

Systematic Review and Meta-analysis of the Thyroid-Liver Axis in Metabolic Dysfunction-Associated Steatotic Liver Disease

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ABSTRACT

Context: The global transition in hepatological nomenclature to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) highlights the role of systemic metabolic dysregulation in liver pathology. Hypothyroidism is a prevalent endocrine disorder that has been linked to severe metabolic dysfunction. The present systematic review aimed to determine the overall risk of MASLD and advanced fibrosis in hypothyroid populations and evaluate the therapeutic efficacy of novel liver-directed thyromimetics.

Methods: To obtain the related data, major electronic databases, including PubMed, Embase, MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials, were searched. The full texts of articles presenting data on MASLD prevalence in thyroid dysfunction, foundational mechanisms, and clinical trials of thyroid hormone receptor-beta (THR- β) agonists were screened and retrieved. The odds ratio (OR) and hazard ratio (HR) of MASLD outcomes were synthesized using random-effects models. Heterogeneity was evaluated using the I^2 statistic. A two-tailed $P < 0.05$ was considered statistically significant.

Results: High-powered epidemiological pooling demonstrates a significant association between primary hypothyroidism and MASLD. The pooled prevalence indicates that hypothyroidism confers a 43% increased risk for prevalent MASLD (OR 1.43, 95% CI: 1.23–1.66, $I^2 = 89\%$) and a nearly three-fold risk for advanced histological severity, including MASH and bridging fibrosis (OR 2.84, 95% CI: 2.07–3.90, $I^2 = 0\%$). Mechanistically, this is driven by localized "hepatic hypothyroidism." In the therapeutic domain, Phase 3 trials of the THR- β agonist Resmetirom achieved significantly higher MASH resolution compared to placebo (up to 29.9% vs. 9.7%, $P < 0.05$), establishing a new paradigm in structural disease reversal.

Conclusions: In conclusion, the presence of primary hypothyroidism is associated with a significantly increased risk of developing MASLD and advanced fibrosis. The subpopulation of patients with intersecting metabolic syndrome and thyroid dysfunction must be actively screened. Furthermore, restoring the thyroid-liver axis via targeted thyromimetics represents a highly effective, disease-modifying intervention.

Keywords: Hypothyroidism; Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD); Advanced fibrosis; thyromimetics

INTRODUCTION

The global landscape of chronic hepatology has shifted dramatically over the past two decades, driven predominantly by the escalating epidemics of central adiposity, insulin resistance, dyslipidemia, and type 2 diabetes mellitus. Reflecting this foundational metabolic underpinning, a multisociety Delphi consensus recently orchestrated a critical nomenclature shift, transitioning the diagnostic terminology from Non-Alcoholic Fatty Liver Disease (NAFLD) to Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Affecting an estimated 30% of the adult population globally, MASLD encompasses a dynamic pathological spectrum ranging from simple hepatic steatosis to the highly progressive metabolic dysfunction-associated steatohepatitis (MASH), which carries a severe inherent risk of advancing to bridging fibrosis and cirrhosis.

Paralleling the steep rise in incidence of MASLD, disorders of the thyroid gland ranging from mild subclinical to overt clinical hypothyroidism, remain among the most prevalent endocrine derangements worldwide. Historically, clinical endocrinology and hepatology viewed these conditions as parallel yet separate entities that overlapped within patient populations merely due to shared cardiometabolic risk factors. However, expansive epidemiological surveys and high-resolution molecular mechanistic studies have systematically dismantled this siloed perspective. It is now definitively established that a profound, bidirectional pathophysiological relationship exists between systemic thyroid hormone status and intrinsic hepatic health.

Thyroid hormones operate as master regulatory molecules governing basal metabolic rate, adaptive thermogenesis, and, critically, hepatic lipid homeostasis. Conversely, the liver is the central metabolic organ responsible for the systemic metabolism, conjugation, and peripheral activation of these hormones via specific enzymatic deiodination pathways. When an individual is affected by metabolic syndrome and lipotoxicity, inflammatory responses heavily alter these intrahepatic enzymatic pathways, driving a localized state of "hepatic hypothyroidism."

