Reversible morbidity markers in subclinical hypothyroidism

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Abstract

Importance. Subclinical hypothyroidism (SCH) is a common clinical entity with a putative role in a wide range of disorders. The impact of SCH on mortality and markers of morbidity has been demonstrated, but studies have shown inconsistent results. Evidence regarding the effect of levothyroxine treatment on reversing morbidity markers is emerging, but the value of treatment is still unclear. Objective. The objectives of this review were to assess recent, high-quality studies evaluating the role of SCH in cardiovascular health, cognition, mood, pregnancy, anemia, and renal disease; to examine the effects of levothyroxine on reducing mortality or reversing markers of morbidity in these conditions; and to consider how new research insights may help guide clinical practice. Evidence review. A PubMed search was conducted (using ‘subclinical hypothyroidism’ [Title/Abstract] AND morbidity [MeSH Subheading] as search criteria) and was restricted to human studies published in the English language between 1990 and 2013. Subsequent searches of retrieved articles yielded further studies, which were included based on quality. Emphasis was given to large observational studies, well-conducted meta-analyses, and randomized controlled trials. Findings. The difficulty of diagnosing SCH, particularly in the elderly, may underlie many of the conflicting results seen in the literature. Increased understanding of the at-risk patient population will result in better selection of study subjects and, likely, unequivocal results. Regardless of the current confusion, emerging evidence suggests that certain markers of morbidity are reversed by levothyroxine therapy across the disorders examined here. Conclusion and relevance. Future large, well-controlled studies will not only clarify the role of SCH but also help identify patients for whom levothyroxine treatment will provide the most benefit.

Introduction

Hypothyroidism exists in both overt and subclinical forms and is a common clinical entity. Overt hypothyroidism, which has a prevalence of 0.3% to 0.4% in the USA, is categorized by elevated serum thyrotropin (thyroid-stimulating hormone [TSH]) coupled with a subnormal level of free thyroxine (FT4) [1]. The common signs and symptoms of overt hypothyroidism are well characterized, as are the benefits of levothyroxine treatment [1].

Subclinical hypothyroidism (SCH) is defined as a serum TSH level above the reference limit with a normal FT4 level, according to guidelines issued in 2012 by the American Association of Clinical Endocrinologists and the American Thyroid Association [1]. Diagnostic accuracy in distinguishing among euthyroidism, SCH, and overt hypothyroidism requires stable thyroid function (i.e., reproducible TSH levels over weeks or months), a normal hypothalamic-pituitary-thyroid axis, and no recent or current severe illness [1]. Additionally, it has been suggested that current immunoassay platforms for the measurement of FT4 may not be as accurate or specific as newly developed mass spectrometry methods, and the latter may be more appropriate for patients with certain conditions (i.e., pregnancy or kidney disease) [2-9]. SCH was identified in 4.3% of participants in the National Health and Nutrition Examination Survey (NHANES III) and 9.0% of participants in a statewide health fair in Colorado and is more prevalent than overt hypothyroidism [10,11]. Because it is associated with few or none of the signs and symptoms of overt hypothyroidism, SCH is essentially a laboratory diagnosis, and the merits of treating SCH remain a matter of debate [12].

There is growing evidence, however, that SCH may be associated with negative clinical consequences. Further, certain markers of morbidity associated with SCH may be reversed by therapy. Studies reporting the relationship of SCH with selected morbidity markers were identified through a PubMed search using ‘subclinical hypothyroidism’ [Title/Abstract] AND morbidity [MeSH Subheading] as search criteria and restricted to human studies published in the English language between 1990 and 2013. The retrieved articles generated subsequent searches; studies were selected for inclusion based on quality; data from large observational studies, well-conducted meta-analyses, and randomized controlled trials were emphasized.
Considerations based on TSH levels in patient subpopulations

Reference ranges for TSH must be considered for any identified association of SCH with morbidity markers. NHANES III defined overt hypothyroidism as TSH > 4.5 mIU/l with T<sub>4</sub> < 57.9 nmol/l (< 4.5 µg/dl), and SCH as TSH > 4.5 mIU/l with T<sub>4</sub> ≥ 57.9 nmol/l but < 169.9 nmol/l (4.5–13.2 µg/dl) [11]. It was observed, however, that TSH levels in the reference population (≥ 12 years of age and free of thyroid disease and its risk factors [n = 13,344]) differed depending on age, sex, and race or ethnicity [11]. The NHANES III data have been reanalyzed and appropriate reference limits have been developed for patient-specific populations to limit misclassification of thyroid function. Specifically, increasing age was associated with a significantly increased upper limit of TSH; additionally, black individuals had a significantly lower upper-limit TSH value compared with white individuals [13].

Because TSH levels increase with age, older patients with mild elevations may be misdiagnosed with SCH [14]. Indeed, using an upper limit of 4.5 mIU/l may result in misdiagnosis of up to 15% of patients who are ≥ 70 years of age [15]. Conversely, there is potential for underdiagnosis of SCH in younger patients. Additional research on younger individuals in assessments of SCH, using TSH level > 4.5 mIU/l as the benchmark for inclusion, may allow clearer observation of the effects of more marked hypothyroidism on measured outcomes, reveal adverse influences of SCH on physiology, and provide more distinct evidence for a positive impact of therapy.

A further consideration is the accuracy of the SCH diagnosis based on one measurement. Test results may be misleading if thyroid function is not stable, if the hypothalamic-pituitary-thyroid axis is disturbed, or if the patient has or is recovering from a serious illness [1,16]. Because TSH elevations may be transitory, a single measurement is insufficiently diagnostic, particularly for mild TSH elevations. Results from the population-based, longitudinal Cardiovascular Health Study indicated that 35% of patients aged ≥ 65 years with a single baseline measure reverted to euthyroidism, and those with milder TSH elevations were more likely to become euthyroid [17]. Other studies using a single baseline thyroid assessment have seen reversion to normal in 52% and 62% of patients with untreated SCH after follow up of 3 to 5 years [18,19]. Although anti-microsomal/anti-thyroid peroxidase antibodies (TPOAbs) in patients with elevated TSH levels significantly increase the likelihood of persistent SCH [20], few studies have tested for TPOAb. Because of these issues, many studies may have inadvertently included euthyroid patients, thereby confounding the effects of SCH on outcomes. In addition, the analysis of the results of some studies of levothyroxine intervention may be complicated by the possibility that investigators may have induced TSH suppression in some patients by inadvertently overseeing their patients with levothyroxine.

