A Review of the Clinical Consequences of Variation in Thyroid Function Within the Reference Range

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Context: Overt thyroid disease is associated with profound adverse health outcomes; however, data are conflicting for studies of borderline/subclinical thyroid dysfunction. Many studies of subclinical thyroid disease have had low power and were prone to selection bias. In contrast, large datasets are available from community studies in healthy individuals. Studies of the effects of variation of thyroid function across the reference range on health outcomes in these populations may provide useful information regarding thresholds for treatment of abnormal thyroid function.

Evidence Acquisition: MEDLINE and the Cochrane Database of Systematic Reviews and Controlled Trials Register were searched for articles studying the effect of variation in thyroid hormone parameters within the reference range on cardiovascular, bone, metabolic, pregnancy, neurological, and psychological outcomes.

Evidence Synthesis: Higher TSH/lower thyroid hormone levels are associated with more cardiovascular risk factors and cardiovascular events and worse metabolic parameters and pregnancy outcomes, whereas lower TSH/higher thyroid hormone levels are associated with reduced bone mineral density and increased fracture risk. The evidence base was good for cardiovascular, metabolic, bone, and pregnancy outcomes; however, high-quality data remained lacking for neurological and psychological outcomes.

Conclusions: Common variation in persons with thyroid function in the normal range are associated with adverse health outcomes. These data suggest, by extrapolation, that carefully monitored treatment of even modest elevations of TSH may have substantial health benefits. Appropriately powered large-scale clinical trials analyzing the risks vs benefits of treating subclinical thyroid disease are required to determine whether these benefits can be achieved with levothyroxine therapy. **(*J Clin Endocrinol Metab* 98: 3562–3571, 2013)**

Thyroid hormone has effects on cardiovascular risk factors, metabolism, bone maintenance, and mental health, as well as pregnancy outcomes and childhood development (1–3). Although it is readily apparent that overt thyroid dysfunction results in adverse health outcomes, it is unclear whether modest variation at the extremes of the normal reference range, or just outside, has sufficient impact on health to justify intervention.

This is an important issue to address. Increased use of thyroid function testing (4) has resulted in many individuals being identified with subclinical thyroid disease. The prevalence of subclinical hypothyroidism is between 4 and 8.5% (5, 6), rising to 15% in elderly populations (1, 7). Subclinical hyperthyroidism is less common, with a prevalence of 1–5% in the elderly (6). Treatments for subclinical thyroid disease are effective, cheap, and easy to mon-

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; fT_3, free T_3; fT_4, free T_4; GFR, glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; OR, odds ratio.

itor; it is the uncertainty regarding the magnitude of the clinical benefit of treatment that has led to divergent opinions regarding screening and management (4, 8–10). Data are lacking due to limited trials in this area with adequate power (1). This is further compounded because the diagnosis of subclinical thyroid disease is based on abnormal TSH levels with normal free T_3 (fT_3) and free T_4 levels (fT_4), and the exact definition of the upper limit of a normal TSH remains contentious (11, 12).

Although subclinical thyroid disease is robustly associated with adverse bone outcomes, atrial fibrillation, and to a lesser extent quality of life (1, 8, 13, 14), it is subclinical hypothyroidism and its impact on cardiovascular outcomes that will drive most clinical management decisions, as well as cost-effectiveness considerations for its detection and treatment (15). A recent meta-analysis (16) identified that subclinical thyroid disease might be associated with adverse coronary heart disease and mortality outcomes, although the point estimates for the relative risk for coronary heart disease extended below equality. Limiting analyses to studies with the more robust methodologies and lower risk of selection bias decreased risk estimates. Although this meta-analysis (16) was unable to confirm a positive association between subclinical thyroid disease and coronary heart disease and mortality in the general population, it did indicate that the negative impact of subclinical hypothyroidism may be more substantial in younger individuals (relative risk = 1.51; 95% confidence interval [CI], 1.09–2.09). Current American Thyroid Association guidelines (17) recommend consideration of levothyroxine therapy at TSH levels less than 10 mU/L when there are clear symptoms of hypothyroidism, positive thyroid antibodies, or evidence of atherosclerotic cardiovascular disease or heart failure (evidence level B), but it is unclear which patients with a TSH between 4.5 and 10.0 mU/L will benefit most (16, 18).

