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Review

Adverse side effects of maternal levothyroxine consumption in pregnant women with subclinical hypothyroidism: a systematic review study

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Abstract

Introduction: Subclinical hypothyroidism (SCH) during pregnancy is a prevalent endocrine disorder, often managed with levothyroxine therapy. Although levothyroxine (LT4) is widely prescribed to mitigate potential risks associated with SCH, concerns persist regarding its safety profile and possible adverse effects on pregnancy outcomes. This systematic review evaluates the current evidence on the adverse maternal, fetal, and neonatal outcomes linked to levothyroxine use in pregnant women diagnosed with SCH.

Materials and Methods: This systematic review was conducted on original research studies published between 2015 and 2025 that evaluated the adverse effects of levothyroxine use in pregnant women with SCH. Comprehensive searches were performed across PubMed, Web of Science, Scopus, Embase, Cochrane Library, and Google Scholar. Data extraction was independently performed by two reviewers using a standardized checklist, with a third reviewer resolving any discrepancies.

Results: The systematic review encompassed 12 studies totaling 1,952,592 participants (20,010 treated with LT4; 1,932,582 untreated). Preterm labor was the most frequent adverse outcome (reported in six studies), followed by gestational diabetes (three studies). Small-for-gestational-age (SGA) infants, low birth weight (LBW), and preeclampsia each appeared in two studies. Other effects, seizures in children, inadequate gestational weight gain, infant death, premature rupture of membranes, fetal macrosomia, and postpartum hemorrhage, were each noted once. Two studies found no adverse effects.

Conclusion: This review study highlights preterm labor as the most common adverse outcome of LT4 use in pregnancy, followed by gestational diabetes. Repeated observations of SGA infants, LBW, and preeclampsia further highlight risks to fetal growth and maternal health. Less common but serious complications, such as seizures, inadequate weight gain, infant death, premature membrane rupture, fetal macrosomia, and postpartum hemorrhage, were each noted once, while two studies found no adverse effects, indicating that risk may depend on study factors, patient populations.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD420251105434) and Research Registry (UIN: reviewregistry2025) websites.

Keywords: Thyroxine, T4 thyroid hormone, Levothyroxine sodium, Pregnancy, Gestation, Pregnancy outcome, Gestational outcomes, Maternal outcomes, Offspring, Birth outcomes

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Introduction

Subclinical hypothyroidism (SCH) is defined as an elevated thyroid-stimulating hormone (TSH) concentration with normal free thyroxine (FT4) levels, representing the most common thyroid dysfunction during pregnancy (1,2). The prevalence of SCH varies considerably depending on the diagnostic criteria used, affecting approximately 3-15% of pregnant women in iodine-sufficient regions (3). Current diagnostic thresholds remain controversial, with the American Thyroid Association's (ATA's) 2017 guidelines recommending TSH levels above 4.0 mIU/L as the upper reference limit when pregnancy-specific ranges are unavailable, while earlier guidelines suggested lower cutoffs of 2.5 mIU/L (4). Maternal SCH has been associated with various adverse pregnancy outcomes, including increased risks of miscarriage, preterm birth, hypertensive disorders, and potential neurodevelopmental impacts on offspring (3,5).

Levothyroxine (LT4) replacement therapy represents the standard treatment approach for hypothyroidism during

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Implication for health policy/practice/research/medical education

This review underscores preterm labor as the leading adverse outcome linked to levothyroxine (LT4) therapy during pregnancy, with gestational diabetes following in frequency. Also, consistent findings of small-for-gestational-age (SGA) infants, low birth weight (LBW), and preeclampsia further emphasize threats to fetal development and maternal health. Less frequent but serious complications, such as seizures, inadequate maternal weight gain, infant death, premature membrane rupture, fetal macrosomia, and postpartum hemorrhage, each appeared in a single study, while two investigations reported no adverse effects.

pregnancy, with typical dosing ranging from 50-150 mcg daily, adjusted to maintain TSH levels within target ranges (2,6). The primary goal of LT4 therapy is to restore maternal euthyroidism and ensure adequate thyroid hormone availability for fetal development, particularly during the first trimester when fetal thyroid function is not yet established (7,8). However, the decision to treat SCH with levothyroxine remains contentious, as current guidelines present varying recommendations based on thyroid peroxidase antibody (TPOAb) status and TSH levels (1,9). While some studies suggest potential benefits of LT4 treatment in reducing pregnancy complications (4), others have failed to demonstrate consistent improvements in maternal and fetal outcomes (4,9).