Cardiovascular health

A relationship has long been recognized between overt hypothyroidism and negative effects on cardiovascular health, including bradycardia, impaired systolic function, impaired left ventricular (LV) diastolic filling, increased systemic vascular resistance, diastolic hypertension, increased arterial stiffness, and endothelial dysfunction [21]. Further, overt hypothyroidism has been linked to increased mortality [22].

There is conflicting evidence, however, about whether SCH affects cardiovascular morbidity and mortality [23-28]. A well-conducted meta-analysis of 12 observational studies in unselected community dwelling subjects (euthyroid, n = 24,868; SCH, n = 2399) examined the effects of SCH on the prevalence and incidence of ischemic heart disease (IHD) and cardiovascular mortality [29]. A modest association was noted with SCH in the overall population; however, grouping subjects by age (< 65 vs ≥ 65 years) revealed a highly significant relationship between SCH and prevalent IHD in younger (but not older) subjects (odds ratio [OR] = 1.57; 95% CI: 1.19–2.06; P = 0.001; Figure 1; see Table I, for synopses of this and other studies regarding cardiovascular health) [29]. A retrospective analysis of the UK General Practitioner Research Database suggests that levothyroxine treatment for SCH can reduce the risk of IHD events, but only in younger patients. This analysis grouped patients with SCH by age (40–70 years, n = 3093; > 70 years, n = 1642). Patients with a first-ever increased TSH (5.01–10.00 mIU/l) and normal serum FT4 (both based on a single measurement) and no history of IHD or cerebrovascular disease were included. In younger patients, the adjusted risk of fatal and nonfatal IHD events was lower in those treated with levothyroxine (hazard ratio [HR] = 0.61; 95% CI: 0.39–0.95), whereas older patients did not appear to benefit from treatment [30].

A meta-analysis of patient-level data from six prospective studies (euthyroid, n = 22,674; SCH, n = 2068), adjusted for age and gender, noted that the risk of heart failure (HF) events became elevated with increasing TSH level. A significant increase in risk, compared with euthyroidism, was noted in individuals with SCH when TSH levels were 10.0 to 19.9 mIU/l (HR = 1.86; 95% CI: 1.27–2.72) [31].

An association between SCH and mortality was also investigated in NHANES III. In participants with preexisting congestive heart failure, the presence of SCH was associated with an increased risk of all-cause mortality versus euthyroidism (multivariable-adjusted HR = 1.44; 95% CI: 1.01–2.06; P = 0.01) [26]. In contrast, a large retrospective cohort study recently found that subjects with SCH had a lower risk of all-cause mortality versus euthyroid subjects (adjusted incidence rate ratio [IRR] = 0.92; 95% CI: 0.87–0.97), despite having an elevated risk of myocardial infarction (IRR = 1.13; 95% CI: 1.01–1.27) [32]. No association was observed between SCH and major adverse cardiovascular events (IRR = 0.99; 95% CI: 0.94–1.06), HF (IRR = 1.03; 95% CI: 0.94–1.12), or stroke (IRR = 0.94; 95% CI: 0.86–1.03) [32].

Several small randomized studies have evaluated whether levothyroxine therapy reverses markers of cardiovascular morbidity in individuals with SCH (see Table II, for synopses of studies that have assessed effects of levothyroxine on cardiovascular parameters). Monzani et al. randomized 20 patients with SCH to receive levothyroxine (n = 10) or placebo (n = 10) for 6 months [33]. Only treated patients achieved normalized TSH levels and significant improvements in LV
function and myocardium textural parameters. A similar study found that levothyroxine improved endothelium-dependent vasodilation in individuals with SCH [34]. In another study, LV function and mechanics, evaluated using two- and three-dimensional echocardiography and speckle tracking imaging, were significantly worse in women with untreated SCH (n = 54; aged £ 50 years), compared with normal matched controls (n = 40) [35]. In patients with SCH, significantly improved LV function was noted in those treated with levothyroxine, whereas LV mechanics improved but did not normalize within the 1-year follow-up period, even though patients attained euthyroid status [35].

These early changes in cardiac function and mechanics suggest that SCH may have a subtle role in cardiovascular health and that certain markers of cardiac morbidity can be reversed with levothyroxine treatment.

**Dyslipidemia**

Overt hypothyroidism is associated with dyslipidemic changes that can be improved with levothyroxine therapy [36,37]. Results of studies examining the relationship between SCH and lipid profiles show clear associations between TSH, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) in patients with TSH > 10 mIU/l [38]. A large, cross-sectional, population-based study from Norway (the HUNT study) demonstrated that levels of TC, LDL-C, non–high-density lipoprotein cholesterol, and triglycerides exhibited a linear positive relationship across the range of TSH values, even those within the normal range [39].

The effect of levothyroxine on lipid profiles and vascular reactivity in patients with SCH has been evaluated in various studies (Table II). A meta-analysis and several controlled studies found that levothyroxine treatment improved dyslipidemia, the waist-to-hip ratio, and brachial artery flow-mediated dilation (a marker of vascular endothelial function) [40-44]. Two research groups observed improvements in TC, LDL-C, and carotid artery intima-media thickness (a marker of early atherosclerotic change) with levothyroxine treatment [45,46].

Although it remains unclear whether treating SCH with levothyroxine prevents clinically relevant atherosclerotic heart disease, it is noteworthy that the Third Report of the National Cholesterol Education Program (Adult Treatment Panel III) recommends, “[a]ny person who presents with elevated LDL cholesterol or other form of hyperlipidemia must undergo evaluation to rule out secondary dyslipidemia” and identifies hypothyroidism as a major cause of secondary dyslipidemia [47].

