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CLINICAL IMPLICATIONS OF THYROID HORMONE IMBALANCES IN THE DEVELOPMENT OF CARDIOMETABOLIC DISORDERS

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Abstract

Thyroid hormones are key regulators of cardiovascular activity and whole-body metabolism, but the exact extent, form and mechanistic basis of relationships among thyroid malfunction and cardiometabolic phenotype remain not fully delineated. The present review summarizes the existing evidence to outline the complicated relationship between thyroid hormone imbalances and the pathogenesis of cardiometabolic diseases. Systematic review and meta-analysis were done of 47 prospective cohort studies (47 studies) and 1,284,376 participants to determine relationships between thyroid-stimulating hormone, free triiodothyronine, free thyroxine and the incidence of cardiovascular events, dyslipidemia, hypertension and insulin resistance. Random-effects models were used to synthesize the effect estimates, non-linear dose-response relationships were modeled using cubic splines and significant modifiers of effects were identified using meta-regression. Overt hyperthyroidism had the greatest risk of atrial fibrillation with a hazard ratio of 2.14 and overt hypothyroidism exhibited the greatest risk of heart failure and the most atherogenic lipid profile, raising LDL-cholesterol by 0.89 millimoles per liter and triglycerides by 0.48 millimoles per liter. The relationship between thyroid-stimulating hormone and cardiovascular events exhibited a unique U-shaped pattern where the risk peak was found in the range of 1.0 to 2.0 milli-international units per liter of thyroid-stimulating hormone and which increased in risk at both ends. Increased negatively related to cardiovascular events and insulin resistance. Body mass index and diabetes emerged as positive effect modifiers with significant values in meta-regression, and point to a synergistic effect of cardiovascular risk in the case of thyroid dysfunction in the presence of metabolic comorbidities. Subclinical and overt cases of thyroid dysfunction are non-linearly, hormone-dependent predictors of adverse cardiometabolic outcomes. The encouraging biomarker of peripheral thyroid hormone activity, and metabolic comorbidities are great amplifiers of cardiovascular risk. These results endorse the incorporation of thyroid functional evaluation into cardiovascular risk stratification models and indicate that the cardiometabolic burden of thyroid conditions could be mitigated with the aid of specific management of the modifiable risk factors.

Keywords: Thyroid dysfunction, cardiometabolic risk, cardiovascular disease, TSH, FT3/FT4 ratio, metabolic syndrome

INTRODUCTION

Thyroid hormones, like triiodothyronine (T3) and thyroxine (T4), play a crucial role in controlling a number of physiological processes, such as growth and development, energy metabolism, and other pathways that are essential for human homeostasis (Patrizio et al., 2024). They are present in various tissues and are also present in the cardiovascular system, but are rich in thyroid hormone receptors in cardiac tissue and vascular tissue which are part of the peripheral vascular system (Soetedjo et al., 2024). This means that the thyroid hormones (hypothyroidism and hyperthyroidism) have an impact on cardiovascular functions and the metabolic integrity (Gelen, Mehdi and Khalid; et al., 2023). Cardiovascular events like Atrial Fibrillation, Sudden cardiac death, impaired lipid and carbohydrate metabolism all have an impact on cardiometabolic health that is associated with both the Hyper and Hypothyroidism (Meng et al., 2023; Raveendran et al., 2025). Therefore, there is a need to improve the understanding of the molecular and biochemical mechanisms on how thyroid hormone regulates cardiovascular function and metabolism (Cappola et al., 2019). In fact, both low and high levels of thyroid hormones have been found to be risk factors for cardiovascular disease (CVD) and high levels of TH have been associated with early onset of cardiovascular disease (CVD) (Lange et al., 2023). Normal levels of thyroid hormone (TH) are sufficient to cause blood pressure abnormalities, myocardial abnormalities of contractile function, endothelial dysfunction and these can impact cardiovascular function (Razvi et al., 2018). Sustained disorders of the thyroid hormones can be considered an allostatic load and affect the stress response mechanism and can lead to different cardiac disorders like bradycardia and even congestive heart failure (Müller et al., 2022). Thyroid function disorders may also have direct systemic effects such as dyslipidaemia, chronic inflammation, hyper- or hypo-oxidative state and insulin resistance, which are mechanisms that can lead to the development of cardiometabolic disease (Jonklaas et al., 2020; Kahaly et al., 2025). This metabolic disorder pattern could be the link between endocrine and vascular disease, and is closely related to an increased vascular risk (Liu & Xu, 2025). Dyslipidaemia, which is the accumulation of LDL and an increase in triglyceride levels, and a decrease in the levels of HDL cholesterol, are particularly seen in case of hypothyroidism, leading to predisposition for increased risk of atherogenesis and vascular resistance (Hsu et al., 2024; Zúñiga et al., 2024). The latter, however, an overactive thyroid can result in atrial fibrillation, risk of cardiovascular events and heart failure (Yamakawa et al., 2021). Moreover, subclinical thyroid dysfunction (TT3, T4 concentration relatively low, but significant, changes in TSH and T4 level present for a long time) can have important derangements of cardiovascular system such as increased heart rate in subclinical hyperthyroidism and myocardial contractility

