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The effect of prenatal maternal distress on offspring brain development: A systematic review

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ABSTRACT

Background: Prenatal maternal distress can negatively affect pregnancy outcomes, yet its impact on the offspring's brain structure and function remains unclear. This systematic review summarizes the available literature on the relationship between prenatal maternal distress and brain development in fetuses and infants up to 12 months of age.

Methods: We searched Central, Embase, MEDLINE, PsycINFO, and PSYNDEXplus for studies published between database inception and December 2023. Studies were included if prenatal maternal anxiety, stress, and/or depression was assessed, neuroimaging was used to examine the offspring, and the offspring's brain was imaged within the first year of life. The quality of the included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-II.

Results: Out of the 1516 studies retrieved, 71 met our inclusion criteria. Although the studies varied greatly in their methodology, the results generally pointed to structural and functional aberrations in the limbic system, prefrontal cortex, and insula in fetuses and infants prenatally exposed to maternal distress.

Conclusions: The hippocampus, amygdala, and prefrontal cortex have a high density of glucocorticoid receptors, which play a key role in adapting to stressors and maintaining stress-related homeostasis. We thus conclude that in utero exposure to maternal distress prompts these brain regions to adapt by undergoing structural and functional changes, with the consequence that these alterations increase the risk for developing a neuropsychiatric illness later on. Future research should investigate the effect of providing psychological support for pregnant women on the offspring's early brain development.

1. Introduction

Maternal psychological distress is common during pregnancy, with 22 % of pregnant women reporting increased symptoms of stress, anxiety, and depression [1]. In high-risk pregnancies, this percentage is almost twice as high [2]. Moreover, prenatal maternal distress can negatively affect pregnancy outcomes (e.g., preeclampsia, preterm delivery) as well as the child's later behavioral, emotional, and cognitive abilities [3–5]. This includes an increased risk for neurodevelopmental and psychiatric disorders, such as attention-deficit/hyperactivity disorder, autism, depression, and schizophrenia [6–8]. Despite the growing evidence of the gravity of maternal distress during pregnancy, the extent to which it affects the offspring's brain continues to be debated.

Previous review articles have focused on the influence of a single dimension of maternal distress on children's brain development, such as anxiety [9], depression [10], or stress [11]. Furthermore, a recent review summarized the available magnetic resonance imaging (MRI) studies on the effects of prenatal maternal physical health, mental health, and drug and medication use on infant brain development [12]. However, it may be argued that other neuroimaging techniques should also be considered when evaluating the neurological outcomes of the offspring, such as diffusion tensor imaging (DTI), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS). To the best of our knowledge, no systematic review to date has provided a comprehensive overview of the brain structure and function of offspring exposed to different dimensions of prenatal distress regardless of the

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neuroimaging technique used. Moreover, given the novelty of the technique, fetal MRI results have not been systematically reviewed within the context of prenatal maternal distress. The present systematic review thus aims to summarize the existing literature on the relationship between prenatal maternal distress and the offspring's brain structure and function between the fetal stage and 12 months of age.

In the following sections, the selected studies are grouped by the type of prenatal distress examined (i.e. anxiety, stress, depression). Studies that used a composite distress factor are discussed separately to highlight potential differences in findings compared to the single-dimension studies. Each section starts with a summary of the structural findings, including MRI and DTI, before discussing the functional data derived from fMRI and fNIRS. Where applicable, EEG and magnetoencephalography (MEG) results are discussed at the end of the section. We also identify gaps in the literature and suggest future directions for this field of research.

2. Methods

The search methods used fulfilled the PRISMA guidelines for systematic reviews.

2.1. Search strategy

A literature search was conducted using the following electronic databases: CENTRAL, Embase, MEDLINE, PsycINFO, and PSYNDEXplus. Literature published up to and including December 2023 was included in the search. The following search terms were used: "infant" and "neuroimaging" and "brain function" and ("prenatal/maternal" and ("stress" or "anxiety" or "mental disease")). The detailed search history can be found in the Supplement.

2.2. Study selection

Two reviewers independently screened the titles and abstracts of each search result for eligibility. Full texts were assessed if the reviewers disagreed or could not determine eligibility based on the study's abstract. Studies were included if (a) the mental health status of pregnant women was assessed, (b) at least one neuroimaging technique was used to examine the offspring, and (c) the offspring's brain was imaged between the fetal stage and a mean age of 12 months. These inclusion criteria were chosen to filter out studies that examined postnatal maternal mental health and/or only assessed the offspring behaviorally. Moreover, we decided to only include offspring up to 12 months of age to reduce the additional influence of postnatal environmental factors on brain development, such as nutrition, pollutants, and infection.

2.3. Risk of bias assessment

Risk of bias in the included studies was assessed with the Quality Assessment of Diagnostic Accuracy Studies-II (QUADAS-II) method [13]. This assessment tool can be used to judge the quality of diagnostic accuracy studies based on four domains: (1) patient/participant selection, (2) index test, (3) reference standard, and (4) flow and timing. Each of these domains is evaluated in terms of the risk of bias; the first three domains are also evaluated in terms of concerns regarding applicability. For the purpose of the present review, the index test refers to the maternal distress questionnaires used and the reference standard refers to either a formal diagnosis of an anxiety-, stress- or mood disorder or the use of established cut-off scores that are consistent with a diagnosis. Two reviewers independently applied the tool to each included study. Any discrepancies in judgements of risk of bias were resolved by discussion to reach consensus between the two review authors. If no consensus could be reached, a third review author acted as an arbiter.

2.4. Data extraction

One reviewer screened each record and transferred the following information from the selected papers onto an Excel spreadsheet: publication details (authors, year of publication, title), study design (sample size, clinical or community sample, country of data collection), participant data (maternal age, gestational age at time of distress assessment, age of offspring at time of outcome assessment), and measurements (maternal assessment, offspring assessment, main findings). The accuracy of the data extraction was verified by two review team members, who compared the information listed in the spreadsheet to the original studies. Due to the heterogeneity in the maternal assessments and neuroimaging techniques used, it was not feasible to conduct a statistical meta-analysis of the study results. Data are therefore descriptively presented in Tables S1–S4.

3. Results

After automatic removal of all duplicates, the literature search yielded 1516 records. Screening the abstracts of these records for eligibility resulted in the exclusion of another 1431 studies. Reasons of exclusion at this stage were no measure of prenatal maternal distress, no original research, wrong age group, involvement of animals, and no neurological outcome in the offspring. We further excluded case reports with no data and studies not written in English. We thus sought 85 studies for retrieval and were able to include 85 in the full-text analysis. Of these, 14 articles were excluded because prenatal maternal distress was only included as a covariate ($N = 10$), cortisol was the only measure of distress, i.e. no complementary maternal mental health assessment was administered ($N = 3$), or the children were older than 12 months on average ($N = 1$). In the end, 71 studies met our inclusion criteria. Fig. 1 depicts a PRISMA flowchart of the full selection process. The 71 records were then categorized by the type of prenatal maternal distress, although several fell into more than one category: anxiety ($N = 20$), stress ($N = 18$), depression ($N = 37$). Ten studies used a composite distress factor.

