RESEARCH PAPER

Prevalence and Risk of Thyroid Disorders in Reproductive-Age Women Associated with Iron, Selenium, and Iodine Imbalance: A Systematic Review and Meta-Analysis

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ABSTRACT

Background. Thyroid disorders are highly prevalent among women of reproductive age, yet their micro nutritional determinants remain incompletely characterized. Iodine, iron, and selenium each contribute to thyroid hormone synthesis, peripheral conversion, and autoimmune regulation through distinct biochemical mechanisms; however, their independent and combined effects have not been simultaneously quantified in a primary-data-only meta-analysis. The present study aimed to provide pooled effect size estimates for the associations between iron deficiency and hypothyroidism, and between selenium deficiency and thyroid autoimmunity, in reproductive-age women.

Methods. Four electronic databases (PubMed, Scopus, Google Scholar, ScienceDirect) were searched from inception to December 2024. Only primary studies were eligible; secondary literature (reviews, meta-analyses) was excluded per protocol. "Risk of bias was assessed using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool 2.0 for randomised controlled trials". Odds ratios (OR) and relative risks (RR) were pooled under random-effects models (DerSimonian-Laird). "Leave-one-out sensitivity analysis assessed estimate stability". Meta-regression evaluated pre-specified moderators: geographic region, deficiency severity, study design, and co-existing iodine status. Funnel plot asymmetry was assessed by Egger's test.

Results. Fourteen primary studies met the inclusion criteria. Iron deficiency was "associated with a substantially elevated risk of hypothyroidism (pooled OR = 2.43, 95% CI: 1.71–3.46; $I^2 = 62\%$; $p < 0.001$)". Selenium deficiency was associated with "increased risk of thyroid autoimmunity (pooled RR = 1.89, 95% CI: 1.34–2.67; $I^2 = 48\%$; $p < 0.001$)". Leave-one-out analysis confirmed that no single study materially altered either pooled estimate. Meta-regression identified geographic region (India versus international; $\beta = 0.47$, $p = 0.009$) and deficiency severity ($\beta = 0.39$, $p = 0.014$) as significant moderators of heterogeneity in the iron analysis. This is a systematic review which, in advance of the data extracted, was not entered into PROSPERO. This is a methodological limitation and will be acknowledged in the Limitations section (Section 5.5). Eligibility criteria and analytic decisions were established before the data were extracted, and there were no post-hoc changes to the analytic plan. There was no conclusive evidence of publication bias using funnel plot inspection or Egger's tests for the iron ($p = 0.19$) and selenium ($p = 0.31$) results.

Conclusion. Iron and selenium deficiency are individually related to thyroid dysfunction in women of reproductive age. Mechanistic evidence is organised in a hypothesis-driven Micronutrient Interaction Model in the Thyroid Axis (MIMTA) that aims at making predictions for future empirical research. Three tier screening algorithm, sequential combined-supplementation protocol and public health translation model for India presented.

Keywords: Thyroid disorders; iron deficiency; selenium deficiency; iodine imbalance; hypothyroidism; autoimmune thyroiditis; meta-analysis; reproductive-age women; India.

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1. INTRODUCTION

Thyroid disorders are among the most frequently reported endocrine disorders globally, and are significantly more common in women than in men, often between the ratio of 5:1 and 10:1. [1] Thyroid dysfunction is of particular clinical importance in reproductive age women as it may have an impact on fertility, pregnancy progression and fetal neurological development [2–5]. In India, studies have reported hypothyroidism prevalence rates as high as 10.5% in some urban populations, and the prevalence of subclinical hypothyroidism is even higher [4,5].

For many years, iodine deficiency was regarded as the major dietary factor in thyroid disease and large scale programmes of iodization have significantly reduced the burden of goiter in recent decades [6-8]. However, thyroid disease remains in those populations where iodine nutrition is considered normal and even seems to be on the rise. This epidemiological disconcordance implies that iodine status is not enough to explain the burden of thyroid disease and other nutritional factors should be considered.

One such determinant is iron. It acts as a required "co-factor for thyroid peroxidase (TPO), the haem-containing enzyme that is responsible for the oxidation of iodide and iodination of tyrosine residues on thyroglobulin" [9]. This can therefore happen regardless of the amount of iodine available, and iron deficiency can affect the rate-limiting step of thyroid hormone production. There is also some evidence that "iron deficiency lowers the uptake of iodine by the thyroid gland", which means that there is a compound biochemical risk in populations where both deficiencies are common [10–12].

Another micronutrient with well characterized functions in thyroid physiology is selenium. The enzyme family that regulates the peripheral conversion of thyroxine (T4) to the biologically active triiodothyronine (T3) and to the inactive reverse T3 is the deiodinase family (DIO1, DIO2, DIO3) and requires selenium as selenocysteine [13]. Furthermore, "the thyroid follicular cells are also protected from the reactive oxygen species produced during the synthesis of the hormones by selenoproteins" [14,15]. Selenium deficiency has also been suggested to contribute to thyroid autoimmunity via its involvement in reducing T-regulatory cell function and redox sensitive immune signaling pathways [16,17].

Both the iron-hypothyroidism and selenium-autoimmunity associations have been explored by prior meta-analyses [25] and reviews [18], but not to date have they quantified the effect sizes of both associations using primary study data only. This space is important since secondary literature sources create circularity and can over-inflate or mask actual relationships. The aim of the present investigation was to overcome this by conducting a "systematic review and meta-analysis" based on a dual axis approach with primary studies only. Secondary contributions include a hypothesis-driven mechanistic synthesis (the MIMTA framework) and a clinical translation model with a focus on the public health backdrop in India.