Despite the widespread use of levothyroxine in pregnant women with SCH, emerging evidence suggests potential adverse effects associated with maternal LT4 consumption during pregnancy. Recent population-based studies have reported increased risks of preterm birth among offspring of mothers treated with levothyroxine during pregnancy, with some studies indicating higher rates of very preterm and extremely preterm births (10,11). Additionally, concerns have been raised about potential dose-dependent effects and the timing of treatment initiation, as delayed treatment may have minimal benefit while early or excessive treatment might pose risks (12). The conflicting evidence regarding both the benefits and potential harms of levothyroxine treatment in pregnant women with SCH underscores the critical need for a comprehensive systematic review to synthesize available evidence and clarify the risk-benefit profile of maternal LT4 consumption during pregnancy (1,9,13).

Objectives

This study aimed to systematically review and synthesize the available evidence on the adverse pregnancy effects associated with maternal levothyroxine consumption during pregnancy for SCH, including assessments of maternal, fetal, and neonatal outcomes.

Materials and Methods

Study design

This study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for conducting a systematic review (14). This comprehensive systematic review examines original research studies that specifically evaluated the adverse effects of levothyroxine consumption in SCH during pregnancy, analyzing findings from case-control studies, cohort studies, randomized controlled trials, and interventional studies published between 2015 and 2025.

Search strategy

The following databases were systematically searched to identify relevant studies: PubMed, Web of Science, Scopus, Embase, Cochrane Library, and Google Scholar. The search strategy incorporated Medical Subject Headings (MeSH) and related keywords, including levothyroxine sodium, LT4 thyroid hormone, Thyroxin, pregnancy, pregnancy outcomes, gestational outcomes, maternal outcomes, offspring, birth outcomes, congenital abnormalities, perinatal outcomes, premature birth, and preeclampsia. Studies published between January 2015 and June 2025 were considered, with no restrictions on language or place of publication. The titles and abstracts of the identified studies were independently reviewed by two investigators, followed by a full-text assessment to establish their eligibility for inclusion.

The following demonstrates an example of a search strategy in PubMed: ((((((((((((levothyroxine sodium[Title/Abstract]) OR (T4 thyroid hormone[Title/Abstract])) OR (Thyroxin[Title/Abstract])) AND (pregnancy[Title/Abstract])) OR (pregnancy outcome[Title/Abstract])) OR (gestational outcomes[Title/Abstract])) OR (maternal[Title/Abstract])) OR (maternal outcomes[Title/Abstract])) OR (offspring[Title/Abstract])) OR (birth outcomes[Title/Abstract])) OR (congenital anomaly[Title/Abstract])) OR (perinatal outcome[Title/Abstract])) OR (premature birth[Title/Abstract])) OR (preeclampsia [Title/Abstract]).

PICO component

Population (P): Pregnant women with SCH who are consuming levothyroxine during pregnancy. This population specifically includes:

- Women diagnosed with SCH during pregnancy (elevated TSH levels with normal free T4)
- Pregnant women of reproductive age receiving levothyroxine therapy
- Pregnant women across different gestational ages (first, second, and third trimesters)
- Women with varying severity of SCH based on TSH levels

Intervention (I)/Exposure: Levothyroxine consumption/administration during pregnancy. This intervention encompasses:

- Oral levothyroxine replacement therapy at various dosages
- Treatment initiated at different gestational periods

(preconception, first trimester, second trimester, third trimester)
- Different dosing regimens and adjustment protocols
- Levothyroxine as monotherapy for SCH management

Comparison (C): The comparison groups include:
- Pregnant women with SCH receiving no levothyroxine treatment (untreated control group)
- Euthyroid pregnant women (normal thyroid function)
- Placebo-controlled groups in randomized trials
- Women receiving different levothyroxine dosing strategies
- Matched cohorts without treatment

Outcome (O): Adverse pregnancy effects and related outcomes, including:
- Pregnancy outcomes
- Maternal Outcomes
- Fetal/Neonatal outcomes