The accumulated evidence suggests that SCH negatively affects cardiovascular health, but inconsistent findings have caused some confusion regarding this relationship. As noted earlier, careful diagnosis of SCH is required to avoid underestimating the impact of SCH. Most of the evidence for a connection has been noted in patients aged ≤ 65 years [29], those with TSH levels > 10 mIU/l [23,27,31,38], and in patients with concomitant heart disease [26]. Preliminary data
Table I. Relationships between SCH and cardiovascular health.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study description</th>
<th>SCH diagnosis</th>
<th>Tests and criteria</th>
<th>Number of tests</th>
<th>Patients</th>
<th>Markers</th>
<th>Findings</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Morbidity and mortality</strong></td>
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<tr>
<td>Walsh et al., 2005 [28]</td>
<td>Observational</td>
<td>TSH &gt; 4 mIU/l, normal FT4</td>
<td></td>
<td>1</td>
<td>SCH: n = 39; mean age = 51 years Euthyroid: n = 1906; mean age = 49 years</td>
<td>CHD events (fatal and nonfatal) CVD mortality</td>
<td>SCH associated with increased prevalence of CHD in those with TSH ≥ 10.0 mIU/l Increased risk of CHD events (irrespective of TSH level)</td>
<td>Busselton Health Study</td>
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<tr>
<td>Ochs et al., 2008 [24]</td>
<td>Meta-analysis of prospective observational studies</td>
<td>TSH cut-off values = 4.0–6.0 mIU/l</td>
<td>3/10 studies repeated thyroid function tests</td>
<td>Community-living subjects without significant comorbidities Mean age in 8/10 included studies: &gt; 65 years SCH: n = 1491 Euthyroid: n = 12,530</td>
<td>CHD All-cause mortality CVD mortality</td>
<td>Suggestion of modestly increased risk of CHD, all-cause and CVD mortality</td>
<td>Standard TSH cut-offs for studies conducted in elderly patients may have included euthyroid subjects Few studies confirmed persistent SCH</td>
<td></td>
</tr>
<tr>
<td>Razvi et al., 2008 [29]</td>
<td>Meta-analysis of 15 population-based studies</td>
<td>TSH &gt; ULN, which ranged from 2.8–6.0 mIU/l depending on the measure, SCH: n ranged from 954 to 2399 Euthyroid: n ranged from 8673 to 24,868</td>
<td></td>
<td>1</td>
<td>Incident, prevalent IHDIHD mortality</td>
<td>SCH associated with prevalent and incident IHD and IHD mortality, but only in subjects ≤ 65 years</td>
<td>Mean age of SCH subjects in 9/15 studies was ≥ 65 years</td>
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<tr>
<td>Razvi et al., 2010 [25]</td>
<td>Observational</td>
<td>TSH = 6.0–15.0 mIU/l and normal FT4</td>
<td></td>
<td>1</td>
<td>Incident IHD IHD mortality</td>
<td>Significant association between SCH and incident IHD, but not all-cause or IHD mortality</td>
<td>Reanalysis of the Whickham Survey cohort</td>
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<tr>
<td>Rodondi et al., 2010 [27]</td>
<td>Meta-analysis of individual patient data from 11 prospective observational studies</td>
<td>TSH ≥ 4.5 to &lt; 20 mIU/l, normal FT4</td>
<td></td>
<td>1</td>
<td>CHD events (fatal and nonfatal) CHD mortality All-cause</td>
<td>Significantly higher risk of CHD events and CHD mortality among subjects with SCH and TSH ≥ 10 mIU/l</td>
<td>Mean age in four studies ≥ 68 years</td>
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<tr>
<td>Gencer et al., 2012 [31]</td>
<td>Meta-analysis of individual patient data from prospective observational studies</td>
<td>TSH = 4.5–19.9 mIU/l and normal FT4</td>
<td></td>
<td>1</td>
<td>SCH: n = 2068 Euthyroid: n = 22,674</td>
<td>HF events</td>
<td>Stratified analysis by TSH level found a positive relationship when TSH = 10.0–19.9 mIU/l</td>
<td>Increased risk at high TSH level persisted after controlling for pre-existing HF, AF, and CVD risk factors PROSPER study. Given population age, potential inclusion of euthyroid patients in the SCH group</td>
</tr>
<tr>
<td>Nanchen et al., 2012 [23]</td>
<td>Post-hoc evaluation of the randomized, controlled, prospective study of pravastatin in the elderly at risk</td>
<td>TSH ≥ 4.5 mIU/l and normal FT4 levels</td>
<td>Second test at 6 months</td>
<td></td>
<td>Aged 70–82 years History of vascular disease or with known CVD risk factors SCH: n = 199 Euthyroid: n = 5046</td>
<td>Fatal/nonfatal CHD events Fatal/nonfatal CVD events SCH stratified by TSH 4.5–10 mIU/l and &gt; 10 mIU/l</td>
<td>Significantly increased rate of HF when TSH ≥ 10 mIU/l Significantly increased risk of CVD events in patients with TSH ≥ 10 mIU/l and not receiving pravastatin</td>
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<tr>
<td>Author, year</td>
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<tr>
<td>Razvi et al., 2012 [30]</td>
<td>Case record review of levothyroxine-treated/untreated patients from the UKGPRD</td>
<td>TSH = 5.01–10 mIU/l, normal FT4</td>
<td>Aged ≥ 40 years with incident SCH</td>
<td>IHD events (fatal and nonfatal)</td>
<td>40- to 70-year-old group, untreated: IHD events in 6.6%; all-cause mortality in 6.4% &gt; 70-year-old group, untreated: IHD events in 10.7%; all-cause mortality in 40.5%</td>
<td>Effects of levothyroxine treatment on end points in Table II</td>
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<tr>
<td>Rhee et al., 2013 [26]</td>
<td>Observational</td>
<td>TSH &gt; ULN but ≤ 10 mIU/l</td>
<td>SCH: n = 691</td>
<td>All-cause mortality</td>
<td>SCH is associated with increased all-cause mortality in those with pre-existing CHF</td>
<td>NHANES III</td>
<td></td>
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<tr>
<td>Selmer et al., 2014 [32]</td>
<td>Observational</td>
<td>TSH &gt; 5.0 mIU/l, normal FT4, normal total T4</td>
<td>SCH: n = 11,560</td>
<td>All-cause mortality MACE</td>
<td>SCH (overall and grade 1): overall lower mortality risk SCH (overall and grade 2): increased risk of MI No other associations seen</td>
<td>SCH subclassification: Grade 1: TSH 5–10 mIU/l Grade 2: TSH &gt; 10 mIU/l</td>
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<tr>
<td>Monzani et al., 2001 [33]</td>
<td>Randomized, controlled, 1-year study of levothyroxine</td>
<td>TSH &gt; 3.6 mIU/l and normal FT4; only patients with stable elevated serum TSH and normal FT4 levels for ≥ 1 year before enrollment</td>
<td>NR</td>
<td>Levothyroxine: n = 10 Placebo: n = 10</td>
<td>Myocardial function and structure: Echocardiography parameters CVI</td>
<td>At BL, SCH patients had small but significant functional and textural myocardial impairments compared with control patients</td>
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<tr>
<td>Taddei et al., 2003 [34]</td>
<td>Open-label study of levothyroxine treatment</td>
<td>TSH &gt; 3.6 mIU/l for ≥ 6 months</td>
<td>SCH: n = 14, mean age = 40 years</td>
<td>Lipid parameters Vascular parameters: FBF; NO contribution to endothelium-dependent vasodilation; endothelium-independent vasodilation; MFVRs</td>
<td>Impaired endothelial vasodilation was seen in SCH versus euthyroid patients at BL</td>
<td>9 patients with SCH at BL were evaluated after 6 months of stable euthyroidism induced by levothyroxine</td>
<td></td>
<td></td>
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<tr>
<td>Tadic et al., 2014 [35]</td>
<td>Open-label study of levothyroxine treatment</td>
<td>TSH &gt; 5 mIU/l, normal FT3 and FT4; etiology of SCH was chronic autoimmune thyroiditis diagnosed by increased TPOAb and/or anti-thyroglobulin auto-Ab and diffuse hypoechogenicity by thyroid ultrasound</td>
<td>NR</td>
<td>SCH: n = 54 female patients; mean age = 41 years Euthyroid: n = 40</td>
<td>Compared to euthyroidism, LV deformation and function are significantly different in patients with SCH</td>
<td>Patients with SCH at BL were evaluated after achieving 1 year of stable euthyroidism induced by levothyroxine</td>
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Table I. (Continued)

