p=.16 Attention: r=-.08, p=.52 RL: r=-.31, p=.02 EL: r=-.22, p=.10 <u>Adjusted results</u>: GIF females : r= -.24, p=.21 GIF males: r= -.12, p=.54 Attention females: r= .05, p=.77 Attention males: r= -.19, p=.32 RL females: r= -.23, p=.24 EC felames: r= -.02, p=.93 RL males: r=-.41, p=.03 EL males: r= -.49, p=.008
on	165 at 6 months 150 at 1.5 years old	1.5 years old	12-24 weeks	Child sex, birthweight and gestational age	Attention, WM	**6 months** <u>Unadjusted</u>: Attention: r=-.08, p>.05 **1.5 years** <u>Unadjusted</u>: Attention: r=.11, p>.05 WM: r=-.08, p>.05 <u>Adjusted</u>: Attention: b=.17, p>.05 WM: b=.05, p>.05
et	3,270	8 years old	n/a	Postnatal depression	Attention, WM	<u>Unadjusted</u>: WM: -.36, p<.05

						Adjusted: Attention: b=-0.01, p=0.53 WM: b=-0.03, p=0.066
ll	6,969	8 years old	32 weeks	Parenting behabiour, maternal age at time of pregnancy, smoking and substance abuse during pregnancy, socioeconomic indicators: maternal education and household crowding, obstetric outcomes: birth weight, gestational age and child gender	WM	Adjusted: WM: b=.01, p>.05
et	104	3 months	30-33 weeks	Maternal age, education, socio–economic status, parity, infants' age, mode of delivery, length of labor, gestational age, birth weight, head circumference, actual weight, postnatal smoke exposure, breastfeeding vs. formula-feeding, maternal emotional availability and IQ, and gestational age at birth	GIF	Unadjusted: r= -0.09, p>.05
t	288	4 years old	28-32 weeks	Minimally adjusted: quality of assessment, child sex, and examiner. Fully adjusted: maternal age at delivery, maternal education, smoking status at 4 years, working status at 4 years assessment, child's sex, prematurity, breastfeeding duration, pre-school attendance, TV watching, birth order at 4 years, number of children in the family, quality of assessment and examiner	GIF, verbal, quantitative and perceptual skills, attention, memory	Unadjusted: GIF: 0.004, p>.05 Attention: .16, p=.02 Minimally adjusted: Verbal skills: b=-.26, p>.05 Perceptual performance: b=-.37, p>.05 Quantitative: b=0.00, p>.05 GIF: b=-.29, p>.05 Memory: b=-.12, p>.05 Attention: b=0.37, p<.05

						Adjusted: Verbal skills: b=.25, p>.05 Perceptual performance: b=.17, p>.05 Quantitative: b=0.52, p>.05 GIF: b=.32, p>.05 Memory: b=.42, p>.05 Attention: .18, p<.05
t	223	18 months	28-32 weeks	Minimally adjusted: quality of assessment, child sex, and examiner. Fully adjusted: maternal age at delivery, maternal education, smoking status at 4 years, working status at 4 years assessment, child's sex, prematurity, breastfeeding duration, pre-school attendance, TV watching, birth order at 4 years, number of children in the family, quality of assessment and examiner	GIF, EL, RL	Minimally adjusted: GIF: b= -0.88 (-1.96, 0.19) RL: b= 0.03 (-0.99, 1.04) EL: b= 1.15 (0.16, 2.14) Fully adjusted: GIF: b= -0.82 (-1.88, 0.25) RL: b= 0.12 (-0.89, 1.12) EL: b= 1.13 (0.15, 2.11)
	358	1 year	< 20 weeks	income, pre-pregnancy body mass index (BMI), education, social support, self-esteem, maternal age, infant sex, gestational age, presence of a spouse/partner, depressive symptoms and perceived stress	GIF, EL, RL, visual skills	Adjusted: GIF: -.2, p>.05 Visual: b=-.2, p>.05 RL: b=-.1, p>.05 EL: b=-.1, p>.05
et	170	3 and 8 months	15-17, 27-28 and 37-38 weeks	Educational level and professional level of the pregnant woman and her partner, pregnancy complications, use of medication during pregnancy, medication that poses risks for the fetus, fertility problems, high blood pressure, in vitro	Attention	**3 months** Unadjusted: r=-.16, p<.05 Adjusted: b=-.29, p<.05 **8 months**