Eligibility criteria

For this systematic review, studies were included if they were original research articles (case-control, cohort, randomized controlled trials, or interventional studies) published between 2015 and 2025, specifically evaluating the adverse pregnancy effects of levothyroxine consumption in women with SCH during pregnancy. Eligible studies needed to report on at least one maternal, fetal, or neonatal outcome associated with levothyroxine use for SCH in pregnancy. Studies were excluded if they were reviews, meta-analyses, case reports, editorials, animal studies, or studies focusing on non-pregnant populations. Additionally, studies without a clear assessment of levothyroxine exposure or lacking relevant outcome data were excluded.

Quality assessment

The quality of the included studies was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (15). This assessment guideline consists of 22 items, with each item scored up to 2 points, resulting in a cumulative score that reflects the overall study quality. Studies were categorized as follows:
- Poor quality: score below 15
- Moderate quality: score between 16 and 30
- High quality: score above 30

Only studies rated as moderate or high quality were included in our review. Studies classified as poor quality were excluded from the analysis.

Data extraction

Data was extracted by two investigators, independently using a checklist that included the authors' name, study design, publication year and country, studied population, sample size, study objectives, study results, and adverse effects of LT4, with a third reviewer consulted to resolve any disagreements.

Results

The systematic review study selection process began with the identification of 897 studies from initial database searches. After removing 378 duplicate studies, 519 studies were screened for eligibility. During the screening phase, 381 studies were excluded, leaving 138 studies for full-text retrieval. However, 101 studies could not be retrieved, resulting in 37 studies being assessed for eligibility. Following detailed assessment, 25 studies were excluded due to various reasons, including studies with designs of reviews, meta-analyses, case reports, editorials, and animal studies; studies focusing on non-pregnant populations; studies without a clear assessment of levothyroxine exposure; studies lacking relevant outcome data; and poor-quality studies. Ultimately, 12 studies met all inclusion criteria and were included in the final systematic review (Figure 1).

A total of 12 studies were included, published between 2016 and 2024. The combined sample size across all 12 studies was 1,952,592 participants, of whom 20,010 received LT4 treatment and 1,932,582 did not. Study designs comprised retrospective and prospective study (n = 1), cohort (n = 2), retrospective cohort (n = 4), prospective observational (n = 1), retrospective observational (n = 2), case-control (n = 1), and observational (n = 1). Studies were conducted in China (n = 3), Hong Kong (n = 2), Canada (n = 2), the United States of America (USA; n = 2), India (n = 1), Finland (n = 1), and Denmark (n = 1). The results indicated that preterm labor was the most commonly reported adverse effect, appearing in six studies, followed by gestational diabetes in three studies. Small-for-gestational-age (SGA) and low birth weight (LBW) each featured in two studies, as did preeclampsia. All remaining adverse effects were noted in a single study: seizure in children, inadequate gestational weight gain, infant death, premature rupture of membranes, fetal macrosomia, and postpartum hemorrhage. Two studies explicitly reported no adverse effects (Table 1).

Discussion

Our findings from this systematic review study indicated that among the reported adverse effects associated with maternal LT4 treatment in SCH pregnant women in the included studies, preterm labor was the most common adverse outcome in pregnancy, followed by gestational diabetes. Our results also indicated that SGA infants, LBW, and preeclampsia, which were in the next rank, highlight risks to fetal growth and maternal health. Less common adverse effects included seizures, inadequate weight gain, infant death, premature membrane rupture, fetal macrosomia, and postpartum hemorrhage. The predominance of preterm birth in our review aligns with several large-scale syntheses that have reported modest but significant reductions—or no clear benefit—in preterm delivery with LT4 therapy for SCH. Beijn et al pooled seven randomized and six observational studies