In the absence of well-designed and adequately powered trials in this area, alternative strategies are required. Analyzing cohorts of individuals identified to have subclinical thyroid disease has key limitations, due to small study size and potential for substantial selection bias. This selection bias arises because subclinical thyroid disease is often asymptomatic, and individuals have their thyroid function measured for a variety of reasons, including screening in patients with diabetes; therefore, individuals who have their thyroid function measured are not representative of the general population.

An alternative approach is to study the phenotypic consequences of variation in thyroid hormone parameters within the general population. Studies here are considerably larger and less prone to selection bias than any available studies in subclinical thyroid disease. This review will therefore highlight the phenotypic consequences of modest variation in thyroid function within the population reference range.

Materials and Methods

Search strategy

Combinations of "TSH," "fT_4," "fT_3," "thyroid function," "blood pressure," "cholesterol," "lipid levels," "cardiovascular disease," "myocardial infarction," "arrhythmia," "stroke," "bone mineral density," "osteoporosis," "osteopenia," "peak bone mass," "fracture," "BMI," "weight," "metabolic syndrome," "ATP-III," "pregnancy," "cancer," "neurological development," "mood," "behavior," "depression," "anxiety," "neurological," separately and in conjunction with the terms "reference-range" and "normal range" were used to search MEDLINE via an Ovid Server and the Cochrane database in September 2012. The references of retrieved papers were also reviewed. Only English-language papers were studied.

Data synthesis

A total of 985 English-language papers were reviewed; studies analyzing associations in thyroid hormone parameters outside the reference range, editorials, and individual case studies were excluded. Forty papers were found to be suitable; no published papers studying variation in thyroid function within the reference range were found to be unsuitable. Information related to authorship, year of publication, number of subjects, study design, and results were extracted and formed the basis for the report. The predominantly narrative nature of this review limited the use of the GRADE scoring criteria (19) because all studies were observational. However, the GRADE criteria for decreasing/increasing evidence levels was used when appraising papers. Evidence quality was regarded as good if derived from several consistent studies from large epidemiological cohorts with adjustment for important confounders. Evidence quality was regarded as moderate if the number of papers on a topic was limited or studies were conflicting, but still from good data sources; finally, evidence was regarded as poor if it was derived from studies with imprecise or sparse data or with a high probability of reporting bias.

We undertook an inverse-variance, fixed-effects, weighted meta-analysis, repeated with random effects, to examine the aggregate odds of developing adverse outcomes in individuals with TSH levels in the upper part of the reference range vs those in the lower part of the reference range across several comparable studies for cardiovascular, metabolic, and bone outcomes.

Cardiovascular Outcomes (Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org)

There is growing evidence that higher levels of TSH are associated with worsening blood pressure (20–22) and lipid levels (23, 24). With an increase in both systolic and diastolic blood pressure of approximately 2 mm Hg per 1

mU/L rise in TSH, over the reference range this difference is equivalent to between 33 and 50% of the blood pressure change observed with antihypertensive monotherapy (25). These associations are also present in children (22), highlighting that TSH influences cardiovascular risk factors throughout life.

The impact of variation in TSH over the reference on lipid levels is more modest, with a change in total cholesterol of only 0.12–0.20 mmol/L between the upper and lower part of the reference range (23). This beneficial impact of thyroid hormone on lipids may have become inflated in current prescribing practice because modest dyslipidemia was found to be a major motivator in prescribing levothyroxine for borderline thyroid function (26).

Analysis in the Nord-Trøndelag Health Study (HUNT Study), one of the largest longitudinal health studies in the world with extensive phenotypic data linked to regional and national disease registers, identified that higher TSH levels within the reference range were associated with higher mortality from coronary heart disease in females (27). This is in keeping with the observed negative impact of rising TSH on blood pressure and lipid levels. Compared to women with a TSH level in the lower third of the reference range, the hazard ratios (HRs) for coronary heart disease mortality were 1.41 (95% CI, 1.02–1.96) and 1.69 (95% CI, 1.14–2.52) for women in the middle third and higher third, respectively (27). After adjusting for age and smoking, the HR for a 1.0 mU/L rise in TSH was 1.37 (95% CI, 1.12–1.68).