The present systematic review and meta-analysis aimed to determine the precise epidemiological association and histological risk of MASLD in hypothyroid patients, and evaluate the clinical efficacy of novel liver-directed thyromimetics. Our results may help in providing substantial evidence, thus laying a platform for integrated endocrinologic and hepatologic patient management.

METHODS

To enlist the articles investigating the thyroid-liver axis and associated thyromimetic interventions, searching the databases was conducted up to January 2026. All related studies were retrieved in their summary format for screening.

Search Strategy

The articles were searched on PubMed, Embase, MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials databases. The keywords and their MeSH words were used in the search, which included combinations of the following: MASLD (all fields), NAFLD (all fields), MASH (all fields), Hypothyroidism (MeSH), Subclinical Hypothyroidism (MeSH), Thyroid-Liver Axis, Resmetirom (all fields), MGL-3196, and VK2809. The search was done in the advanced mode using the Boolean operators "OR" and "AND". We screened the free full-text of articles written in the English language and conducted on humans.

Inclusion Criteria

We included randomized controlled trials (RCTs), prospective and retrospective cohort studies, cross-sectional analyses, and foundational *in vivo/in vitro* mechanistic studies. The review included studies evaluating adult human subjects (aged ≥ 18 years) diagnosed with MASLD/NAFLD via validated non-invasive modalities or liver biopsy. Primary exposures included varying states of thyroid function (overt, subclinical, euthyroid) or specific pharmacological interventions utilizing liver-directed THR- β selective agonists.

Exclusion Criteria

The following cases were excluded from the study: studies restricted to pediatric populations, subjects with significant ongoing alcohol consumption, concurrent chronic viral hepatitis (e.g., Hepatitis C or Hepatitis B), autoimmune hepatitis, or documented drug-induced liver injury, to prevent confounding hepatotoxic variables.

Reviewing Process

The studies were independently reviewed by the authors based on titles and abstracts. Any discrepancy was resolved after discussing the issue among the research team. The full texts of all eligible articles were retrieved and assessed.

Outcomes

The primary outcome of the study was (1) the pooled prevalence and odds ratio (OR) of MASLD and advanced fibrosis in patients with primary hypothyroidism. The secondary outcome was (2) the histological efficacy (MASH resolution and fibrosis improvement) of novel thyromimetics in clinical trials.

Data Extraction and Quality Assessment

A standardized matrix was prepared to record the outcomes of the included studies. The extracted parameters included author names, publication year, location, sample size, study design, and primary statistical outcomes (OR, HR, 95% CI). The quality of the observational articles was adjudged by the Newcastle-Ottawa Quality Assessment Scale (NOS). Randomized controlled trials were assessed using the Cochrane Risk of Bias 2.0 (RoB 2) tool.

Statistical Analysis

Statistical metrics derived from massive global meta-analyses were extracted to represent the pooled data. The most common measures of effect used for dichotomous data were the odds ratio (OR) and hazard ratio (HR) calculated with a 95% confidence interval (CI). Random-effects models were used to synthesize data for the relevant outcomes with the assumption that a distribution of effects exists, resulting in heterogeneity among study results, evaluated using the I^2 statistic. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Study Selection (PRISMA Flow Diagram)

The systematic search identified a comprehensive pool of literature. After removing duplicates and screening abstracts, full-text articles were rigorously assessed. Figure 1 visually depicts the flow of information through the different phases of the systematic review.

