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# Coronary Artery Disease in Postmenopausal Women with Hypothyroidism: Interaction of Estrogen Deficiency and Thyroid Insufficiency

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**Abstract:** Objective: to systematize data on the mechanisms by which estrogen deficiency and thyroid insufficiency potentiate coronary artery disease (CAD), and to summarize available evidence on the cardiovascular significance of subclinical hypothyroidism in postmenopausal women.

Materials and methods: a structured narrative review was conducted using PubMed, Scopus, eLIBRARY.RU and CyberLeninka databases for the period 2000–2024. Search terms included: hypothyroidism, menopause, coronary artery disease, estrogen deficiency, dyslipidemia, endothelial dysfunction. Inclusion criteria: cohort and case-control studies ($n \geq 100$), meta-analyses (≥ 5 primary studies), systematic reviews with described methodology. A total of 23 sources were included in the final analysis.

Results: overt hypothyroidism increases total cholesterol by up to 50%; subclinical hypothyroidism raises it by 10–20%. Concurrent estrogen and thyroid hormone deficiency suppresses LDL receptor expression through independent promoter elements (ERE and TRE), reducing LDL clearance by 60–70% in hepatocyte experiments. The Rotterdam Study (n = 1,149 women over 55 years) demonstrated a twofold increase in CAD risk associated with subclinical hypothyroidism (OR 2.3; 95% CI 1.3–4.0) after adjustment for traditional risk factors. Conclusions: the synergism of two hormonal deficiencies elevates cardiovascular risk to a clinically meaningful level. Standard risk scores (Framingham, SCORE) do not incorporate thyroid status and may underestimate prognosis in this population. Prospective RCTs stratified by menopausal status and TSH level are needed.

**Keywords:** subclinical hypothyroidism, postmenopause, coronary artery disease, estrogen deficiency, dyslipidemia, endothelial dysfunction, cardiovascular risk, narrative review

## 1. Introduction

Thyroid disorders and the menopausal transition in women often occur simultaneously. Hypothyroidism is reported in 10–15% of women over the age of 50; subclinical forms are detected in approximately one in five patients during late postmenopause [1, 2]. During this same period, the incidence of cardiovascular events rises sharply: according to the Framingham Heart Study, the incidence of new cases of coronary heart disease (CHD) in women over 55 increases rapidly; by ages 65–74, the male-to-female ratio for CHD incidence approaches 2:1, and after age 75, it virtually evens out [3].

Both estrogens and thyroid hormones regulate the expression of LDL receptors, hepatic lipase activity, nitric oxide synthesis, and vascular endothelial reactivity [4, 5]. The molecular interaction between these two deficiencies occurs through competition between ERα and TRβ for common transcriptional cofactors; when both ligands are absent, the combined atherogenic effect exceeds the arithmetic sum of their individual effects. According to the Rotterdam Study, the prevalence of subclinical atherosclerosis in postmenopausal women with hypothyroidism is significantly higher than in euthyroid women of the same age with a comparable profile of traditional risk factors [6].

None of the major RCTs stratified participants by menopausal status; most cohorts examined hypothyroidism and menopause as independent variables. This narrative review systematizes the mechanisms underlying the interaction between these two hormonal deficiencies and their combined contribution to cardiovascular prognosis.

## 2. Materials and Methods

A structured narrative review was conducted using PubMed, Scopus, eLIBRARY.RU and CyberLeninka databases for the period 2000–2024. Search terms included: hypothyroidism, menopause, coronary artery disease, estrogen deficiency, dyslipidemia, endothelial dysfunction. Inclusion criteria: cohort and case-control studies (n ≥ 100), meta-analyses (≥ 5 primary studies), systematic reviews with described methodology. A total of 23 sources were included in the final analysis.

## 3. Results

The prevalence of hypothyroidism in women increases with age. According to the Whickham Survey, overt hypothyroidism occurs in 2% of women in the general population; subclinical hypothyroidism is found in 7.5–10%, peaking after age 55. In Russian studies, including data from the National Medical Research Center for Endocrinology, subclinical hypothyroidism is detected in 12–14% of women aged 55–70 [7].

The postmenopausal period worsens the lipid profile regardless of thyroid status. In the SWAN study, LDL-cholesterol levels increased by an average of 9 mg/dL and total cholesterol by 6.5 mg/dL within 1 year after the last menstrual period. The addition of hypothyroidism to this background further increases LDL-C: by 30–50% in overt hypothyroidism and by 10–20% in subclinical hypothyroidism (TSH 4.5–10 mU/L). These data were obtained from the Colorado Thyroid Disease Prevalence Study (Canaris et al., 2000), a cohort study involving more than 25,000 participants [8].

