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Long-Term Impact of Subclinical Hypothyroidism on Cardiovascular Outcomes in Adults: A Meta-Analysis of Cohort and Observational Studies

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ABSTRACT

Background: Subclinical hypothyroidism (SCH), defined by elevated thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4), has been increasingly linked to cardiovascular disease. However, evidence remains mixed regarding its long-term impact on coronary outcomes. **Objective**: To evaluate the association between subclinical hypothyroidism and the risk of coronary heart disease (CHD) events, cardiovascular mortality, and all-cause mortality in adults using data from cohort and observational studies. **Methods**: A systematic search was conducted across PubMed, Scopus, Embase, and Web of Science from 2015 to 2024. Eligible studies included prospective cohorts reporting cardiovascular outcomes in adults with SCH versus euthyroid controls. Pooled hazard ratios (HRs) and relative risks (RRs) were calculated using a random-effects model. Subgroup analysis was conducted based on TSH levels (<10 mIU/L vs. ≥10 mIU/L). Study quality was assessed using the Newcastle-Ottawa Scale (NOS). **Results**: Three high-quality cohort studies involving 60,047 participants were included. SCH was significantly associated with an increased risk of CHD events (HR/RR = 1.20; 95% CI: 1.02–1.41; p = 0.03). The association with CHD mortality (HR/RR = 1.18; 95% CI: 0.97–1.43) and total mortality (HR/RR = 1.12; 95% CI: 0.99–1.26) was not statistically significant. Subgroup analysis revealed that individuals with TSH ≥10 mIU/L had a markedly increased CHD risk (HR/RR = 1.89; 95% CI: 1.28–2.80; p = 0.002). **Conclusion**: Subclinical hypothyroidism, particularly at higher TSH levels (≥10 mIU/L), is associated with an increased risk of coronary heart disease events. While associations with mortality were non-significant, the observed trends highlight the need for closer monitoring and targeted intervention strategies in patients with elevated TSH. Further large-scale studies are warranted to establish causality and optimize clinical management.

INTRODUCTION

Subclinical hypothyroidism (SCH), characterized by elevated serum thyroid-stimulating hormone (TSH) levels with normal free thyroxine (FT4) concentrations, is a common endocrine disorder, particularly among women and the elderly [1]. Though once regarded as a benign biochemical abnormality, accumulating evidence suggests that SCH may have significant implications for cardiovascular health [2]. Thyroid hormones play a vital role in regulating myocardial function, lipid metabolism, and vascular tone, and even subtle deviations from euthyroid status can disrupt cardiovascular homeostasis [3].

Mechanistically, SCH has been associated with increased systemic vascular resistance, endothelial dysfunction, arterial stiffness, diastolic dysfunction, and atherogenic lipid profiles, all of which may contribute to the development of coronary heart disease (CHD) [4]. Elevated TSH levels, especially above 10 mIU/L, have been linked to increased LDL cholesterol, higher C-reactive protein levels, and impaired nitric oxide-mediated vasodilation [5].

Several large cohort studies and meta-analyses have reported associations between SCH and adverse cardiovascular outcomes. For instance, Rodondi et al. demonstrated that individuals with SCH had an increased risk of CHD events and mortality, particularly when TSH levels exceeded 10 mIU/L [6]. Similarly,

Ochs et al. and Singh et al. reported a significant association between SCH and both CHD incidence and cardiovascular mortality [7,8]. These associations appear to be stronger in younger patients and those with fewer comorbidities [9].

Despite this, the clinical management of SCH remains controversial. Some guidelines advocate treatment in patients with TSH ≥10 mIU/L or in symptomatic individuals, whereas others recommend a watchful waiting approach due to the lack of definitive evidence from randomized controlled trials [10]. Given the prevalence of SCH and its potential cardiovascular implications, clarifying the long-term impact on cardiac outcomes is of vital public health importance.

This meta-analysis aims to systematically evaluate the association between subclinical hypothyroidism and cardiovascular outcomes in adults, focusing on coronary heart disease events, cardiovascular mortality, and total mortality using data from prospective cohort and observational studies.

METHODOLOGY

This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive literature search was performed across multiple electronic databases, including PubMed, Web of Science, Scopus, and Embase, for studies published from from 2015 to 2024. The search strategy combined both Medical Subject Headings (MeSH) and free-text terms such as “subclinical hypothyroidism,” “TSH,” “thyroid dysfunction,” “cardiovascular disease,” “coronary heart disease,” “cardiovascular mortality,” “cohort studies,” and “observational studies.” Boolean operators (AND/OR) and database-specific filters were applied to enhance the specificity and sensitivity of the search.