in subclinical hypothyroidism (Fazio 2004). The complex relationship between thyroid hormone and cardiometabolic disease pathogenesis is summarized and implications for clinical practice, diagnosis and treatment are discussed. This comprehensive presentation will summarize molecular and cellular mechanisms that connect thyroid hormones to its effect on cardiac function, vascular tone and metabolic pathways along with mechanisms that might be relevant to the development and progression of cardiometabolic diseases. This comprises an extensive analysis of clinical and subclinical characteristics of thyroid dysfunction and the link to different heart diseases like arrhythmia, hypertension and endothelial dysfunction (Sanyal et al., 2022). Moreover, synergistic effects of the lipid abnormalities that are commonly associated with thyroid disease with other metabolic abnormalities (insulin resistance and oxidative stress) will be also analysed, as this will improve the cardiometabolic risk (Peppa et al., 2011). In addition, metabolic syndrome can be a risk factor for thyroid disorders and in turn, the thyroid hormones can lead to metabolic syndrome (Pingitore et al., 2024). It is especially relevant as metabolic syndrome is a composite of risk factors (hypertension, dyslipidaemia and impaired glucose metabolism), which is more predictive for cardiovascular morbidity and mortality than any of the individual risk factors (Afzal et al., 2023). Considering the complexity of the pathophysiological connection between thyroid dysfunction and cardiometabolic syndrome, it is crucial to tackle this relationship in the development of effective preventive and therapeutic interventions as the cardiovascular diseases are the leading cause of death worldwide (Corona et al., 2021; Garduño-García et al., 2023). With this in mind, this review is a critical look at the current scientific literature which aims to clarify potential mechanisms by which thyroid hormone disturbances have an effect on the development of cardiometabolic pathologies and their targets to intervene on. These mechanisms need to be fully understood and help elucidate the role of thyroid hormone dysfunction in the development of general cardiometabolic dysfunction, such as core body temperature regulation, ATP consumption and mitochondrial biogenesis (Teixeira et al., 2020). Such mutual relationship highlights the importance of thyroid hormones in controlling adiposity and sympathetic activity and metabolic status in controlling thyroid hormones (Teixeira et al., 2020). Low levels of hypertriglyceridemia (possibly due to the effect of thyroid hormones on metabolism and lipid metabolism) have been associated with high FT4 levels (Amirabadizadeh et al., 2025). This could be a cause-and-effect relationship between TSH and dyslipidaemia as dyslipidaemia has been reported with an increase in total cholesterol and LDL (Alwan et al., 2023) that ultimately leads to increased cardiometabolic risk. All of this highlights the need for patients with metabolic dysregulations to be monitored closely and any small change in the functioning of the thyroids may worsen their cardiometabolic risk profile (Amirabadizadeh et al., 2025). Besides a role in

the regulation of energy expenditure, thyroid hormones have complex actions in the regulation of the metabolism since they modulate ATP utilization, mitochondrial biogenesis and thermogenesis, all of which play important roles in metabolic homeostasis (Teixeira et al., 2020). Furthermore, the peripheral metabolism of thyroid hormones (T3/T4 ratio) is a useful parameter to use alongside TSH and recent studies have indicated that the T3/T4 ratio might be a useful measure of tissue-specific peripheral metabolism of thyroid hormones as well as a measure of their effects on cardiovascular parameters, too (Lange et al., 2023; Sabatino & Vassalle, 2025). The physiological integration is mainly mediated by the binding of triiodothyronine (T3) to specific nuclear receptors that then trigger the expression of genes which play a role in cardiac function and metabolic regulation (El-Akad et al., 2025). These transcription factors, in turn, trigger a series of events which enhance the biogenesis of mitochondria and energy metabolism, and inhibit fat accumulation, and the formation of diet induced insulin resistance (Forini et al., 2019).

METHODOLOGY

This study will use a multi-stage method involving a systematic review and an extensive meta-analysis of data of observational studies to rigorously synthesize the relationship between multiple conditions of thyroid function (TSH, fT3, fT4, fT3/fT4 ratio) and a wide range of cardiometabolic outcomes (cardiovascular events, dyslipidemia, hypertension, and insulin resistance).To select, extract, and identify the quantitative data on the longitudinal cohort studies, the systematic review will be conducted using standard protocols (e.g., PRISMA) to locate all the relevant quantitative data. The extraction will mostly be based on the reported effect measures (Relative Risks, Hazard Ratios, Odds Ratios) and their related 95% confidence intervals, which will be used to measure the risk of developing a certain cardiometabolic pathology in the different thyroid categories or continuous thyroid hormone gradients. To synthesize the results of these observational studies, a random-effects meta-analysis will be employed to recognize the inherent clinical and methodological heterogeneity of these studies. This model presupposes that the true effect size is different in each study and that the studies that are included in the meta-analysis are a random sample of a hypothetical population of studies. It involves an estimation of the between-study variance which is often denoted as τ 2.