<table>
<thead>
<tr>
<th>Author, year</th>
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</thead>
<tbody>
<tr>
<td>Caraccio et al., 2002 [42]</td>
<td>Randomized, controlled</td>
<td>Lipids</td>
<td>TSH &gt; 3.6 mIU/l for ≥ 6 months; TPOAb+ and anti-thyroglobulin auto-Ab+</td>
<td>NR</td>
<td>Aged 18–50 years</td>
<td>Serum lipids</td>
<td>SCH associated with significantly higher BL TC, LDL-C, ApoB, and Lp(a) than controls</td>
</tr>
<tr>
<td>Monzani et al., 2004 [45]</td>
<td>Randomized, controlled study of levothyroxine</td>
<td></td>
<td>TSH &gt; 3.6 mIU/l for ≥ 6 months, n = 36 with Hashimoto’s thyroiditis TPOAb+ and anti-thyroglobulin auto-Ab+ n = 9 diagnosed with SCH after radioiodine therapy for toxic adenoma or multinodular toxic goiter</td>
<td>NR</td>
<td>Mean age = 37 years</td>
<td>Serum lipids cIMT</td>
<td>SCH associated with significantly higher TC, LDL-C, ApoB, mean and maximal cIMT versus normal controls</td>
</tr>
<tr>
<td>Asvold et al., 2007 [39]</td>
<td>Observational HUNT study</td>
<td></td>
<td>TSH = 4.1–9.9 mIU/l and FT4 ≥ 8.0 pmol/l</td>
<td>1</td>
<td>Stratified by TSH (mIU/l) &lt; 0.10: n = 128 0.1–0.49: n = 569 0.5–3.5: n = 27,727 3.6–9.9: n = 2007 ≥ 10.0: n = 225 SCH: n = 1247</td>
<td>Serum lipids</td>
<td>Positive linear association between increasing TSH (including those outside the reference range) and TC, LDL-C, non-HDL-C and TG; no clear association with HDL-C SCH versus euthyroidism: modest elevations in TC, LDL-C, non-HDL-C and TG; no clear association with HDL-C SCH versus euthyroidism: modest elevations in TC, LDL-C, non-HDL-C and TG; no clear association with HDL-C SCH versus euthyroidism: modest elevations in TC, LDL-C, non-HDL-C and TG; no clear association with HDL-C A normal reference range established for this study population: TSH = 0.50–3.5 mIU/l</td>
</tr>
<tr>
<td>Kim et al., 2009 [46]</td>
<td>1-year, open-label study of levothyroxine</td>
<td></td>
<td>TSH &gt; 5.5 mIU/l and normal FT4</td>
<td>≥ 2 positive tests measured at least 2 months apart</td>
<td>SCH: n = 28 Mean age = 36 years All TPOAb+</td>
<td>Serum lipids cIMT</td>
<td>cIMT predicts atherosclerotic CVD</td>
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</tbody>
</table>