The association between TSH and cardiovascular mortality appears to be mediated by components other than lipids and blood pressure because adjusting for age, smoking, serum creatinine, cholesterol, use of hypertensives, systolic blood pressure, and diastolic blood pressure resulted in only a modest fall in the HR for a 1.0 mU/L rise in TSH to 1.30 (95% CI, 1.06–1.60).

The lack of an observed association between TSH and cardiovascular mortality in males may be due to insufficient power because there were more than twice the number of females in this study as males; however, there was weak evidence of interaction by sex. Extending the observation period for 4 more years (28) identified that the association between TSH and mortality from coronary heart disease in women remained similar over the increased follow-up time and demonstrated stronger evidence of interaction by sex. This study also identified that, compared to women with a TSH level in the lower third of the reference range, the risk of mortality from coronary heart disease was higher in women with subclinical hypothyroidism (HR = 1.76; 95% CI, 1.21–2.56) or subclinical hyperthyroidism (HR = 2.29; 95% CI, 1.27–4.13). The relationship between TSH and cardiovascular mortality is therefore U-shaped, and if individuals are excessively treated with levothyroxine for subclinical hypothyroidism, which results in a suppressed TSH, then any benefit on cardiovascular mortality may be lost and mortality may even be potentially increased. A similar U-shaped association with TSH for both cardiovascular outcomes and fracture incidence has been observed in individuals on levothyroxine (29).

Despite this positive association between TSH levels and coronary heart disease mortality (28), there was no evidence of association between TSH levels and the risk of being hospitalized with a first myocardial infarction (MI). This finding therefore does not confirm the suggestion that low thyroid function within the reference range is associated with an increased risk of MI. This finding is difficult to explain. It may be underpowered, but another possible explanation is that higher TSH levels within the reference range may increase the risk of heart disease, but this is mechanistically distinct from a typical MI—for example silent MI or diastolic dysfunction. This is to some extent supported by a large meta-analysis showing an increased risk of heart failure in individuals with subclinical hypothyroidism (30), although evidence for a substantial impact of TSH variation within the population on heart failure is limited at present. It needs highlighting that all these studies examined the association with cardiovascular outcomes for TSH only. Although higher TSH was associated with worse cardiovascular risk factors and higher mortality, data are limited and conflicting for fT_4 and fT_3 levels (31–33). Although data have been obtained for key cardiovascular risk factors and outcomes, more information is still required for other important health outcomes—in particular, stroke. This is particularly relevant because higher thyroid hormone levels are associated with atrial fibrillation (3, 29), a key stroke risk factor.

Metabolic Outcomes (Supplemental Table 2)

Weight/body mass index (BMI)

The relationship between pathological thyroid dysfunction and weight is well established. Cross-sectional studies in population cohorts identified that variation in thyroid function within the population reference range has a substantial impact on weight and BMI, with higher levels of TSH being associated with increased BMI (34, 35) and rising TSH levels associated with increased weight gain (36, 37). Baseline TSH may be associated with weight gain over time, although this may not be apparent for several years (34). Consistent with this, fT_4 was strongly negatively associated with BMI (34).

Metabolic syndrome

Cross-sectional analysis in cohort studies highlighted that the odds of metabolic syndrome as defined by the Adult Treatment Panel-III (ATP-III) criteria are positively associated with TSH levels within the reference range (38–40); however, this may be due to reverse causation through the impact of the metabolic syndrome on the hypothalamic-pituitary-thyroid axis. Prospective cohort studies with serial measurements of thyroid function and metabolic properties assessing the change in thyroid hormone status and change in ATP-III score over time are therefore required.