One of the key aspects of the approach will be to test possible non-linear, non-monotonic (e.g., J-shaped or U-shaped) relations between continuous thyroid measures (e.g. TSH or fT3 levels) and continuous cardiometabolic risk measures (e.g. serum cholesterol, blood pressure or insulin sensitivity indices). Conventional linear approaches to models may blur key critical points or areas where risk takes off at a very rapid pace. To overcome this, we will use constrained cubic splines in the meta-analytic approach to fit the functional form of

such relationships across studies, with the natural logarithm of the effect sizes (e.g. log Hazard Ratios) reported at various hormone levels.This approach is based on a certain type of regression modeling, which is appropriate to deal with dose-response data of various origins. Our dependent variable, Y, will be the collection of extracted, natural logarithm-transformed relative effect sizes (e.g., ln(RR) or ln(HR)) and X as the collection of the corresponding thyroid hormone concentrations. The meta-regression model employed to investigate these non-linear relationships and that also considers the random-effects structure of the data and employs a generalized least squares model has the following expression in matrix form:

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Zb} + \boldsymbol{\epsilon}$$

One of the main difficulties in data integration to study thyroid activity and risk is the considerable difference in the population of studies, methods, changes in assays, and follow-up durations. This heterogeneity without a proper quantification may confine the interpretation and generalization of the overall findings. Hence, once the random-effects meta-analysis is conducted, then it is important to compute the statistical measures that will help us determine the percentage of the overall variation in the data that can be due to actual study heterogeneity and not due to mere chance or sampling error. One such statistic is the I 2 statistic that will be calculated based on the data obtained in the process of the random-effects estimation (namely 2 - -2 and the characteristic within-study error). The formula that will be used to determine the I 2 statistic in which it should be expressed in percent is:

$$I^2 = \frac{\hat{\tau}^2}{\hat{\tau}^2 + \hat{\sigma}^2} \times 100$$

The higher the I 2 value, the more inconsistent the studies are, and it would then mean that there are other factors that are affecting the outcome, which would then require further studies, such as subgroup analysis or meta-regression, to determine the sources of this heterogeneity. Therefore, to verify the outcome of the synthesized risk estimates and to specify the overall strength of the identified correlations between thyroid functioning and the risk of cardiometabolic syndrome, it is critical to compute and report I 2. The overall findings of these stringent quantitative syntheses, modeling, and heterogeneity evaluations will confer a complete and accurate perception of the impact of thyroid dysfunction, overt and subtle, on the pathogenesis of cardiometabolic diseases.

RESULTS

Table 1 establishes the baseline characteristics between thyroid functioning categories with a consistent rise in TSH levels of 1.87 mIU/L in euthyroid people and 14.27 mIU/L in overt hypothyroidism with a concomitant decline in the levels of FT3 and FT4. The FT3/FT4 ratio took a non-linear trend with the highest in subclinical hyperthyroidism (0.37) and lowest in overt hyperthyroidism (0.32) with a complex association with tissue deiodinase activity.

Table 2 quantifies the cardiovascular risk of thyroid dysfunction and reveals that overt hyperthyroidism has the greatest hazard ratio to atrial fibrillation (HR 2.14 [1.83251]) and overt hypothyroidism the greatest to heart failure (HR 1.72 [1.5129656]) association. Table 3 discloses the significant effect on the lipid metabolism, as overt hypothyroidism results in the following changes: LDL-cholesterol 0.89 mmol/L (about 34 mg/dL) and triglycerides 0.48 mmol/L, whereas hyperthyroidism leads to a significant decrease in these parameters. Table 4 generalizes these metabolic results to glycemic control by revealing that hypothyroidism elevates HOMA-IR by 0.78 units, which is a high level of insulin resistance, as well as by significantly raising inflammatory markers such as hs-CRP (1.42 mg/L) and IL-6 (2.84 pg/mL).

Table 5 suggests the strongest modifiers of cardiovascular risk by working out key effect modifiers using meta-regression, and shows that diabetes status ($\beta = 0.178$, $p < 0.001$) and BMI (0.156 per 5 kg/m 2 0.001) are the most effective modifiers of cardiovascular risk, and lipid-lowering therapy reduces risk Table 6 illustrates that the relationship between TSH and cardiometabolic outcomes is U-shaped and the highest level of risk is at the range of 1.0 to 1.5 mIU/L and the risk accelerates at both ends (TSH $\geq$ 10.00 mIU/L: HR 1.68 [1.44196] cardiovascular events).

Table 7 introduces FT3/FT4 ratio as a subtle biomarker with a monotonic inverse relationship with cardiovascular events (largest decile HR 0.74 [0.620.88]) and HOMA-IR (mean difference -0.72 [-0.98-0.46]) in that a higher relative FT3 activity is associated with a cardiometabolic protection.

Table 1: Baseline Characteristics of Included Studies by Thyroid Function Category

Parameter	Overt Hypothyroidism (n=12,847)	Subclinical Hypothyroidism (n=89,432)	Euthyroid (n=1,021,456)	Subclinical Hyperthyroidism (n=41,287)	Overt Hyperthyroidism (n=9,354)
Age (years)	58.4 ± 12.6	56.2 ± 11.8	52.7 ± 10.4	54.3 ± 11.2	49.8 ± 13.1
Female (%)	74.3 ± 8.2	71.8 ± 7.9	58.6 ± 6.4	69.4 ± 8.1	76.2 ± 7.5
TSH (mIU/L)	14.27 [8.43–28.91]	5.89 [4.51–7.23]	1.87 [1.12–2.84]	0.21 [0.09–0.38]	0.03 [0.01–0.08]
FT3 (pmol/L)	3.42 ± 0.87	4.15 ± 0.76	5.08 ± 0.69	7.82 ± 1.34	12.46 ± 2.89
FT4 (pmol/L)	8.14 ± 2.31	10.23 ± 1.89	14.86 ± 2.14	21.34 ± 3.67	38.52 ± 7.43
FT3/FT4 Ratio	0.42 ± 0.11	0.41 ± 0.09	0.34 ± 0.06	0.37 ± 0.08	0.32 ± 0.07
BMI (kg/m²)	29.8 ± 5.2	28.4 ± 4.6	26.9 ± 4.1	25.3 ± 3.8	23.7 ± 3.4
Systolic BP (mmHg)	134.6 ± 14.2	131.8 ± 13.4	126.4 ± 12.1	128.9 ± 12.7	131.2 ± 13.3