3.1. Risk of bias in studies

Out of the 71 studies included in the present review, more than 90 % of studies were identified at low risk of bias for participant selection and index test used. With regard to the reference standard, 66 % of studies were identified at unclear risk of bias, as most studies relied solely on self-report questionnaires and thus provided insufficient information in this domain. Finally, 41 % of studies were at low risk of bias, 42 % at unclear risk of bias, and 17 % at high risk of bias for flow and timing of participant recruitment and maternal assessment. Table A.1 in the Appendix displays the risk-of-bias judgment for each individual study.

3.2. Demographics

All included studies used community sampling as their participant selection method, recruiting pregnant women during routine obstetrical appointments at local clinics or hospitals and through digital advertisements and flyers. Most studies were conducted in the United States ($N = 32$), with hotspots in California, New York, and Washington D.C. Two large birth cohorts, namely the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) cohort and the FinnBrain cohort, resulted in 13 studies being conducted in Singapore and 10 studies in Finland. Other countries of data collection were Canada ($N = 5$), United Kingdom ($N = 5$), South Africa ($N = 2$), Bangladesh ($N = 1$), Brazil ($N = 1$), China ($N = 1$), and Italy ($N = 1$). The studies were all published between 2006 and 2023 in peer-reviewed journals, with 49 out of the 71 included studies (69 %) having been published since 2020.

The sample size varied between studies from 14 to 413 mother-child dyads, with the offspring at the time of assessment aged between 28.1

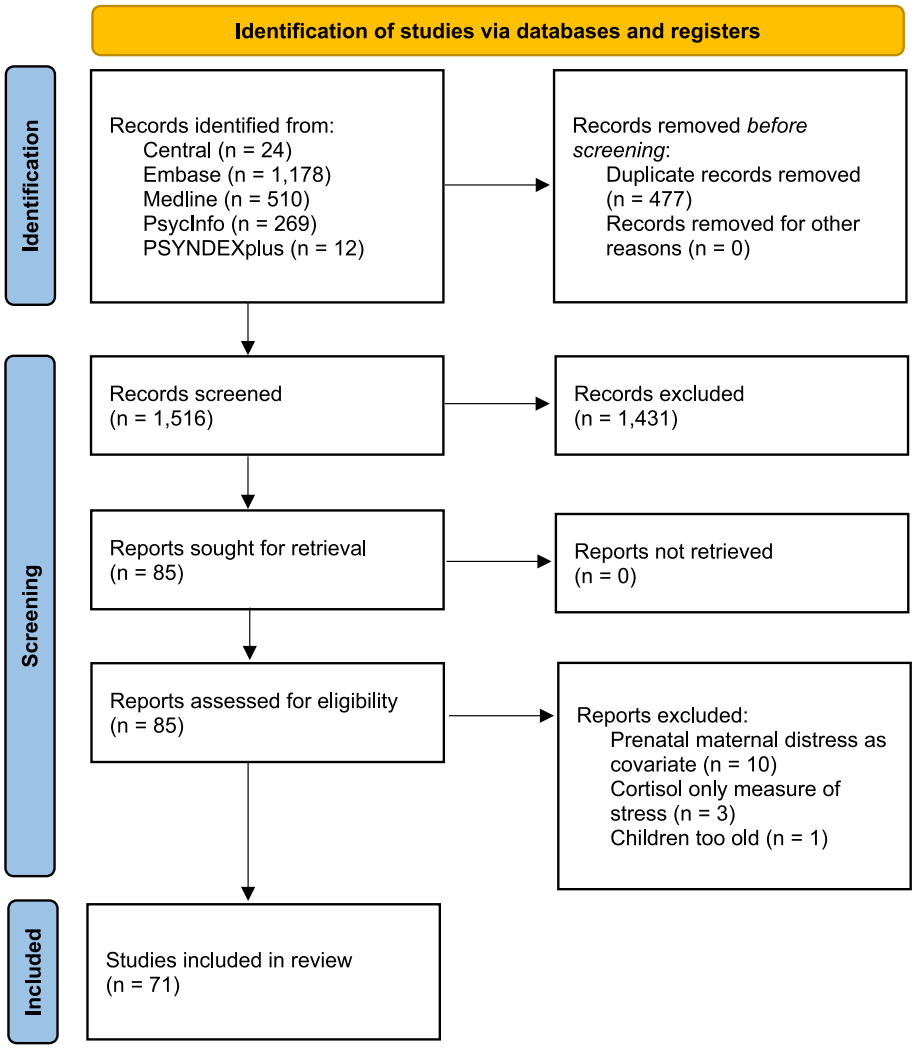

Fig. 1. PRISMA flowchart of study selection process.

gestational weeks and 9.7 months. The average maternal age was 29.5 years. The studies investigated 7924 dyads in total, including 2142 with anxiety exposure, 2368 with stress exposure, 3160 with depression exposure, 554 with "distress" exposure, and 1219 healthy controls. It is important to note here that some children were exposed to more than one dimension of distress (e.g. depression and anxiety).

Forty out of the 71 studies also reported maternal race/ethnicity. Among them, 31.5 % self-identified as Non-Hispanic White/Caucasian, 19.3 % as Black/African-American, 3.9 % as Hispanic or Latina, 41.0 % as Asian or Pacific Islander, and 3.9 % as Mixed/Other. Sixteen of these studies with 2392 study participants overall controlled their analyses for maternal ethnicity or included it as a covariate. None of the studies reported significant ethnic differences in the effect of prenatal maternal distress on fetal or infant brain measures.

3.3. Maternal assessments

Maternal characteristics were assessed either during pregnancy or retrospectively at the time of the child's scan using one or more dimensional scales. Overall, 29 different assessments were used to determine prenatal maternal distress status of the participating women (Table 1). However, the overwhelming majority of studies administered the Edinburg Postnatal Depression Scale (EPDS), Perceived Stress Scale (PSS), and/or State-Trait Anxiety Inventory (STAI).