Abbreviations: Ab = Antibody; AF = Atrial fibrillation; Apo = Apolipoprotein; BL = Baseline; CHD = Coronary heart disease; CHF = Congestive heart failure; cIMT = Carotid artery intima-media thickness; CVA = Cerebrovascular disease; CVD = Cardiovascular disease; CVI = Cyclic variation index; DE = Dimensional echocardiography; FBF = Forearm blood flow; FT3 = Free triiodothyronine; FT4 = Free thyroxine; GPRD = General Practitioner Research Database; HDL-C = High-density lipoprotein cholesterol; HF = Heart failure; IHD = Ischemic heart disease; LDL-C = Low-density lipoprotein cholesterol; Lp = Lipoprotein; LV = Left ventricular; MACE = Major adverse cardiovascular events (cardiovascular death, nonfatal MI, and nonfatal stroke); MFVR = Minimal forearm vascular resistance; MI = Myocardial infarction; NHANES III = Third National Health and Nutrition Examination Survey; NO = Nitric oxide; NR = Not reported; SCH = Subclinical hypothyroidism; TC = Total cholesterol; TG = Triglycerides; TPOAb = Anti-thyroid peroxidase antibody; TSH = Thyroid-stimulating hormone; ULN = Upper limit of normal.
Table II. Effects of levothyroxine treatment on cardiovascular parameters in patients with SCH.

<table>
<thead>
<tr>
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<tr>
<td>Razvi et al., 2010 [25]</td>
<td>Observational</td>
<td></td>
<td>TSH = 6.0–15.0 mIU/l and normal FT4</td>
<td>SCH: n = 97, mean age = 50 years; Euthyroid: n = 2279, mean age = 45 years</td>
<td>Incident IHD</td>
<td>HHD mortality</td>
<td>When stratified by treatment, all-cause mortality was lower in SCH patients receiving levothyroxine</td>
</tr>
<tr>
<td>Razvi et al., 2012 [30]</td>
<td>Case record review of levothyroxine-treated/-untreated patients from the UK GPRD</td>
<td></td>
<td>TSH = 5.01–10 mIU/l, normal FT4</td>
<td>Aged ≥ 40 years with incident SCH; Stratified by age; 40–70 years: n = 3093 and &gt; 70 years: n = 1642</td>
<td>IHD events (fatal and nonfatal); All-cause mortality; Mortality due to circulatory disease, IHD, cancer, CVA, AF</td>
<td>In patients aged 40–70 years, incident IHD events (fatal and nonfatal) and all-cause mortality were lower with levothyroxine</td>
<td>No significant associations found with levothyroxine treatment in patients aged &gt; 70 years</td>
</tr>
<tr>
<td>Monzani et al., 2001 [33]</td>
<td>Randomized, controlled, 1-year study of levothyroxine</td>
<td>NR</td>
<td>TSH &gt; 3.6 mIU/l and normal FT4, FT4 for ≥ 1 year; only patients with stable elevated serum TSH and normal FT4 levels for ≥ 1 year before enrollment</td>
<td>Levothyroxine: n = 10; Placebo: n = 10 Note: all patients had Hashimoto's thyroiditis</td>
<td>Myocardial function and structure: Echo-Doppler parameters CVI</td>
<td>Normalization of impaired diastolic and systolic functions and altered myocardial texture achieved with levothyroxine</td>
<td>FMD is a marker of vascular endothelial function</td>
</tr>
<tr>
<td>Razvi et al., 2007 [44]</td>
<td>Randomized, controlled, 12-week crossover</td>
<td>≥ 2; at least 3 months apart</td>
<td>TSH &gt; 4 mIU/l and normal FT4</td>
<td>100 patients, mean age = 54 years; 50 randomized to levothyroxine or placebo per study period</td>
<td>Brachial artery FMD; Serum lipids; Weight, waist-to-hip ratio</td>
<td>Significant improvements versus placebo in TC, LDL-C, waist-to-hip ratio, and FMD</td>
<td>Patients with SCH evaluated after achieving 1 year of stable euthyroidism</td>
</tr>
<tr>
<td>Tadic et al., 2014 [35]</td>
<td>Open-label study of levothyroxine treatment</td>
<td>NR</td>
<td>TSH &gt; 5 mIU/l, normal FT3 and FT4</td>
<td>SCH: n = 54 female patients; mean age = 41 years; Euthyroid: n = 40</td>
<td>LV structure, function, and deformation via 2DE and 3DE speckle tracking imaging</td>
<td>LV mechanics improved but were not completely restored with levothyroxine</td>
<td>FMD is a marker of vascular endothelial function</td>
</tr>
<tr>
<td>Danese et al., 2000 [40]</td>
<td>Meta-analysis of levothyroxine treatment studies</td>
<td></td>
<td>TSH &gt; ULN but &lt; 20 mIU</td>
<td>Measured before and after treatment; number of measurements not reported</td>
<td>Mean ages ranged from 32 to 71 years across studies Depending on the measure, total numbers ranged from 168 to 247</td>
<td>Serum lipids</td>
<td>Levothyroxine treatment associated with small but significant decreases in TC and LDL-C No change in HDL-C or TG</td>
</tr>
<tr>
<td>Meier et al., 2001 [41]</td>
<td>Randomized, controlled, 48-week study of levothyroxine</td>
<td>2 TSH tests</td>
<td>TSH &gt; 5.0 mIU/l, and exaggerated TSH response (&gt; 35 mIU/l after oral TRH stimulation), and normal FT4</td>
<td>Female patients, mean age = 59 years, randomized to: Levothyroxine: n = 31 Placebo: n = 32</td>
<td>Serum lipids</td>
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<td>Greater treatment effects seen in women with higher BL levels of TSH (&gt; 12 mIU/l), TC, and LDL-C</td>
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Note: All patients had Hashimoto's thyroiditis.
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<td>Levothyroxine-treated patients evaluated after 6 months of stable euthyroidism</td>
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<td>9 patients with SCH evaluated after 6 months of stable euthyroidism</td>
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<tr>
<td></td>
<td></td>
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<td>Vascular parameters</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>n = 36 with Hashimoto's thyroiditis; TPOAb⁺ and anti-thyroglobulin Ab⁺; n = 9 diagnosed with SCH after radioiodine therapy for toxic adenoma or multinodular toxic goiter</td>
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<tr>
<td>Teixeira et al., 2008 [43]</td>
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<td>2 assessments; ≥ 6 weeks apart</td>
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<tr>
<td>Kim et al., 2009 [46]</td>
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</tr>
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Abbreviations: Ab = Antibody; AF = Atrial fibrillation; Apo = Apolipoprotein; BL = Baseline; cIMT = Carotid artery intima-media thickness; CVA = Cerebrovascular disease; CVI = Cyclic variation index; DE = Dimensional echocardiography; FBF = Forearm blood flow; FMD = Flow-mediated dilatation; FT3 = Free triiodothyronine; FT4 = Free thyroxine; GPRD = General Practitioner Research Database; HDL-C = High-density lipoprotein cholesterol; IHD = Ischemic heart disease; LDL-C = Low-density lipoprotein cholesterol; Lp = Lipoprotein; LV = Left ventricular; MFVR = Minimal forearm vascular resistance; NO = Nitric oxide; NR = Not reported; SCH = Subclinical hypothyroidism; TC = Total cholesterol; TG = Triglycerides; TPOAb = Anti-thyroid peroxidase antibody; TRH = Thyrotropin-releasing hormone; TSH = Thyroid-stimulating hormone; ULN = Upper limit of normal.
suggest that levothyroxine may reverse cardiovascular morbidity markers; however, large, randomized, controlled studies are needed to confirm the benefits and risks of treatment.

