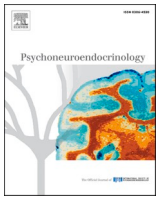
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Perinatal depression, maternal thyroid status and fetus/infant health and development: A systematic review

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ABSTRACT

Background: Thyroid hormones are known to influence both maternal depression and child developmental outcomes, while maternal depression independently affects child outcomes. The potential interaction between thyroid dysfunction and depression in shaping child development remains insufficiently explored. The present study addresses such interplay.

Methods: Following PRISMA 2020 and JBI guidelines, three databases were searched through December 2025 for primary studies on maternal thyroid status, perinatal depression, and child development. Risk of bias (RoB) was assessed using validated tools. Due to clinical and methodological heterogeneity, data were synthesized narratively following SWiM guidelines.

Results: Eleven studies were included. Beyond independent risks for preterm birth and behavioral problems, limited evidence supports a synergistic model, while most studies likely reflect the simple co-occurrence of risks. Maternal thyroid peroxidase antibodies (TPO-Ab) were associated with child externalizing problems exclusively in the presence of clinical depression. High depressive symptoms also attenuated the cognitive benefits of prenatal iodine supplementation. Thyroid status appears to function as a risk moderator rather than a mediator. However, 50% of observational studies presented high RoB, primarily due to participant attrition.

Conclusion: Findings are still scarce to support a synergistic risk model where specific maternal thyroid parameters (i.e. thyroid autoimmunity and iodine status) may moderate the impact of depressive symptoms on child development. Despite the high RoB in half of the studies, results highlight the need for integrated screening protocols. Simultaneously assessing mental health and thyroid status may optimize risk stratification for high-risk mother-infant dyads.

1. Introduction

1.1. The public health burden

Perinatal depression, encompassing prenatal depression (PD) and postpartum depression (PPD), represents a major public health concern, with global prevalence estimates spanning from 3% to 38% (Figueiredo and Conde, 2011; Howard et al., 2014; Hahn-Holbrook et al., 2018; Alsaeed et al., 2023; Vesga-López et al., 2008). PD is particularly prevalent throughout pregnancy, often showing its highest incidence early on; studies indicate that prevalence rates in the first trimester range from 18% to 33% (Figueiredo and Conde, 2011; Guo et al., 2021; Huang et al., 2023; Redinger et al., 2018). Although these rates may fluctuate as gestation progresses, the third trimester remains a period of significant concern, with reported prevalence varying between 11% and 20% across diverse populations (Figueiredo and Conde, 2011; Huang et al., 2023; Zhang et al., 2021; Zikic et al., 2024). The presence of PD is a key variable influencing PPD risk (Gelaye et al., 2016; Liu et al., 2022; O'Hara and McCabe, 2013). Furthermore, severe prenatal depression is linked to adverse obstetric outcomes, including an elevated risk of spontaneous preterm birth (Dadi et al., 2020; Li et al., 2009; Shahhosseini et al., 2012; Venkatesh et al., 2019). Maternal depression during the perinatal period can impair parenting ability, leading to enduring adverse effects on the child's development across emotional, cognitive, and physical domains (O'Hara and McCabe, 2013; Humphreys et al., 2018; Silva Costa et al., 2026). Prenatal depressive symptoms have been consistently associated with child psychopathology, specifically through a positive association with both internalizing and externalizing

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problems (Fisher et al., 2015; Pietikäinen et al., 2020; Silva Costa et al., 2026).

Parallel to the burden of depression, subtle thyroid dysfunction, including subclinical hypothyroidism and the presence of anti-thyroid antibodies, affects up to 5% and 15% of pregnancies, respectively (Basraon and Costantine, 2011), and maternal thyroid status serves as a critical determinant of fetal neurodevelopment. Thyroid hormones are essential for the proper development of the fetal central nervous system, particularly during the first half of pregnancy (Bernal, 2025; Moog et al., 2017; Li et al., 2026). Suboptimal maternal thyroid status has been consistently linked to poor birth outcomes, such as premature delivery, low birth weight, and impaired fetus neurodevelopment (Johns et al., 2018, Korevaar et al., 2017; De Leo and Pearce, 2018), and to cognitive and psychomotor impairment in the infant (Costeira et al., 2011; Huget-Penner and Feig, 2020; Min et al., 2016; Wang et al., 2016). Iodine is a micronutrient required for the synthesis of thyroid hormones, and several studies have associated iodine deficiency with poorer cognitive outcomes of the progeny (Bougma et al., 2013; Grossklaus et al., 2023; Li et al., 2010).

1.2. The interconnection and synergistic hypothesis

The interconnectedness between maternal mental health and thyroid function highlights a shared biological vulnerability. Thyroid hormones are pivotal in mood regulation, and their presence in brain regions like the amygdala is essential for the therapeutic action of antidepressant drugs, which have been shown to modulate regional thyroid hormone concentrations (Henley and Koehnle, 1997; Singh and Sundaresh, 2022). As a potent psychosocial stressor, prenatal depression, often accompanied by physiological anxiety, activates the hypothalamic-pituitary-adrenal (HPA) axis (Gelman et al., 2015; Laurent et al., 2018). This prolonged activation can, in turn, disrupt the hypothalamic-pituitary-thyroid (HPT) axis activity, as high levels of glucocorticoids are known to inhibit the HPT axis (Fekete and Lechan, 2014). Longitudinal evidence also indicates that hyperactivation of the HPA axis, marked by altered cortisol trajectories, is significantly predictive of increased prenatal depressive symptoms throughout pregnancy (Laurent et al., 2018). Concurrently, maternal thyroid status, including subclinical hypothyroidism and iodine deficiency, has been independently associated with increased emotional distress and depressive symptoms (Basraon and Costantine, 2011; Brantsæter et al., 2022).

Given the established link between and independent risks associated with both maternal depression and thyroid dysfunction, it is hypothesized that their co-occurrence may create a synergistic risk profile. Under this framework, maternal thyroid status and depressive symptoms may interact or act as mutual moderators, where the adverse effects on fetal neurodevelopment are amplified when both risk factors coexist. This perspective suggests that the biological burden on the child could be greater than the sum of each factor alone, necessitating an integrated analysis of these interconnected pathways.

1.3. Research gap

Although it is clinically plausible that maternal thyroid dysfunction acts both as a direct cause and as a moderator or risk amplifier in populations already vulnerable due to maternal depressive symptoms, there is a lack of research examining the combined or interactive effects of perinatal depression and suboptimal maternal thyroid status on offspring outcomes.

1.4. Clinical relevance and rationale for joint screening

The current clinical guidelines for perinatal care often recommend separate and sequential screening for depressive symptoms and thyroid dysfunction. However, the emerging evidence suggesting a synergistic risk profile supports the need for a re-evaluation of this compartmentalized approach. Identifying this dual risk is critical, as it allows clinicians to accurately stratify maternal patients into high-risk groups requiring more intensive monitoring and earlier intervention.

1.5. Objectives

The purpose of this systematic review is to comprehensively analyze the current empirical evidence regarding the interaction between maternal depression and thyroid status on infant health and developmental outcomes. Specifically: Evaluate the evidence for an interaction effect (moderation) between perinatal depression and thyroid status on infant health and development; Assess whether thyroid status has a mediating role in the association between depression and infant development (or vice-versa); Determine if the interaction effect varies across specific types of developmental problems (e.g., internalizing versus externalizing problems).

2. Methods

This systematic review was conducted in accordance with the methodological guidance from the JBI Manual for Evidence Synthesis (Aromataris et al., 2024) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement (Page et al., 2021). The study protocol was pre-registered in the Open Science Framework (OSF) Registries (available at: https://osf.io/bh568).

2.1. Eligibility criteria

Inclusion criteria: Empirical primary studies that assessed the association between perinatal depression, maternal thyroid status and fetus/infant health and development, irrespectively of the study design. Maternal thyroid status included suboptimal thyroid hormone levels, presence of anti-thyroid antibodies, iodine deficiency, and/or goiter. Fetus/infant/child health and development included cognitive scores, motor skills, behavioral problems, and psychopathology. For perinatal depression all measures were considered. The established inclusion limit focused on neurodevelopmental outcomes emerging within the first 36 months of life (early childhood). However, neurobehavioral outcomes, such as externalizing behaviors, often emerge gradually during the preschool and school-age periods; and given the nature of fetal programming, studies were included regardless of the child's age at follow-up.

Exclusion criteria: Non-original research (review articles and meta-analyses); Studies focused exclusively on the pharmacological treatment for depression or hormonal conditions without assessing the co-occurrence effects on the child outcome; Studies that did not include both maternal depression and maternal thyroid status as variables in relation to child development; Studies that only assessed adults without a focus on child/offspring outcomes.