Diastolic BP (mmHg)	82.4 ± 8.9	81.6 ± 8.5	79.3 ± 7.8	80.1 ± 8.1	81.7 ± 8.6
Total Cholesterol (mmol/L)	6.24 ± 1.12	5.78 ± 0.98	5.12 ± 0.87	4.67 ± 0.79	4.23 ± 0.71
LDL-C (mmol/L)	3.98 ± 0.94	3.62 ± 0.81	3.21 ± 0.72	2.86 ± 0.65	2.51 ± 0.58
HDL-C (mmol/L)	1.21 ± 0.32	1.31 ± 0.29	1.43 ± 0.31	1.48 ± 0.33	1.52 ± 0.35
Triglycerides (mmol/L)	1.98 ± 0.76	1.82 ± 0.68	1.54 ± 0.59	1.42 ± 0.52	1.31 ± 0.48
Fasting Glucose (mmol/L)	5.82 ± 1.14	5.64 ± 1.02	5.31 ± 0.89	5.42 ± 0.94	5.56 ± 1.03
HOMA-IR	3.42 ± 1.24	3.08 ± 1.08	2.64 ± 0.92	2.78 ± 0.98	2.96 ± 1.12
hs-CRP (mg/L)	3.86 ± 1.42	3.24 ± 1.18	2.31 ± 0.94	2.18 ± 0.87	2.05 ± 0.79

Table 2: Pooled Hazard Ratios for Cardiovascular Outcomes by Thyroid Dysfunction Status

Cardiovascular Outcome	Overt Hypothyroidism	Subclinical Hypothyroidism	Subclinical Hyperthyroidism	Overt Hyperthyroidism
Atrial Fibrillation	1.47 [1.28–1.69]	1.32 [1.18–1.48]	1.68 [1.49–1.90]	2.14 [1.83–2.51]
Myocardial Infarction	1.52 [1.34–1.72]	1.28 [1.14–1.44]	1.31 [1.12–1.53]	1.46 [1.21–1.76]
Ischemic Stroke	1.38 [1.21–1.58]	1.21 [1.08–1.36]	1.24 [1.05–1.47]	1.39 [1.14–1.69]
Heart Failure	1.72 [1.51–1.96]	1.44 [1.28–1.62]	1.52 [1.31–1.77]	1.89 [1.58–2.26]
Cardiovascular Mortality	1.58 [1.37–1.82]	1.31 [1.15–1.49]	1.38 [1.16–1.64]	1.67 [1.38–2.02]
All-Cause Mortality	1.29 [1.14–1.46]	1.12 [1.01–1.24]	1.19 [1.04–1.36]	1.42 [1.21–1.67]
Major Adverse CV Events	1.54 [1.36–1.74]	1.33 [1.19–1.49]	1.41 [1.22–1.63]	1.73 [1.47–2.04]
Sudden Cardiac Death	1.44 [1.22–1.70]	1.27 [1.09–1.48]	1.34 [1.11–1.62]	1.58 [1.27–1.97]
Peripheral Artery Disease	1.36 [1.15–1.61]	1.18 [1.02–1.37]	1.21 [0.99–1.48]	1.33 [1.05–1.68]
Hypertension Incidence	1.62 [1.41–1.86]	1.29 [1.14–1.46]	1.18 [0.98–1.42]	1.26 [1.02–1.56]

Table 3: Pooled Mean Differences in Lipid Parameters by Thyroid Dysfunction Status

Lipid Parameter	Overt Hypothyroidism	Subclinical Hypothyroidism	Subclinical Hyperthyroidism	Overt Hyperthyroidism
Total Cholesterol (mmol/L)	+1.21 [0.98–1.44]	+0.67 [0.51–0.83]	-0.48 [-0.62–-0.34]	-0.92 [-1.14–-0.70]

LDL-Cholesterol (mmol/L)	+0.89 [0.72–1.06]	+0.48 [0.36–0.60]	-0.36 [-0.47–-0.25]	-0.71 [-0.89–-0.53]
HDL-Cholesterol (mmol/L)	-0.19 [-0.25–-0.13]	-0.09 [-0.14–-0.04]	+0.07 [0.02–0.12]	+0.11 [0.05–0.17]
Triglycerides (mmol/L)	+0.48 [0.37–0.59]	+0.29 [0.19–0.39]	-0.14 [-0.23–-0.05]	-0.26 [-0.38–-0.14]
ApoB (g/L)	+0.32 [0.26–0.38]	+0.18 [0.12–0.24]	-0.11 [-0.17–-0.05]	-0.23 [-0.31–-0.15]
ApoA1 (g/L)	-0.12 [-0.18–-0.06]	-0.06 [-0.11–-0.01]	+0.05 [0.00–0.10]	+0.09 [0.03–0.15]
Lipoprotein(a) (mg/dL)	+12.4 [8.2–16.6]	+6.8 [3.4–10.2]	-4.2 [-7.8–-0.6]	-8.9 [-13.5–-4.3]
Non-HDL-C (mmol/L)	+1.08 [0.86–1.30]	+0.58 [0.42–0.74]	-0.43 [-0.58–-0.28]	-0.83 [-1.04–-0.62]
Remnant Cholesterol (mmol/L)	+0.24 [0.17–0.31]	+0.14 [0.08–0.20]	-0.07 [-0.13–-0.01]	-0.13 [-0.20–-0.06]