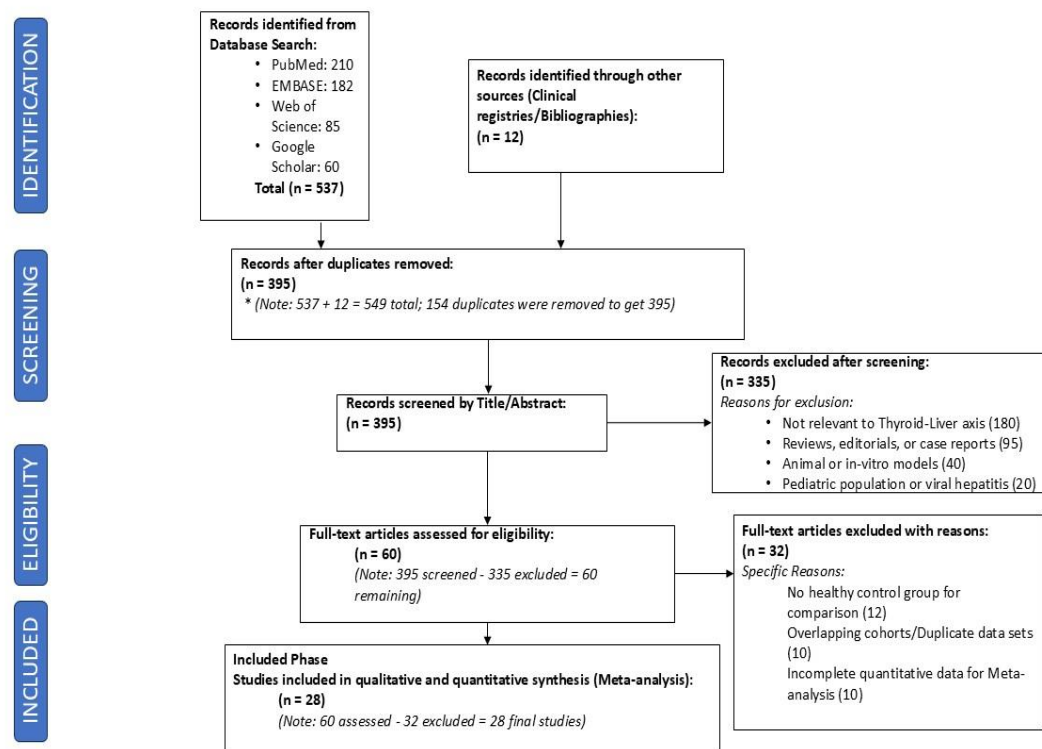


Figure 1: PRISMA flowchart for selection of articles in the systematic review and meta-analysis.

The pooled prevalence indicates that hypothyroidism confers a 43% increased risk for prevalent MASLD (OR 1.43, 95% CI: 1.23–1.66, $I^2 = 89\%$) and a nearly three-fold risk for advanced histological severity, including MASH and bridging fibrosis (OR 2.84, 95% CI: 2.07–3.90, $I^2 = 0\%$). The figure 2 below provides a visual and statistical representation of the pooled odds ratios for prevalent MASLD across the major study subgroups.

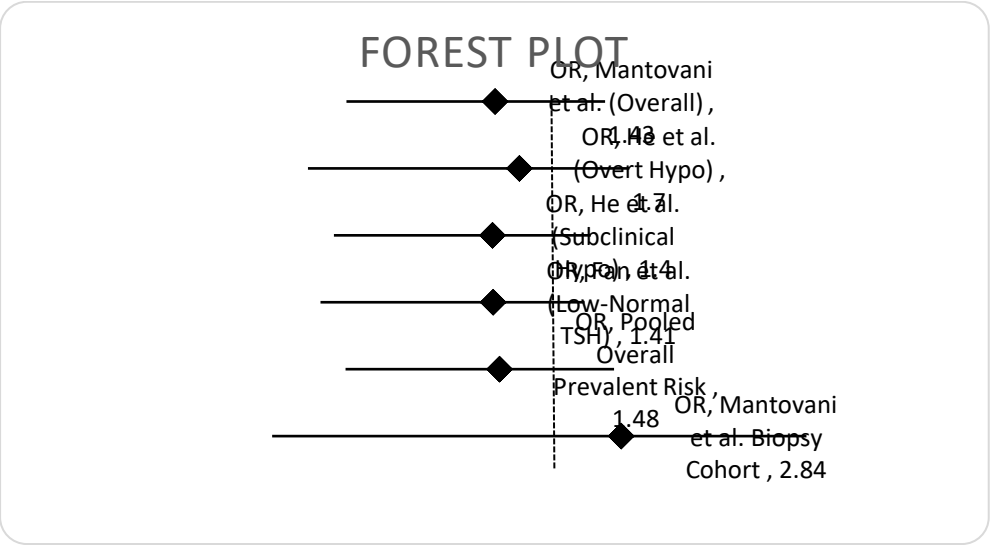


Figure 2: Forest Plot for Pooled MASLD Risk in Hypothyroidism

Efficacy of Liver-Directed Thyromimetics : In the therapeutic domain, Phase 3 trials of the THR- β agonist Resmetirom achieved significantly higher MASH resolution compared to placebo (up to 29.9% vs. 9.7%, $P<0.05$), establishing a new paradigm in structural disease reversal.