2.2. Information sources and search strategy

An electronic search was performed in January 2026 across three databases (PubMed, Web of Science and Scopus) for empirical articles published from inception until December 2025. The search combined key words and controlled vocabulary (MeSh terms) using the following equation: (prenatal OR prenatal OR postnatal OR postpartum OR perinatal OR puerper* OR pregnan*) AND (depress*) AND (thyroid* OR tsh OR t4 OR t3 OR "free t4" OR "free t3" OR "antithyroid antibodies" OR "anti-TG antibodies" OR "anti-TPO antibodies" OR goiter OR goitre OR iodi?e OR thyroxine OR triiodothyronine OR "thyroid-stimulating hormone*" OR thyrotropin OR thyroglobulin OR thyreotropin OR thyroperoxidase OR hypothyroidism OR hyperthyroidism OR ioduria) AND (fetus OR fetal OR infan* OR baby OR babies OR toddler* OR child* OR

newborn* OR neonat* OR progeny). The search was limited to articles published in English, Portuguese, French, and Spanish. The references were managed and duplicates were removed using Rayyan (Ouzzani et al., 2016).

2.3. Selection process

The eligibility process was conducted in two stages. First, the titles and abstracts of the identified records were independently screened by two reviewers (C.S.C. and M.J.C.) following a blinded protocol. Second, the full text of potentially relevant reports was independently assessed for eligibility based on the predefined criteria. Any disagreements between the primary reviewers were resolved through consensus upon further opinion by B.F. and J.A.P.

2.4. Data collection process and data items

Following the final selection, the first and second authors extracted data using a standardized sheet. The extraction was performed by the first author and independently cross-checked by the second author to ensure accuracy. Data items retrieved included: authorship, country, sample size, measurement tools, and key findings. Reported effects were categorized into: 1. Isolated effects (Depression or maternal thyroid status - Child Outcome); 2. Interaction effects (Moderation) (Depression X maternal thyroid status - Child Outcome); and 3. Mediation effects (Depression - maternal thyroid status - Child Outcome, or maternal thyroid status - Depression - Child Outcome).

2.5. Study risk of bias assessment

The methodological rigor and risk of bias (RoB) of the included studies were assessed independently by two authors (C.S.C. and M.J.C.). Due to the inclusion of both observational studies and a randomized controlled trial (RCT), study-specific risk of bias tools were applied. The ROBINS-E tool (Risk of Bias in Non-randomized Studies of Exposures) (Higgins et al., 2024) was utilized to examine biases across seven specific domains (e.g., confounding, selection of participants, measurement of exposure). For the randomized controlled trial, the Cochrane RoB 2 tool (Sterne et al., 2019) was applied to assess the risk of bias across five domains (e.g., randomization process, deviations from intended interventions). The visualization of these assessments was generated using the robvis web app (McGuinness and Higgins, 2021).

2.6. Synthesis methods

Given the clinical and methodological heterogeneity of the included studies, which ranged from varied thyroid indicators, different child outcomes and disparate child assessment ages to diverse study designs (e.g., traditional cohorts, multi-cohort investigations, and case-control studies), a formal meta-analysis was not feasible. A narrative synthesis approach was therefore used to address the primary research questions, following the Synthesis Without Meta-analysis (SWiM) reporting guidelines (Campbell et al., 2020). Results were systematically grouped and summarized based on the type of association reported (e.g., isolated effects, interaction/moderation, or mediation) and the specific child outcome measured (e.g., internalizing vs. externalizing behaviors, cognitive vs. motor development, and physical neonatal morbidity). This approach focused on identifying consistent trends in the reported associations and the role of specific biological markers (including TPO-Ab, thyroid stimulating hormone (TSH), and iodine status) in the interactive effects.

3. Results

3.1. Study selection

In the first stage, the initial database search yielded 731 records. After removing 185 duplicates, the first and second authors independently evaluated the titles and abstracts of the remaining 546 unique records to assess potentially relevant references. Abstracts that did not address the association among perinatal depression, maternal thyroid status, and child development, as well as those involving animal models, were excluded at this stage (n = 491), with an agreement rate of 92%. In the second stage, the 55 articles selected for full-text evaluation were independently assessed by both authors to determine their inclusion based on the predefined criteria. One report (n = 1) could not be retrieved. Of the remaining 54 reports, 43 were excluded because they did not meet all criteria, such as being study protocols (n = 2) or not assessing the triple association of interest (n = 41). The agreement rate at this stage was 91%. In all stages, disagreements were resolved by consensus through discussion. Ultimately, 11 studies met all eligibility criteria and were included (see Fig. 1; Haddaway et al., 2022).

3.2. Study characteristics

The evidence synthesis is summarized in Table 1.

Sample and Location The included studies presented substantial diversity in terms of sample size, geographical setting, and socioeconomic background. Large-scale cohorts were primarily situated in East Asia, with samples including 4663 pregnant women examining prenatal depression and perinatal outcomes (Chen et al., 2021) and 2055 participants involved in machine learning predictive modeling in Chengdu (Zhang et al., 2025); notably, the latter reflected a predominantly urban, educated population with over 65% holding university degrees. Western and North American contexts were represented by a multi-cohort investigation involving 949 participants across the United States and Puerto Rico (Moog et al., 2025), which captured significant internal disparities, ranging from high-income cohorts to disadvantaged samples in Puerto Rico and Archives of Research on Child Health (ARCH) cohort (about 50% of families with low annual incomes). This was complemented by two prospective studies from the Netherlands involving 442 mothers (Endendijk et al., 2017) and 204 mother-neonate dyads (Kooistra et al., 2006), typically representing middle-class community samples. The review also incorporated findings from vulnerable and low-resource global contexts, such as a cluster RCT with 1220 women in Ethiopia facing severe poverty and low schooling (Mohammed et al., 2020), a case-control study with 545 women in the United Arab Emirates (Nandagopal et al., 2025), and two investigations in India, including a prospective study with 400 women (Aishwarya et al., 2025) and a retrospective analysis of 155 records in rural Bhubaneswar (Samanta et al., 2025). Smaller-scale investigations were also represented in Egypt (n = 120; Saleh et al., 2012) and Brazil (n = 51; Bernardi et al., 2024), where most participants belonged to lower economic strata. As such, this review encompasses studies with broad geographical dispersion, representing a variety of healthcare systems, nutritional landscapes, and diverse socioeconomic gradients.

Exposure Measures (Depression and Maternal Thyroid Status) The studies utilized multiple approaches to measure the key maternal exposures: depressive symptoms and thyroid status. Depression was assessed during both the prenatal and postpartum periods. The most common self-report instruments included the Edinburgh Postnatal Depression Scale (EPDS), the Zung Self-Rating Depression Scale (SDS), the Center for Epidemiological Studies Depression Scale (CES-D), and the 9-item Patient Health Questionnaire (PHQ−9). In clinical studies, depression was defined by specific cutoffs (e.g., EPDS≥13), while the multi-cohort study harmonized depression using a continuous T-score measure linked to the PROMIS Depression metric (Moog et al., 2025). In clinical and retrospective settings, depression and anxiety were also