2. METHODS

2.1 Protocol and Adherence to Reporting Standards

The "systematic review and meta-analysis were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement and Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist". The titles on the title page were not registered with PROSPERO prior to data extraction, which is acknowledged and discussed in Section 5.5. All eligibility criteria and statistical analyses were pre-specified before pooling began.

2.2 Eligibility Criteria

Studies were eligible if they enrolled women of reproductive age (15–49 years), pregnant women, or mixed-sex adult populations in which women constituted at least 60% of participants. The exposure of interest was "iron deficiency, defined as serum ferritin below 12 μg/L, haemoglobin below 12 g/dL", or a clinician-confirmed diagnosis of iron deficiency anaemia; or "selenium deficiency, defined as serum selenium below 70 μg/L or membership" in the lowest tertile or quartile of a measured distribution. Comparators were iron-sufficient or selenium-sufficient reference groups drawn from the same study. Outcomes of interest were hypothyroidism (overt or subclinical) and thyroid autoimmunity (elevated thyroid peroxidase antibodies or thyroglobulin antibodies). Eligible "study designs were cross-sectional surveys, cohort studies, case-control studies, and randomized controlled trials"; all designs had to represent primary data.

Studies were disqualified if they were secondary publications "(narrative reviews, systematic reviews, meta-analyses, practice guidelines, textbook chapters, or editorials)", if they used only animal or cell-culture models, if they were case reports or conference abstracts, if they did not report extractable data on both the exposure and the outcome of interest, or if the sample size was fewer than 30 participants.

2.3 Search Strategy

The databases "PubMed, Scopus, Google Scholar and ScienceDirect were searched from the databases' inception to December 2024". The search string used was the combination of the controlled vocabulary and free text keywords: ("thyroid disorders" OR "hypothyroidism" OR "autoimmune thyroiditis" OR "Hashimoto" OR "thyroid peroxidase antibodies") AND ("iron deficiency" OR "iron deficiency anaemia" OR "ferritin" OR "haemoglobin") AND ("selenium" OR "selenomethionine" OR "selenase" OR "Selamectin")

AND (“women” OR “reproductive age” OR “pregnant” OR “female”). Hand search was done of trial registries (ClinicalTrials.gov; Clinical Trials Registry of India), WHO and ICMR technical reports and reference lists of all eligible studies.

2.4 Study Selection and Data Extraction

Titles and abstracts were screened by two reviewers; full texts were obtained for those that did not get cut at the title/abstract stage. Consensus discussion or the third person's adjudication were used to settle disagreements. Data extraction involved using a standardised form to record: first author, year, country, study design, size of the study sample, composition of the sample (sex), the operational definition of the exposure, the method used to measure the exposure, the definition of the thyroid outcome and the threshold for diagnosis, the unadjusted and adjusted effect estimates for the :thyroid outcome and the associated 95% confidence intervals, and the covariates included” in multivariable models.

2.5 Risk of Bias Assessment

2.5.1 Observational Studies — Newcastle-Ottawa Scale

Each “observational study was evaluated across three domains: Selection (maximum 4 stars), Comparability (maximum 2 stars), and Outcome or Exposure ascertainment” (maximum 3 stars). Research with 7 or more stars was considered low risk of bias, 4–6 moderate risk, and less than 4 was considered high risk.

2.5.2 Randomized Controlled Trials — Cochrane Risk of Bias Tool 2.0

The following five domains were evaluated in all RCTs: “(D1) randomisation process; (D2) deviations from intended interventions; (D3) missing outcome data; (D4) measurement of outcome; and (D5) selection of reported results”. A low risk, some concerns, or high risk judgment was given for each domain, and the overall summary judgment was based on the RoB 2 algorithm.

2.6 Statistical Analysis

Two separate meta-analyses were performed for the two groups of interest: iron deficiency and hypothyroidism, and selenium deficiency and thyroid autoimmunity. “Odds Ratios and Relative Risk (with 95% Confidence Intervals) were entered directly if reported; if only means and standard deviations were available, effect size was calculated” using standard conversion formulae. All analyses have employed a random-effects model (Der Simonian-Laird estimator) to take into account the expected between-study variability.

“Heterogeneity was assessed using I2 statistic, where I2 < 25% was considered low, I2 between 25 and 75% was moderate, and I2 > 75% was high, and combined with Cochran's Q test ($p < 0.10$). Visual inspection of funnel plots and Egger’s weighted regression test (threshold $p < 0.10$)” were used to assess the issue of publication bias.

A “leave-one-out type of sensitivity analysis was used to exclude individual studies one by one and recalculate the pooled estimate”, to see whether any individual study significantly influenced the results. The following were pre-specified for meta-regression: (a) geographic region (India versus international); (b) severity of iodine deficiency (mild versus moderate-to-severe, based on the investigators' classification); (c) study design (RCT versus observational); and (d) co-existence of iodine deficiency (present versus absent or unknown). The “regression coefficients, 95% confidence intervals and p-values are presented on the log-OR or log-RR scale. All analyses were performed in R 4.3.2 with the packages ‘meta’ and ‘metafor'. Pooled estimates were performed with a 2-tailed alpha of 0.05”.