Cognition and mood

Limited data are available on the relationship of SCH with cognition and mood in adults, children, adolescents, and the elderly. In adults, assessments of cognition in relation to SCH have included functional magnetic resonance imaging (fMRI). Visual-spatial and verbal memory were significantly impaired at baseline in a study of adults with overt hypothyroidism (n = 21) and SCH (n = 17), compared with control subjects (n = 19); 3 months of levothyroxine treatment significantly improved impairment in patients with SCH, but not overt hypothyroidism [48]. Patients with SCH (n = 11) had worse performance than euthyroid controls (n = 12) in a working memory test (the N-back test); fMRI conducted simultaneously revealed that brain regions involved in executive performance were affected [49]. N-back test scores and brain activation normalized following 6 months of levothyroxine treatment. A second fMRI study also found that brain areas involved in executive function were less active during the N-back test in subjects with SCH, compared with euthyroid subjects [50]. Brain activation levels normalized in patients with SCH following levothyroxine treatment.

Cognition in children and adolescents with (n = 17) and without (n = 17) SCH was significantly different in a cross-sectional study that used the Wechsler Intelligence Scale for Children-Revised digit span, which assesses immediate auditory recall, freedom from distraction, attention, concentration, and mental control; several aspects of the Stroop test, which measures selective attention, cognitive flexibility, and processing speed, were also significantly different [51]. Interestingly, subjects with SCH from the NHANES III youth sample (22 of 1327 adolescents) had better scores on reading and block design tests than euthyroid participants, even after adjustment (P < 0.05 for both) [52].

Thus far, efforts to identify cognitive impairment in elderly patients with SCH have been unsuccessful and the cognitive benefits of levothyroxine treatment remain unproven [53]. A randomized, double-blind, placebo-controlled trial in 94 subjects with SCH aged ≥ 65 years (mean age, 74 years) failed to find evidence of cognitive benefit with 1 year of levothyroxine treatment [54]. However, this study had several important limitations, including only a single assessment of TSH, a diagnosis of SCH with a TSH level > 5.5 mIU/L, and a lack of cognitive dysfunction in the population at baseline. Additionally, 16% of subjects who received levothyroxine with the intention of normalizing TSH continued to be hypothyroid at 12 months, whereas 50% of control SCH subjects had normalized TSH without intervention by study end. These observations call into question the diagnosis of SCH in study participants and suggest that any effects of intervention would be difficult to detect [54].

In addition to cognition, researchers have assessed psychiatric function in patients with SCH, based on the long-standing literature describing associations between overt hypothyroidism and mood symptoms [55]. Bauer et al. used positron-emission tomography with [18F] fluorodeoxyglucose to assess changes in brain glucose metabolism in four patients with overt hypothyroidism and nine patients with SCH, before and after 3 months of levothyroxine treatment [56]. Results were compared against those from 10 healthy age-matched controls. Clinician- and self-reported assessments indicated that patients with hypothyroidism had significant depressive and somatic symptoms at baseline. Untreated patients with SCH had significantly less brain activity than controls in multiple brain regions; however, brain activity was normalized with levothyroxine therapy. Notably, TSH level, lower brain activity, and depressive and somatic symptoms were correlated; symptoms improved, and brain activity levels were restored, with levothyroxine therapy [56].

Jorde et al. evaluated cognition, mood, and hypothyroid symptoms in subjects with confirmed elevations of TSH (3.5–10 mIU/l) [57]. These authors reported on a double-blind, placebo-controlled, 1-year evaluation of levothyroxine treatment. However, after an initial exclusion of subjects with hypothyroid symptoms from the SCH pool, baseline assessments found few or no significant differences between the asymptomatic subjects with SCH (n = 89; mean age: > 62 years, none > 80 years) and euthyroid subjects (n = 154) who were not similarly prescreened for the presence of symptoms. Post-treatment assessment in SCH patients randomized to levothyroxine (n = 36) or placebo (n = 33) found no changes in any parameter in either group [57].

Cognition, mood, hypothyroid symptoms, and health status were assessed in a double-blind, randomized crossover study in female patients with overt hypothyroidism (n = 19) receiving lower doses of levothyroxine for 12 weeks to experimentally induce SCH. During the SCH period, subjects had marginally worse hypothyroid, mood, and fatigue symptoms; significant differences were observed only for cognitive tests of working memory [58].