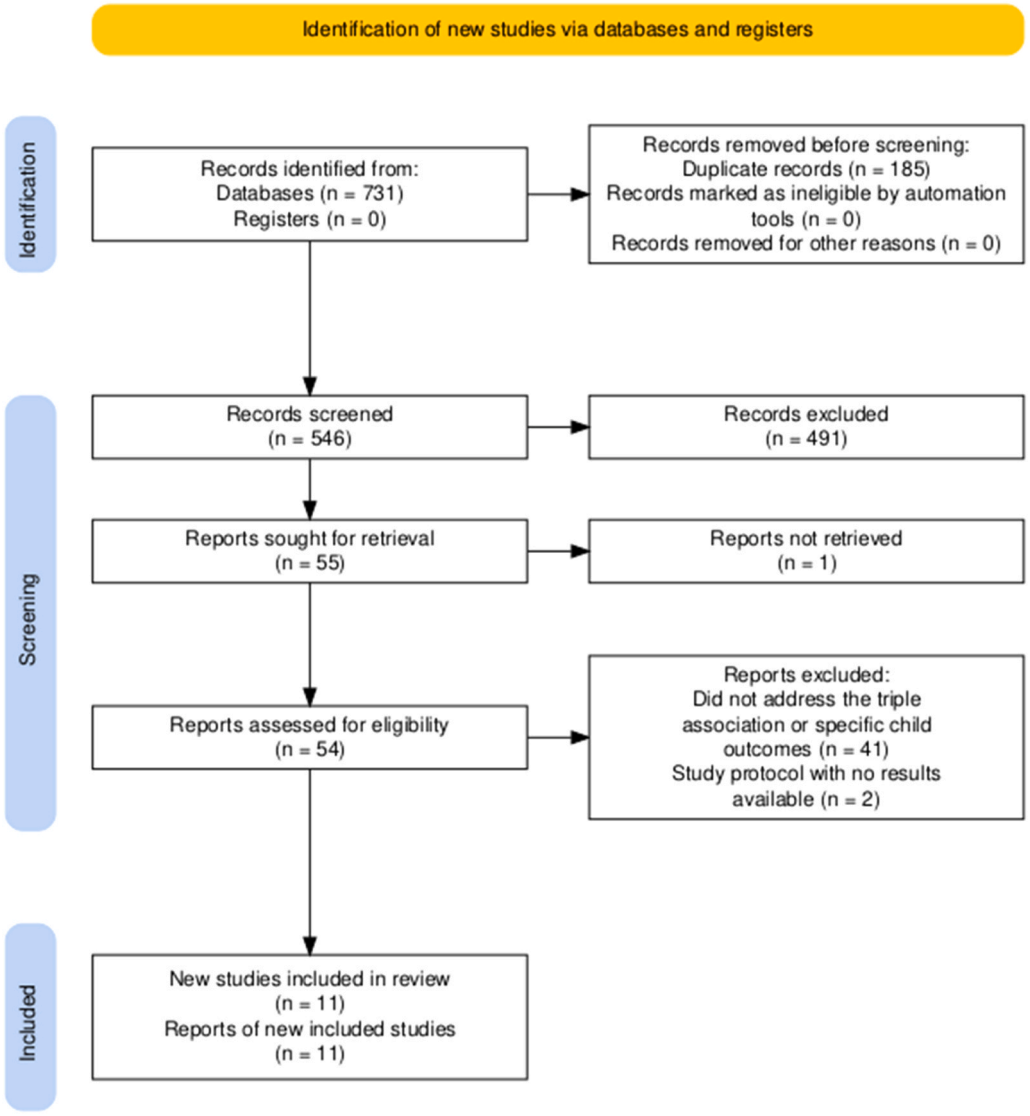


Fig. 1. PRISMA 2020 flow diagram of the study selection.

identified through documented indicators in hospital discharge summaries (Samanta et al., 2025) or via validated self-administered questionnaires specifically addressing postpartum depression (Nandagopal et al., 2025).

Regarding maternal thyroid status, the most frequently measured parameters were TSH, free thyroxine (fT4), and thyroid peroxidase antibodies (TPO-Ab). Measures also included formal diagnoses of thyroid disorders based on medical records and established clinical guidelines (Nandagopal et al., 2025; Samanta et al., 2025). Thyroid function assessment occurred predominantly during the first half of pregnancy ($\leq$ 20 weeks), but also included assessments at specific trimesters (12, 24, and 36 weeks) and postpartum (1 and 3 months). Additionally, Saleh et al. (2012) assessed the triiodothyronine (T3) level one week postpartum, while Mohammed et al. (2020) utilized urinary iodine concentration (UIC) as an indicator of iodine status during pregnancy.

Outcome Measures (Infant/Child Development) Child developmental outcomes were assessed using standardized measures across a broad age range. Internalizing and Externalizing problems (i.e., behavioral problems) were widely assessed using the Child Behavior Checklist (CBCL), with assessment ages ranging from 2 to 7.5 years. Cognitive and motor development were measured with the Bayley Scales of Infant and Toddler Development III (Bayley III) in children between 2 and 13 months old (Mohammed et al., 2020). The neonatal neurobehavioral profile was evaluated using the Neonatal Behavioral Assessment Scale (NBAS), focusing on the orientation cluster, at 3 weeks of age (Kooistra et al., 2006), and the Infant Visuomotor Behavior Assessment Scale was utilized to classify visual fixation abilities in 1-month-old infants (Bernardi et al., 2024). Additionally, clinical studies incorporated neonatal physical outcomes, including birth weight, gestational age at delivery to identify preterm birth, and the presence of neonatal respiratory distress (RDS) or the need for Neonatal Intensive Care Unit (NICU) admission (Samanta et al., 2025; Nandagopal et al., 2025). These outcomes were determined through medical records and clinical observation during the immediate postnatal period.

3.3. Risk of bias assessment

The overall risk of bias assessment is summarized in Fig. 2 (for observational studies, using ROBINS-E) and Fig. 3 (for the RCT, using RoB 2). As shown, all observational studies presented a low risk of bias with respect to post-exposure interventions and selection of the reported result. However, significant concerns were identified in the missing data domain, where 60% of the studies showed some concerns and 20% reached a high risk of bias. Regarding the overall evaluation of observational evidence, 50% of the studies were classified as 'High risk' and 50% as 'Some concerns', primarily driven by limitations in measuring

Table 1
Summary of the Characteristics and Main Findings of Included Studies.

Author (Year)	Study Design & Country	Sample (N)	Maternal Measures (Depression & Thyroid)	Child Outcome & Age of Assessment	Key Findings (Interaction/Main Effects)
Nandagopal et al. (2025)	Case-control; United Arab Emirates	545	Self-administered questionnaire (Stress/PPD); Thyroid disorders	Preterm birth & RDS; Neonatal	**Synergistic Risk Path:** Thyroid disorders independently predicted preeclampsia (aOR 4.34; $p < 0.001$), which was significantly associated with postpartum depression (11.8%) and neonatal RDS (27.5%).
Samanta et al. (2025)	Retrospective observational; India	155	Clinical records (Depression/Anxiety); Maternal Thyroid disorders	Birth weight & NICU stay; Neonatal	**Co-occurrence:** High prevalence of thyroid disorders (31%) and depression (58.7%); preterm birth significantly linked to lower birth weight (49%; $p = 0.032$).
Moog et al. (2025)	Multi-cohort Meta-analysis (ECHO); USA/PR	949	PROMIS (Depression); fT4, TSH, TPO-Ab	Internalizing & Externalizing (CBCL/SDQ); 2–7.5 y	**Synergistic Interaction:** TPO-Ab positively associated with externalizing problems only in children of mothers with clinically relevant depression.
Zhang et al. (2025)	Retrospective (Machine Learning); China	2055	Zung SDS; TSH, TPO-Ab	Birth weight & Apgar scores; Neonatal	**Predictive Reciprocity:** Elevated TSH and low TPO-Ab, alongside adverse neonatal outcomes, predicted postpartum depression (PPD).
Aishwarya et al. (2025)	Prospective Cohort; India	400	EPDS, BDI-II; TSH, fT3, fT4	Fetal distress & Apgar scores; Birth	**Joint Risk:** High depression scores correlated with both maternal hypothyroidism and fetal distress, suggesting cumulative stressor impact.
Bernardi et al. (2024)	Prospective Cohort; Brazil	51	EPDS; Serum T3, T4	Visuomotor behavior (Gagliardo Scale); 1 month	**Main Effect Only:** Higher maternal T4 associated with better visual conduct; no association found between infant visual fixation and depression.
Chen et al. (2021)	Prospective Cohort; China	4663	Zung SDS; Clinical diagnosis (Hyper/Hypo)	Preterm birth & birth weight; Birth	**Co-occurrence:** Severe depression linked to 11x risk of preterm birth; moderate depression co-occurred with gestational hyperthyroidism.
Mohammed et al. (2020)	Cluster RCT; Ethiopia	1220	CES-D; UIC & Goiter	Cognitive, Language, Motor (Bayley III); 2–13 months	**Effect Modification:** High maternal depression attenuated the cognitive benefits of iodized salt intervention (thyroid status).
Endendijk et al. (2017)	Prospective Cohort; Netherlands	442	EDS/EPDS; TSH & fT4 trajectories	Internalizing & Externalizing (CBCL); 23–60 months	**Synergistic Interaction:** Flattened thyroid trajectories associated with more mood symptoms and higher child internalization. TSH in 1st trimester positively linked to attention problems in boys.
Saleh et al. (2012)	Cross-sectional; Egypt	120	EPDS, DSM-IV; Serum T3	Health indicators (weight, Apgar, illness); Neonatal	**Biological Association:** PPD severity positively correlated with T3 levels; depressed group had higher prevalence of low-weight/unhealthy infants.
Kooistra et al. (2006)	Prospective Cohort; Netherlands	204	EPDS, RDC interviews; fT4, TSH, TPO-Ab	Neurobehavioral profile (NBAS); 3 weeks	**Joint Risk:** Both 1st trimester hypothyroxinemia (low fT4) and psychological stress predicted lower neonatal orientation scores.

exposure and addressing missing data. For the single RCT included, the overall assessment indicated 'Some concerns', specifically due to the missing outcome data domain, while all other domains (randomization, deviations from interventions, measurement of the outcome, and selection of the reported result) were rated as low risk.