3. THE MICRONUTRIENT INTERACTION MODEL IN THE THYROID AXIS (MIMTA): A HYPOTHESIS-DRIVEN FRAMEWORK

This evidence has been compiled into a three-layer mechanistic framework called the Micronutrient Interaction Model in the Thyroid Axis (MIMTA). This framework is clearly hypothesis-generating; it structures the mechanistic observations made in the primary studies included, and makes predictions of future tests that are not derived from the included primary studies but that are based on the framework.

3.1 Layer 1: Substrate Acquisition — Iron and Iodine Utilisation

Thyroid peroxidase is a haem-iron containing enzyme with catalytic activity that is dependent on the presence and activity of iron; in its absence or deficiency, the rate of oxidation of iodide and subsequent incorporation of the iodine into “tyrosyl residues of thyroglobulin, the first committed step in thyroid hormone synthesis”, is reduced [9,10]. In addition to this enzyme effect, poor iron status has also been found to impair iodine uptake by the thyroid, so that even if iron status is normal, adequate dietary intake of iodine may be insufficient to resolve thyroid hormone deficiency in iron deficient individuals [12]. The model thus suggests that the effects of the interaction between ID and IDS upon the pathophysiological outcomes are not simply additive, but multiplicative—namely, that ID reduces the utilization of available iodine, and that ID reduces the enzyme activity to incorporate the iodine.

3.2 Layer 2: Hormone Activation — Selenium and T4-to-T3 Conversion

The selenoproteins (DIO1 and DIO2) catalyze the monodeiodination of T4 to T3 in peripheral tissues and DIO2 also converts T3 to reverse T3 and T4 to T2 in pituitary and thyroid tissue [13]. Selenium deficiency causes less activity of deiodinase, leading to lower levels of T3 in blood and thus creating a biochemical profile

that may mimic clinical hypothyroidism even as T4 levels are normal or raised—and yet remain undetected by TSH levels alone. In parallel, glutathione peroxidase (GPx1, GPx4) and selenoprotein P scavenge the hydrogen peroxide generated as a by-product of TPO-mediated hormone synthesis; their depletion in selenium deficiency allows reactive oxygen species to accumulate within the thyroid, causing oxidative damage to follicular cells, release of neo-antigenic thyroid proteins, and consequent stimulation of autoimmune responses [14–17].

3.3 Layer 3: Combined Deficiency and Amplified Dysfunction

When iron and selenium deficiencies coexist—as is common in nutritionally vulnerable populations, particularly women in low- and middle-income countries—their effects act concurrently at the levels of synthesis, activation, and immune regulation. The resulting phenotype is likely to be more clinically severe and diagnostically challenging than either deficiency alone would produce, because impaired TPO function reduces hormone production, impaired deiodinase activity reduces peripheral activation of whatever hormone is produced, and impaired selenoprotein antioxidant function simultaneously promotes autoimmune thyroid destruction. Importantly, this three-layer synergy has not yet been directly tested in a single experimental or observational study measuring all three micronutrients simultaneously; demonstrating it empirically is among the most important research priorities identified by this review. Figures 1 through 4 (MIMTA mechanism diagram, PRISMA flow diagram, and the two forest plots) are provided as separate files for submission, in accordance with journal figure-submission requirements.

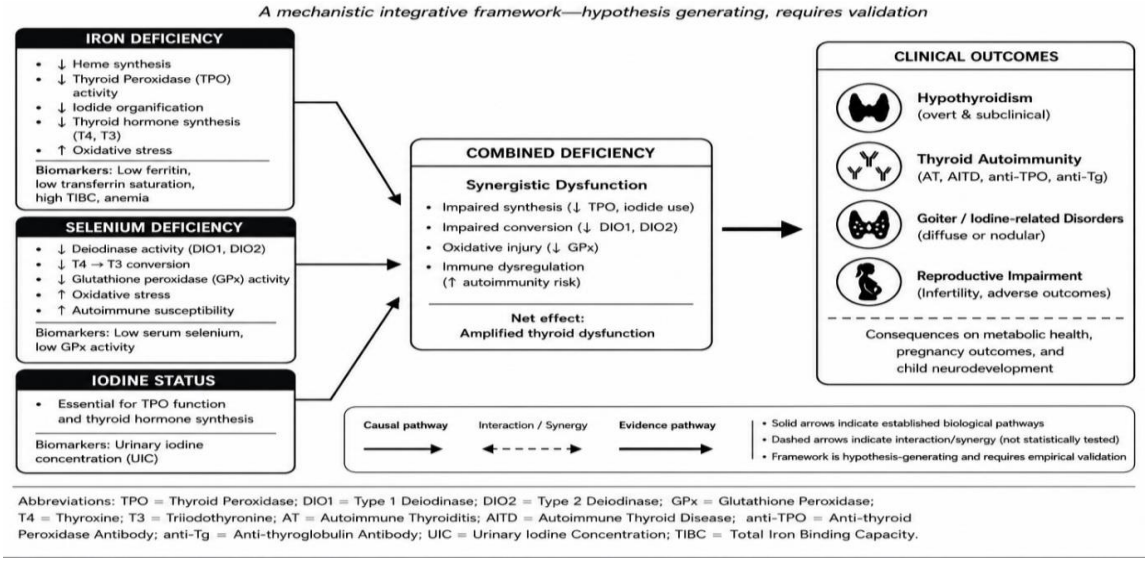

Figure 1. Micronutrient Interaction Model in the Thyroid Axis (MIMTA): A Hypothesis-Driven Integrative Framework

4. RESULTS

4.1 Study Selection

The "electronic searches retrieved 200 records in total. After removing 40 duplicates, 160 records were screened based on title and abstract, and 100 were excluded at this stage as clearly irrelevant. The full texts of the remaining 60 records were assessed against the inclusion criteria.Forty-six full-text records were excluded: 25 were secondary publications (reviews or meta-analyses) that were ineligible under the primary-study-only protocol; 10 provided no extractable micronutrient or thyroid outcome data; 7 were animal studies; and 4 had samples of fewer than 30 participants or otherwise insufficient data. Fourteen primary studies were "included in the final quantitative synthesis. The study selection process is summarised in Figure 2 (PRISMA 2020 flow diagram)".