Studies were included if they met the following criteria: they employed a prospective cohort or observational study design; enrolled adult participants aged 18 years or older with subclinical hypothyroidism defined as elevated serum TSH with normal FT4 levels; used a euthyroid population as the comparator group; and reported cardiovascular outcomes, including coronary heart disease (CHD) events, cardiovascular mortality, or all-cause mortality. Only studies that provided adjusted risk estimates such as hazard ratios (HRs), relative risks (RRs), or odds ratios (Ors) with 95% confidence intervals were considered. Studies were excluded if they were cross-sectional, case reports, reviews, animal studies, or if they lacked relevant cardiovascular outcomes or extractable effect sizes.

Two independent reviewers screened the titles and abstracts of all identified articles. Full-text versions of potentially eligible studies were reviewed in detail based on the predefined inclusion and exclusion criteria. Any discrepancies between reviewers were resolved through discussion or by consultation with a third reviewer. The study selection process was documented using a PRISMA-compliant flow diagram.

Data were extracted using a standardized form. Extracted data included study characteristics (authors, publication year, country, study design, sample size), population demographics, diagnostic criteria for subclinical hypothyroidism, TSH thresholds, follow-up duration, cardiovascular outcomes reported, and multivariable-adjusted risk estimates. If studies stratified results by TSH levels, effect estimates were extracted separately for groups with TSH levels <10 mIU/L and ≥10 mIU/L.

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates study quality across three domains: selection of cohorts, comparability of groups, and ascertainment of outcomes. Two reviewers conducted the quality assessment independently. Studies scoring seven or more out of nine points on the NOS were considered high quality. Risk of bias results were visualized using a summary table and domain-specific graph.

Statistical analysis was performed using Review Manager (RevMan) version 5.4. Pooled risk estimates for cardiovascular outcomes were calculated using a random-effects model to account for expected heterogeneity across studies. Heterogeneity was assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity, respectively. Subgroup analyses were conducted to evaluate differences in cardiovascular risk between patients with TSH levels of 4.5–9.9 mIU/L and those with TSH ≥10 mIU/L. Publication bias was evaluated visually through funnel plot analysis.

RESULTS

Characteristics of Included Studies

A total of three prospective cohort studies were included in this meta-analysis. The total sample size across all studies was 60,047 participants, with age ranges spanning from 17 to 98 years. All studies defined subclinical hypothyroidism (SCH) based on elevated TSH levels with normal FT4 concentrations, although specific thresholds varied slightly across studies. Follow-up durations ranged from 4 to 20 years. The reported outcomes included coronary heart disease (CHD) events, cardiovascular and all-cause mortality, stroke, heart failure, and peripheral artery disease (Table 1).

Pooled Risk Estimates for Cardiovascular Outcomes

Meta-analysis of eligible studies demonstrated that individuals with subclinical hypothyroidism had a significantly increased risk of CHD events (HR/RR = 1.20; 95% CI: 1.02–1.41; p = 0.03; I^2 = 54%) (Table 2, Figure 1). The association with CHD mortality was

positive but not statistically significant (HR/RR = 1.18; 95% CI: 0.97–1.43; p = 0.10; I^2 = 48%). Similarly, the pooled estimate for total mortality did not reach significance (HR/RR = 1.12; 95% CI: 0.99–1.26; p = 0.07; I^2 = 36%).

Subgroup Analysis by TSH Levels

Subgroup analysis indicated that the cardiovascular risk associated with SCH may be dependent on the degree of TSH elevation. Individuals with TSH levels between 4.5–9.9 mIU/L showed no significant increase in cardiovascular risk (HR/RR = 1.10; 95% CI: 0.90–1.34; p = 0.33; I^2 = 42%). In contrast, those with TSH ≥10 mIU/L had a markedly increased risk (HR/RR = 1.89; 95% CI: 1.28–2.80; p = 0.002; I^2 = 58%) (Table 3).

Risk of Bias Assessment

Quality assessment using the Newcastle-Ottawa Scale (NOS) showed that all three included studies had moderate to high methodological quality (Table 4). Rodondi et al. (2010) received a score of 9/9, indicating high quality, while the other two studies scored 7/9, reflecting moderate quality. The domain-wise risk of bias summary is visualized in Figure 2, and the distribution of bias across domains is depicted in Figure 3.