3.4. What are the isolated effects of depression and thyroid dysfunction on infant development?

Maternal depressive symptoms in the perinatal period were consistently associated with adverse infant outcomes, specifically predicting higher scores on internalizing problems and, to a lesser extent, externalizing behaviors (Moog et al., 2025; Endendijk et al., 2017). This association persisted even when controlling for sociodemographic factors (Moog et al., 2025). In terms of birth outcomes, severe prenatal depression was linked to a significantly elevated risk of spontaneous preterm birth (Chen et al., 2021), as well as lower fetal weight, lower Apgar scores, and fetal distress (Zhang et al., 2025; Aishwarya et al., 2025; Saleh et al., 2012). Additionally, a reciprocal relationship was observed where women experiencing preterm delivery and high-risk neonatal outcomes exhibited higher rates of psychological distress during the postnatal period (Samanta et al., 2025; Zhang et al., 2025). However, no association was found between maternal depression and neonatal visual fixation abilities at 1 month of age (Bernardi et al., 2024).

Regarding maternal thyroid status, indicators of dysfunction, including subclinical hypothyroidism and the presence of anti-thyroid antibodies (TPO-Ab), were linked to developmental challenges (Zhang et al., 2025; Moog et al., 2025; Endendijk et al., 2017). Specifically, studies reported associations between maternal hypothyroxinemia during the first trimester and lower infant orientation scores (Kooistra et al., 2006), while higher TSH levels were linked to attention problems in boys (Endendijk et al., 2017). Beyond neurodevelopmental scores, maternal thyroid disorders were identified as independent predictors for preeclampsia (Nandagopal et al., 2025) and as risk factors for preterm labor and clinical neonatal morbidity (Samanta et al., 2025). When considering the potential effects of subtle variations within the clinical normal range, and after adjusting for sociodemographic factors, Moog et al. (2025) showed that the latter are more robust predictors of child outcomes than subtle euthyroid fluctuations. Finally, biological markers such as elevated TSH and declined TPO-Ab levels were identified as primary predictors for the risk of maternal postpartum depression (Zhang et al., 2025).

3.5. Is there evidence of an interaction effect between perinatal depression and thyroid status on infant development?

(1) Studies testing formal interaction/moderation effects: The synthesis of the included studies provides limited and parameter-specific, rather than generalized, evidence of an interaction effect between maternal thyroid status and perinatal depression. This synergistic risk is most clearly found with respect to thyroid autoimmunity. Specifically, Moog et al. (2025) described that maternal TPO-Ab concentrations were associated with child externalizing problems exclusively in the offspring of mothers with clinical depression. In this cohort, TPO-Ab had no independent effect on child behavior in the absence of depression, suggesting that the risk to fetal and infant development is interactive rather than merely additive.

Another form of interaction was observed regarding nutritional thyroid status. In Ethiopia, Mohammed et al. (2020) found that maternal depression symptoms attenuated the positive impact of

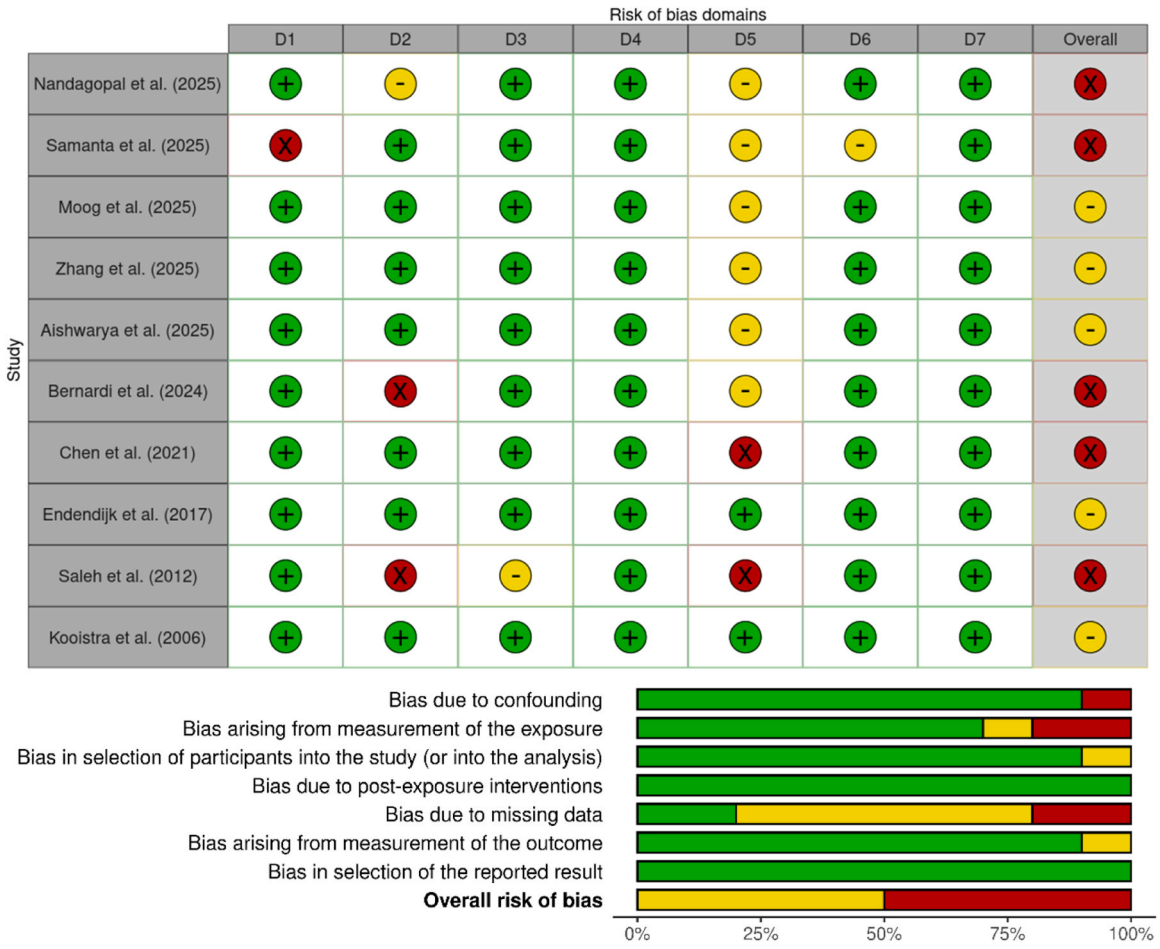


Fig. 2. Risk of Bias Assessment for Observational Studies (ROBINS-E). **Note.** (A) Traffic light plot presenting individual domain judgements for each included study. (B) Summary plot illustrating the percentage of risk of bias across domains. D1: Confounding; D2: Measurement of exposure; D3: Selection of participants; D4: Post-exposure interventions; D5: Missing data; D6: Measurement of outcomes; D7: Selection of reported result. Green (+) = low risk; Yellow (-) = some concerns; Red (X) = high risk.

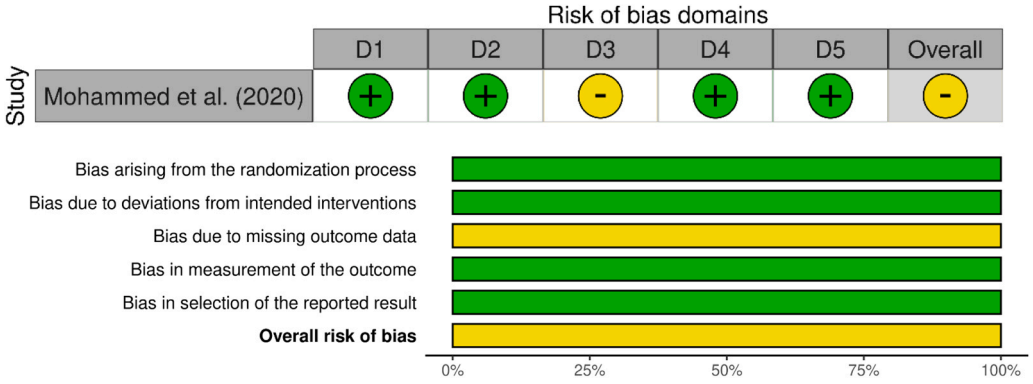


Fig. 3. Risk of Bias Assessment for the Randomized Controlled Trial (RoB 2). **Note.** (A) Traffic light plot presenting individual domain judgements for the included randomized controlled trial. (B) Summary plot illustrating the percentage of risk of bias across domains. D1: Bias arising from the randomization process; D2: Bias due to deviations from intended interventions; D3: Bias due to missing outcome data; D4: Bias in measurement of the outcome; D5: Bias in selection of the reported result. Green (+) = low risk; Yellow (-) = some concerns; Red (X) = high risk.

iodized salt on child cognitive development, suggesting that psychological distress may block the protective benefits of adequate iodine intake.