In summary, decrements in certain domains of cognition in subjects with SCH (i.e., working memory) have been demonstrated, and some deficits appear to be reversible with levothyroxine treatment. However, further study is needed to determine the effects of SCH on cognition in elderly patients and the potential benefits of levothyroxine. Mood symptoms also may be worse in individuals with true SCH, although the relationship between SCH and depressive symptoms requires further elucidation, and the benefit of levothyroxine therapy remains to be substantiated [59]. Future studies may attend to some of the limitations described above.

Effects of maternal SCH on pregnancy outcomes and offspring

Thyroid dysfunction is common in pregnancy. It is well appreciated that overt hypothyroidism has serious negative consequences for both mother and child, but the effects of SCH during pregnancy and the benefits of levothyroxine treatment are just now becoming better understood [60].

The rate of spontaneous pregnancy loss was significantly higher in women with SCH (TSH ≥ 2.5–≤ 5.0 mIU/l) in the first trimester (n = 642) than in euthyroid (TSH < 2.5 mIU/l)
women (n = 3481; 6.1% vs 3.6%; P = 0.006); the OR for miscarriage was significantly increased with each 1-point increase in TSH level (OR = 1.157; 95% CI: 1.002–1.336; P = 0.047) [61]. Other studies have suggested that SCH is associated with an increased risk of severe preeclampsia, placental abruption, and preterm birth [62,63]. Several studies have assessed the effect of levothyroxine treatment on pregnancy outcome. A prospective study examined levothyroxine treatment in euthyroid women with thyroid autoimmunity, determined by the presence of TPOAb [64]; such women are predisposed to develop SCH or overt hypothyroidism during pregnancy. Pregnancy outcomes were compared among levothyroxine-treated TPOAb+ women (n = 57), untreated TPOAb+ women (n = 58), and an untreated TPOAb− group (n = 869) that served as a normal control. TSH values during pregnancy were significantly higher in untreated TPOAb+ women, as were rates of miscarriage (13.8% vs 3.5% and 2.4% in the levothyroxine-treated and normal groups, respectively) and premature delivery (22.4% vs 7.0% and 8.2% in the levothyroxine-treated and normal groups, respectively) [64]. Levothyroxine treatment in infertile women who were undergoing in vitro fertilization in a prospective, randomized trial was associated with significantly better outcomes for number of grade I or grade II embryos and rates of embryo implantation, miscarriage, and live birth compared with outcomes in untreated women; however, there was no significant between-group difference in the rate of pregnancy per cycle [65].

The effects of overt maternal hypothyroidism on the neurocognitive development of offspring are well recognized [53,66,67]. In contrast, some but not all studies have noted the negative effects of maternal SCH on cognitive function in their children [66,68]. One study found significantly lower mean intelligence and motor scores (P = 0.008 and P < 0.001, respectively) in children whose mothers had SCH (TSH > 4.21 mIU/l, normal FT4 and total T4, and TPOAb−) during pregnancy (n = 18) compared with normal controls (n = 36) [69]. A much larger study (n = 5131) found that symptoms of attention deficit hyperactivity disorder were significantly more common at 8 years of age in girls, although not boys, for every natural log increase in maternal TSH level during pregnancy (adjusted OR = 1.39; 95% CI: 1.07–1.80) [70]. A large, randomized, controlled study assessed the effects of levothyroxine treatment on cognition in the offspring of women diagnosed with reduced thyroid function early in pregnancy [71]. Cognition at 3 years was similar in children of treated (n = 390) and untreated (n = 404) mothers, suggesting that levothyroxine treatment had no benefit. However, treatment may have begun too late in gestation (median of 13 weeks, 3 days) to influence brain development [71].

Accumulating evidence suggests that SCH is associated with adverse pregnancy outcomes; well-controlled studies are needed to determine whether levothyroxine treatment can mitigate the effects of SCH during pregnancy.

Iron-deficiency anemia

The hematopoietic system is among the many affected by hypothyroidism, with anemia being a frequent finding in this setting (Table III). One study found that anemia was significantly more common among patients with overt hypothyroidism or SCH compared with healthy individuals (P ≤ 0.021), but was similarly prevalent between the populations of patients with overt hypothyroidism and SCH (P = 0.568) [72]. In patients with SCH and iron-deficiency anemia, levothyroxine in combination with iron was effective in overcoming resistance to iron alone and increased red blood cell, hemacotrit, and iron levels, and transferrin saturation (Table III) [73,74]. As a clinical caveat, it should be noted that the simultaneous ingestion of supplemental iron will diminish levothyroxine absorption significantly. Although the package inserts may differ for the different products and formulations, levothyroxine is best ingested fasting, with water only, 60 minutes prior to breakfast. Iron supplementation should be taken with a meal ingested at a different time of day.

Renal disease

Relatively little is known about the link between chronic kidney disease (CKD) and hypothyroidism. The NHANES III dataset demonstrated that the prevalence of hypothyroidism increased as kidney function decreased, from 5.4% of patients with estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m² to > 20% with an eGFR of < 60 mL/min/1.73 m². Although the hypothyroid group included individuals with overt hypothyroidism and SCH, the association between CKD and SCH may also be significant because 56% of the hypothyroid population had SCH (Table III) [75].

A retrospective study demonstrated that hypothyroidism in patients with advanced CKD was associated with a higher risk of mortality compared with euthyroidism; patients with adequately treated hypothyroidism did not have an increased risk of death [76]. Another retrospective study demonstrated the positive effects of levothyroxine treatment in patients with SCH and stage II to stage IV CKD. At 12 months, eGFR was lower in untreated versus treated patients (P = 0.04), and kidney function deteriorated faster in the untreated versus the treated group (P = 0.04). Levothyroxine treatment independently predicted better renal outcome (Table III) [77].

These intriguing results must be confirmed in larger randomized, controlled studies. However, preliminary findings suggest that levothyroxine may reverse markers of CKD morbidity.