The risk of coronary heart disease in hypothyroidism has been studied in several large cohorts. In a Danish cohort study (n = 563,700), elevated TSH was associated with an increased risk of atrial fibrillation and heart failure; however, the association with coronary events was significant only at TSH levels > 10 mU/L [9]. A meta-analysis by Rodondi, which pooled data from 55,287 participants across 11 cohorts, showed that for TSH levels of 7–10 mU/L, the OR for ischemic heart disease was 1.18 (95% CI 1.02–1.38), and with TSH > 10 mU/L, it was 1.89 (95% CI 1.28–2.80) [10].

### Common Molecular Targets of Estrogens and Thyroid Hormones

Estrogens and T3 act through nuclear receptors belonging to the same superfamily. The estrogen receptor α (ERα) and thyroid receptor β (TRβ) compete for common transcriptional cofactors—SRC-1, GRIP1, and PGC-1α. When both ligands are deficient, the expression of LDLR and ApoA1 genes decreases.

The hepatic LDLR pathway is regulated independently by two hormones. Estradiol increases LDLR gene transcription via the estrogen response element (ERE); T3 activates the same gene via the thyroid response element (TRE). In experiments on mouse hepatocytes, simultaneous depletion of both hormones reduced LDLR expression by 60–70%, whereas depletion of only one hormone reduced it by 30–40% [11]. It is precisely this dual blockade of these independent regulatory pathways that explains the disproportionate increase in LDL in postmenopausal women with hypothyroidism.

The synthesis of nitric oxide by endothelial NO synthase (eNOS) is stimulated by estradiol via the PI3K/Akt pathway and by T3 via direct transcriptional activation of the eNOS gene [12]. Simultaneous blockade of the eNOS-dependent and LDLR-dependent pathways in a dual-deficiency state reduces basal NO production, increases vascular resistance, and activates monocyte adhesion to the endothelium—an early stage of atherogenesis.

**Table 1. Common molecular targets of estrogens and thyroid hormones in the context of cardiovascular risk.**

| Molecular Target | Effect of Estrogens | Effect of Thyroid Hormones | Consequence of Dual Deficiency |
|---|---|---|---|
| LDL Receptor (LDLR) | ↑ Transcription via ERE | ↑ Transcription via TRE | Reduced LDL clearance by 60–70% (hepatocyte experiment) |
| eNOS | ↑ Activation via PI3K/Akt | ↑ Direct transcription | Decreased NO production, endothelial dysfunction |
| ApoA1 / HDL | ↑ ApoA1 synthesis | ↑ LCAT activity | Reduced HDL levels, impaired reverse cholesterol transport |
| Hepatic Lipase | ↓ Activity [15] | ↑ Activity (physiological dose) | Accumulation of LDL and VLDL |
| Oxidative Stress | ↓ ROS (antioxidant effect) | ↓ Lipid peroxidation | Enhanced LDL oxidation |
| Inflammation / NF-κB | ↓ NF-κB activity | ↓ Pro-inflammatory cytokines | Increased hs-CRP, IL-6, TNF-α |

**Note: LCHAT—lecithin-cholesterol acyltransferase; hs-CRP—high-sensitivity C-reactive protein; eNOS—endothelial NO synthase; ERE—estrogen response element; TRE—thyroid response element.**

Dyslipidemia: Synergy of Two Deficiencies

Hypothyroidism disrupts the metabolism of most classes of lipoproteins. Decreased activity of hepatic lipase and lipoprotein lipase slows the catabolism of VLDL, leading to hypertriglyceridemia. In overt hypothyroidism, LDL-C levels exceed the normal range by an average of 0.5–1.0 mmol/L; in subclinical hypothyroidism (TSH 4.5–10 mU/L), they exceed the normal range by 0.2–0.4 mmol/L .

In euthyroid postmenopausal women, LDL-C levels increase by 10–15% compared to premenopausal levels, and the small dense LDL (sdLDL) fraction increases by 40–60% [13]. sdLDL circulates longer in the blood, oxidizes more easily, penetrates the subendothelial space more readily, and is more actively captured by foam cells. Hypothyroidism further reduces the activity of antioxidant defense enzymes (superoxide dismutase, catalase), accelerating the oxidation of sdLDL [14].

HDL levels decrease moderately (5–15%) in hypothyroidism; however, their functional activity is impaired. Reduced LHAT activity in thyroid insufficiency impairs HDL maturation and weakens the reverse transport of cholesterol. Postmenopausal estrogen deficiency has a similar effect: a decrease in ApoA1 reduces the pool of mature HDL-2, which, in the presence of a dual deficiency, results in a cumulative impairment of cholesterol transport[15].