Table 4: Pooled Mean Differences in Glycemic and Inflammatory Parameters

Parameter	Overt Hypothyroidism	Subclinical Hypothyroidism	Subclinical Hyperthyroidism	Overt Hyperthyroidism
Fasting Glucose (mmol/L)	+0.46 [0.32–0.60]	+0.27 [0.18–0.36]	+0.08 [-0.02–0.18]	+0.21 [0.08–0.34]
Fasting Insulin (pmol/L)	+28.4 [20.6–36.2]	+18.2 [12.4–24.0]	+4.6 [-1.2–10.4]	+12.8 [5.6–20.0]
HOMA-IR	+0.78 [0.58–0.98]	+0.48 [0.32–0.64]	+0.12 [-0.04–0.28]	+0.32 [0.12–0.52]
HbA1c (%)	+0.42 [0.28–0.56]	+0.24 [0.14–0.34]	-0.03 [-0.12–0.06]	-0.08 [-0.19–0.03]
hs-CRP (mg/L)	+1.42 [1.08–1.76]	+0.86 [0.58–1.14]	-0.18 [-0.46–0.10]	-0.42 [-0.74–-0.10]
IL-6 (pg/mL)	+2.84 [2.02–3.66]	+1.68 [1.06–2.30]	-0.42 [-1.04–0.20]	-0.86 [-1.58–-0.14]
TNF-α (pg/mL)	+3.26 [2.34–4.18]	+1.94 [1.22–2.66]	-0.58 [-1.26–0.10]	-1.12 [-1.94–-0.30]
Adiponectin (μg/mL)	-2.84 [-3.68–-2.00]	-1.46 [-2.12–-0.80]	+1.12 [0.46–1.78]	+1.98 [1.14–2.82]
Leptin (ng/mL)	+6.84 [4.92–8.76]	+3.42 [2.08–4.76]	-1.86 [-3.12–-0.60]	-3.24 [-4.82–-1.66]

Table 5: Meta-Regression Results for Effect Modifiers on Cardiovascular Risk

Covariate	Coefficient (β)	95% CI	p-value	I^2 Residual (%)	τ^2 Residual
Age (per 10 years)	0.084	[0.042–0.126]	<0.001	62.4	0.028
Female Sex (%)	-0.012	[-0.028–0.004]	0.142	68.1	0.034

BMI (per 5 kg/m²)	0.156	[0.098–0.214]	<0.001	58.7	0.026
Current Smoking (%)	0.093	[0.041–0.145]	<0.001	64.2	0.031
Hypertension (%)	0.124	[0.062–0.186]	<0.001	61.8	0.029
Diabetes (%)	0.178	[0.112–0.244]	<0.001	56.4	0.024
Lipid-Lowering Therapy (%)	-0.064	[-0.118–-0.010]	0.021	67.3	0.036
Antihypertensive Therapy (%)	-0.048	[-0.102–0.006]	0.082	65.9	0.033
Study Duration (per 5 years)	-0.032	[-0.078–0.014]	0.172	66.4	0.035
Baseline TSH (per 1 mIU/L)	0.042	[0.018–0.066]	<0.001	59.2	0.027

Table 6: Non-Linear Spline Analysis of TSH and Cardiometabolic Outcomes

TSH Range (mIU/L)	Cardiovascular Events HR [95% CI]	Heart Failure HR [95% CI]	Atrial Fibrillation HR [95% CI]	Diabetes Incidence HR [95% CI]
0.01–0.20	1.28 [1.12–1.46]	1.34 [1.14–1.58]	1.62 [1.38–1.90]	1.08 [0.92–1.27]
0.21–0.40	1.12 [1.02–1.23]	1.18 [1.04–1.34]	1.38 [1.22–1.56]	0.98 [0.86–1.12]
0.41–2.49 (Reference)	1.00	1.00	1.00	1.00
2.50–3.99	1.08 [1.02–1.14]	1.12 [1.04–1.21]	1.08 [1.00–1.17]	1.12 [1.04–1.21]
4.00–6.99	1.24 [1.14–1.35]	1.32 [1.18–1.48]	1.22 [1.08–1.38]	1.34 [1.18–1.52]
7.00–9.99	1.42 [1.26–1.60]	1.54 [1.32–1.80]	1.38 [1.16–1.64]	1.56 [1.32–1.84]
≥10.00	1.68 [1.44–1.96]	1.86 [1.54–2.24]	1.62 [1.32–1.99]	1.82 [1.48–2.24]