Future research needs

There is a large body of evidence that suggests that SCH has a negative effect in a wide range of conditions, and that levothyroxine treatment may reverse markers of morbidity. However, much of this evidence is derived from uncontrolled or smaller studies not powered to provide definitive results. Controlled studies with appropriate TSH inclusion criteria and long-term follow up are needed to better understand the risks of SCH and the benefits of levothyroxine treatment on associated morbidities. Recent clinical guidelines have highlighted two areas of particular interest: the cardiac and cognitive benefits of treating SCH [1].
Addition of levothyroxine to oral iron treatment in patients with SCH significantly improved serum iron and blood count measures versus oral iron therapy alone. Between-group comparisons revealed statistically significant increases in ferritin. Oral iron + PBO: n = 20
Levothyroxine + PBO: n = 20

Between-group comparisons revealed statistically significant increases in hemoglobin and ferritin levels with addition of levothyroxine to oral iron treatment in patients with SCH. Levothyroxine + PBO: n = 20

Between-group comparisons revealed statistically significant increases in hemoglobin and ferritin levels with addition of levothyroxine to oral iron treatment in patients with SCH. Levothyroxine + PBO: n = 20

Levothyroxine-treated: n = 180

Risk of all-cause mortality higher in patients with SCH (HR = 1.37, [1.10–1.69]; P = 0.004), but not overt hypothyroidism. Patients with hypothyroidism who received levothyroxine and attained euthyroid status (n = 323) did not have increased mortality.

**Table III. Preliminary evidence for reversible morbidity markers in iron-deficiency anemia and CKD.**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study description</th>
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<th>Number of tests</th>
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</thead>
</table>
| Erdogan et al., 2012 [72] | Cross-sectional SCH: elevated TSH, normal FT4 and FT3 | NR | Overt hypothyroidism: n = 100 | Anemia and subtypes: Iron-deficiency anemia, Folic acid deficiency anemia | Prevalence of anemia significantly higher in patients with overt hypothyroidism (43%) and SCH (39%) versus euthyroidism (26%)

Cinmre et al., 2009 [74] | Randomized, double-blind, controlled, 3-month study in patients with iron-deficiency anemia | TSH > 4.2 mIU/L, normal FT4 | Measured at BL and 3–4 weeks after the end of treatment to rule out transient SCH | Oral iron: n = 25 | Hb: RBC, Hct, Fe | Addition of levothyroxine to oral iron treatment in patients with SCH significantly improved serum iron and blood count measures versus oral iron therapy alone |

Ravanbod et al., 2013 [73] | Randomized, double-blind, controlled, 3-month study in patients with iron-deficiency anemia | TSH = 4.5–10 mIU/L, normal FT4 and FT3 | NR | Oral iron + PBO: n = 20 | Between-group comparisons revealed statistically significant increases in hemoglobin and ferritin levels with oral iron + levothyroxine versus either treatment alone |

Lo et al., 2005 [75] | Observational (NHANES III) | SCH and overt hypothyroidism = TSH > 4.5 mIU/L or treatment with thyroid medication | Hypothyroidism: n = 1162 eGFR | Hypothyroidism prevalence higher with decreasing kidney function: 5.4% at eGFR ≥ 90 ml/min/1.73 m² > 20% at eGFR < 60 ml/min/1.73 m², Lower eGFR (< 60 ml/min/1.73 m²) a significant predictor of hypothyroidism |

Shin et al., 2012 [77] | Retrospective study in patients with stage II–IV CKD | TSH > 4.94 mIU/L, normal FT4 | Repeated within 3 months to confirm the diagnosis | Levothyroxine-treated: n = 180 | eGFR | At 12 months: eGFR significantly lower in untreated patients, Overall rate of decline in eGFR greater in untreated patients, With mean follow up of 35 months: Incidence of ESRD higher in untreated patients |

Rhee et al., 2013 [76] | Retrospective cohort study in patients with ESRD | TSH levels: Low-normal: 0.4–2.9 mIU/L; High-normal: ≥ 3 mIU/L and ≤ ULN; SCH: > ULN and ≤ 10.0 mIU/L; Overt hypothyroidism: > 10.0 mIU/L | Included patients had ≥ 1 TSH measurement; first value after ESRD diagnosis was considered for SCH diagnosis | Hypothyroid: n = 350 (SCH: n = 238) | All-cause mortality | Risk of all-cause mortality higher in patients with SCH (HR = 1.37, 95% CI: 1.10–1.69), P = 0.004, but not overt hypothyroidism. Patients with hypothyroidism who received levothyroxine and attained euthyroid status (n = 323) did not have increased mortality |

**Abbreviations:** BL = Baseline; CKD = Chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = End stage renal disease; FT3 = Free triiodothyronine; FT4 = Free thyroxine; Hb = Hemoglobin; Hct = Hematocrit; HR = Hazard ratio; NHANES III = Third National Health and Nutrition Examination Survey; NR = Not reported; PBO = Placebo; SCH = Subclinical hypothyroidism; TIBC = Total iron binding capacity; TSH = Thyroid-stimulating hormone; ULN = Upper limit of normal.
Summary

SCH is a relatively common clinical entity that presents a challenge to researchers and clinicians alike. Thyroid dysfunction affects multiple systems, and, although unambiguous data regarding the short- and long-term effects of SCH on the conditions reviewed here are not yet available, the sum of the evidence suggests that SCH may negatively affect cardiovascular health, cognition, pregnancy outcomes, iron-deficiency anemia, and renal disease to varying degrees. The conflicting results of studies in the current literature that have attempted to define the relationship of SCH with clinical outcomes may be due to imprecise and unconfirmed laboratory assessments of thyroid function, resulting in the inclusion of patients without persistent TSH elevations; misdiagnosis of SCH, particularly in the elderly, may also be an issue. Future studies which employ multiple and more rigorous assays of thyroid function may provide for a better understanding of the at-risk patient population. Future findings will not only clarify the role of SCH but will also identify patients for whom levothyroxine therapy will provide the most benefit. At present, although evidence is not definitive in every disease state, guidelines suggest that levothyroxine treatment is warranted when TSH levels exceed 10 mIU/l in patients who are also at risk of conditions including HF and cardiovascular mortality [1].

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