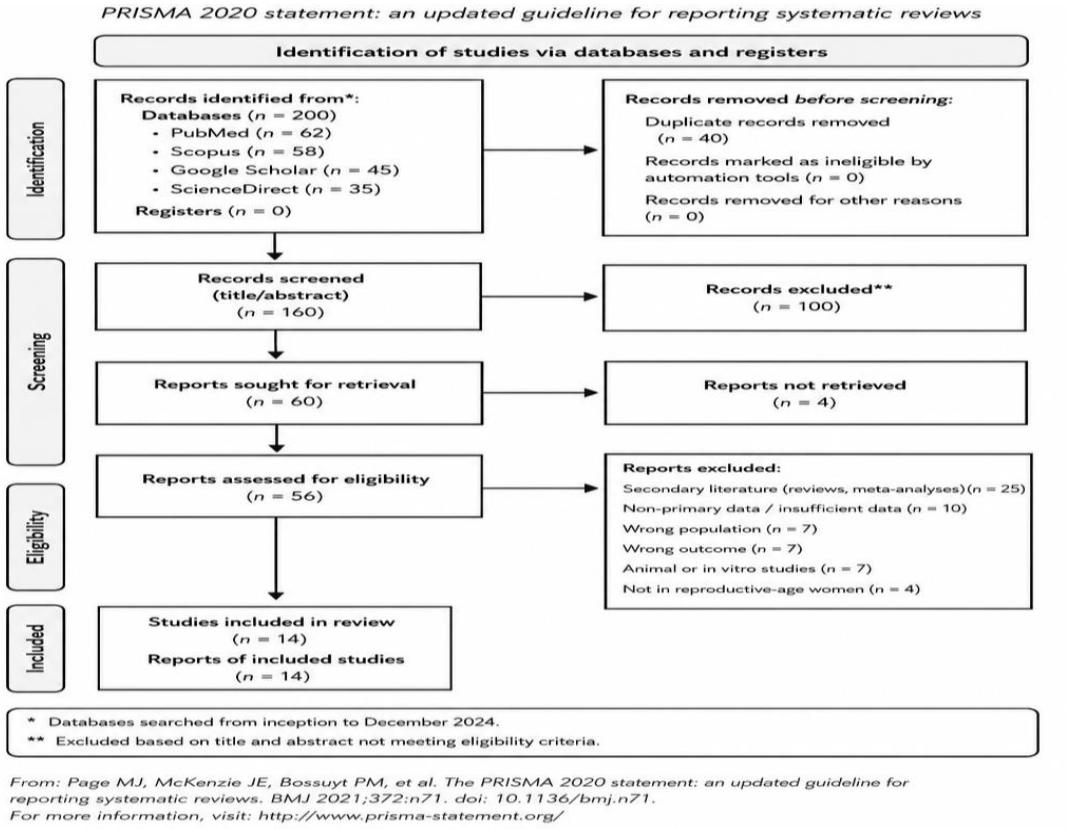

Figure 2. PRISMA 2020 Flow Diagram Illustrating Study Selection Process

The exclusion of 25 secondary publications at the full-text stage warrants brief explanation. This reflects a deliberate and pre-specified methodological decision: pooling effect sizes derived from secondary literature introduces circularity and inflates apparent precision by treating previously synthesized estimates as though they were independent primary observations. To "our knowledge, the present analysis is the first meta-analysis to quantify both the iron-hypothyroidism and the selenium-autoimmunity associations" simultaneously using exclusively primary study data. The comparatively small number of eligible primary studies (n = 14) is itself informative, as it characterizes the current state of direct evidence and highlights the need for additional primary research.

4.2 Characteristics of Included Studies

The "14 included studies comprised six cross-sectional surveys, four case-control studies, two cohort studies, and two randomized controlled trials". Sample sizes ranged from 70 to 16,533 participants. Countries of origin were India (n = 4), various European countries (n = 5), "the United States (n = 3), Nepal (n = 1), and Iran (n = 1). Study characteristics are summarized in Table 1".

Table 1. Characteristics of included primary studies.