Glomerular filtration rate (GFR)

Variation in TSH within the population reference range was positively associated with changes in GFR and a higher prevalence of chronic kidney disease (41), with the strength of this association being magnified over the subclinical and overt hypothyroid range. The association between TSH and GFR was approximately the same in thyroid peroxidase- positive and -negative individuals, indicating that immunological processes are unlikely to explain this association. It has been previously observed that GFR increases after T_4 treatment for hypothyroidism (42, 43) and decreases after treatment for hyperthyroidism (42) or after withdrawal of T_4 therapy, indicating that variation in thyroid hormone status drives this association. This association between GFR and thyroid status may, however, be explained at least partially by a diminished ability to excrete free water (44, 45) in hypothyroidism leading to changes in volume status.

Bone Phenotypes and Fracture Risk (Supplemental Table 3)

Cross-sectional analyses have identified that lower levels of TSH and higher levels of thyroid hormone within the population reference range are associated with an increased risk of osteoporosis (46–50) and fracture (47, 51). Data from these studies are largely from healthy postmenopausal women; although this represents the group at greatest risk, generalizability is limited. Even modest variations of 1 U in TSH and thyroid hormone levels were associated with a substantial change in the odds of osteoporosis and fracture. There may, however, be a "threshold effect" because the prevalence of vertebral fracture was only substantially increased in individuals with a TSH lower than 1.0 mU/L (51). In keeping with these findings, greater bone loss occurs in levothyroxine-treated patients with suppressed TSH levels than in those without suppression (29, 52). This reinforces the hypothesis that the potential advantages of treating subclinical hypothyroidism may be lost if patients develop high-normal or subclinical hyperthyroidism through overreplacement.

Data from these studies also highlighted that low levels of TSH, independent of thyroid hormone levels, may have an adverse effect on bone (46, 51) even in younger individuals (53). This is particularly relevant because peak bone mass determines the structural strength of bone in later life (54) and is a major determinant of an individual's risk of osteoporosis and fracture. The relationship between fT_3 and fracture may be more complex than previously believed because fT_3 was strongly positively associated with handgrip and balance (47), key protective factors in determining an individual's risk of falls.

Neuropsychological Outcomes (Supplemental Table 4)

Although thyroid dysfunction results in impaired central nervous system development (55) and possibly mood disturbance (13), the impact of variation within the population reference range is less clear. Analysis in the HUNT study identified that there may be interaction by sex on the association between TSH and mood (56). In this study (56), there was an inverse association between serum TSH and depression in males, but no evidence of association in females. In females on levothyroxine, TSH was positively associated with both depression and anxiety. Analysis of neuropsychological outcomes in cohorts of children (57, 58) and older individuals have been inconclusive (59–63), most likely due to lack of power because these cohorts have been smaller and are prone to type-2 error or type-1 error and subsequent publication bias.

A meta-analysis identified a positive association between depression and FT_4 within the reference range (odds ratio [OR] = 1.12; 95% CI, 1.02–1.22; $P = .01$) (63). This is in keeping with the observed inverse association between TSH and depression in males in the HUNT study (56), but in contrast to traditional thinking that higher levels of TSH are associated with increased levels of depression. Studies of selective cohorts of individuals with depression are inconsistent; individuals with serum TSH concentrations in the upper 25th percentile of the normal range were more likely to have more episodes of major depression, longer duration of depression, and a higher number of suicide attempts than patients who had serum TSH concentrations below the upper 25th percentile of the reference range (64). However, in another cohort of individuals with depression, those with a high-normal TSH (≥2.5 mU/L) had lower depression as measured by Hamilton Depression Rating scores, fewer anxiety symptoms,

and less suicidal ideation than those with low-normal TSH (<2.5 mU/L) (65). These data are not from the general population, and observed associations may be due to selection bias, medication effects, and reverse causation through the effects of major depression on the hypothalamic-pituitary-thyroid axis.