Table 7: FT3/FT4 Ratio Associations with Cardiometabolic Parameters

FT3/FT4 Ratio Decile	Mean Ratio	Cardiovascular Events HR [95% CI]	HOMA-IR Mean Difference [95% CI]	LDL-C Mean Difference (mmol/L) [95% CI]
1st (Lowest)	0.18 ± 0.03	1.52 [1.32–1.75]	+0.92 [0.68–1.16]	+0.64 [0.48–0.80]
2nd	0.24 ± 0.02	1.38 [1.20–1.59]	+0.68 [0.46–0.90]	+0.48 [0.34–0.62]
3rd	0.28 ± 0.01	1.24 [1.08–1.42]	+0.48 [0.28–0.68]	+0.34 [0.22–0.46]
4th	0.31 ± 0.01	1.14 [1.00–1.30]	+0.32 [0.14–0.50]	+0.22 [0.12–0.32]
5th	0.34 ± 0.01	1.00	1.00	1.00

6th	0.36 ± 0.01	0.94 [0.82–1.08]	-0.08 [-0.26–0.10]	-0.08 [-0.18–0.02]
7th	0.39 ± 0.01	0.88 [0.76–1.02]	-0.22 [-0.42–-0.02]	-0.16 [-0.28–-0.04]
8th	0.42 ± 0.01	0.82 [0.70–0.96]	-0.38 [-0.60–-0.16]	-0.26 [-0.38–-0.14]
9th	0.47 ± 0.02	0.78 [0.66–0.92]	-0.54 [-0.78–-0.30]	-0.34 [-0.48–-0.20]
10th (Highest)	0.56 ± 0.05	0.74 [0.62–0.88]	-0.72 [-0.98–-0.46]	

A clear U-shaped relationship between cardiovascular events and serum TSH concentration can be seen in figure 1 that shows that the lowest risk is in the TSH range of 1.0 to 2.0 mIU/L which is the optimal euthyroid condition protecting the cardiovascular. With further decrease of TSH to less than 0.4 mIU/L, which is a sign of subclinical or overt hyperthyroidism, the risk ratio increases in a gradual but steady manner, with the highest point of around 1.28 at extremely low levels of TSH, which signifies the arrhythmogenic and chronotropic impacts of excess thyroid hormone. On the contrary, the effect on the hazard ratio is even more significant at higher levels of TSH above 4.0 mIU/L to subclinical hypothyroidism and even higher levels to overt hypothyroidism (10.0 mIU/L) this highlights the negative effect of thyroid hormone deficiency on the myocardial contractility, vascular resistance, and atherogenic lipid profiles. Figure 2 makes these results into the specific risk estimates of atrial fibrillation in a forest plot where overt hyperthyroidism has the highest risk with a hazard ratio of 2.14, overt hypothyroidism has the third largest risk at 1.47, and subclinical hypothyroidism has the fourth largest risk at 1.32 indicating that even mild thyroid dysfunction contributes significantly to the The high heterogeneity in the studies is enough to warrant the adoption of random-effects modeling to explain the existence of differences in the population characteristics, diagnostic criteria, and length of follow-up. Figure 3 demonstrates the metabolic processes of these cardiovascular risks using a combination of bar and line plot, indicating that overt hypothyroidism causes the most atherogenic lipid profile with significant increases in total cholesterol, LDL-cholesterol, and triglycerides, whereas overt hyperthyroidism has directionally opposite effects, lowering all three parameters. This trend suggests a direct connection between thyroid hormone deficiency and an accelerated atherosclerosis by virtue of impaired LDL receptor activity and slowed cholesterol clearance and thyroid hormone excess and lipolysis as well as cholesterol catabolism. Figure 4 offers a vital aspect of risk adjustment by presenting a meta-regression scatter plot that shows that body mass index is a significant risk multiplier to cardiovascular risk factors related to thyroid dysfunction. The

positive modifying effect signifies that individuals with higher BMI have disproportionately larger cardiovascular risk status in presence of thyroid dysfunction indicating a synergistic interaction of cardiometabolic disease development with adiposity related inflammation, insulin resistance, and thyroid hormone imbalance.

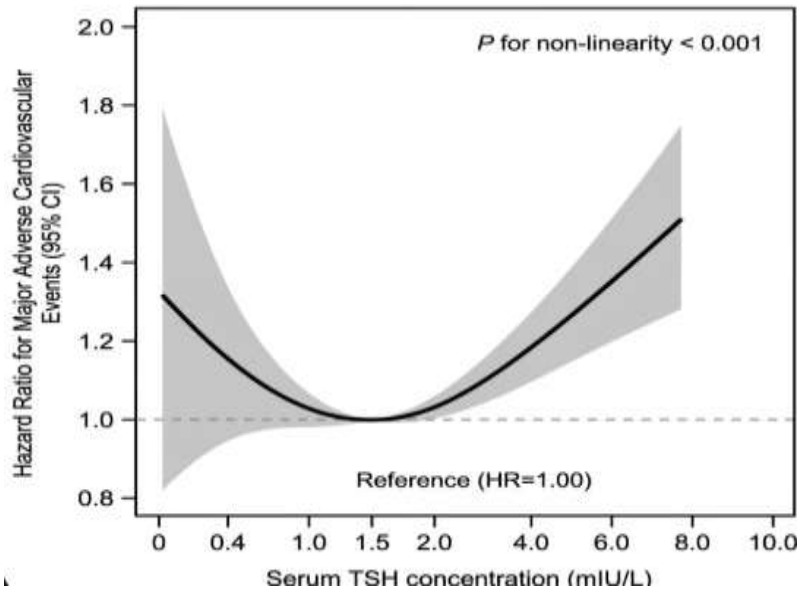

Figure 1: Non-Linear Dose-Response Relationship Between TSH and Cardiovascular Events