(2) Studies examining the co-occurrence of exposures: In contrast, other studies highlighted the coexistence of risks without formally confirming an interaction. For instance, Nandagopal et al. (2025) and Samanta et al. (2025) reported that although maternal thyroid disorders and psychological distress are common in high-risk pregnancies, their associations with neonatal complications—such as RDS (affecting 27.5% of preeclamptic pregnancies) and low birth weight—were examined as

independent predictors or main effectors, rather than as interacting or synergistic factors.

(3) Studies demonstrating independent effects: Similarly, while Kooistra et al. (2006) reported that both maternal hypothyroxinemia and anxiety predicted lower neonatal orientation scores, these were identified as independent factors in the regression models.

Finally, gender-specific findings appear limited and specific to thyroid parameters. Endendijk et al. (2017) found that higher first-trimester TSH levels were related to attention problems specifically in boys, though the study did not find an interaction between thyroid trajectories and child sex. These findings emphasize that while the co-occurrence of these conditions is clinically relevant, formal evidence of a synergistic interaction is scarce and parameter-specific, precluding the generalization into a unified synergistic framework based on the current literature.

3.6. Does thyroid status have a mediating role in the association between depression and infant development (or vice versa)?

While evidence for simple, unidirectional mediation was scarce across the 11 included studies (Mohammed et al., 2020; Moog et al., 2025), the synthesis revealed support for complex pathways, often involving moderation rather than direct mediation (Moog et al., 2025).

Regarding the hypothesis that maternal thyroid status mediates the effect of depression, limited evidence for direct significant mediation was reported. Instead, findings from Moog et al. (2025) pointed toward a moderating role; the presence of TPO-Ab did not function as a mediator but rather amplified the effect of depression on externalizing behaviors, acting as a moderator that dictates the magnitude of risk.

A different pattern emerges when considering whether perinatal depression mediates the effect of maternal thyroid status on child outcomes. While formal mediation models were rarely tested, clinical data suggests potential indirect pathways through obstetric complications. Specifically, maternal thyroid disorders were identified as predictors for preeclampsia and preterm labor (Nandagopal et al., 2025; Samanta et al., 2025), conditions which are subsequently associated with increased maternal psychological distress and postnatal depression (Samanta et al., 2025; Zhang et al., 2025). This suggests a feedback loop where thyroid-related physiological stressors may contribute to a depressive environment, indirectly impacting on infant development.

Despite these clinical observations, robust empirical support for a definitive mediating role, either of thyroid status on depression or vice versa, remains limited within the current body of research (Moog et al., 2025; Nandagopal et al., 2025).

3.7. Does the interaction effect vary across specific types of developmental problems (e.g., internalizing vs. externalizing)?

The synthesis reveals that the interaction effect does not manifest uniformly across all types of developmental outcomes. Regarding behavioral domains, the findings suggest that the interactive risk is associated with externalizing behaviors only. When maternal depression co-occurs with thyroid autoimmunity (TPO-Ab), a robust association is found with increased risks for aggression and disruptive behavior (Moog et al., 2025). While higher TSH levels were linked to attention symptoms specifically in boys, no synergy with depression was confirmed for this specific gender-based outcome (Endendijk et al., 2017).

While internalizing problems, such as anxiety, were reliably associated with maternal depression alone, the evidence for a synergistic interaction involving thyroid status on these specific mood-related outcomes was weak (Moog et al., 2025; Endendijk et al., 2017). When considering neonatal physical morbidity, the co-occurrence of thyroid dysfunction—specifically in the context of preeclampsia—and psychological distress was associated with a higher prevalence of acute clinical complications, such as RDS and low birth weight (Nandagopal et al., 2025; Samanta et al., 2025).

4. Discussion

4.1. Summary of main findings and contextualization

The primary objective of this systematic review was to synthesize the evidence concerning the potential interaction between maternal perinatal depression and thyroid status on offspring developmental outcomes. Despite its relevance, this hypothesis remains understudied, underscoring the need for research specifically designed to examine this interaction. The available evidence, here summarized, provides limited, parameter-specific support for a model of synergistic risk, though the broader literature predominantly captures the co-occurrence of independent risks rather than formal synergy. The potential synergistic effect of thyroid function and maternal psychological distress is suggested to impact not only on neonatal morbidity (specifically low birth weight and RDS) (Nandagopal et al., 2025; Samanta et al., 2025) but also on externalizing behavioral problems (Moog et al., 2025).

It also shows, as expected and well documented, that both perinatal depressive symptoms and maternal thyroid dysfunction independently confer risks to the offspring (Pop et al., 1999; Madigan et al., 2018).

4.2. Interpreting the mechanisms: moderation and biological plausibility

From a mechanistic standpoint, while depression alone serves as a powerful psychosocial stressor, its combination with maternal thyroid dysfunction, particularly the presence of TPO-Ab, is hypothesized to heighten biological vulnerability (Chen et al., 2021; Moog et al., 2025). As a marker of thyroid autoimmunity, TPO-Ab often signals chronic immune activation and subclinical inflammation (Chaker et al., 2017), which may reduce the maternal physiological threshold to withstand psychological distress.

This combined endocrine and psychosocial stress likely increases systemic inflammation, potentially impacting on the fetus through two pathways. First, via the HPA axis and placental signalling, it negatively impacts the developing fetal brain (Moog et al., 2025; Ruiz et al., 2003). Second, it can compromise vascular and placental integrity, as evidenced by the higher incidence of preeclampsia and RDS observed in comorbid or high-risk cases (Nandagopal et al., 2025; Samanta et al., 2025).

In this model, the autoimmune/inflammatory component dictates the magnitude by which depressive symptoms translate into developmental harm. The HPA and HPT axes are deeply interconnected; dysregulation in the HPA axis due to chronic stress influences thyroid signalling and potentially reduces fetal circulating thyroid hormones (Lemaire et al., 2000; Zoeller, 2003). The scarcity of evidence for simple mediation models (Moog et al., 2025) reinforces the need to view this pathway as a complex, dynamic interplay of factors rather than a unidirectional cause-and-effect chain. As none of the included primary studies directly measured cortisol, inflammatory markers, or placental function, these biological links remain conceptual hypotheses.

4.3. Heterogeneity in outcomes and methodological diversity

This review highlights a significant heterogeneity in the assessed outcomes, which limits the ability to analyse the data in an aggregated manner, specifically due to the wide diversity of instruments used to evaluate both exposures and developmental domains. Regarding exposures, while the EPDS was the most frequent measure for maternal distress, other studies employed a mix of the Zung SDS, PHQ−9, or structured clinical interviews (e.g., DSM−5), complicating the threshold for "depression" across the sample. Thyroid status was captured through varied markers, ranging from standard TSH and fT4 levels to the specific presence of TPO-Ab, and goiter. As for the assessment of offspring outcomes, while behavioral domains were predominantly evaluated

through parent-report tools like the CBCL or the Strengths and Difficulties Questionnaire (SDQ) (Endendijk et al., 2017; Moog et al., 2025), clinical and physical outcomes relied on objective neonatal records, such as Apgar scores and birth weight metrics, further complicating direct comparisons across these different developmental spheres. This exposure heterogeneity implies that the included studies may not reflect the same underlying biological phenomenon. Maternal TPO-Ab positivity captures a chronic autoimmune and inflammatory pathway. Gestational iodine deficiency reflects a nutritional limitation in thyroid hormone synthesis, whereas standalone TSH or fT4 alterations capture metabolic shifts in homeostasis. These disparate exposures are likely mediated by distinct pathophysiological mechanisms, and the narrative synthesis should not be interpreted as a single, unified biological construct.

Despite this methodological diversity, distinct patterns emerge across the reviewed findings regarding how these combined risks manifest in the offspring. As for neurodevelopment, the combined risk profile showed a markedly stronger association with externalizing behaviors, while the association with internalizing problems was primarily driven by maternal depression alone (Moog et al., 2025). As previously discussed (see Section 4.2), this suggests that the combined effect of endocrine and psychological stress may preferentially disrupt neurodevelopmental processes related to impulse control and executive function (Ghassabian et al., 2011; Modesto et al., 2015). This aligns with neurobiological theories suggesting that early exposure to combined stress hormones and inflammatory signals can alter the structure and function of brain regions like the prefrontal cortex and amygdala, which are critical for behavioral regulation (Lemaire et al., 2000; Zoeller, 2003).

Given the current methodological heterogeneity, it remains unclear whether these findings reflect domain-specific vulnerabilities or a broader, generalized neurodevelopmental vulnerability.

As for immediate clinical outcomes, the co-occurrence of thyroid dysfunction and psychological distress in high-risk pregnancies manifests as acute physical morbidity, including higher rates of RDS and low birth weight (Nandagopal et al., 2025; Samanta et al., 2025). These clinical manifestations likely reflect the compromised vascular and placental integrity associated with comorbid states, where endocrine disruption and maternal stress may synergistically impair fetal growth signalling and nutrient transfer.