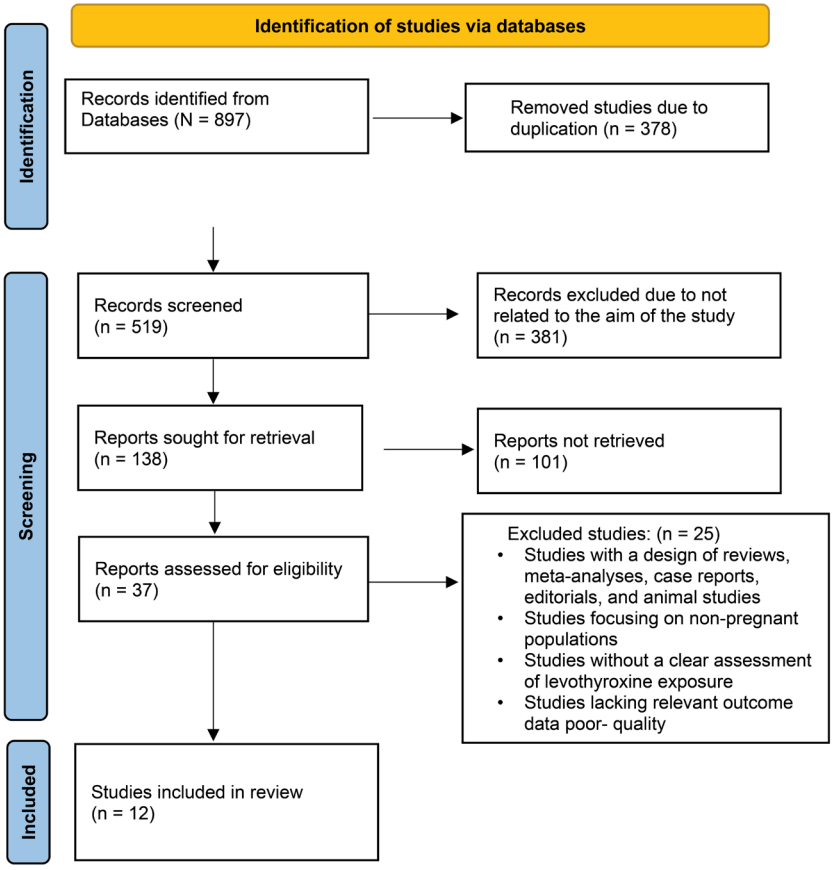

Figure 1. PRISMA flowchart of the study selection.

and found no statistically significant risk difference for preterm delivery after treatment (RR 0.92, 95% CI 0.71–1.19) (2). A 2024 meta-analysis by Sankoda et al, limited to randomized trials, likewise showed neutral effects overall, but a subgroup with baseline TSH >4 mIU/L experienced fewer preterm births (RR 0.47, 95% CI 0.20–1.10) (12). Against this backdrop, our finding that preterm labor remains the most frequent adverse event underscores that LT4 therapy does not fully mitigate prematurity risk. In contrast, earlier aggregated data suggested a protective effect on preterm birth when SCH is defined using the 2011—rather than 2017—ATA thresholds (9); these discrepant patterns likely reflect evolving diagnostic cut-offs and heterogeneous treatment timing across trials.

Gestational diabetes emerged as the second most common adverse outcome in our analysis, echoing increasingly consistent signals that LT4 exposure may predispose to dysglycemia in pregnancy. A retrospective cohort noted a three-fold rise in gestational diabetes among LT4-treated SCH women versus euthyroid controls (OR 3.43, 95% CI 1.12–10.56) (19). Although earlier meta-analyses found no effect on gestational diabetes incidence (RR 0.80, 95% CI 0.51–1.25) (28), those pooled studies rarely stratified by treatment initiation before 9 weeks' gestation—an interval now implicated in altered glucose metabolism (29). Our observation that growth-related outcomes (SGA and LBW) cluster just behind preterm birth is consistent with reports that LT4 does not significantly change birth-weight distributions overall (28), yet may confer modest protection against fetal growth restriction in antibody-positive cohorts (30). The intermediate ranking of preeclampsia parallels pooled risk estimates hovering around unity (RR 1.10, 95% CI 0.61–1.97) (28), suggesting no decisive benefit or harm. Rarer sequelae such as seizures, membrane rupture, and postpartum hemorrhage have been individually described but remain too infrequent for robust synthesis; their appearance in our dataset likely reflects expanded surveillance rather than causal attribution.