3.4. Neuroimaging techniques

To examine the offspring's brain structure and function, numerous non-invasive neuroimaging techniques were used. The most common techniques were MRI ($N = 22$), DTI ($N = 19$), functional MRI (fMRI; $N = 16$), fetal MRI ($N = 6$), fetal fMRI (N = 6), and EEG (N = 6). Three studies used MEG (N = 1), fNIRS (N = 1), or diffuse optical tomography (DOT; N = 1). Nine studies included more than one imaging technique (fetal MRI/fMRI = 1; fetal fMRI/neonatal fMRI = 1; MRI/DTI = 4; fMRI/DTI = 3).

3.5. Child outcomes

The following sections summarize the literature on the neurological outcomes of children exposed to maternal anxiety, stress, and/or depression in utero. The neurological findings, including alterations in brain structure and function, are grouped by the neuroimaging technique used. All of the included studies were correlational. Effect sizes of the correlations are reported in Tables S1 to S4, where available.

3.6. Anxiety

Anxiety is a prevalent mental health concern in pregnant women. Pregnancy is associated with higher rates of certain anxiety disorders, such as generalized anxiety disorder. However, there is a significant

Table 1
Assessments used to screen for prenatal maternal distress status.

Maternal assessment	Distress dimension assessed	Number of studies
Beck Anxiety Inventory	Anxiety	1
Beck Depression Inventory	Depression	7
Center for Epidemiologic Studies Depression Scale	Depression	7
Childhood Trauma Questionnaire	Distress	1
COPE Stress	Stress	1
Crisis in Family Systems	Stress	1
Edinburgh Postnatal Depression Scale	Depression	39
Everyday Discrimination Scale	Stress	1
Hamilton Rating Scale for Depression	Depression	3
Life Stressor Checklist	Stress	1
Lifetime Events Checklist for DSM-5	Stress	1
Maternal Frailty Inventory	Anxiety	1
Medical history/Clinical records	Stress, Depression	4
Modified PTSD Symptoms Scale	Stress	1
Penn State Worry Questionnaire	Anxiety	2
Perceived Stress Scale	Stress	21
Pregnancy Distress Questionnaire	Distress	1
Pregnancy Experiences Scale	Stress	2
Pregnancy-Related Anxiety Questionnaire	Anxiety	4
PROMIS Anxiety Scale	Anxiety	1
Reynolds Adolescent Depression Scale	Depression	1
Satisfaction with Life Scale	Stress	2
Schedule for Affective Disorders and Schizophrenia	Depression	1
State-Trait Anxiety Inventory	Anxiety	22
Stress and Adversity Inventory	Stress	3
Stressful Life Events Questionnaire	Anxiety, Stress	2
Structured Clinical Interview for DSM-5	Depression	3
Symptom Checklist-90	Anxiety, Depression	6
Traumatic Birth Experiences	Stress	1

amount of variation in anxiety during pregnancy that the categories of anxiety listed in the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) cannot explain. This type of anxiety is also known as pregnancy-related anxiety, and it describes emotional and cognitive attributes of anxiety related to fetal health and loss, childbirth, body image, and perceived control [14]. The studies reviewed in this section examine either generalized anxiety or pregnancy-related anxiety.

Twenty studies with 2371 mother-child dyads (2416 exposed, 229 controls) investigated the influence of prenatal maternal anxiety on child brain development (Table S1). Three fetal MRI studies examined fetal hippocampal and white matter volume based on maternal state- and trait-anxiety (STAI) scores during pregnancy. State-anxiety refers to the participant's current feelings, whereas trait-anxiety relates to the participant's characteristic patterns of feeling, which tend to remain stable over time [15]. Whereas two studies found elevated levels of prenatal maternal state- and trait-anxiety to correlate with smaller hippocampal volumes in both hemispheres [16,17], another study found only trait-anxiety to be significantly associated with smaller right hippocampal volume [18]. Moreover, Wu et al. [16] reported a correlation of both higher state- and trait-anxiety with lower white matter volume, while Lu et al. [17] could only demonstrate a significant negative association between trait-anxiety and white matter volume. One fetal MRI study focused on the association between state- and trait anxiety and alterations in regional cortical thickness [19]. This study found increased maternal anxiety to correlate with cortical thickening in parahippocampal and limbic areas, and with cortical thinning in medial prefrontal regions. However, none of these associations survived multiple comparisons correction. In terms of resting-state functional connectivity in the fetus, higher maternal anxiety has been associated with hyperactivity in the limbic system, including the amygdala and hippocampus, and with hypoactivity in higher-order cortical areas related to emotion regulation, such as the medial prefrontal cortex (PFC) [20,21].

Six studies on prenatal maternal anxiety used structural MRI to assess neurological outcomes in infants. Several of those studies drew participants from one of two large birth cohorts, namely the FinnBrain cohort or the GUSTO cohort. In the FinnBrain cohort, one study found maternal pregnancy-related anxiety to be associated with sexually dimorphic alterations in the offspring's amygdalar volume [22]. More specifically, higher scores on the Pregnancy-Related Anxiety Questionnaire (PRAQ) during the second trimester were associated with a larger left relative amygdalar volume in girls compared to boys. In contrast, a UK study and a GUSTO cohort study did not find an association between prenatal maternal anxiety and amygdalar or hippocampal volume [23,24]. However, the GUSTO study reported slower bilateral hippocampal volume growth in the first six months of life in the offspring of mothers with elevated levels of anxiety during pregnancy [24].

Three MRI studies also considered the child's genetics in their analyses [25–27]. One research group found a significant interaction effect between a genetic oxytocin receptor variant (rs53576) in the offspring and the mother's Symptom Checklist-90 sum scores on right hippocampal volumes [25]. A higher score was positively associated with right hippocampal volume in A-allele carriers, but not in GG-homozygotes. Within the GUSTO cohort, it was demonstrated that prenatal maternal anxiety interacted with an infant gene variant (Val66Met) and that maternal anxiety was a significant source of variation in DNA methylation across the genome among carriers of the methionine (Met) allele. In terms of brain structure, neonatal DNA methylation co-varied with right amygdalar volume among Met/Met carriers and with left hippocampal volume in valine (Val)/Val carriers [26]. It was also shown that variation in the catechol-*O*-methyltransferase gene modulated the association between prenatal maternal anxiety and neonatal cortical thickness in prefrontal and parietal regions. For instance, the Met-homozygous neonates exposed to high levels of prenatal maternal anxiety demonstrated cortical thinning in the right ventrolateral prefrontal region, whereas the Val-homozygous infants showed cortical thickening [27].

Sylvester et al. [28] also looked at the impact of prenatal maternal anxiety on the offspring's functional connectivity. They used an oddball paradigm to assess brain activity in response to deviant auditory stimuli in sleeping infants and found a positive correlation between trait-anxiety exposure in utero and activity in the bilateral anterior insula, anterior cingulate cortex, and the ventrolateral PFC. The study also demonstrated lower activity in occipital and posterior parietal regions in infants with higher levels of trait-anxiety exposure during pregnancy.