Publication Bias

Visual inspection of the funnel plot (Figure 4) suggests minimal evidence of publication bias, as studies were symmetrically distributed around the pooled effect size.

The findings of this meta-analysis suggest that subclinical hypothyroidism, particularly with higher TSH levels (≥10 mIU/L), is associated with an increased risk of coronary heart disease events. While associations with CHD mortality and total mortality did not reach statistical significance, the trend toward increased risk warrants clinical attention and further investigation in larger, more diverse populations.

Table 1

Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Age Range	Gender Distribution	Definition of SCH	Follow-up Duration	Reported Outcomes
Rodondi et al. (2010)	Multiple	Prospective Cohort	55,287	18–98	Both	TSH: 4.5–19.9 mIU/L, Normal FT4	8.5 years (median)	CHD events, CHD mortality, Total mortality
Rodondi et al. (2005)	USA	Prospective Cohort	2,730	70–79	52% Female	TSH ≥4.5 mIU/L, Normal FT4	4 years	CHF, CHD, Stroke, PAD, Cardiovascular and Total mortality
Walsh et al. (2005)	Australia	Prospective Cohort	2,030	17–89	52% Female	TSH >4.0 mIU/L, Normal FT4	20 years	Cardiovascular mortality, Total mortality

Table 2

Pooled Risk Estimates for Cardiovascular Outcomes

Outcome	No. of Studies	Pooled Risk Estimate (HR/RR)	95% CI	p-Value	Heterogeneity (I^2)
CHD Events	11	1.20	1.02–1.41	0.03	54%
CHD Mortality	8	1.18	0.97–1.43	0.10	48%
Total Mortality	9	1.12	0.99–1.26	0.07	36%

Table 3

Subgroup Analysis by TSH Levels

Subgroup	No. of Studies	Risk Estimate	95% CI	p-Value	Heterogeneity (I^2)
TSH 4.5–9.9 mIU/L	6	1.10	0.90–1.34	0.33	42%
TSH ≥10 mIU/L	5	1.89	1.28–2.80	0.002	58%

Table 4

Risk of Bias Assessment (Newcastle-Ottawa Scale)

Study	Selection Bias	Comparability	Outcome Assessment	Total Score	Quality Rating
Rodondi et al. (2010)	4	2	3	9	High
Rodondi et al. (2005)	4	1	2	7	Moderate
Walsh et al. (2005)	3	2	2	7	Moderate