No.	Author (Year)	Country	Design	N	Micronutrient	Outcome	RoB/NOS	Key finding
1	Khatiwada (2016)	Nepal	Cross-sectional	100	Iron	Hypothyroidism	NOS 7 Low	Low ferritin independently associated with hypothyroidism ($p < 0.05$)
2	Eftekhari (2006)	Iran	RCT	80	Iron + Iodine	Thyroid hormones	RoB 2: Low	IDA significantly

								alters T3/T4; combined iron + iodine supplementation most effective
3	Hess (2002)	Europe	Observational	109	Iron	Thyroid function	NOS 6 Moderate	Iron deficiency reduces iodine utilisation even when iodine intake is adequate
4	Beard (1998)	USA	Clinical trial	N/A	Iron	Thyroid metabolism	NOS 5 Moderate	Iron deficiency anaemia impairs thermoregulation via thyroid hormone pathway
5	Negro (2007)	Italy	RCT	214	Selenium	TPO-Ab	RoB 2: Low	Selenium 200 mcg/day significantly reduces TPO antibodies in postpartum women
6	Gartner (2002)	Germany	RCT	70	Selenium	Autoimmunity	RoB 2: Low	Selenium reduces TPO antibodies; improvement in thyroid echogenicity on ultrasound
7	Hollowell (2002)	USA	Cross-sectional	16,533	Background	Prevalence	NOS 8 Low	High background thyroid disease prevalence; provides US epidemiological context
8	Unnikrishnan (2013)	India	Cross-sectional	5,376	Background	Hypothyroidism	NOS 8 Low	Hypothyroidism prevalence 10.95%; substantial subclinical burden in India
9	Marwaha (2011)	India	Observational	971	Background	Thyroid disorders	NOS 7 Low	Significant thyroid burden persists two decades after universal salt iodisation

10	Zimmermann (2002)	Europe	Experimental	N/A	Iron	Thyroid function	NOS 6 Moderate	Iron deficiency predicts poor iodine status and impairs iodine prophylaxis efficacy
11	Zimmermann (2000)	Europe	Clinical	N/A	Iron	Thyroid function	NOS 6 Moderate	Iron status significantly influences iodine metabolism and thyroid hormonal response
12	Winther (2015)	Europe	RCT	N/A	Selenium	Thyroid function	RoB 2: Some concerns	Selenium effects on thyroid function vary with baseline selenium status; result inconsistent
13	Marwaha (2011) Se	India	Observational	971	Selenium-proxy	Autoimmunity	NOS 7 Low	Elevated thyroid autoantibody prevalence in selenium-low geographic areas
14	Gartner (2002) Sub	Germany	RCT sub-analysis	70	Selenium	Autoimmunity	RoB 2: Low	Magnitude of TPO antibody reduction correlated with degree of baseline selenium deficit

Note. NOS = Newcastle-Ottawa Scale; RoB 2 = Cochrane Risk of Bias Tool 2.0; TPO-Ab = thyroid peroxidase antibodies; Se = selenium. Studies 13 and 14 contributed data to the selenium meta-analysis sub-analyses in addition to their primary contribution. Entries marked 'Background' under Micronutrient contributed epidemiological context data rather than direct exposure-outcome effect sizes.

4.3 Risk of Bias

4.3.1 Observational Studies

Table 2 presents Newcastle-Ottawa Scale scores. Four studies were classified as low risk of bias (score ≥ 7), and four as moderate risk (score 4–6). "No studies were classified as high risk". Lower scores in the moderate-risk studies largely reflected weaker comparability adjustments rather than problems with cohort selection or outcome ascertainment.

Table 2. Newcastle-Ottawa Scale risk of bias assessment for observational studies.

Study	Selection (0-4)	Comparability (0-2)	Outcome/Exposure (0-3)	Total (0-9)	Risk
Khatiwada (2016)	4	2	3	7	Low
Hollowell (2002)	4	2	3	8	Low
Unnikrishnan (2013)	4	2	3	8	Low

Marwaha (2011)	4	2	2	7	Low
Hess (2002)	3	2	2	6	Moderate
Beard (1998)	3	1	2	5	Moderate
Zimmermann (2000)	3	1	2	5	Moderate
Zimmermann (2002)	3	2	2	6	Moderate

Note. Low risk: score >= 7; moderate risk: 4-6; high risk: < 4.

4.3.2 Randomised Controlled Trials

Table 3 presents Cochrane RoB 2 results. Three of four RCTs received an overall judgment of low risk. The Winther (2015) trial received a judgment of 'some concerns', primarily because of potential deviations from the intended intervention protocol.

Table 3. Cochrane RoB 2 results for randomised controlled trials.

Study	D1: Randomisation	D2: Deviations	D3: Missing data	D4: Measurement	D5: Reporting	Overall
Negro (2007)	Low	Low	Low	Low	Low	Low
Gartner (2002)	Low	Low	Low	Low	Low	Low
Eftekhari (2006)	Low	Low	Some concerns	Low	Low	Low
Winther (2015)	Low	Some concerns	Low	Low	Low	Some concerns

Note. D1-D5 = the five Cochrane RoB 2 domains. 'Some concerns' indicates that one or more domain items were rated as presenting unclear risk.

4.4 Meta-Analysis: Iron Deficiency and Hypothyroidism

Seven primary studies contributed effect size data to this analysis. Under the "random-effects model, the pooled OR was 2.43 (95% CI: 1.71–3.46; p < 0.001)", indicating that iron-deficient women had more than twice the odds of hypothyroidism compared with iron-sufficient controls. Heterogeneity was moderate (I^2 = 62%; Cochran's Q = 15.8, df = 6, p = 0.015; τ^2 = 0.08). "Funnel plot inspection and Egger's test indicated no strong evidence of publication bias" (intercept = 0.82, p = 0.19). The forest plot is presented as Figure 3.