DTI studies have reported various findings in infant brain microstructure, even though the STAI questionnaire was used consistently to assess prenatal maternal anxiety. Negative correlations between STAI scores and fractional anisotropy were found in the right insula, right middle occipital and inferior temporal regions, and in bilateral superior temporal and left postcentral regions [29] as well as the left prefrontal and middle frontal gyrus white matter [30]. These remained significant when depression scores were controlled for. One GUSTO study found an interaction effect between rs2034254 and rs1900247 within the ASB3 gene and the STAI scores on neonatal hippocampal radial diffusivity in the right hemisphere [31]. Positive associations between STAI scores and fractional anisotropy within the anterior cingulate white matter tract have also been reported [32]. In contrast, Lautarescu et al. [33] did not find a significant association between maternal trait anxiety and uncinate fasciculus microstructural properties or inferior longitudinal fasciculus diffusion properties.

One DOT study found a strong negative correlation between PRAQ scores at 24, but not 34, gestational weeks and infant total hemoglobin responses to sad speech in areas inferior and superior to the left temporoparietal junction [34]. Moreover, Shephard et al. [35] conducted a resting-state EEG study with six-month-old infants of adolescent mothers living in poverty in Brazil and found that a higher score on the Beck Anxiety Inventory was associated with stronger theta power at frontal and posterior electrode clusters and weaker oscillatory

connectivity in alpha-range networks.

Overall, MRI and DTI studies on prenatal maternal anxiety point to structural alterations in the hippocampus, amygdala, and PFC of the offspring, including smaller volume, cortical thinning, and decreased fractional anisotropy. However, a couple of studies also found increases in volume, particularly in the amygdala, while some studies reported no relationship between prenatal maternal anxiety and brain structure of the offspring. Functional imaging studies also showed contrasting results, including both hyper- and hypoactivity in frontal-limbic and insular regions.

3.7. Stress

Prenatal maternal stress can be divided into chronic and acute stress, as well as objective and subjective stress. Chronic stress refers to ongoing events in the pregnant woman's life, such as unemployment or familial conflict, while acute stress refers to sudden changes in her daily routine, such as the sudden death of a spouse, a prenatal diagnosis, or a global event like the COVID-19 pandemic. Objective stress quantifies the amount of stress that the woman experiences, including the length of the event or the extent to which her daily routine is affected. Subjective stress, on the other hand, refers to the woman's psychological reaction to the event, which can vary greatly between individuals.

The following subsections review 18 studies with 2607 mother-child dyads (2368 exposed, 229 controls) on different types of prenatal maternal stress, including acute stress, like the COVID-19 pandemic and receiving a prenatal diagnosis, and chronic stress, such as lifetime adversity and trauma (Table S2).

3.7.1. Acute stress

Ten studies examined acute prenatal maternal stress, including pregnancy-specific stress and stressful events that occurred during but were unrelated to the pregnancy. These studies predominantly assessed women's reaction to the event, or subjective stress, using the PSS.

With regard to brain structure, several studies reported stress-related changes in subcortical brain volume, particularly in the hippocampus, cerebellum, and brainstem [16–18,36,37]. For example, Wu et al. [18] compared the stress levels of women who had received a prenatal diagnosis of fetal congenital heart disease to healthy controls and found that maternal stress was associated with smaller fetal hippocampal and cerebellar volumes, but only in women with the prenatal diagnosis. Similarly, studies investigating perceived maternal stress within the context of the COVID-19 pandemic also found reductions in hippocampal, cerebellar, and white matter volumes [17] as well as increased brainstem volume in the offspring [36]. One study examined the effect of perceived maternal stress on regional cortical thickness in low-risk pregnancies and found cortical thinning in the supramarginal gyrus, middle occipital-, and medial orbital frontal regions, and cortical thickening in the parahippocampal gyrus. However, these findings did not survive multiple comparisons correction [19].

Concerning functional connectivity, studies observed correlations between acute prenatal maternal stress and aberrations in the frontoparietal, temporoparietal, and striatal networks, as well as decreased cerebellar-insular connectivity [38,39]. Rajagopalan et al. [36] found higher prenatal maternal stress during the COVID-19 pandemic to be associated with lower temporal variability in the fetal brain, pointing to reduced resting-state functional connectivity. In neonates, studies found elevated stress levels to correlate with decreased connectivity between the hippocampus and anterior cingulate cortex [40], and with stronger amygdala connectivity to the PFC and the insula [41].

3.7.2. Chronic stress

Eight studies investigated the effect of chronic maternal stress on offspring brain development. Three of those studies recruited participants from the Early Life Adversity, Biological Embedding, and Risk for Developmental Precursors of Mental Disorders (eLABE) cohort. The eLABE study examines maternal exposure to adversity during pregnancy using two constructs: social disadvantage and psychosocial stress. The social disadvantage construct encompasses health insurance status, highest educational level, income-to-needs ratio, area deprivation index, and maternal nutrition. The psychosocial stress construct includes measures of perceived stress, depression, lifetime stress exposure, and racial discrimination.

The common finding across the eLABE reports was that even though social disadvantage and psychosocial stress during pregnancy were positively correlated, psychosocial stress alone did not influence infant brain development [42–44]. Social disadvantage, however, was found to be negatively associated with cortical and subcortical gray and white matter volume [44], and with mean diffusivity in the bilateral dorsal and inferior cingulum bundle, bilateral uncinate fasciculus, and the right fornix [42]. One study, which did not recruit eLABE participants but used similar maternal adversity constructs, also did not find psychosocial stress to correlate with EEG power in six-month-old infants [45].

Three studies used stressful life events questionnaires to assess chronic maternal stress. Regarding structural changes in the infant brain, it was found that maternal stressful life events were positively associated with uncinate fasciculus microstructure [33] but not with gray matter volume [23]. In terms of functional alterations, high levels of chronic maternal stress during pregnancy correlated with weaker connectivity between the amygdala and the PFC [46].

Sanjuan et al. [47] focused specifically on the effect of maternal posttraumatic stress disorder (PTSD) on child outcome. They used the Lifetime Events Checklist for DSM-V (LEC-5) to assess maternal exposure to 16 index traumas but modified the checklist to ask whether each traumatic event occurred prior to, during, or after becoming pregnant. Moreover, the study asked about traumatic birth experiences, such as miscarriage, fetal demise, and stillbirth. Lastly, the researchers administered the Modified PTSD Symptoms Scale (MPSS), with the symptom period restricted to the time since the participant found out that she was pregnant with the study infant. PTSD symptom severity was the sum of the frequency and severity scores for all symptoms. Children's left hemisphere was assessed with resting-state MEG at six months of age. The study found a significant positive correlation between maternal PTSD severity during pregnancy and left anterior temporal resting theta power in six-month-old infants, which the authors interpret as a sign of delayed brain maturation.