4.4. Clinical implications and future directions

This review strengthens the need of targeted studies to address the hypothesis of the synergistic effects of maternal thyroid dysfunction and depression on offspring health. To resolve the identified methodological heterogeneity, future research must rely on more rigorous and standardized designs. Specifically, longitudinal studies should incorporate repeated endocrine and psychological assessments across multiple timepoints in pregnancy to capture dynamic trajectories rather than isolated snapshots, as well as employ standardized developmental outcomes and ensure formal statistical interaction testing to avoid confounding co-occurrence with synergistic effects. Finally, incorporating mechanistic biomarkers, such as inflammatory profiles, placental function indicators, and HPA stress-axis markers, will be critical to clarifying the underlying biological pathways linking maternal thyroid status, perinatal depression, and child development. If these studies confirm the hypothesis of the synergistic effects, they will have clinical implications.

Current clinical guidelines often recommend targeted screening for thyroid disease in pregnancy only for women at high risk (Alexander et al., 2017), while depressive symptoms are managed through separate mental health protocols. The current limited and heterogeneous evidence base does not warrant advocating for an immediate restructuring of clinical guidelines; instead, these insights justify the development of pilot studies to evaluate the feasibility, cost-effectiveness, and logistical viability of integrated screening protocols. Identifying patients with this dual risk within pilot frameworks will allow clinicians to accurately stratify mother-infant dyads into a high-risk category requiring intensified monitoring (Moog et al., 2025; Nandagopal et al., 2025), not only for neurodevelopmental risks but also for obstetric complications (Nandagopal et al., 2025; Samanta et al., 2025). In addition, clinical care of pregnant women should include management of depressive symptoms and of thyroid status (Moog et al., 2025).

4.5. Strengths and limitations

The strength of this review lies in its attempt to integrate evidence from diverse study designs, capturing the complex interplay between perinatal depression, maternal thyroid status, and offspring development. By focusing specifically on this triple association, this review provides a unique perspective that is often missing from research focusing only on individual risks. The inclusion of studies with wide follow-up age ranges, from neonatal neurobehavior to early childhood, was meant to capture the persistent effects of fetal programming.

A significant limitation within the compiled literature is that true statistical interactions have only been formally tested in a minority of the reviewed studies, with much of the current literature focusing instead on the independent effects or simple co-occurrence of maternal risks. Furthermore, none of the included primary research directly quantified cortisol trajectories, inflammatory biomarkers, or placental functioning parameters within a combined framework. Therefore, the proposed synergistic mechanisms remain conceptually hypothetical.

Regarding the quality of the evidence, all observational studies have concerns, half of which presenting high risk — mainly due to participant attrition and missing data (D5). This reflects a common challenge in longitudinal perinatal research, where maternal depressive symptoms may themselves interfere with long-term study engagement and retention (Gordon-Hacker et al., 2022; Zeedyk and Blacher, 2017). Because participant attrition in perinatal cohorts is often non-random and frequently tied to higher depression severity or lower compliance with thyroid monitoring, this missing data domain poses a significant threat to internal validity, potentially distorting or obscuring the true magnitude and nature of the combined risk. These constraints limit confidence in the findings and highlight the need for improved retention and reporting strategies in future research.

Another limitation, which is also a strength, must be acknowledged. The total number of studies included is small, reflecting the novelty of this specific research area and the need for additional studies. The heterogeneity of measurement, including varying cutoffs for depression, different timing of thyroid sampling across trimesters, and diverse child assessment tools, precluded a formal meta-analysis and complicates the establishment of a uniform sensitive window for these interactions. Furthermore, results from studies utilizing indirect nutritional markers (e.g., UIC) must be interpreted with caution, as these reflect recent dietary intake rather than stable thyroid homeostasis. Finally, despite multivariable adjustments in the primary studies, the reliance on observational designs means that residual confounding cannot be entirely dismissed. Collectively, these limitations highlight that while an interactive risk is supported, the precise magnitude and causal pathways require further standardized investigation.

5. Conclusion

This systematic review offers limited preliminary support for the hypothesis that the risk imposed by maternal perinatal depression on offspring development may be amplified by specific altered maternal thyroid status. Rather than a generalized phenomenon, the synthesis points to a restricted model of moderation where specific indicators (namely thyroid autoimmunity and iodine status) act as risk multipliers, while other parameters may simply co-occur without verified synergy. This potential synergy increases the likelihood of adverse outcomes across two distinct domains: immediate clinical morbidity, such as low birth weight and neonatal RDS, and long-term neurodevelopmental

challenges. While current evidence primarily links this synergy to externalizing behavioral problems, a broader neurodevelopmental vulnerability cannot be ruled out.

These findings highlight a critical need to move beyond compartmentalized clinical approaches in future studies

CRediT authorship contribution statement

Cláudia Silva Costa: Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Joana Almeida Palha:** Writing – review & editing, Validation, Supervision, Methodology. **Maria José Costeira:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Bárbara Figueiredo:** Writing – review & editing, Validation, Supervision, Methodology.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

References

Aishwarya, S., Vinodhini, V.M., Renuka, P., Saravanan, R.A., Anuradha, M., Gomathi, T., Amuthavalli, V., 2025. Investigating the impact of endocrine-disrupting compounds on antepartum mental health at the Nexus of genetic insights and maternal-fetal outcomes: A prospective study. General. Hosp. Psychiatry 94, 174–183. https://doi.org/10.1016/j.genhosppsych.2025.03.009.

Alexander, E.K., Pearce, E.N., Brent, G.A., Brown, R.S., Chen, H., Dosiou, C., Grobman, W.A., Laurberg, P., Lazarus, J.H., Mandel, S.J., Peeters, R.P., Sullivan, S., 2017. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 27 (3), 315–389. https://doi.org/10.1089/thy.2016.0457.

Alsaeed, J.K., Zayed, A.M., Buhassan, Z.H., Alhadrami, S.H., Naguib, Y., Husni, M., Naguib, Y.M., 2023. Hyperthyroidism masking depression and panic disorder symptoms during pregnancy: A case report. Cureus 15 (12). https://doi.org/10.7759/cureus.50582.

Aromataris, E., Lockwood, C., Porritt, K., Pilla, B., Jordan, Z., 2024. JBI manual for evidence synthesis. JBI. https://doi.org/10.46658/JBIMES-24-01.

Basraon, S., Costantine, M.M., 2011. Mood disorders in pregnant women with thyroid dysfunction. Clin. Obstet. Gynecol. 54 (3), 506–514. https://doi.org/10.1097/GRF.0b013e3182273089.

Bernal, J., 2025. Thyroid hormones in brain development and function (et al). In: Feingold, K.R. (Ed.), Endotext. MDText.com, Inc.. https://www.ncbi.nlm.nih.gov/books/ (et al).

Bernardi, F.R., Lucion, M.K., Dalle Mole, R., Machado, T.D., Loreto, B.B.L., Farias, B.L., Silveira, P.P., 2024. Relationship between maternal biological features, environmental factors, and newborn neuromotor development associated with visual fixation abilities. Brain Cogn. 180, 106202. https://doi.org/10.1016/j.bandc.2024.106202.

Bougma, K., Aboud, F.E., Harding, K.B., Marquis, G.S., 2013. Iodine and mental development of children 5 years old and under: A systematic review and meta-analysis. Nutrients 5 (4), 1384–1416. https://doi.org/10.3390/nu5041384.

Brantsæter, A.L., Garthus-Niegel, S., Brandlistuen, R.E., Caspersen, I.H., Meltzer, H.M., Abel, M.H., 2022. Mild-to-moderate iodine deficiency and symptoms of emotional distress and depression in pregnancy and six months postpartum–Results from a large pregnancy cohort. J. Affect. Disord. 318, 347–356. https://doi.org/10.1016/j.jad.2022.09.009.

Campbell, M., McKenzie, J.E., Sowden, A., Katikireddi, S.V., Brennan, S.E., Ellis, S., Hartmann-Boyce, J., Ryan, R., Shepperd, S., Thomas, J., Welch, V., Thomson, H., 2020. Synthesis without meta-analysis (SWiM) in systematic reviews: Reporting guideline. BMJ 368, l6890. https://doi.org/10.1136/bmj.l6890.

Chaker, L., Bianco, A.C., Jonklaas, J., Peeters, R.P., 2017. Hypothyroidism. Lancet 390 (10101), 1550–1562. https://doi.org/10.1016/S0140-6736(17)30703-1.

Chen, X.N., Hu, Y., Hu, W.H., Xia, X., Li, X.T., 2021. Risk of adverse perinatal outcomes and antenatal depression based on the zung self-rating depression scale. Reprod. Dev. Med. 5 (01), 23–29. https://doi.org/10.4103/2096-2924.313683.