The Effect of Variation in Thyroid Function Within the Reference Range on Pregnancy and Oncological Outcomes (Supplemental Table 5)

Pregnancy outcomes

TSH levels between 2.5 and 5.0 mU/L in thyroid antibody-negative women were associated with a significant increase in the rate of spontaneous pregnancy loss compared with first-trimester thyroid antibody-negative women with TSH levels less than 2.5 mU/L (66). Furthermore, treatment of pregnant women in this trial who were thyroid antibody-positive with TSH levels of 2.5 mU/L or above resulted in a decrease in both maternal and neonatal complications (67). A narrower reference range may be appropriate during pregnancy and is endorsed by current American and European guidelines (68, 69). Low thyroid hormone levels during pregnancy have also been associated with impaired fetal neurological development (55). However, maternal treatment with levothyroxine for TSH levels, just outside the reference range (median gestational age at levothyroxine initiation, 13 wk and 3 d) did not result in improved cognitive function in children at 3 years of age (70).

Cancer risk

There was a substantially higher HR of both prostate (HR = 2.60; 95% CI, 1.36–4.99) and lung cancer (HR = 2.91; 95% CI, 1.49–5.70) in individuals with a TSH less than 0.5 mU/L compared to the rest of the reference range, even after adjusting for key confounders including age and smoking (71). These results require replication, especially because smoking has been shown to be associated with lower TSH levels (72), and although smoking was adjusted for in models, there may be residual confounding. Furthermore, no association was observed between TSH levels and cancer outcomes in another, albeit smaller, cohort of patients aged over 60 (73).

Results Summary

An overview of the phenotypic associations of variation in thyroid function within the reference range is shown in Table 1. A fixed-effects meta-analysis of the ORs of adverse heath outcomes for higher TSH levels within the reference range compared to lower levels of TSH is shown in Figure 1. There was very strong evidence in the fixed-effects meta-analysis that individuals with TSH levels in the upper part of the reference range had increased odds of adverse cardiovascular outcomes (OR = 1.21; 95% CI, 1.15–1.27; $P = 7.99 \times 10^{-15}$) and adverse metabolic outcomes (OR = 1.37; 95% CI, 1.27–1.48; $P = 5.99 \times 10^{-15}$) but lower odds of adverse bone outcomes (OR = 0.55; 95% CI, 0.41–0.72; $P = 1.93 \times 10^{-05}$) compared to individuals with TSH levels in the lower part of the reference range. Similar but more modest associations were observed in the random-effects model (Supplemental Figure 1).

Discussion

We have highlighted that variation in thyroid hormone levels within the population reference range is associated with a wide range of adverse health outcomes. Higher TSH levels are associated with worse cardiovascular risk factors, metabolic parameters, and pregnancy outcomes, whereas lower TSH levels are associated with reduced bone mineral density (BMD) and increased risk of osteoporosis and fracture. The evidence base for our findings was generally good for cardiovascular, metabolic, bone, and pregnancy outcomes, being derived from large population cohorts; however, high-quality data remain lacking for neurological outcomes, and most psychological outcome studies were underpowered.

A key aim in studying the relationships between thyroid function within the general population and health outcomes was to take advantage of large study populations without selection bias to inform the debate on thresholds for treating subclinical thyroid disease. Hence, it might be expected that effects attributable to variation in thyroid function across the reference range would be similar if not greater in subjects with thyroid function outside this range. The data collated in this report suggest that, at least at the population level, treatment of subclinical thyroid disease could potentially improve health outcomes. However, important limitations need to be taken into account in extrapolating data from the reference range to assess risk of adverse outcomes for individuals with subclinical thyroid disease. Most studies in this report have been in individuals of white European ancestry, which limits generalizability. Most studied associations were also with TSH only; data are still lacking on the phenotypic consequences of variation in fT_3 and fT_4. Furthermore, a substantial proportion of identified associations were from

Table 1. Summary of the Associations Between Variation in Thyroid Hormone Parameters Within the Population Reference Range and Key Phenotypic Outcomes