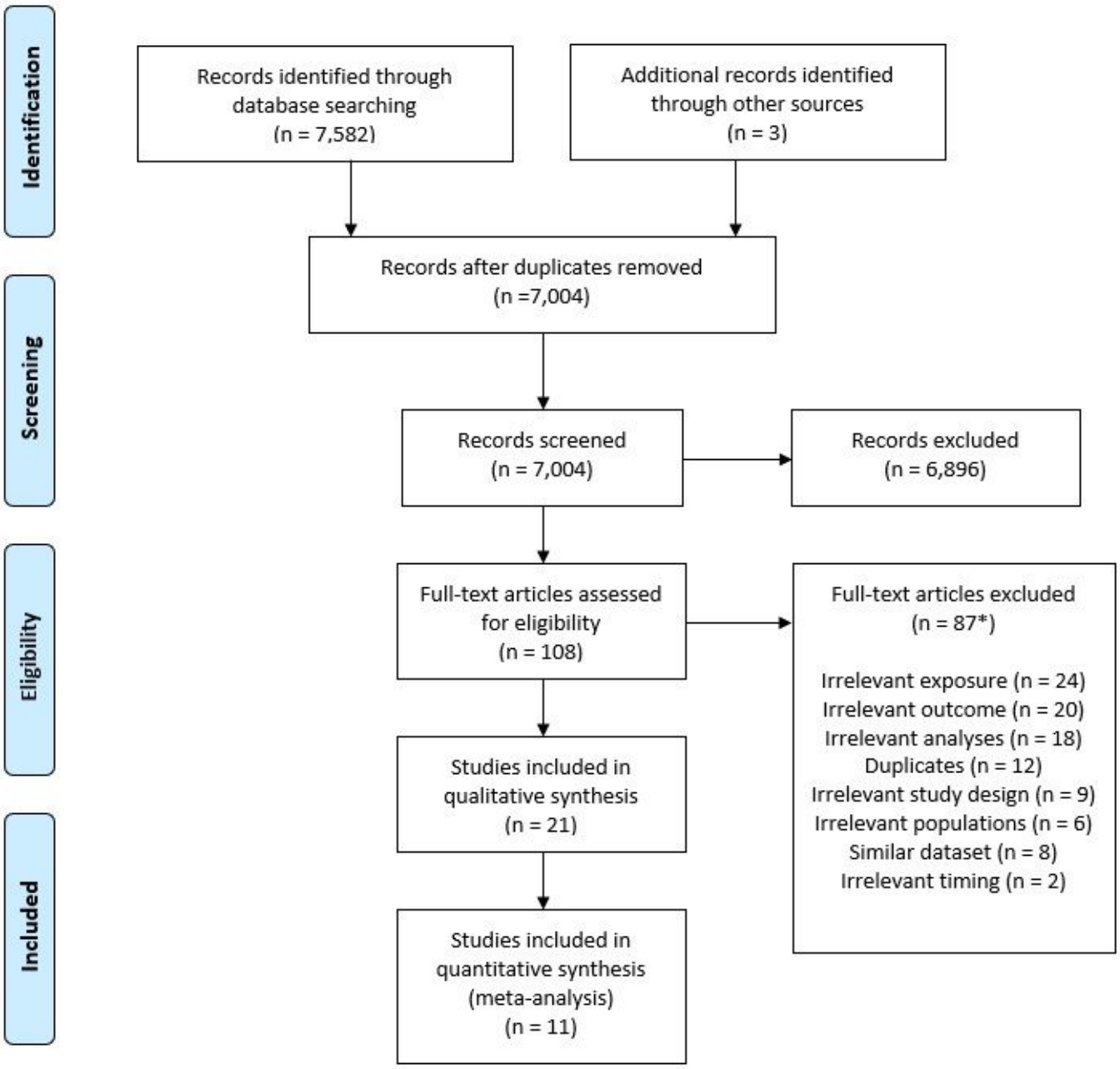
				fertilisation, gestational diabetes mellitus, gynecological risk, pre-existing disease, smoking during pregnancy, alcohol use during pregnancy, birth weight, gestational age at birth, complications during delivery, gender, breast-feeding, psychological well-being, and perceived stress of the mother at 3 and 8 months after childbirth and postnatal depression scores of the mother		Unadjusted: r=-.18, p<.05 Adjusted: b=-.10, p>.05
g	113	6-7 years	15–17, 27–28 and 37–38 weeks	child's gender, gestational age, and	Learning and memory	Unadjusted: r=-.10, p>.05 Adjusted: b=-.16, p>.05
et	82-90	2 years old	28 weeks	Maternal education, fetal sex, prenatal depression and stress, postnatal depression and stress	GIF	Unadjusted: STAI: r=.16, p>.05 POMS: r=.29, p<.05 Adjusted: Composite anxiety: b=2.59, p<.05
t	46	3 months	26-38 weeks	Trait anxiety Considered but not significant: maternal age, parental education, pregnancy complications, smoking and drinking habits during pregnancy, birth order of the unborn child, infant birth weight, length of infant	Attention	Unadjusted: Trait: r=-.13, p>.05 State: -.33, p<.05 Adjusted: Trait: b=-.15, p>.05 State: b=-.34, p>.05
t	3,298	8 years old	32 weeks	n/a	Verbal skills	Unadjusted: Females: -.05, p<.05 Males: -.04, p>.05