Costeira, M.J., Oliveira, P., Santos, N.C., Ares, S., Saenz-Rico, B., de Escobar, G.M., Palha, J.A., 2011. Psychomotor development of children from an iodine-deficient region. J. Pediatr. 159 (3), 447–453. https://doi.org/10.1016/j.jpeds.2011.02.034.

Dadi, A.F., Miller, E.R., Bisetegn, T.A., Mwanri, L., 2020. Antenatal depression and its association with adverse birth outcomes in low and middle-income countries: A systematic review and meta-analysis. PLoS. One 15 (1), e0227323. https://doi.org/10.1371/journal.pone.0227323.

De Leo, S., Pearce, E.N., 2018. Autoimmune thyroid disease during pregnancy. Lancet Diabetes Endocrinol. 6 (7), 575–586. https://doi.org/10.1016/S2213-8587(17)30402-3.

Endendijk, J.J., Wijnen, H.A., Pop, V.J., van Baar, A.L., 2017. Maternal thyroid hormone trajectories during pregnancy and child behavioral problems. Horm. Behav. 94, 84–92. https://doi.org/10.1016/j.yhbeh.2017.06.007.

Fekete, C., Lechan, R.M., 2014. Central regulation of hypothalamic-pituitary-thyroid axis under physiological and pathophysiological conditions. Endocr. Rev. 35 (2), 159–194. https://doi.org/10.1210/er.2013-1087.

Figueiredo, B., Conde, A., 2011. Anxiety and depression in women and men from early pregnancy to 3-months postpartum. Arch. Women's. Ment. Health 14 (3), 247–255. https://doi.org/10.1007/s00737-011-0217-3.

Fisher, S.D., Brock, R.L., O'Hara, M.W., Kopelman, R., Stuart, S., 2015. Longitudinal contribution of maternal and paternal depression to toddler behaviors: Interparental conflict and later depression as mediators. Couple Fam. Psychol. Res. Pract. 4 (2), 61. https://doi.org/10.1037/cfp0000037.

Gelaye, B., Rondon, M.B., Araya, R., Williams, M.A., 2016. Epidemiology of maternal depression, risk factors, and child outcomes in low-income and middle-income countries. Lancet Psychiatry 3 (10), 973–982. https://doi.org/10.1016/S2215-0366(16)30284-X.

Gelman, P.L., Flores-Ramos, M., López-Martínez, M., Fuentes, C.C., Grajeda, J.P.R., 2015. Hypothalamic-pituitary-adrenal axis function during perinatal depression. Neurosci. Bull. 31 (3), 338–350. https://doi.org/10.1007/s12264-014-1508-2.

Ghassabian, A., Bongers-Schokking, J.J., Henrichs, J., Jaddoe, V.W., Visser, T.J., Visser, W., Tiemeier, H., 2011. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. Pediatr. Res. 69 (7), 454–459. https://doi.org/10.1203/PDR.0b013e3182125b0c.

Gordon-Hacker, A., Bar-Shachar, Y., Egotubov, A., Uzefovsky, F., Gueron-Sela, N., 2022. Trajectories and associations between maternal depressive symptoms, household chaos and children's adjustment through the COVID-19 pandemic: A four-wave longitudinal study. Res. Child. Adolesc. Psychopathol. 51 (1), 103–117. https://doi.org/10.1007/s10802-022-00954-w.

Grosskläus, R., Liesenkötter, K.P., Doubek, K., Völzke, H., Gaertner, R., 2023. Iodine deficiency, maternal hypothyroxinemia and endocrine disrupters affecting fetal brain development: A scoping review. Nutrients 15 (10), 2249. https://doi.org/10.3390/nu15102249.

Guo, J., Zheng, A., He, J., Ai, M., Gan, Y., Zhang, Q., Kuang, L., 2021. The prevalence of and factors associated with antenatal depression among all pregnant women first attending antenatal care: a cross-sectional study in a comprehensive teaching hospital. BMC Pregnancy Childbirth 21 (1), 713. https://doi.org/10.1186/s12884-021-04090-z.

Haddaway, N.R., Page, M.J., Pritchard, C.C., McGuinness, L.A., 2022. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. Campbell Syst. Rev. 18 (2), e1230. https://doi.org/10.1002/cl2.1230.

Hahn-Holbrook, J., Cornwell-Hinrichs, T., Anaya, I., 2018. Economic and health predictors of national postpartum depression prevalence: a systematic review, meta-analysis, and meta-regression of 291 studies from 56 countries. Front. Psychiatry 8, 248. https://doi.org/10.3389/fpsyt.2017.00248.

Henley, W.N., Koehnle, T.J., 1997. Thyroid hormones and the treatment of depression: an examination of basic hormonal actions in the mature mammalian brain. Synapse 27 (1), 36–44. https://doi.org/10.1002/(SICI)1098-2396(199709)27:1<36::AID-SYN4>3.0.CO;2-E.

Higgins, J.P.T., Morgan, R.L., Rooney, A.A., Taylor, K.W., Thayer, K.A., Silva, R.A., Lemeris, C., Akl, E.A., Bateson, T.F., Berkman, N.D., Glenn, B.S., Hróbjartsson, A., LaKind, J.S., McAleenan, A., Meerpohl, J.J., Nachman, R.M., Obbagy, J.E., O'Connor, A., Radke, E.G., Sterne, J.A.C., 2024. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). Environ. Int. https://doi.org/10.1016/j.envint.2024.108602.

Howard, L.M., Molyneaux, E., Dennis, C.L., Rochat, T., Stein, A., Milgrom, J., 2014. Non-psychotic mental disorders in the perinatal period. Lancet 384 (9956), 1775–1788. https://doi.org/10.1016/S0140-6736(14)61276-9.

Huang, X., Wang, Y., Wang, Y., Guo, X., Zhang, L., Wang, W., Shen, J., 2023. Prevalence and factors associated with trajectories of antenatal depression: a prospective multicenter cohort study in Chengdu, China. BMC Pregnancy Childbirth 23 (1), 358. https://doi.org/10.1186/s12884-023-05672-9.

Huget-Penner, S., Feig, D.S., 2020. Maternal thyroid disease and its effects on the fetus and perinatal outcomes. Prenat. Diagn. 40 (9), 1077–1084. https://doi.org/10.1002/pd.5684.

Humphreys, K., King, L., Choi, P., Gotlib, I., 2018. Maternal depressive symptoms, self-focus, and caregiving behavior. J. Affect. Disord. 238, 465–471. https://doi.org/10.1016/j.jad.2018.05.072.

Johns, L.E., Ferguson, K.K., Cantonwine, D.E., Mukherjee, B., Meeker, J.D., McElrath, T.F., 2018. Subclinical changes in maternal thyroid function parameters in pregnancy and fetal growth. J. Clin. Endocrinol. Metab. 103 (4), 1349–1358. https://doi.org/10.1210/jc.2017-01698.