Outcome	Association	Parameter	Comment	Refs.	Evidence Quality
Blood pressure	Yes	TSH	Positively associated with blood pressure, approximately a 5-mm Hg increase in systolic blood pressure across the reference range.	20–22	Good
Cholesterol and lipid levels	Yes	TSH	Positively associated with cholesterol and lipid levels although effect modest, approximately 0.2 mmol/L increase in total cholesterol across the reference range.	23, 24	Good
Cardiovascular mortality	Possible	TSH	Positively associated with cardiovascular mortality in women, but not men. No association identified between TSH and hospitalization for myocardial infarction.	27, 28	Moderate
BMI	Yes	TSH	Positively associated with BMI and odds of obesity. Those with TSH levels in the upper 1/3 of reference range have a BMI of approximately 1.9 kg/m^2, higher than the lower 1/3. Increasing TSH over time is also associated with increased weight gain.	34–37	Good
Metabolic syndrome	Yes	TSH	Positively associated with increased odds of fulfilling the diagnostic ATP III criteria.	24, 38	Moderate
Pregnancy outcomes	Yes	TSH	The proportion of spontaneous pregnancy loss in individuals with a TSH less than 2.5 mU/L was 3.6%, vs 6.1% in individuals with a TSH between 2.5 and 5.0 mU/L; $P = .006$.	66	Moderate
BMD	Probable	TSH	TSH was positively associated with BMD at both the spine and the hip and reduced odds of osteoporosis/ osteopenia and vertebral fracture. However, 1 study with the highest proportion of men found no evidence of association between TSH and BMD.	46, 48–51, 84	Good in females. Moderate in males
BMD	Probable	fT_3, fT_4	fT_3 consistently associated with low BMD; $\beta = -0.08$; $P = 0.02$, but not fT_4.	47, 53	Moderate
Depression	Unclear	TSH	Inverse association between serum TSH and depression score in males but not in females. Also appears to be a different relationship between TSH and depression in individuals on levothyroxine. Other studies are conflicting.	56	Poor

cross-sectional analyses, which are prone to unmeasured/ residual confounding and reverse causation.

When considering whether to treat subclinical hypothyroidism, there also needs to be careful consideration of the complexities of thyroid hormone replacement. For instance, the population reference range by far exceeds the variation of the intraindividual set-point (74), and although levothyroxine treatment will restore an individual's TSH levels to within the "normal population range," this may be outside their genetically determined set-point (75). It is also unclear whether treatment with levothyroxine in individuals with subclinical hypothyroidism will normalize the odds of developing adverse outcomes; for instance, treating individuals with levothyroxine will substantially reduce their T_3:T_4 ratio (76), and the long-term consequences of this in patients with subclinical hypothyroidism are currently unclear. The pituitary response as measured by changes in TSH may not fully reflect the