Note. GIF =General intellectual skills; RL=Receptive language; EL=Expressive language; WM=Working memory; ns=Non-significant; STAI=Spielberger State Anxiety Scale; POMS= Profile

Moods Scale, anxiety subscale

*Composite anxiety=STAI and the anxiety subscale of POMS

Figures



Note. * Some studies were excluded for more than one reason and thus reported more than once

Figure 1

PRISMA Study Flow Diagram for the Systematic Review

Figure 2

Association between All types of Exposure and Language Outcomes in Offspring

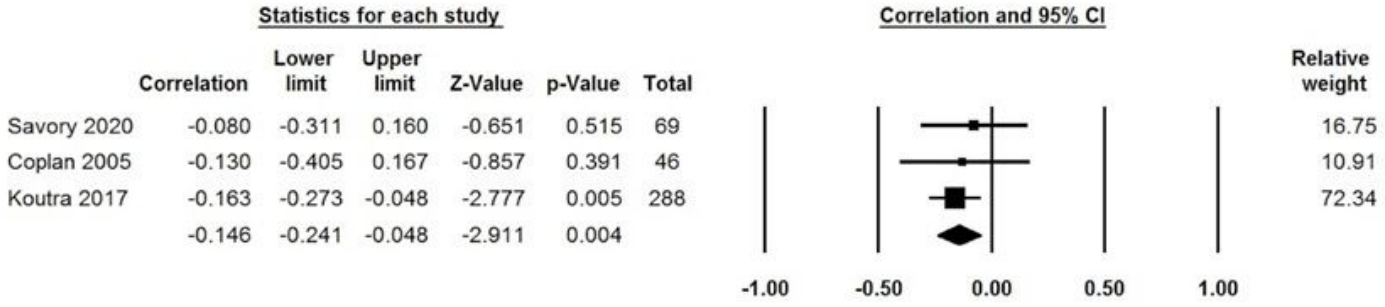


Figure 3

Association between Trait anxiety and sustained attention

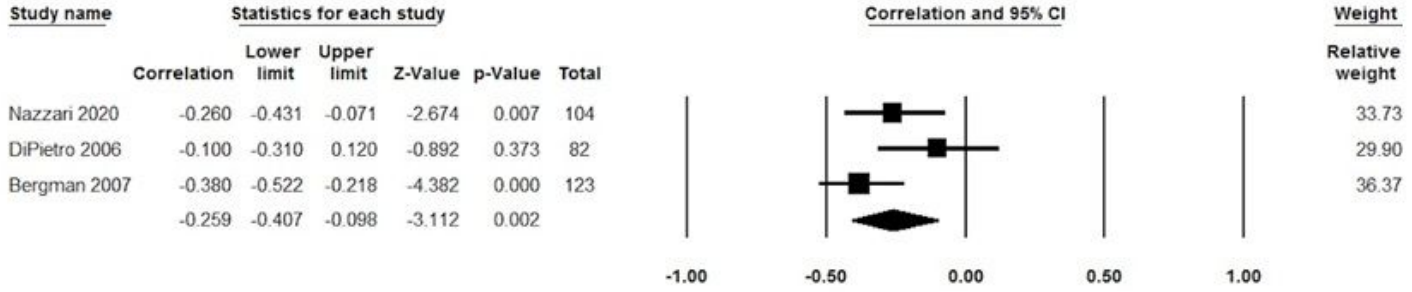


Figure 4

Association between Stress and General intellectual functions

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementtables.pdf