In sum, acute prenatal stress seems to particularly affect the structural and functional integrity of the offspring's brain, including smaller hippocampal and cerebellar volumes, weaker connectivity between the cerebellum and the insula as well as between the hippocampus and the anterior cingulate cortex, and stronger connectivity between the amygdala and the PFC.

3.8. Depression

An estimated 6 % of adult women suffer from major depressive disorder, characterized by long-term loss of pleasure or interest in life and a persistently depressed mood [48]. Approximately 20 % of pregnant women experience prenatal maternal depressive symptoms, which includes impaired cognitive functioning, loss of appetite, and feeling sad, irritable, or hopeless [1]. This distinction is important within the context of the present review, as 30 studies investigated the effect of prenatal maternal depressive symptoms and seven studies focused specifically on clinical depression (Table S3). Depressive symptoms were most often assessed with the Edinburgh Postnatal Depression Scale (EPDS), the Center for Epidemiologic Studies Depression Scale (CES—D), and the Beck Depression Inventory (BDI). In cases of clinical depression, either the Structured Clinical Interview for DSM-5 or existing medical records were used.

3.8.1. Depressive symptoms

Thirteen MRI studies investigated the association between prenatal

maternal depressive symptoms and the offspring's brain volume structure. Eight of those studies reported alterations in amygdalar and hippocampal volumes in fetuses and infants, although the direction of change remains contested [17,49–54]. While some studies found larger amygdalar and/or hippocampal volumes [49,50], others reported volume reductions [17]. With regard to cortical thickness, De Asis-Cruz et al. [19] found cortical thickening in the inferior frontal and superior occipital regions in the left hemisphere, but this result did not survive multiple comparisons correction.

Within the GUSTO cohort, five studies found significant interaction effects between prenatal maternal depressive symptoms and the child's genetic risk for major depressive disorder on amygdalar and/or hippocampal volume [31,51–54]. In contrast, two studies from the FinnBrain birth cohort did not find a significant effect of prenatal maternal depressive symptoms or child genotype on infants' amygdalar, hippocampal, or striatal volumes [55,56].

The functional connectome also appears to be affected in prenatally exposed infants, with studies reporting both increased and decreased functional connectivity between various subcortical and cortical regions [40,57–59]. For example, Scheinost et al. [40] found prenatal depressive symptoms to correlate with reduced connectivity between the hippocampus and posterior cingulate cortex, whereas Qiu et al. [59] showed stronger functional connectivity between the amygdala and the left temporal cortex, insula, bilateral anterior cingulate cortex, and ventromedial PFC. Moreover, Posner et al. [57] found increased inverse functional connectivity between the amygdala and the dorsal PFC. Kim et al. [60], on the other hand, did not find prenatal depressive symptoms to have any significant effect on infants' functional connectivity patterns.

Infant studies have further reported associations between prenatal depressive symptoms and microstructural properties of the corpus callosum genu [61], the fornix [30], the uncinate fasciculus [62], the sagittal stratum [63], and the amygdala [64,65]. Studies have also reported decreased structural connectivity between the amygdala and the PFC and a decreased density of local connections in the default mode network [57,66]. One study from the GUSTO cohort found a gene x depression interaction effect on right hippocampal axial- and radial diffusivity [31].

Two EEG studies did not find prenatal maternal depressive symptoms to be predictive of EEG activity between birth and six months of age [35,67]. However, chronic maternal depressive symptoms (i.e. including postnatal period) were linked to altered EEG frontal activity in six-month-old infants [67]. The severity of prenatal maternal depressive symptoms has also been examined, with one study reporting increased network modularity for viewing happy compared to sad faces in infants exposed to high levels of prenatal maternal depressive symptoms and decreased network modularity in infants exposed to low levels of prenatal depressive symptoms [68]. Moreover, one study found the prenatally depressed mother's interaction style with their infant to have an effect on the offspring's brain activity, with infants of withdrawn mothers showing increased right frontal EEG activity and infants of intrusive mothers displaying increased left frontal EEG activity [69]. Finally, one study utilized fNIRS to examine the relationship between prenatal maternal depressive symptoms and infant functional connectivity and found lower connectivity in the frontal-parietal and temporal-parietal regions of the left hemisphere [70].

3.8.2. Clinical depression

Out of the seven studies on clinical depression and selective reuptake inhibitor (SSRI) antidepressants, only one study investigated brain volume in the exposed offspring [71]. This study found depression-exposed infants to have significantly larger subcortical gray matter volumes and smaller midbrain volumes compared to unexposed infants. It did not, however, find volumetric differences between infants of mothers taking SSRI antidepressants and infants of depressed mothers not taking antidepressants. Regarding brain function, one fMRI study found depression-exposed infants to show unchanged or greater activation to sad sounds and reduced or unchanged activation to happy sounds in frontal-limbic regions, including the superior temporal gyrus, amygdala, parahippocampal gyrus, and putamen in the left hemisphere and the medial orbitofrontal cortex in the right hemisphere [72]. Moreover, Rotem-Kohavi et al. [73] found increased functional connectivity in the anterior cingulate cortex, insula, and caudate in depression-exposed infants, and in Heschl's gyrus in SSRI-exposed infants.

In contrast, four studies found only infants prenatally exposed to SSRI antidepressants to show brain aberrations, compared to infants exposed to untreated maternal depression and unexposed infants. Podrebarac et al. [74] reported increased fractional anisotropy in the superior white matter and decreased fractional anisotropy in the basal ganglia and thalamus, and Lugo-Candelas et al. [75] found increased white matter structural connectivity between the amygdala and the insula. A third DTI study reported decreased fractional anisotropy and increased diffusivity in the corticothalamic and corticofugal projection tracts [76]. Finally, Videman et al. [77] found only SSRI-exposed infants to show reduced EEG activity in the frontal lobe.

In sum, depressive symptoms, clinical depression, and SSRI intake during pregnancy can have significant effects on the offspring's brain structure and function. Similar to anxiety and stress exposure, depression appears to particularly target frontal-limbic regions, including the amygdala, hippocampus, cingulate cortex, and PFC.

3.9. Distress

Prenatal maternal distress is an umbrella term for elevated symptoms of anxiety, stress, and/or depression during pregnancy. While the previously reviewed studies examined these symptoms separately, the following 10 studies calculated a distress composite factor (Table S4). Four of those studies combined measures of anxiety, stress, and depression [78–81], whereas the other six studies used only measures of anxiety and depression to create a distress composite [82–87].