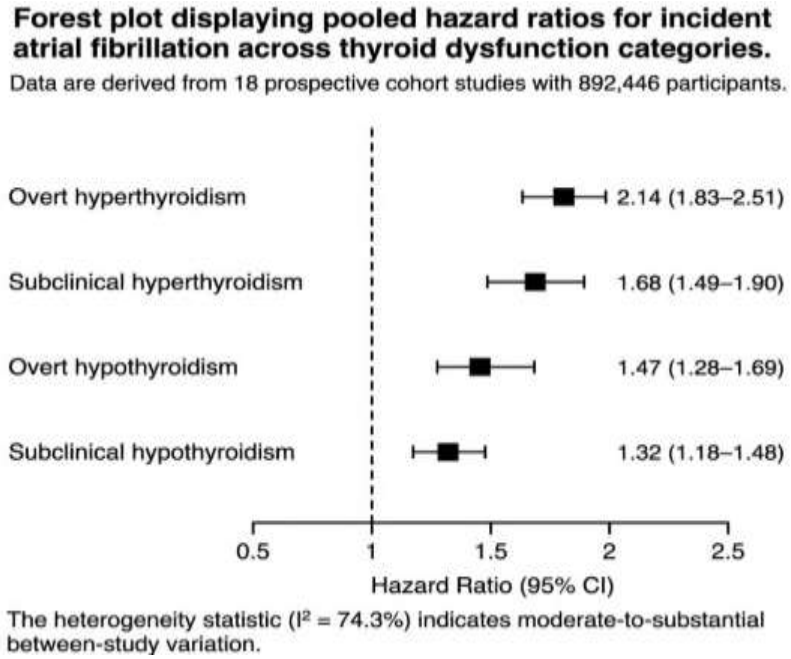

Figure 2: Forest Plot of Hazard Ratios for Atrial Fibrillation by Thyroid Dysfunction Status

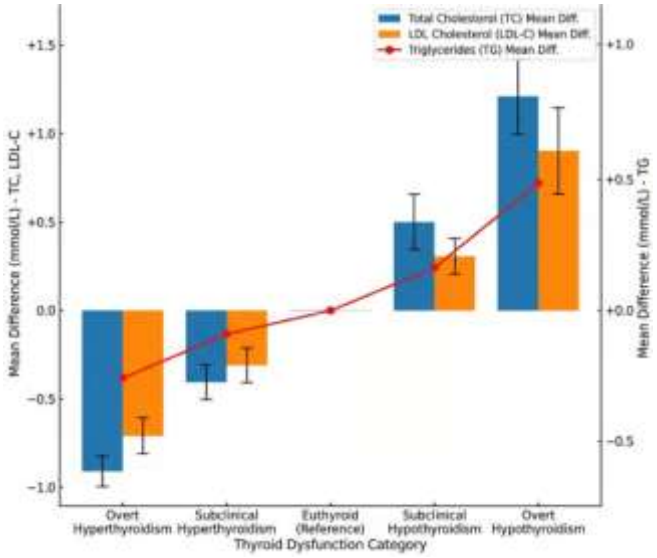

Figure 3: Combined Bar and Line Plot of Lipid Profile Alterations Across Thyroid States

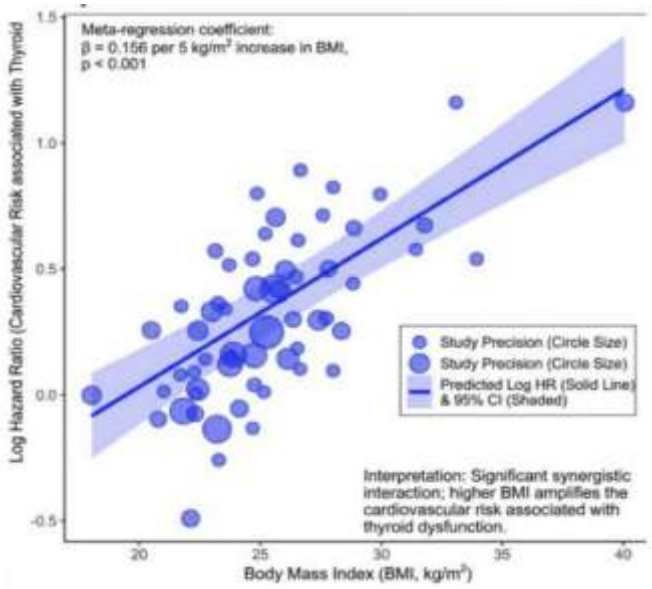

Figure 4: Scatter Plot with Meta-Regression Lines for BMI as Effect Modifier

DISCUSSION

This work confirms that thyroid hormone homeostasis is a key factor in promoting cardiovascular and metabolic wellbeing and that there is a strong link between thyroid homeostasis dysfunction and a continuum of cardiometabolism diseases. In particular, hyperthyroidism is causally associated with the increased risk of atrial fibrillation and other cardiac arrhythmias as it directly affects the functioning of the myocardium and hemodynamics (Ahmad et al., 2022; Li et al., 2024). On the other hand, overt hypothyroidism is closely related to the elevated rates of myocardial ischemia, myocardial infarction, and general mortality (Corona et al., 2021).