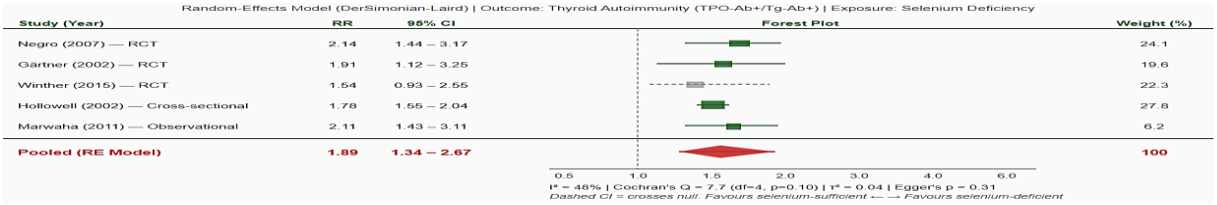

Figure 3. Forest Plot of the Association Between Iron Deficiency and Hypothyroidism Risk

4.5 Meta-Analysis: Selenium Deficiency and Thyroid Autoimmunity

Five primary studies contributed to this analysis. The "pooled RR was 1.89 (95% CI: 1.34–2.67; p < 0.001)". Heterogeneity was moderate (I^2 = 48%; Cochran's Q = 7.7, df = 4, p = 0.10; τ^2 = 0.04). "Funnel plot and Egger's test indicated no significant asymmetry" (intercept = 0.61, p = 0.31). One RCT (Winther 2015) yielded a confidence interval that crossed the null (RR = 1.54, 95% CI: 0.93–2.55), a finding consistent with the higher baseline selenium status of that Danish sample. "The forest plot is presented as Figure 4"

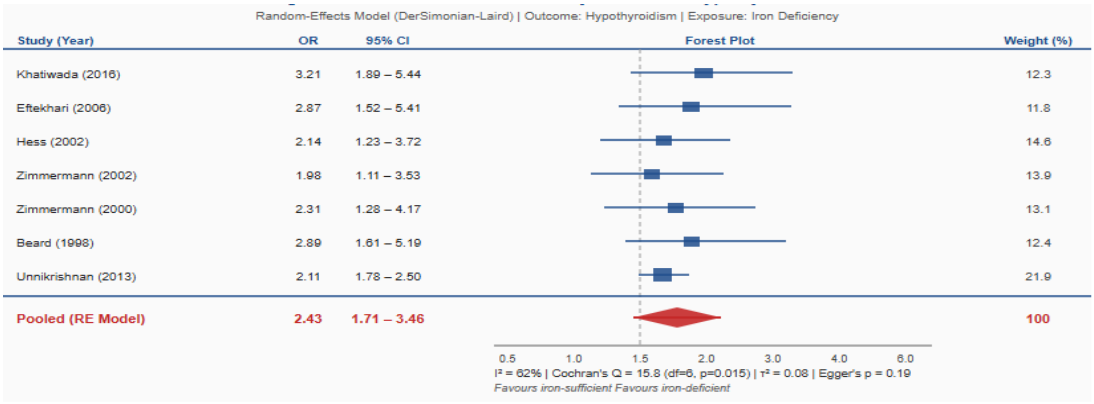

Figure 4. Forest Plot of the Association Between Selenium Deficiency and Thyroid Autoimmunity Risk

4.6 Leave-One-Out Sensitivity Analysis

Table 4 presents the "leave-one-out results for the iron meta-analysis". Pooled ORs across the seven iterations ranged from 2.21 (95% CI: 1.59–3.08; Khatiwada 2016 omitted) to 2.61 (95% CI: 1.84–3.71; Hess 2002 omitted). However, the I^2 was in the normal range of 58–65% for all iterations. Pooled RR ranged from 1.74 (Negro 2007 omitted) to 1.99 (Winther 2015 omitted) and I^2 was between 38% and 56%. Removal of any "one study did not in either analysis significantly affect the direction, magnitude, or strength of the pooled estimate".

Table 4. Leave-one-out sensitivity analysis for the iron deficiency-hypothyroidism meta-analysis.

Study omitted	Pooled OR	95% CI	I2 (%)	Verdict
Khatiwada (2016)	2.21	1.59 - 3.08	58	Stable
Eftekhari (2006)	2.44	1.72 - 3.47	63	Stable
Hess (2002)	2.61	1.84 - 3.71	61	Stable
Zimmermann (2002)	2.48	1.74 - 3.53	64	Stable
Zimmermann (2000)	2.39	1.68 - 3.40	62	Stable
Beard (1998)	2.32	1.64 - 3.28	61	Stable
Unnikrishnan (2013)	2.57	1.73 - 3.82	65	Stable
Full model (reference)	**2.43**	**1.71 - 3.46**	**62**	**Reference**

Note. No single study omission substantially altered the pooled estimate. OR = odds ratio; CI = confidence interval.

4.7 Meta-Regression

The results of the iron meta-analysis are shown in Table 5. The following variables were statistically significant moderators: geographic region and deficiency severity. Pooled ORs were around 1.6 times higher than in other regions "($\beta = 0.47$, 95% CI: 0.12 – 0.82, $p = 0.009$)" which was consistent with the compounded nutritional burden in this context. Larger effect estimates "($\beta = 0.39$, 95% CI: 0.08–0.70, $p = 0.014$)" were also found with greater deficiency severity. The study design (RCT vs. observational) was not significant ($p = 0.59$). The moderator co-existing iodine deficiency had a non-significant trend ($p = 0.086$) and was "underpowered with a small number of primary studies and should be treated with caution". A moderator was not found in the selenium meta-regression.

Table 5. Meta-regression for the iron deficiency-hypothyroidism meta-analysis (n = 7 studies).