With regard to the anxiety/stress/depression composite, one fetal MRI study found a smaller left hippocampal volume in distress-exposed compared to unexposed fetuses [81]. Sex differences were also reported, with prenatal maternal distress positively correlating with bilateral amygdalar volumes and hippocampal-parietal functional connectivity in female, but not male, offspring [78,80]. In contrast, Hendrix et al. [79] found no correlation between prenatal maternal distress and neonatal functional connectivity, regardless of sex.

The anxiety/depression studies all examined structural or functional connectivity. Two studies found increased diffusivity in frontal white matter, and lower fractional anisotropy in female and higher fractional anisotropy in male neonates in the corona radiata, superior-frontal white matter, and the splenium of the corpus callosum [82,83]. Moreover, three fMRI studies showed prenatal maternal distress to correlate with decreased functional connectivity in neonates, especially in amygdalar, prefrontal, and frontoparietal regions [84,86,87]. Only one study using a depression/anxiety composite reported increased functional activity in the medial PFC [85].

4. Discussion

This systematic review summarizes the literature on the effect of prenatal maternal distress, including anxiety, stress, and depression, on fetal and infant brain structure and function. Overall, 71 studies were included, examining 7924 mother-child dyads in total.

Although the studies varied greatly in their methodology, the results generally pointed to alterations in the limbic system, PFC, and insula, particularly in infant offspring (Fig. 2). Regarding brain structure, both fetal and infant studies described reductions in volume, especially in the hippocampus. However, larger volumes, particularly in the amygdala and insula, were reported as well. Infant studies examining white matter microstructure repeatedly found changes in fractional anisotropy and

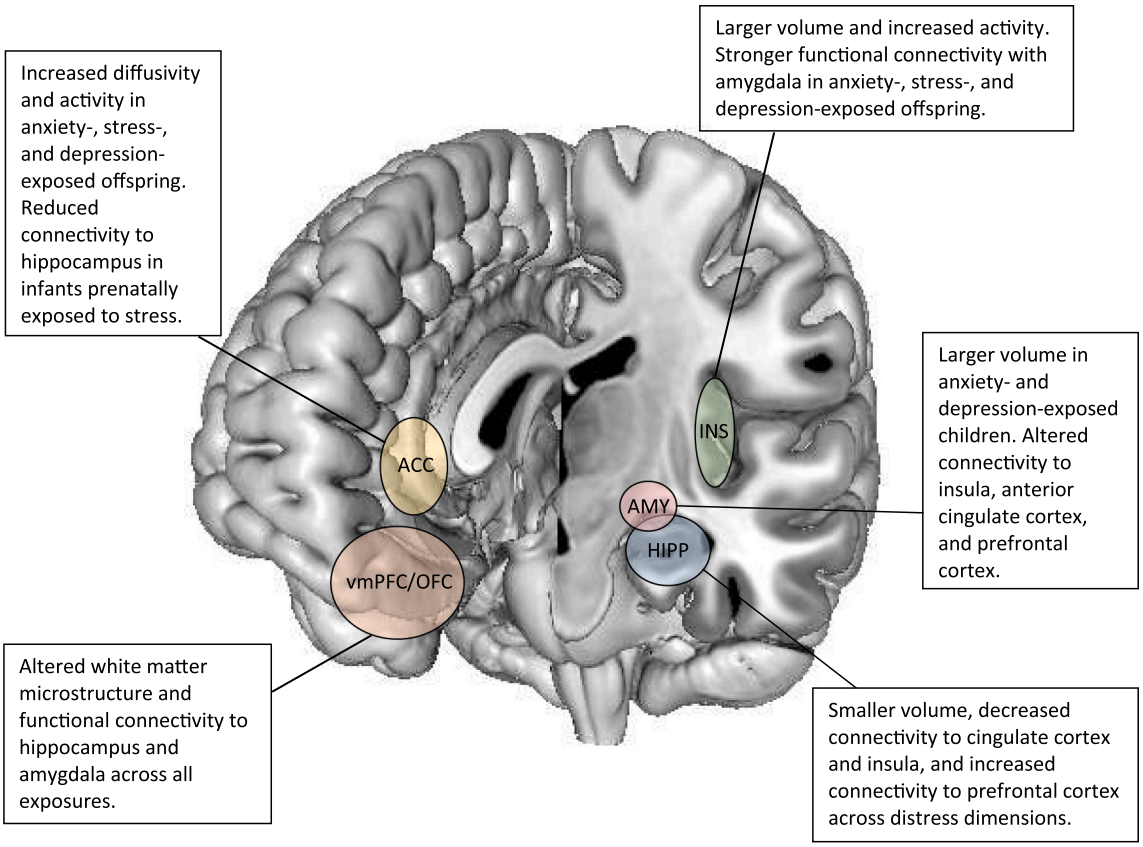

Fig. 2. Summary of findings from neuroimaging studies on prenatal maternal distress. ACC: anterior cingulate cortex; AMY: amygdala; HIPP: hippocampus; INS: insula; vmPFC/OFC: ventromedial prefrontal cortex/orbitofrontal cortex.

diffusivity in the anterior cingulate cortex, insula, hippocampus, amygdala, and PFC. But the direction of change remains contested, as some studies reported increases in fractional anisotropy and diffusivity, while others reported decreases. The functional imaging results are also complex, with fetal and infant studies describing both stronger and weaker connectivity within and between the aforementioned regions.

Moreover, the subgroup of studies that controlled for maternal ethnicity in their analyses did not find ethnic differences in the effect of prenatal maternal distress on fetal or infant brain measures. This finding not only suggests that pregnant women may experience prenatal distress regardless of their ethnic background, but also that offspring brain development may be independent of maternal ethnicity. However, we cannot exclude the possibility that maternal ethnicity can influence the fetal and infant brain, as previous studies have demonstrated associations between ethnicity and early brain development [88–90]. These findings may arise as a consequence of numerous factors, such as access to prenatal care, maternal prenatal discrimination, or acculturation experiences.