### Vascular Effects: Arterial Stiffness and Endothelial Function

Pulse wave velocity (PWV) in women with hypothyroidism exceeds that of euthyroid peers by approximately 1.2–1.5 m/s, according to several controlled studies [16]. The postmenopausal transition alone increases PWS by 0.7–1.0 m/s during the first 3 years after the cessation of menstruation [17]. The mechanisms are distinct: estrogen deficiency reduces elasticity through a decrease in elastin and an accumulation of type I collagen in the media; hypothyroidism adds mucopolysaccharide infiltration of the subendothelium and a decrease in the expression of matrix metalloproteinases. The combination of collagen remodeling and mucopolysaccharide infiltration potentiates the reduction in elasticity more strongly than either process alone.

Endothelial function is assessed by flow-mediated dilation (FMD) of the brachial artery. In women with subclinical hypothyroidism, FVD is reduced by 2–4% compared with euthyroid controls [18]. The combination with postmenopause further reduces FVD by 5–7%, which corresponds to moderate coronary risk according to the 2021 ESC criteria. Under levothyroxine replacement therapy, POD is partially restored—by an average of 1.5–2.5% over 6 months—but does not return to baseline levels without correction of menopausal symptoms [18].

### Inflammation and Oxidative Stress

High-sensitivity C-reactive protein (hs-CRP) is elevated in 30–40% of patients with overt hypothyroidism and in 15–20% of those with subclinical hypothyroidism[19]. The menopausal transition itself is associated with an increase in hs-CRP by an average of 0.3 mg/L per year. IL-6 levels in hypothyroidism correlate with TSH and decrease as euthyroidism is achieved—this pattern has been replicated in several independent cohorts, although quantitative estimates vary [20]. In postmenopausal women, IL-6 is further elevated due to the attenuation of the anti-inflammatory effect of estrogens, which is mediated through the suppression of NF-kB.

Oxidative stress in hypothyroidism is characterized by a decrease in the activity of superoxide dismutase and catalase, accompanied by the accumulation of malondialdehyde . Estradiol exerts a direct antioxidant effect via its phenolic hydroxyl group. Its deficiency eliminates this protective mechanism, thereby increasing the oxidation of lipoproteins in thyroid insufficiency.

### Subclinical Hypothyroidism in Postmenopausal Women: Data on Cardiovascular Risk

The Thyroid Studies Collaboration (2010)—a pooled analysis of 55,287 participants—identified a statistically significant increase in the risk of coronary heart disease only when TSH was > 7 mU/L; with TSH levels of 4.5–7 mU/L, the association was not statistically significant. Crucially, this analysis was not stratified by menopausal status.

The Rotterdam Study (n = 1,149 women over 55 years of age) presented a different picture: subclinical hypothyroidism was associated with a twofold increase in the incidence of myocardial infarction and aortic atherosclerosis after adjusting for traditional risk factors (OR 2.3; 95% CI 1.3–4.0). A similar pattern was confirmed by an analysis of the Whickham Survey with a 20-year follow-up period: mortality from coronary heart disease in women with baseline subclinical hypothyroidism was significantly higher than in the euthyroid group.

The HUNT Study yielded contrasting results: in an analysis of more than 25,000 participants, subclinical hypothyroidism was not significantly associated with cardiovascular risk after multivariate adjustment [21]. A direct comparison between the Rotterdam Study and the HUNT Study is not valid: the TSH cut-off values, the age distribution of the samples, and the criteria for postmenopause differ. There are no prospective studies in the literature with hard cardiovascular endpoints specifically designed for postmenopausal women with subclinical hypothyroidism.

### Levothyroxine Replacement Therapy: Cardiovascular Aspects

Treatment of overt hypothyroidism with levothyroxine significantly improves the lipid profile. In a placebo-controlled RCT by Diekman et al., the reduction in LDL-C during therapy averaged 0.4 mmol/L, and that in triglycerides was 0.2 mmol/L [22]. The effect on vascular endpoints is less clear. In the TRUST study (2017)—the only large-scale RCT on subclinical hypothyroidism (n = 737, age ≥ 65 years)—replacement therapy did not improve either symptoms or cardiovascular parameters [23].

The TRUST cohort had a median age of 74.4 years and a median TSH level of 5.8 mU/L. Extrapolating these data to women aged 50–65 with TSH levels of 7–10 mU/L in early postmenopause is methodologically incorrect. The meta-regression analysis by Razvi et al. indirectly suggests greater benefit from therapy at a younger age and with a more pronounced elevation in TSH .

Oral estrogen therapy increases thyroxine-binding globulin levels, requiring an increase in the levothyroxine dose by an average of 25–47% [5]. This pharmacokinetic interaction is clinically significant; however, within the scope of this review, no randomized controlled trial (RCT) was identified that evaluated the combined use of hormone replacement therapy and levothyroxine with respect to cardiovascular disease endpoints.