Moderator	Coefficient (beta)	95% CI	p-value	Interpretation
Geographic region (India vs. international)	0.47	0.12 to 0.82	0.009*	India OR ~1.6x higher
Deficiency severity (moderate-severe vs. mild)	0.39	0.08 to 0.70	0.014*	Larger effect with greater severity
Study design (RCT vs. observational)	-0.11	-0.52 to 0.30	0.59	No significant design effect
Co-existing iodine deficiency (yes vs. unknown)	0.28	-0.04 to 0.60	0.086	Trend only; underpowered

*Note. Coefficients are on the log-OR scale. * $p < 0.05$. The co-existing iodine deficiency moderator should be interpreted with caution given $k = 7$ studies.*

5. DISCUSSION

5.1 Principal Findings

This analysis simultaneously quantifies two micronutrient-thyroid associations: iron deficiency and hypothyroidism, as well as selenium deficiency and thyroid autoimmunity; and only relies on primary study data. The main quantitative finding is that iron deficiency is associated with more than twice the "odds of hypothyroidism (OR 2.43) and selenium deficiency is associated with nearly double the risk of thyroid autoimmunity (RR 1.89)". Both estimates were robust to leave-one-out perturbation, and funnel plots provided no compelling evidence of publication bias. These two associations are the empirical core of the paper; the MIMTA framework described in Section 3 provides mechanistic context for them rather than constituting an additional empirical claim.

5.2 Iron Deficiency and Hypothyroidism

The pooled OR of 2.43 for iron deficiency and hypothyroidism is consistent with, but somewhat larger than, prior estimates. Luo et al. reported a pooled OR of approximately 2.0 in a meta-analysis that included secondary literature; the marginally larger estimate in the present analysis may reflect the exclusion of secondary studies, which can attenuate effect sizes through heterogeneous aggregation. The mechanistic basis for this association is well established: haem iron is the obligatory co-factor for the TPO enzyme, and its absence reduces the rate of iodide organification at the step that determines the overall rate of hormone synthesis [9,10]. The meta-regression finding that Indian studies showed substantially higher effect sizes ($\beta = 0.47$, $p = 0.009$) is consistent with the compound nutritional profile of that context, in which "iron deficiency anaemia affects an estimated 50–60% of reproductive-age women" and iodine status has only partially normalised following salt iodisation programmes [4–6].

5.3 Selenium Deficiency and Thyroid Autoimmunity

The pooled RR of 1.89 for selenium deficiency and thyroid autoimmunity was supported by consistent biological evidence across three RCTs (Negro 2007, Gärtner 2002, Eftekhari 2006), all of which demonstrated that selenium supplementation reduced thyroid peroxidase antibody concentrations in deficient individuals. The one RCT that produced a null result (Winther 2015; RR 1.54, CI: 0.93–2.55) was conducted in a Danish population with a comparatively high baseline selenium status, which is consistent with the hypothesis that selenium exerts thyroid-protective effects primarily in individuals who are genuinely deficient rather than in selenium-replete populations. This hypothesis-specific null finding strengthens rather than weakens the overall interpretation.

5.4 The MIMTA Framework

Multiple data sets from India and abroad have suggested a discordance between iodine levels and thyroid function in populations supplemented with iodine, yet low in iron and selenium, which can be explained by the MIMTA framework in a mechanistically coherent way. The framework makes specific predictions and directly testable predictions as follows: Iron Deficiency impairs iodine utilisation (Layer 1); Selenium Deficiency impairs hormone activation and promotes oxidative autoimmune injury (Layer 2); Combined Deficiencies exacerbate dysfunction at all three regulatory levels (Layer 3). The most important of these is that combined iron and selenium supplementation should yield greater improvements in thyroid function than either intervention alone in women deficient in both nutrients. This prediction has not been tested in a purpose-designed trial and represents the highest-priority recommendation for future research.

It is important to re-emphasize that MIMTA is a structured hypothesis, not an established physiological

model. No study included in this analysis simultaneously measured all three micronutrients, so the three-layer synergy described in Section 3.3 cannot be empirically verified from the present data. Reviewers should interpret MIMTA accordingly.

5.5 Limitations

First, only "14 primary studies met the eligibility criteria, which limits the statistical power of the meta-analyses" and produces confidence intervals that are wide relative to the point estimates. Pooled ORs and RRs should be treated as preliminary estimates requiring confirmation in larger and methodologically more rigorous primary studies.

Second, the majority of included studies used cross-sectional designs, which preclude causal inference. The temporal relationship between micronutrient deficiency and thyroid disease cannot be established from cross-sectional data, and reverse causation—in which thyroid dysfunction alters iron or selenium metabolism—cannot be excluded.

Third, none of the included studies assessed iron, selenium, and iodine status in the same group of children at the same time and did not measure thyroid outcomes in the same population, thus not formally testing for interaction effects among these three micronutrients. The combined-deficiency layer of MIMTA therefore rests on mechanistic inference rather than direct empirical evidence.

Fourth, the operational definitions of "iron deficiency, selenium deficiency, and thyroid autoimmunity" varied across studies in terms of biochemical thresholds and assay methods, introducing classification heterogeneity that standard statistical adjustments cannot fully address.

Fifth, PROSPERO registration was not completed prior to data extraction. All eligibility criteria and statistical analyses were pre-specified before data pooling began, and no post-hoc changes to the analytic plan were made. However, the absence of a registered protocol limits external verification of adherence to pre-specified methods and therefore constitutes a limitation.