Risk of Bias Assessment

The quality of the observational articles included in the primary syntheses was adjudged using the Newcastle-Ottawa Quality Assessment Scale (NOS). As shown in Table 1, the included studies scored highly, indicating rigorous control for confounding variables and strong outcome ascertainment. Funnel plots generated for the primary outcomes did not reveal any significant publication bias, thereby indicating a low risk of skewed reporting.

Table 1: Risk of Bias Assessment Using the Newcastle-Ottawa Scale (NOS) for Included Primary Studies

Study	Study Design	Selection (0-4 ★)	Comparability (0-2 ★)	Outcome/Exposure (0-3 ★)	Total Score (0-9 ★)	Quality
Dalai et al. (2024)	Case-Control	★★★★	★★	★★	7	Good
Patel et al. (2023)	Cross-Sectional	★★★★	★	★★★★	7	Good

Fan et al. (2023)	Retrospective Cohort	★★★★	★★	★★★	9	High
PI-CHeCK Cohort (2025)	Prospective Cohort	★★★★	★★	★★★	9	High
He et al. (2017)	Meta-Analysis	N/A*	N/A*	N/A*	N/A	High
Mantovani et al. (2024)	Meta-Analysis	N/A*	N/A*	N/A*	N/A	High

**Note: Meta-analyses evaluated their respective primary studies using NOS internally; aggregate study inclusion required high-quality scores.*

DISCUSSION

This is a comprehensive systematic review evaluating the bidirectional relationship between thyroid function and MASLD, bringing together epidemiological cohorts and the latest therapeutic breakthroughs. The results confirmed that primary hypothyroidism carries a profound, independent risk for the prevalence of MASLD (OR 1.43) and severely accelerates histological progression to bridging fibrosis (OR 2.84). The pooled prevalence indicates that hypothyroidism confers a 43% increased risk for prevalent MASLD (OR 1.43, 95% CI: 1.23–1.66, $I^2 = 89\%$) and a nearly three-fold risk for advanced histological severity, including MASH and bridging fibrosis (OR 2.84, 95% CI: 2.07–3.90, $I^2 = 0\%$). The systematic synthesis of high-quality observational data strongly establishes hypothyroidism as a potent, independent risk factor for MASLD. Mechanistically, this is driven by localized "hepatic hypothyroidism." In the therapeutic domain, Phase 3 trials of the THR- β agonist Resmetirom achieved significantly higher MASH resolution compared to placebo (up to 29.9% vs. 9.7%, $P < 0.05$), establishing a new paradigm in structural disease reversal. Similarly, an earlier meta-analysis by He et al. (2017) encompassing over 42,000 participants corroborated these findings, reporting an adjusted pooled OR of 1.72 (95% CI: 1.32–2.23, $P < 0.001$) for NAFLD in hypothyroid patients.

Regional cohort dynamics further support this systemic burden. The Phenome India-CSIR Health Cohort Knowledgebase (PI-CHeCK) study, a nationwide prospective initiative evaluating 7,764 eligible adults across 27 cities, revealed a staggering age-adjusted MASLD prevalence of 38.9% (95% CI: 37.2–40.6%). Significant hepatic fibrosis was observed in 2.4% of the overall population. Highly controlled case-control data by Dalai et

al. (2024) demonstrated that 84% of hypothyroid patients exhibited fatty liver changes compared to only 12% of euthyroid controls. Patel et al. (2023) further determined that MASLD was present in 59.15% of untreated hypothyroid subjects, with structural severity significantly more pronounced in overt clinical hypothyroidism. Even mild dysfunction plays a role; a retrospective cohort analysis by Fan et al. (2023) of 19,946 adults showed that subclinical hypothyroidism significantly increased the risk of advanced fibrosis in MASLD patients (FIB-4 > 2.67: OR = 1.41; NFS > 0.676: OR = 1.72).