4.1. Limbic system

The limbic system is a collection of structures that subserves several key functions, including emotional processing, memory formation, and homeostatic maintenance. While it is still debated which structures should be considered part of the limbic system, it is generally said to include the parahippocampal and cingulate cortex, hippocampal formation, amygdala, septal area, and hypothalamus [91]. In the present review, 33 studies found alterations in hippocampal and amygdalar structure and function in offspring prenatally exposed to maternal distress, which suggests that these brain structures are particularly vulnerable to prenatal stressors. This vulnerability may be attributed to higher fetal exposure to maternal cortisol, which increases during times of distress through upregulation of the maternal hypothalamic-pituitary-adrenal axis activity [92]. This increase in cortisol may differentially activate the amygdala and hippocampus, which have a high density of glucocorticoid receptors, and in turn affect their structure and function [93]. Interestingly, studies in rats have shown that prolonged exposure to glucocorticoids in the hippocampus leads to dendritic atrophy and neuronal death [94] whereas glucocorticoid exposure in the amygdala leads to dendritic hypertrophy and synapse formation [95]. This aligns with the present overall finding of decreased hippocampal volume and increased amygdalar volume in prenatally exposed fetuses and infants. However, glucocorticoid receptors are not the only receptors involved in the effects of maternal anxiety, stress, or depression on the fetal brain. Fetal and adult receptors for sex steroids include those for estrogen, and it is now established that glucocorticoid and estrogen actions occur synergistically [96]. Maternal stress affects levels of fetal sex hormones, which may in turn also influence the development and organization of neural pathways and networks, and the development of certain brain structures, such as the hippocampus and the amygdala [97]. Moreover, structural and functional alterations in the amygdala and hippocampus have repeatedly been associated with anxiety and mood disorders in adults [98]. Taken together, prenatal maternal distress may particularly affect hippocampal and amygdalar development, which in turn may lead to an increased susceptibility to later stress-related disorders in the offspring.

Nine studies also showed exposure to prenatal depression and anxiety to be associated with altered activity in the cingulate cortex, which is a cortical limbic structure that plays an important role in the appraisal, generation, and regulation of emotion [99]. The majority of studies reported increased activity in the anterior cingulate cortex, which is particularly involved in emotion regulation and often implicated in

stress-related disorders [100]. One study also found reduced connectivity between the hippocampus and the posterior cingulate cortex, which constitutes a part of the default mode network that is commonly altered in major depressive disorder [101]. These findings further suggest that prenatal maternal distress may lead to alterations in functional connectivity in the offspring, particularly between regions involved in emotion processing, such as the hippocampus, amygdala, and anterior cingulate cortex.

4.2. Prefrontal cortex

Aside from the limbic system, 18 of the presently reviewed studies also found the PFC to be affected by prenatal distress exposure. The PFC can be divided into three main regions: the dorsolateral PFC, the medial PFC, and the ventral, or orbitofrontal, PFC. However, as the medial and ventral PFC are highly interconnected, they are often referred to as one structure, namely the ventromedial PFC. The dorsolateral PFC has widespread connections to higher-order cortical areas and thus plays an important role in cognitive control and executive functioning. The ventromedial PFC, on the other hand, has extensive connections to lower-order subcortical structures, such as the amygdala, nucleus accumbens, and hypothalamus, and is responsible for emotion regulation [102].

Along with the hippocampus and amygdala, the PFC, and particularly the ventromedial PFC, has one of the highest densities of glucocorticoid receptors. In turn, numerous studies have also found this brain region to be particularly vulnerable to stress exposure, undergoing both structural and functional changes in an attempt to adapt (please see Arnsten [103] for a review). In adults, aberrations in both the dorsolateral and ventromedial PFC have repeatedly been associated with mood and anxiety disorders [104–106]. An altered PFC in fetuses and infants may thus be the brain's early attempt to respond and adapt to external stressors, with the trade-off that these structural and functional adaptations increase the risk for developing a neuropsychiatric illness later on.

4.3. Insula

Finally, 11 of the studies found the insula's structure and/or connectivity to other cortical areas to be altered in fetuses and infants exposed to prenatal maternal distress. The insula, which is located deep within the Sylvian fissure, is interconnected with several areas involved in emotion processing and addiction, including the amygdala, basal ganglia, thalamus, and ventromedial PFC [107]. In adult imaging studies, depression and anxiety have been associated with increased activation of the insula as well as hypo- and hyper-connectivity to the amygdala and anterior cingulate cortex [108,109]. It is therefore not surprising that the present review found a larger, thicker insula as well as increased amygdala-insular structural and functional connectivity to be common in the offspring of distressed mothers. Since abnormal amygdala-insula connectivity is associated with anxiety and mood disorders, a structurally- and functionally altered circuit in the fetal and infant brain may further predict later mental health issues.

4.4. Limitations

This review also has several limitations that may influence the present conclusions. To start, most studies had small sample sizes, which could affect the generalizability of the results. Moreover, the studies differed in the neuroimaging techniques and maternal mental health assessments used, making comparisons difficult. While structural and functional MRI were the most common methods, the analyses often differed between the studies, with some using predefined brain regions and others taking a whole-brain approach. In terms of the mental health assessments, there were commonalities within each mental health category, such as the STAI for anxiety and the EPDS for depression. While these are valid screening tools, they look at one mental health disorder in isolation and do not consider comorbidity. This can be problematic since mental health issues often co-occur [110]. It is important to note, however, that several studies did try to account for comorbidity by screening depressed mothers for substance use, for example. Another limitation is that only three studies formally diagnosed their subjects using the Structured Clinical Interview for DSM-5. Since the severity of symptoms greatly varied within and between studies and different cut-off scores were used, "prenatal exposure" could not be uniformly defined across studies. On top of that, only 18 out of the 71 studies included a separate control group, which is necessary to identify brain alterations that are specific to the effect of prenatal maternal distress on the offspring's development. Finally, we restricted the offspring outcome data to the first 12 months of age to reduce the potential influence of postnatal environmental factors. However, in doing so, we were unable to draw conclusions about the long-term consequences of prenatal maternal distress on children's neurological outcome.

4.5. Future directions

To better understand the influence of prenatal maternal distress on the offspring, future studies should include larger sample sizes and neuroimaging assessments at multiple time points beyond 12 months of age, while controlling for postnatal environmental factors that may also influence brain development. The neuroimaging techniques should also be more homogeneous, both in terms of the paradigm (e.g., resting-state, tasked-based) and in terms of the analysis (e.g., region-of-interest, whole-brain). We also recommend the administration of a standardized, comprehensive mental health screening during pregnancy to account for potential comorbidity of mental health issues. Lastly, there are several mental disorders whose effect on the offspring's development has not been assessed, such as episodic mood disorders (e.g., bipolar disorder), several fear-related disorders (e.g., panic disorder, specific phobia), obsessive-compulsive disorders, dissociative disorders, and personality disorders. Future studies should therefore examine the influence of these mental disorders on infant's brain development as well.

5. Conclusions

This is a comprehensive review of the current literature on the effect of prenatal maternal distress on the offspring's neurological development between the fetal stage and a mean age of 12 months. It was shown that limbic, prefrontal, and insular regions are especially affected, with studies reporting alterations in volume, cortical thickness, white matter microstructure, and functional connectivity within and between these brain areas. These brain regions play important roles in emotion processing and regulation, and abnormalities in these areas have also been reported in adults with mood, anxiety, and stress-related disorders. It is therefore possible that the brain aberrations found in fetuses and infants exposed to prenatal distress have a predictive value for later behavioral and emotional dysregulation. Overall, our review supports the notion that prenatal maternal distress can have a significant effect on the very early brain structure and function of the offspring, underlining the importance of psychological support for pregnant women and early interventions for the affected offspring.