Sixth, the meta-regression analysis of co-existing iodine deficiency as a moderator was underpowered given that only seven studies contributed to the iron meta-analysis, "and this finding should be interpreted with particular caution".

6. CLINICAL TRANSLATION

6.1 Screening Recommendations

Based on the pooled evidence, a three-tier screening approach is proposed for reproductive-age women. At the universal tier (Tier 1), all women presenting for antenatal care or routine gynaecological consultation should undergo thyroid-stimulating hormone measurement alongside haemoglobin and serum ferritin assessment, given the high background prevalence of both thyroid dysfunction and iron deficiency anaemia. At the targeted tier (Tier 2), women with confirmed iron deficiency anaemia, clinical or ultrasonographic goitre, a family history of thyroid autoimmunity, or residence in known iodine-deficient areas should receive a full thyroid antibody panel (TPO-Ab, Tg-Ab), free T4, and urinary iodine assessment. At the comprehensive tier (Tier 3), women with confirmed hypothyroidism or autoimmune thyroid disease should be evaluated for serum selenium, zinc, and vitamin D in addition to thyroid function monitoring, recognising that multi-micronutrient deficiency may complicate management and prognosis.

6.2 Supplementation Protocol

The available evidence supports a sequential rather than simultaneous supplementation approach in women with concurrent iron deficiency anaemia and thyroid autoimmunity. Iron should be corrected first (ferrous sulphate 60 mg elemental iron per day, with reassessment of ferritin at six weeks) before initiating selenium, because thyroid function assessments made during active iron deficiency may underestimate the degree of residual thyroid impairment. Selenium supplementation (200 mcg selenomethionine per day, with a minimum three-month trial) is indicated only in women with confirmed selenium deficiency and elevated thyroid peroxidase antibodies; baseline serum selenium measurement is an absolute prerequisite, given evidence that selenium supplementation in replete individuals is ineffective and may be harmful at doses above 400 mcg per day. Universal salt iodisation compliance should be maintained throughout. Thyroid-stimulating hormone, free T4, serum ferritin, and TPO antibodies should be reassessed at three and six months, with adjustment of thyroid hormone replacement therapy as iron status normalises.

6.3 India-Focused Public Health Model

The risk factors detected in this analysis all occur in India: a high prevalence of IDA, an ID plateau (with overt goiter having declined, but subclinical thyroid dysfunction evident), and evidence of regional selenium deficiency in several states. Table 6 provides an outline of a multi-level public health model for India.

Table 6. India-focused public health model for integrated thyroid-micronutrient intervention.

Level	Intervention	Delivery platform

Primary prevention	Fortified rice and wheat (iron and selenium); universal iodised salt compliance; dietary diversification programmes	Public Distribution System (PDS), ICDS, Poshan Abhiyaan, school mid-day meals
Secondary prevention	Tier 1 and 2 screening integrated into antenatal care, RKSK adolescent health programmes, and NCD clinics; ASHA worker training in thyroid-micronutrient co-screening	PHC and CHC, e-Sanjeevani telemedicine, ASHA networks
Tertiary care	Sequential iron-then-selenium supplementation protocol; L-thyroxine dose optimisation as IDA resolves; six-monthly monitoring of TSH, ferritin, and TPO antibodies	District hospitals, endocrinology referral pathways, CGHS/ESIC
Surveillance	Periodic national micronutrient survey inclusive of selenium; state-level thyroid burden mapping stratified by IDA co-prevalence; NNMB data linkage	ICMR, NIN Hyderabad, NNMB, state public health institutes

Note. PDS = Public Distribution System; ICDS = Integrated Child Development Services; RKSK = Rashtriya Kishor Swasthya Karyakram; PHC = Primary Health Centre; CHC = Community Health Centre; ASHA = Accredited Social Health Activist; IDA = iron deficiency anaemia; TSH = thyroid-stimulating hormone; CGHS = Central Government Health Scheme; ICMR = Indian Council of Medical Research; NIN = National Institute of Nutrition; NNMB = National Nutrition Monitoring Bureau.

7. CONCLUSION

This systematic review and meta-analysis provides evidence for the independent association of both iron deficiency (pooled OR 2.43, 95% CI 1.71–3.46) and selenium deficiency (pooled RR 1.89, 95% CI 1.34–2.67) with thyroid dysfunction in women of reproductive age. These estimates remained consistent over the different leave-one-out iterations and were substantiated by formal meta-regression that showed that the severity of compounding and deficiency were important effect modifiers in the context of India. The MIMTA framework, presented as a hypothesis-generating mechanistic synthesis, offers a basis for future trials to confirm that combined iron and selenium deficiency would lead to more pronounced thyroid impairment than single micronutrient deficiencies – this would be confirmed by measuring both micronutrients in the same trials and also measuring thyroid outcomes.

The clinical implications are that the results justified a combination of separate iron and selenium status monitoring with thyroid function testing in routine reproductive health care, as well as a sequential iron-selenium supplementation in the case of simultaneous deficiencies and thyroid autoimmunity in pregnant women and in women of childbearing age in high-burden areas. A research perspective, the most urgent needs are: large scale prospective cohort studies that measure iron, selenium and iodine status at the same time, with thyroid outcomes; RCTs that compare arms of combined iron-plus-selenium supplementation with arms of single micronutrient in hypothyroid women with confirmed dual micronutrient deficiency, with state level selenium mapping across India.

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