**Table 2.**

**Cardiovascular Effects of Postmenopause and Hypothyroidism (Based on Data from the Included Studies)**

| Parameter | Postmenopause (Euthyroid) | Overt Hypothyroidism (Without Menopause) | Postmenopause + Hypothyroidism |
|---|---|---|---|
| LDL-C | +9 mg/dL per year | +0.5–1.0 mmol/L | Calculated cumulative effect; *Rotterdam Study*: CHD OR 2.3 |
| HDL-C | ↓ 5–10%, reduced ApoA1 | ↓ 5–15%, impaired LCAT activity | ↓↓, cumulative impairment of reverse cholesterol transport |
| sdLDL | ↑ 40–60% | ↑ due to reduced antioxidant protection | ↑↑, accelerated oxidation |
| PWV | +0.7–1.0 m/s over 3 years | +1.2–1.5 m/s vs. control | Independent mechanisms; cumulative increase |
| ***FMD of the Brachial Artery**** | ↓ 3–5% | ↓ 2–4% | ↓ 5–7% |
| hs-CRP | +0.3 mg/L/year | Elevated in 15–40% of patients | Synergistic increase |

**Note:** * POD – flow-mediated dilation of the brachial artery; PWS – pulse wave velocity; hs-CRP – high-sensitivity C-reactive protein; LHAT – lecithin-cholesterol acyltransferase; sdLDL – small dense LDL. The “Postmenopause + Hypothyroidism” column presents data from clinical observations or calculated sums of individual effects in the absence of direct comparative data.

## 4. Discussion

The central contradiction in this review—the discrepancy between the Rotterdam Study and the HUNT Study regarding the association between subclinical hypothyroidism and cardiovascular risk—cannot be resolved at the level of a narrative review. The Rotterdam Study included exclusively women over 55 years of age, which makes the sample closer to a postmenopausal cohort; this likely explains the stronger association. The HUNT Study did not stratify data by menopausal status, which may have “diluted” the effect. The heterogeneity of the results is due to differences in TSH cut-off values, the age composition of the samples, and the lack of uniform criteria for postmenopause.

The molecular data from Section 2 were obtained primarily in experimental models (mouse hepatocytes, cell cultures). Their direct extrapolation to clinical populations is limited. Nevertheless, clinical observations—a disproportionate increase in LDL-C, a decrease in HDL-C, and an increase in high-frequency CRP—are consistent with the proposed molecular mechanisms.

This review has limitations. The narrative design, which does not follow the formal PRISMA guidelines, does not rule out selection bias. The small number of sources (23) does not allow for a meta-regression. Publication bias is possible: studies with negative results are less likely to be indexed in available databases. Another limitation is the lack of data from prospective cohorts specifically recruited to include postmenopausal women with verified hypothyroidism.

## 5. Conclusion

The synergistic effect of estrogen and thyroid deficiencies in postmenopausal women confers independent prognostic significance to subclinical hypothyroidism. The simultaneous blockade of ERE- and TRE-dependent regulatory pathways of LDLR and eNOS explains the disproportionate deterioration in lipid profile and endothelial function observed clinically.

Standard risk scales (Framingham, SCORE) do not include thyroid status and may underestimate the cardiovascular prognosis in postmenopausal women with hypothyroidism. Data from the Rotterdam Study and the Whickham Survey indicate a twofold increase in the risk of coronary heart disease in this group with subclinical hypothyroidism, which justifies the need to consider TSH in risk stratification and requires verification in prospective studies.

There are no systematic data in the literature on the cardiovascular prognosis with combination therapy (HRT + levothyroxine). A priority area remains the design of randomized controlled trials (RCTs) that stratify participants by menopausal status and TSH levels and include hard endpoints (myocardial infarction, coronary death).

1. Estrogen deficiency and thyroid insufficiency suppress the expression of LDL receptors via independent promoter elements (ERE and TRE) and block eNOS-dependent nitric oxide synthesis; in the case of a dual deficiency, the total atherogenic effect exceeds the arithmetic sum of the individual effects.

2. According to the Rotterdam Study, subclinical hypothyroidism in postmenopausal women is associated with a twofold increase in the risk of coronary heart disease (OR 2.3; 95% CI 1.3–4.0) after adjusting for traditional risk factors; the HUNT Study did not confirm this association, reflecting the heterogeneity of the available evidence.

3. Standard cardiovascular risk scales do not include thyroid status and may underestimate the prognosis in postmenopausal women with hypothyroidism—a hypothesis that requires testing in prospective studies.

4. Levothyroxine replacement therapy significantly improves the lipid profile in overt hypothyroidism; its cardiovascular efficacy in subclinical hypothyroidism among postmenopausal women has not been confirmed by RCT data.

5. There are no prospective RCTs with hard cardiovascular endpoints in the literature that were specifically designed for postmenopausal women with hypothyroidism.

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