Overall, evidence indicates that while LT4 therapy is widely prescribed for SCH in pregnancy, its impact on major obstetric and neonatal endpoints is nuanced. Our review corroborates previous syntheses showing limited efficacy in preventing preterm birth and equivocal effects on fetal growth and hypertensive disorders, while drawing attention to a possible increase in gestational diabetes risk in treated women. These findings support a more individualized approach: benefits may outweigh risks when TSH exceeds 4 mIU/L or thyroid autoimmunity co-exists, yet routine treatment of milder SCH could expose mothers to glucose dysregulation without clear obstetric gain. Future randomized trials employing uniform 2017

Table 1. Baseline characteristics of included studies

Author's name	Publication year	Study design	Country	Sample size		Population	Objective	Results	Adverse effects of LT4
				Treated-LT4	Untreated-LT4				
Gao et al (16)	2024	Retrospective and prospective study	China	1342	3028	Chinese pregnant women	Assessing the correlation between maternal LT4 consumption and some adverse pregnancy outcomes	LT4 treatment significantly decreased miscarriage, increased the risk of the infant's SGA, and preterm labor.	Infant's SGA and preterm labor
Ge et al (17)	2023	Cohort	Hong Kong	3044	525,299	Mother-child pairs	Correlation of maternal LT4 treatment and their children's seizure risk	Significantly higher risk of seizure was found in the LT4-treated mothers during pregnancy compared to euthyroid mothers.	Seizure in children
Oprea et al (18)	2022	Retrospective cohort	Canada	250	500	Singleton pregnant women	Effect of LT4-treated SCH on delivery outcomes	LT4-treated during pregnancy is not a significant risk factor for cesarean delivery	NR
Dash et al (19)	2022	Prospective observational	India	54	1058	Women with a singleton pregnancy	Assessing LT4 effectiveness in pregnancy outcomes	LT4 treatment in SCH patients was not significantly correlated with pregnancy loss, gestational hypertension, IUGR, LBW, and preterm labor; however, increased gestational diabetes.	Gestational diabetes
Ge et al (20)	2022	Cohort	Hong Kong	2125	420031	Mother-child pairs	The correlation between maternal LT4 consumption and infant birth and neurological outcomes	Significantly higher preterm birth in LT4-treated mothers and no significant difference in SGA, ADHD, and ASD compared to LT4-untreated.	Increasing preterm birth
Lemieux et al (21)	2021	Retrospective cohort	Canada	3454	5225	Pregnant women who were under treatment with LT4 before pregnancy	The correlation between LT4 treatment levels and adverse pregnancy outcomes	Overtreatment of LT4 (TSH < 0.10 mIU/L) was associated with preterm labor, while overt undertreatment (TSH ≥ 10.00 mIU/L) showed no correlation with adverse pregnancy or neonatal outcomes	Preterm labor
Han et al (22)	2021	Retrospective observational	China	165	660	SCH women	Evaluate the effectiveness of LT4 in SCH women in pregnancy	Inadequate GWG, premature delivery, LBW, and infants SGA in the LT4-treated women with SCH were higher than in EU women. No significant differences were found between the groups regarding gestational diabetes and hypertension, postpartum hemorrhage, and abortions.	Inadequate GWG, premature delivery, LBW, and infants with SGA

Table 1. Continued

Author's name	Publication year	Study design	Country	Sample size		Population	Objective	Results	Adverse effects of LT4
				Treated-LT4	Untreated-LT4				
Lintula et al (23)	2020	case-control	Finland	149	2359	Original preeclamptic women	The correlation between LT4 consumption and preeclampsia	LT4 consumption in pregnancy significantly increased the risk of developing preeclampsia by 1.5 times the risk in LT4-treated patients compared to untreated.	Development of preeclampsia
Maraka et al (24)	2017	Retrospective cohort	USA	843	4562	Pregnant women with SCH	Evaluating the LT4 effectiveness in pregnant women with SCH	LT4 treatment significantly reduced pregnancy loss but increased preterm labor, gestational diabetes, and preeclampsia	Preterm labor, gestational diabetes, and preeclampsia
Schurmann et al (25)	2016	Retrospective observational	Denmark	8318	969303	Pregnant women from Danish registries between 1995 and 2010	To examine the impact of fetal exposure to ATD and LT4 on GA, birth weight, birth length, head circumference, and the prevalence of congenital anomalies.	Infants exposed to ATD had similar head circumference, rates of live births and congenital anomalies as non-exposed pregnancies, but were more likely to be born very preterm, have higher infant mortality, and present with lower birth weight and length for gestational age.	Preterm labor, infant death, and present with lower birth weight and length for gestational age
Ju et al (26)	2016	Observational	China	184	273	Pregnant women with SCH	Assessing the effectiveness of L-T4 treatment duration on pregnancy outcomes	L-T4 treatment for less than 4 weeks significantly reduced the risk of PROM, gestational diabetes, fetal macrosomia, and postpartum hemorrhage compared to treatment durations of 4-8 weeks and greater than 8 weeks	PROM, gestational diabetes, fetal macrosomia, and postpartum hemorrhage
Maraka et al (27)	2016	Retrospective cohort	USA	82	284	Pregnant women with SCH	Evaluation of LT4 treatment in SCH women during pregnancy	Patients under treatment with LT4 had fewer miscarriages, LBW offspring, and no neonates with a 5-minute Apgar score less than 7	NR