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CRediT authorship contribution statement

Sophie Mandl: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Conceptualization.

Johanna Alexopoulos: Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Stephan Doering:** Writing – review & editing, Supervision, Conceptualization. **Brigitte Wildner:** Writing – review & editing, Software, Methodology, Investigation. **Rainer Seidl:** Writing – review & editing, Supervision. **Lisa Bartha-Doering:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

None declared.

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Appendix A

Table A.1
Risk of bias assessment of each included study.

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD
Acosta, Kantojarvi, Hashempour, et al. (2020)	☺	☺	?	?	☺	☺	?
Acosta, Kantojarvi, Tuulari, et al. (2020)	☺	☺	?	?	☺	☺	?
Acosta et al. (2021)	☺	☺	?	?	☺	☺	?
Acosta et al. (2023)	☺	☺	☹	☺	☺	☺	?
Borchers et al. (2021)	☺	☺	?	☹	☺	☺	?
Canini et al. (2023)	?	☺	?	?	☺	☺	?
Chen et al. (2015)	☺	☺	?	?	☺	☺	?
Craig et al. (2022)	☺	☺	☹	☹	☺	☺	☺
De Asis-Cruz et al. (2020)	☺	☺	?	☺	☺	☺	?
De Asis-Cruz et al. (2023)	☺	☺	?	☺	☺	☺	?
Dean et al. (2018)	☺	☺	?	☺	☺	☺	?
Dean et al. (2021)	☺	☺	?	☺	☺	☺	?
Demers et al. (2021)	☺	☺	?	☺	☺	☺	?
Diego et al. (2006)	☺	☺	☹	☺	☺	☺	?
Donnici et al. (2023)	☺	☺	☹	☺	☺	☺	?
Graham et al. (2020)	☺	☺	☹	☺	☺	☺	?
Groenewold et al. (2022)	?	☺	☺	☺	☺	☺	☺
Hashepour et al. (2023)	☺	☺	?	?	☺	☺	?
Hendrix et al. (2021)	?	☺	?	?	☺	☺	?
Hendrix et al. (2022)	?	☺	☺	☺	☺	☺	☺
Humphreys et al. (2020)	☺	☺	?	?	☺	?	?
Jensen et al. (2021)	☺	☺	?	?	?	☺	?
Jha et al. (2016)	☺	?	☺	☹	☺	?	☺

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD
Kim et al. (2022)	☺	?	?	☹	☺	☺	☺
Lautarescu et al. (2020)	☺	☺	?	☹	☺	☹	?
Lautarescu et al. (2021)	☺	☺	?	☹	☺	☹	?
Lautarescu et al. (2022)	☺	☺	?	☺	☺	☺	☺
Lean et al. (2022)	☺	☺	?	☹	☺	☺	?
Lee et al. (2019)	☺	☺	?	?	☺	☺	?
Lehtola et al. (2022)	☺	☺	?	☹	☺	☺	?
Lu et al. (2022)	☺	☺	?	☺	☺	☺	☺
Lugo-Candelas et al. (2018)	☺	☺	?	☹	☺	☺	?
Manning et al. (2022)	☺	☺	?	☺	☺	☺	?
Maria et al. (2020)	☺	☺	?	☹	☺	☺	?
Marr et al. (2023)	☺	☺	?	☹	☺	☺	?
Moog et al. (2021)	☺	☺	?	☹	☺	☺	?
Na et al. (2023)	☺	☺	☺	☺	☺	☺	☺
Ong et al. (2019)	☺	☺	☺	☺	☺	☺	☺
Parikh et al. (2022)	☺	☺	?	?	☺	☺	?
Podrebarac et al. (2017)	☺	☺	?	?	☺	☺	?
Posner et al. (2016)	☺	☺	☺	☺	☺	☺	☺
Qui et al. (2013)	☺	☺	☺	?	☺	☺	☺
Qui, Anh, et al. (2015)	☺	☺	?	?	☺	☺	?
Qui, Tuan, et al. (2015)	☺	☺	?	?	☺	☺	?
Qui et al. (2017)	☺	☺	?	☺	☺	☺	?
Qui et al. (2021)	☺	☺	?	?	☺	☺	?
Rajagopalan et al. (2022)	☺	☺	?	?	☺	☺	?
Rajasilta et al. (2023)	☺	☺	☺	☺	☺	☺	☺

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PARTICIPANT SELECTION	INDEX TEST	REFERENCE STANDARD
Rifkin-Graboi et al. (2013)	☺	☺	☺	☺	☺	☺	☺
Rifkin-Graboi et al. (2015)	☺	☺	☺	☺	☺	☺	☺
Roos et al. (2022)	☺	☺	☺	☺	☺	☺	☺
Rotem-Kohavi et al. (2019)	☺	☺	?	?	☺	☺	?
Rotem-Kohavi et al. (2021)	☺	☺	?	?	☺	☺	?
Sanjuan et al. (2016)	☺	☺	☺	?	☺	☺	☺
Scheinost et al. (2016)	☺	☺	☺	?	☺	☺	☺
Scheinost et al. (2020)	☺	☺	☺	?	☺	☺	☺
Sethna et al. (2021)	☺	☺	?	?	☺	☺	?
Shephard et al. (2019)	☺	☺	?	?	☺	☺	?
Soe et al. (2016)	☺	☺	?	?	☺	☺	?
Sylvester et al. (2021)	☺	☺	?	?	☺	☺	?
Thomason et al. (2021)	☺	☺	?	?	☺	☺	?
Triplett et al. (2022)	☺	☺	?	?	☺	☺	?
Tuulari et al. (2023)	☺	☺	☺	☺	☺	☺	☺
Van den Heuvel et al. (2021)	☺	☺	?	?	☺	☺	?
Videman et al. (2017)	☺	☺	?	?	☺	☺	?
Wang et al. (2018)	☺	☺	?	☺	☺	☺	?
Wang et al. (2022)	☺	☺	☺	☺	☺	☺	☺
Wu, Kapse, et al. (2020)	☺	☺	☺	☺	☺	☺	☺
Wu, Lu, et al. (2020)	☺	☺	☺	☺	☺	☺	☺
Wu et al. (2021)	☺	☺	?	☺	☺	☺	?
Wu et al. (2022)	☺	☺	☺	☺	☺	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2024.106009.

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