Kooistra, L., Crawford, S., van Baar, A.L., Brouwers, E.P., Pop, V.J., 2006. Neonatal effects of maternal hypothyroxinemia during early pregnancy. Pediatrics 117 (1), 161–167. https://doi.org/10.1542/peds.2005-0227.
Korevaar, T.I., Medici, M., Visser, T.J., Peeters, R.P., 2017. Thyroid disease in pregnancy: New insights in diagnosis and clinical management. Nat. Rev. Endocrinol. 13 (10), 610–622. https://doi.org/10.1038/nrendo.2017.93.
Laurent, H., Goodman, S.H., Stowe, Z.N., Halperin, M., Khan, F., Wright, D., Knight, B., 2018. Course of ante-and postnatal depressive symptoms related to mothers' HPA axis regulation. J. Abnorm. Psychol. 127 (4), 404. https://doi.org/10.1037/abn0000348.
Lemaire, V., Koehl, M., Le Moal, M., Abrous, D., 2000. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc. Natl. Acad. Sci. 97 (20), 11032–11037. https://doi.org/10.1073/pnas.97.20.11032.
Li, D., Liu, L., Odouli, R., 2009. Presence of depressive symptoms during early pregnancy and the risk of preterm delivery: A prospective cohort study. Human. Reprod. 24 (1), 146–153. https://doi.org/10.1093/humrep/den342.
Li, Y., Shan, Z., Teng, W., Yu, X., Li, Y., Fan, C., Hua, T., 2010. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25–30 months. Clin. Endocrinol. 72 (6), 825–829. https://doi.org/10.1111/j.1365-2265.2009.03743.x.
Li, X., Yao, S., Pan, P., Zhou, J., Wang, J., 2026. Effects of thyroid hormones on brain development: Cytoarchitecture and neurodevelopmental disorders. FASEB J. 40 (2), e71487. https://doi.org/10.1096/fj.202503736R.
Liu, X., Wang, S., Wang, G., 2022. Prevalence and risk factors of postpartum depression in women: A systematic review and meta-analysis. J. Clin. Nurs. 31 (19–20), 2665–2677. https://doi.org/10.1111/jocn.16121.
Madigan, S., Oatley, H., Racine, N., Fearon, R.P., Schumacher, L., Akbari, E., Tarabulsy, G.M., 2018. A meta-analysis of maternal prenatal depression and anxiety on child socioemotional development. J. Am. Acad. Child. Adolesc. Psychiatry 57 (9), 645–657. https://doi.org/10.1016/j.jaac.2018.06.012.
McGuinness, L.A., Higgins, J.P., 2021. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res. Synth. Methods 12 (1), 55–61. https://doi.org/10.1002/jrsm.1411.
Min, H., Dong, J., Wang, Y., Wang, Y., Teng, W., Xi, Q., Chen, J., 2016. Maternal hypothyroxinemia-induced neurodevelopmental impairments in the progeny. Mol. Neurobiol. 53 (3), 1613–1624. https://doi.org/10.1007/S12035-015-9101-X.
Modesto, T., Tiemeier, H., Peeters, R.P., Jaddoe, V.W., Hofman, A., Verhulst, F.C., Ghassabian, A., 2015. Maternal mild thyroid hormone insufficiency in early pregnancy and attention-deficit/hyperactivity disorder symptoms in children. JAMA Pediatr. 169 (9), 838–845. https://doi.org/10.1001/jamapediatrics.2015.0498.
Mohammed, H., Marquis, G.S., Aboud, F., Bougma, K., Samuel, A., 2020. Pre-pregnancy iodized salt improved children's cognitive development in randomized trial in Ethiopia. Matern. Child. Nutr. 16 (3), e12943. https://doi.org/10.1111/mcn.12943.
Moog, N.K., Entringer, S., Heim, C., Wadhwa, P.D., Kathmann, N., Buss, C., 2017. Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience 342, 68–100. https://doi.org/10.1016/j.neuroscience.2015.09.070.
Moog, N.K., Mansolf, M., Sherlock, P., Adibi, J.J., Barrett, E.S., Entringer, S., program collaborators for Environmental influences on Child Health Outcomes, 2025. Maternal thyroid dysfunction and depressive symptoms during pregnancy and child behavioral and emotional problems–an ECHO multi-cohort investigation. J. Affect. Disord. 380, 475–486. https://doi.org/10.1016/j.jad.2025.03.163.
Nandagopal, P., Sanaullah, A.A.R., Nandagopal, S., Wazil, S.M., Muhammed, S.A., Sreejith, A., 2025. Unveiling the risks and outcomes of preeclampsia: A case-control study in the UAE. BMC Pregnancy Childbirth 25 (1), 1247. https://doi.org/10.1186/s12884-025-08448-5.
O'Hara, M.W., McCabe, J.E., 2013. Postpartum depression: Current status and future directions. Annu. Rev. Clin. Psychol. 9 (1), 379–407. https://doi.org/10.1146/annurev-clinpsy-050212-185612.
Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan—a web and mobile app for systematic reviews. Syst. Rev. 5 (1), 210. https://doi.org/10.1186/s13643-016-0384-4.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372. https://doi.org/10.1136/bmj.n71.
Pietikäinen, J.T., Kiviruusu, O., Kylliäinen, A., Pölkki, P., Saarenpää- Heikkilä, O., Paunio, T., Paavonen, E.J., 2020. Maternal and paternal depressive symptoms and children's emotional problems at the age of 2 and 5 years: A longitudinal study. J. Child. Psychol. Psychiatry 61 (2), 195–204. https://doi.org/10.1111/jcpp.13126.
Pop, V.J., Kuijpens, J.L., van Baar, A.L., Verkerk, G., van Son, M.M., de Vijlder, J.J., Vader, H.L., 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin. Endocrinol. 50 (2), 149–155. https://doi.org/10.1046/j.1365-2265.1999.00639.x.
Redinger, S., Norris, S.A., Pearson, R.M., Richter, L., Rochat, T., 2018. First trimester antenatal depression and anxiety: prevalence and associated factors in an urban population in Soweto, South Africa. J. Dev. Orig. Health Dis. 9 (1), 30–40. https://doi.org/10.1017/S204017441700071X.
Ruiz, R.J., Fullerton, J., Dudley, D.J., 2003. The interrelationship of maternal stress, endocrine factors and inflammation on gestational length. Obstet. Gynecol. Surv. 58 (6), 415–428. https://doi.org/10.1097/01.OGX.0000071160.26072.DE.
Saleh, E.S., El-Bahei, W., Del El-Hadidy, M.A., Zayed, A., 2012. Predictors of postpartum depression in a sample of Egyptian women. Neuropsychiatr. Dis. Treat. 15–24. https://doi.org/10.2147/NDT.S37156.
Samanta, S., Ghosh, U., Ghosh, S., Rath, K., Behera, A., Dash, R., Mall, M., 2025. Assessment of determinants and causes of preterm births among postnatal mothers: A retrospective study. Cureus 17 (9). https://doi.org/10.7759/cureus.91731.
Shahhosseini, Z., Esmaeeli Douki, Z., Vaezzadeh, N., Keshavarz, Z., 2012. Maternal depression and preterm delivery. World Appl. Sci. J. 18 (1), 15–20. https://doi.org/10.5829/idosi.wasj.2012.18.01.199.
Silva Costa, C., Pinto, T.M., Field, T., Figueiredo, B., 2026. Low paternal postpartum depression buffers the association between maternal prenatal depression and preschoolers' internalizing and externalizing symptoms. Infant. Ment. Health J. 47 (1), e70070. https://doi.org/10.1002/imhj.70070.
Singh, B., Sundaresh, V., 2022. Thyroid hormone use in mood disorders: revisiting the evidence. J. Clin. Psychiatry 83 (5), 22ac14590. https://doi.org/10.4088/JCP.22ac14590.
Sterne, J.A.C., Savović, J., Page, M.J., Elbers, R.G., Blencowe, N.S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M.S., Eldridge, S.M., Hernán, M.A., Hopewell, S., Hróbjartsson, A., Junqueira, D.R., Jüni, P., Kirkham, J.J., Lasserson, T., Li, T., McAleenan, A., Higgins, J.P.T., 2019. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ 366, l4898. https://doi.org/10.1136/bmj.l4898.
Venkatesh, K.K., Meeker, J.D., Cantonwine, D.E., McElrath, T.F., Ferguson, K.K., 2019. Association of antenatal depression with oxidative stress and impact on spontaneous preterm birth. J. Perinatol. 39 (4), 554–562. https://doi.org/10.1038/s41372-019-0317-x.
Vesga-Lopez, O., Blanco, C., Keyes, K., Olfson, M., Grant, B.F., Hasin, D.S., 2008. Psychiatric disorders in pregnant and postpartum women in the United States. Arch. General. Psychiatry 65 (7), 805–815. https://doi.org/10.1001/archpsyc.65.7.805.
Wang, P., Gao, J., Zhao, S., Guo, Y., Wang, Z., Qi, F., 2016. Maternal thyroxine Levels during pregnancy and outcomes of cognitive development in children. Mol. Neurobiol. 53 (4), 2241–2248. https://doi.org/10.1007/S12035-015-9189-Z.
Zeedyk, S.M., Blacher, J., 2017. Longitudinal correlates of maternal depression among mothers of children with or without intellectual disability. Am. J. Intellect. Dev. Disabil. 122 (5), 374–391. https://doi.org/10.1352/1944-7558-122.5.374.
Zhang, R., Liu, Y., Zhang, Z., Luo, R., Lv, B., 2025. Interpretable machine learning model for predicting postpartum depression: retrospective study. JMIR Med. Inform. 13, e58649. https://doi.org/10.2196/58649.
Zhang, L., Wang, L., Cui, S., Yuan, Q., Huang, C., Zhou, X., 2021. Prenatal depression in women in the third trimester: prevalence, predictive factors, and relationship with maternal-fetal attachment. Front. Public. Health 8, 602005. https://doi.org/10.3389/fpubh.2020.602005.
Zikic, O., Stojanov, J., Kostic, J., Nikolic, G., Tosic Golubovic, S., Simonovic, M., Binic, I., 2024. Depression in the perinatal period: course and outcome of depression in the period from the last trimester of pregnancy to one year after delivery in Primiparous mothers. Medicina 60 (6), 970. https://doi.org/10.3390/medicina60060970.
Zoeller, R.T., 2003. Transplacental thyroxine and fetal brain development. J. Clin. Investig. 111 (7), 954–957. https://doi.org/10.1172/JCI200318236.