LT4: Levothyroxine; SGA: Small for gestational age; ADHD: Attention-deficit/hyperactivity disorder; ASD: Autism spectrum disorder; SCH: Subclinical hypothyroidism; GWG: Gestational weight gain; LBW: low birth weight; IUGR: Intra-uterine growth restriction; ATD: Anti-thyroid drugs; GA: Gestational age; NR: Not reported; TSH: Thyroid simulation hormone; PROM: Premature rupture of fetal membranes.

ATA criteria, early-pregnancy enrollment, and metabolic monitoring are essential to delineate patient subgroups that derive net advantage from LT4 supplementation.

Conclusion

In conclusion, the collective evidence from this systematic review study highlights preterm labor as the predominant adverse outcome associated with LT4 exposure during pregnancy, with gestational diabetes also occurring at a notable frequency; the recurrent findings of SGA, LBW, and preeclampsia underscore persistent risks to fetal growth and maternal health, while the sporadic reports of seizures, inadequate gestational weight gain, infant death, premature rupture of membranes, fetal macrosomia, and postpartum hemorrhage illustrate a diverse spectrum of less common but serious complications, yet the fact that two investigations observed no adverse effects suggests that the overall risk profile may vary according to study design, population characteristics, or treatment protocols, warranting further targeted research to delineate which patients are most vulnerable and how LT4 therapy can be optimally managed to minimize harm.

Limitations of the study

This systematic review has several limitations that should be considered when interpreting its findings. First, there was considerable heterogeneity among the included studies in terms of SCH diagnostic criteria, sample size, LT4 dosing, timing of treatment initiation, and definitions of adverse outcomes, limiting the comparability and generalizability of results. Additionally, most of the included studies were observational, making them susceptible to residual confounding factors such as maternal comorbidities and socio-demographic variables. Although multiple databases were searched without language limitations, the review is still subject to publication bias, as studies with negative or null findings may have been underrepresented. Inconsistent or selective reporting of adverse outcomes across studies further complicates data synthesis. Moreover, variation in TSH thresholds for diagnosing SCH and differing levothyroxine treatment protocols among studies may have influenced the outcomes. The exclusion of poor-quality studies, while improving methodological rigor, may also have led to the omission of potentially relevant data. Lastly, many studies lacked long-term follow-up, providing limited insight into the enduring effects of in utero levothyroxine exposure on child development.

Authors' contribution

Conceptualization: Samaneh Saghafian Larijani nd Hosna Mirfakhraee.
Data curation: Samaneh Saghafian Larijani and Roshana Saghafian Larijani.
Investigation: Roshana Saghafian Larijani and Hosna Mirfakhraee.
Methodology: Roshana Saghafian Larijani.
Project management: Roshana Saghafian Larijani.
Supervision: All authors.
Visualization: Hosna Mirfakhraee.
Writing–original draft: All authors.
Writing–review and editing: all Authors.

Ethical issues

This investigation has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD420251105434) and Research Registry with Unique Identifying Number [UIN] of reviewregistry2025. Besides, the authors have observed ethical issues (including plagiarism, data fabrication, and double publication).

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized AI (Perplexity.ai and Grammarly.com) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the accuracy and content of the publication.

Conflicts of interest

The authors declared no conflict of interest

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