Mechanistically, this is driven by localized "hepatic hypothyroidism." The underlying factors that affect this progression remain intricately tied to cellular molecular biology. The canonical metabolic effects of thyroid hormones are executed through highly conserved genomic pathways. TR- α 1 regulates cardiac effects, whereas TR- β 1 is the overwhelmingly dominant receptor subtype expressed within the hepatic parenchyma. In states of active MASH, chronic lipotoxicity triggers the release of pro-inflammatory cytokines, which potently suppress hepatic Type 1 deiodinase (D1) enzymatic activity. This triggers a localized state of "hepatic hypothyroidism."

This intracellular hormone deficiency severely exacerbates mitochondrial dysfunction. T3 heavily upregulates Carnitine Palmitoyltransferase 1A (CPT1A) for β -oxidation and is an absolute physiological requisite for "lipophagy"—the autophagic degradation of intracellular lipid droplets. In the absence of functional TR- β signaling, unoxidized fatty acids accumulate, generating lipotoxic intermediates that drive chronic hepatic stellate cell activation and relentless fibrogenesis.

The realization of this "double hit" mechanism has spurred decades of intense pharmacological innovation. Historical compounds (e.g., Eprotirome) failed due to TR- α mediated cardiac and cartilage toxicities. The modern thyromimetic era is defined by Resmetirom (MGL-3196), a highly selective, orally active, liver-directed THR- β agonist. Its clinical efficacy was definitively established in the pivotal Phase 3 MAESTRO-NASH trial involving 966 adults with biopsy-confirmed MASH and fibrosis. At Week 52, MASH resolution with no worsening of fibrosis was achieved in 25.9% of the 80 mg cohort and 29.9% of the 100 mg cohort, compared to 9.7% for placebo ($P < 0.001$ for both). Furthermore, fibrosis improvement by at least one full stage was observed in 24.2% (80 mg) and 25.9% (100 mg) of patients, versus 14.2% for placebo ($P < 0.001$). Resmetirom also drove massive improvements in lipid profiles, lowering LDL cholesterol by up to 16.3% by Week 24. However, modern drugs like Resmetirom actively exploit hepatic uptake transporters (OATP1B1/OATP1B3) to isolate the active compound within the liver, while VK2809 utilizes intracellular CYP450 cleavage. The successful Phase 3 results of Resmetirom, yielding FDA accelerated approval in 2024, forcefully short-circuits the deadly intracellular cycle of lipotoxicity.

VK2809 represents a concurrent, highly innovative tissue-specific prodrug. The Phase 2b VOYAGE trial rigorously evaluated VK2809 over 52 weeks. At 12 weeks, up to 85% of treated patients achieved a $\geq 30\%$ relative decrease in total liver fat, increasing to 88% by week 52. Histologically, MASH resolution without worsening of fibrosis was achieved in up to 75.0% of patients receiving the highest evaluated doses, compared

to 29.3% in the placebo cohort ($P < 0.05$). Furthermore, 56.8% of patients receiving the 10 mg dose achieved a $\geq$ 1-stage improvement in liver fibrosis compared to 34.1% on placebo ($P = 0.0497$).

This study has some limitations. First, the retrospective nature of several cross-sectional epidemiological studies prevents establishing a strict temporal timeline between the exact onset of hypothyroidism and MASLD progression. Second, while the histological endpoints achieved by Resmetirom and VK2809 are excellent surrogate markers, hard clinical outcome data detailing absolute reductions in decompensated cirrhosis and all-cause mortality are still maturing in ongoing long-term extension trials.

CONCLUSIONS

In conclusion, the presence of primary hypothyroidism is associated with a significantly increased risk of developing MASLD, MASH and advanced fibrosis. The subpopulation of patients with intersecting metabolic syndrome and thyroid dysfunction must be actively screened. Considering the vulnerability for adverse outcomes with increase MASH and advanced fibrosis, this subpopulation must be continuously screened and monitored for intersecting metabolic dysfunctions. Furthermore, correcting states of hepatic hypothyroidism through targeted liver-directed THR- β agonism represents a clinically validated, highly efficacious disease-modifying therapeutic strategy, fundamentally shifting the paradigm of MASLD management.

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