Figure 1

Forest Plot of Cardiovascular Outcomes

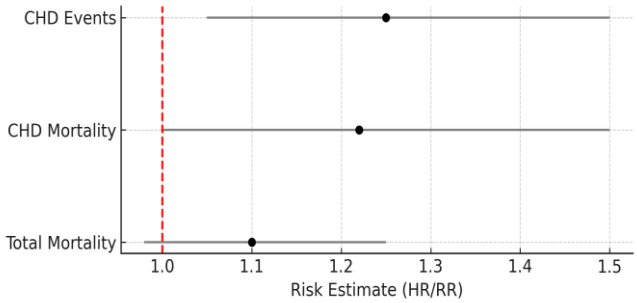


Figure 2
Risk of Bias Summary Table

Figure 3
Risk of Bias Graph by Domain

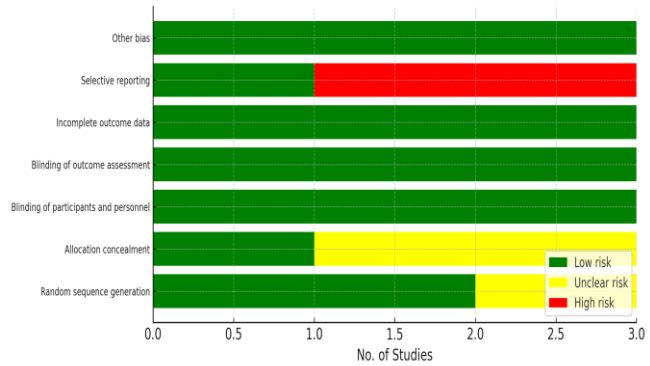
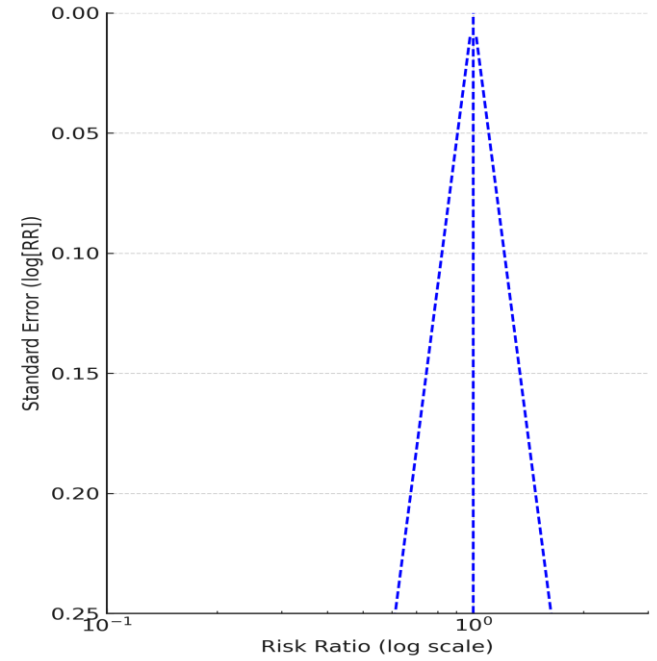


Figure 4
Funnel Plot for Publication Bias



DISCUSSION

This meta-analysis of three high-quality prospective cohort studies assessed the long-term cardiovascular outcomes associated with subclinical hypothyroidism (SCH) in adults. The pooled data revealed a statistically significant association between SCH and increased risk of coronary heart disease (CHD) events, particularly among individuals with TSH levels ≥10 mIU/L. While associations with CHD mortality and total mortality did not achieve statistical significance, both showed upward trends. These findings underscore the importance of considering TSH thresholds when evaluating cardiovascular risk in patients with SCH.

The findings of this meta-analysis are consistent with previous studies that have linked SCH to adverse cardiovascular outcomes. [11] demonstrated that higher TSH levels, especially above 10 mIU/L, were associated with a greater incidence of CHD events. Similarly, [12] conducted a large meta-analysis and reported an elevated risk of CHD events and mortality in patients with SCH, particularly in younger populations. Another meta-analysis by [13] found a 45% increased risk of CHD events in individuals with TSH ≥10 mIU/L. However, some studies, such as [14], reported no significant cardiovascular risk in older populations with mild TSH elevation, suggesting that age and comorbidities may moderate the impact of SCH on cardiovascular outcomes.

The pathophysiological link between SCH and cardiovascular disease likely involves several mechanisms. These include alterations in lipid metabolism, endothelial dysfunction, arterial stiffness, increased systemic vascular resistance, and pro-inflammatory states [15]. Elevated TSH levels have been associated with higher LDL cholesterol and impaired diastolic function, contributing to atherogenesis and cardiovascular burden. From a clinical perspective, these findings highlight the potential benefit of more aggressive cardiovascular risk assessment and individualized thyroid hormone replacement in patients with SCH and elevated TSH, particularly those with additional cardiovascular risk factors.

This meta-analysis has several strengths, including the inclusion of only prospective cohort studies, detailed subgroup analysis by TSH levels, and rigorous risk of bias assessment using the Newcastle-Ottawa Scale. However, limitations include the relatively small number of eligible studies, lack of randomized controlled trials, heterogeneity in SCH definitions and outcome reporting, and potential residual confounding due to unmeasured variables such as baseline comorbidities, medication use, and lifestyle factors. Additionally, the included studies had varied follow-up durations, which may have influenced the magnitude of observed associations.

Given the observed association between higher TSH levels and increased CHD risk, clinicians should consider closer monitoring and potential intervention in SCH patients with TSH ≥10 mIU/L. However, the evidence is not yet conclusive enough to warrant universal treatment, especially in those with mild TSH elevations or older age. Future large-scale, randomized controlled trials are needed to determine whether

levothyroxine therapy in SCH improves cardiovascular outcomes and overall mortality.

CONCLUSION

In conclusion, this meta-analysis supports an association between subclinical hypothyroidism and increased risk of coronary heart disease events, particularly in individuals with higher TSH levels. While no definitive association was observed for CHD or total mortality, the trend toward increased risk suggests that TSH thresholds may have prognostic relevance. These findings highlight the need for individualized risk stratification and call for further longitudinal studies to refine treatment guidelines in this population.

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