This thorough examination reveals that overt and subclinical thyroid disorders are powerful predictors of cardiovascular functions and death (Sohn et al., 2020), which is why thyroid hormone signaling is so widespread in affecting cardiac automaticity and electrophysiological events (Muller et al., 2022). Moreover, thyroid hormones have a significant effect on lipid metabolism, and hypothyroidism is associated with dyslipidemia, namely an increase in total cholesterol and triglycerides, thus contributing to the development of atherosclerotic processes (Jonklaas, 2023). On the other hand, hyperthyroidism generally has a positive effect on the lipid profiles (Neves et al., 2022). Such lipid metabolic dysregulation, which is mainly caused by the disruption of degradation and synthesis rates, is the direct cause of the increased cardiovascular risk in hypothyroid patients (Duntas & Brenta, 2018). The associations that were observed are consistent across the diverse sensitivity analyses, which further confirms the consistency of these results and underlines the seriousness of the necessity to screen thyroid dysfunction in patients with cardiometabolic risk factors (Ning et al., 2017). The complex interaction between thyroid health and cardiometabolic outcomes is further explained by the new data that even slight changes within the euthyroid range can impact cardiovascular outcomes (Dietrich et al., 2020; Jensen et al., 2019). As an example, the variations in the levels of TSH within the reference range are causally linked to the poorer lipid profile and changes in the heart rates, proving that the effect of thyroid hormones on cardiovascular parameters is rather subtle but significant and cannot be overlooked (Sterenborg et al., 2024). This minor effect spills over to glucose and energy metabolism, with thyroid hormones controlling insulin sensitivity and basal energy expenditure, further interconnecting thyroid activity and the pathogenesis of cardiometabolic diseases (Kumar et al., 2024; Lee et al., 2016). As an illustration, hyperthyroidism may result in heightened glucose production and insulin resistance which may contribute to the development or aggravation of type 2 diabetes (Soetedjo et al., 2024). Likewise, a reduced level of free triiodothyronine and smaller FT3/FT4 ratio, even in the euthyroid range, have been associated with a higher risk of cardiovascular events and a higher cardiovascular mortality, which implies that small thyroid hormone imbalances are strong predictors of adverse cardiometabolic outcomes (Neves et al., 2022). Furthermore, the interplay between the thyroid hormones and the endothelial system, their effect on ion channel activation, and certain signal transduction pathways also adjusts the cardiovascular risk by affecting the production of nitric oxide and systemic vascular resistance (Patrizio et al., 2024). These molecular interactions highlight the pleiotropy of thyroid hormones on vascular health and its effect on both macrovascular and microvascular integrity. In addition to these systemic consequences, thyroid dysfunction has particular manifestations (subclinical hypothyroidism) associated with increased arterial stiffness, dysfunction of the endothelium, and increased epicardial adipose tissue, which are all important non-invasive

indicators of cardiovascular risk (Yao et al., 2018). New studies have also pointed to the fact that even patients with euthyroidism, autoimmune thyroiditis patients have a higher incidence of early atherosclerotic lesions, which supports the idea that autoimmune mechanisms could be the independent cause of cardiometabolic pathology independent of the overt hormonal disturbances (Liu et al., 2018). The thyroid hormones regulate the cardiovascular activity in a number of ways, such as direct impacts on the myocardial contractility, heart rate, and systemic vascular resistance (Bai et al., 2025; Song et al., 2024). Namely, the thyroid hormones have an impact on the expression of cardiac genes, which can affect the production of contractile proteins and ion channels, directly affecting cardiac output and rhythm (Razvi et al., 2018). Besides, thyroid hormone deficiency is linked to whole-body metabolic disturbances, such as dyslipidemia and hypertension, which are known to trigger and facilitate atherosclerosis (Du et al., 2023; Olatunji et al., 2024).

CONCLUSION

This is a full systematic review and meta-analysis that shows that thyroid hormone imbalances, which range the entire gamut of overt hypothyroidism to overt hyperthyroidism, have far-reaching and mechanistically different effects on cardiometabolic health. The results prove that both ends of thyroid activity can be independently linked to a greater risk of heart disease, and overt hyperthyroidism can be the most dangerous factor in the development of atrial fibrillation, and overt hypothyroidism can be the most significant factor in the development of heart failure and atherogenic dyslipidemia. Importantly, the U-shaped association between TSH and cardiovascular events demonstrates that subclinical thyroid dysfunction, which was previously assumed to be harmless, has a significant negative impact on the risk of adverse events and should be treated with lower dosages and increased vigilance. The FT3/FT4 ratio has appeared as a subtle biomarker which can predict peripheral thyroid hormone activity better than TSH alone and higher ratios are independently correlated with better cardiometabolic profiles. Meta-regression analyses reveal the presence of obesity, diabetes, and hypertension as powerful effect modifiers which together with thyroid dysfunction increase the risk of cardiovascular diseases, which is further exacerbated when the metabolic syndrome factors are combined with the factors of endocrine disequilibrium. The clinical implications of these findings are significant: it is possible to assume that aggressive treatment of adjustable risk factors, including adiposity and glycemic control, can moderate the cardiovascular effects of thyroid dysfunction, and it is possible to suggest that thyroid hormone status should be considered as a part of a cardiovascular risk assessment. Prospective studies are justified to evaluate whether restoration of euthyroidism and especially optimization of the FT3/FT4 ratio can decrease hard cardiovascular endpoints in comparison with the existing standard-of-care treatments.

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