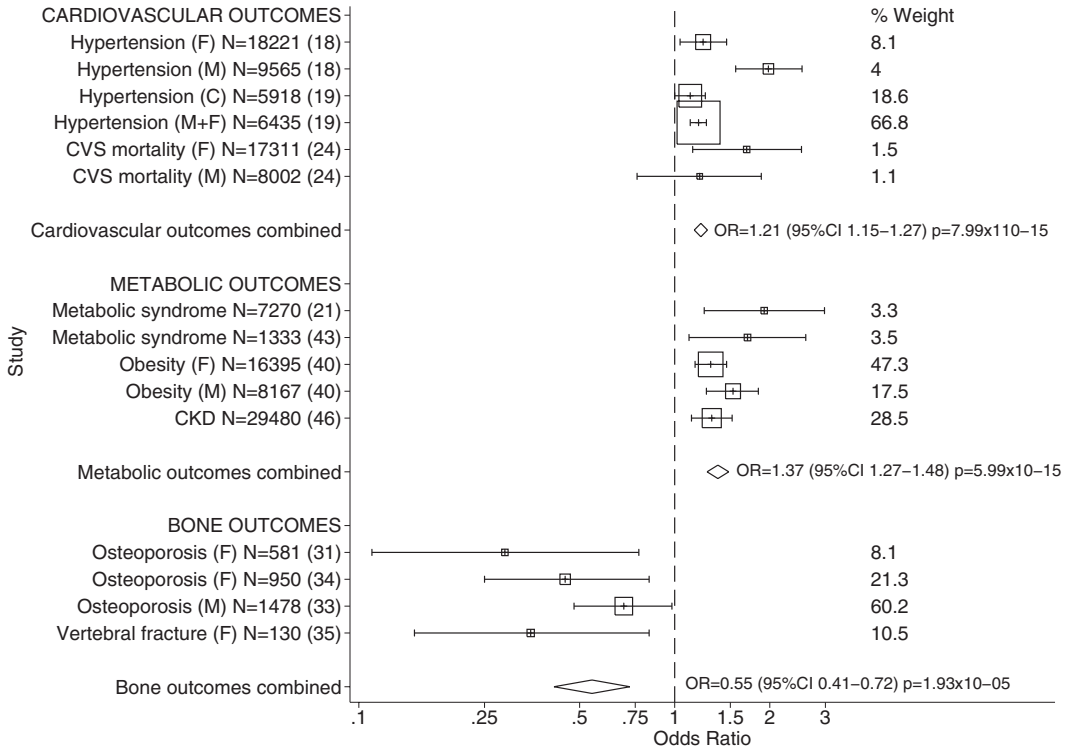

Figure 1. The odds of adverse outcomes for higher TSH levels within the reference range compared to lower levels of TSH within the reference range with fixed-effects meta-analysis. (Reference numbers for the relevant papers are in parentheses.)

thyroid status in other key organs; for example, common variation in *DIO2* has been shown to influence mood and response to combination T_3/T_4 therapy (77) and osteoarthritis risk (78), but it has no effect on serum thyroid hormone levels (77). Hence, it is possible that improving outcomes for cardiovascular disease may at the same time increase the risk of osteoporosis in the same individual, and the optimal TSH (or indeed the premorbid TSH) may be difficult to determine. Furthermore, with current practice, 40–48% of hypothyroid patients on levothyroxine do not achieve target TSH values (5, 79) with many individuals overtreated. Taken together, the data reviewed in this article provide a strong rationale for the treatment of subclinical thyroid disease, but large, carefully designed, long-term, randomized clinical trials will be needed to determine the true balance of benefits and risks and the optimal thresholds for intervention.

The continuum of effects across the reference range of thyroid function suggest that it might be more appropriate to consider thyroid hormone levels as "risk factors" for disease (similar to blood pressure or cholesterol in cardiovascular disease), rather than consider a particular level to be "normal" or "abnormal." In this way of thinking, the net benefit of intervention at a particular TSH level can be related to an individual's comorbidities. For example, more net benefit might be obtained in initiating levothyroxine therapy for subclinical hypothyroidism in an adult with multiple cardiovascular risk factors than in one with osteoporosis. This approach might then suggest that younger adults with cardiovascular risk factors should be screened for thyroid disease because this will increase the likelihood of identifying patients with subclinical disease who might benefit most from intervention (80, 81).

Considering thyroid hormone levels as continuously distributed risk factors for different health outcomes may also help inform the debate on the upper limit of "normal" TSH. The National Academy of Clinical Biochemists highlighted that 95% of individuals without evidence of thyroid disease or autoantibodies had TSH concentrations below 2.5 mU/L (82), leading for calls to lower it to this level (11). However, it has been argued that lowering the upper TSH limit is unnecessary because treating individuals with high-normal TSH is unwarranted and routine levothyroxine treatment is not currently recommended for subclinical hypothyroidism (12). Identifying TSH levels at which net benefit for intervention can be obtained by treatment in different patient groups by prospective studies may be a more relevant goal.

Although no large prospective intervention studies have been performed in subclinical hypothyroidism, there have been cohort studies in this area. A large individual patient data meta-analysis (n = 55 287) from 11 population cohorts (83) identified that the impact of subclinical hypothyroidism on coronary heart disease event only became apparent between a TSH level of 7.0 and 9.9 mU/L (HR = 1.17; 95% CI, 0.96–1.43), with no clear effect

observed for TSH levels between 4.50 and 6.99 mU/L (HR = 1.00; 95% CI, 0.86–1.18). However, levothyroxine treatment at TSH levels lower than 7.00 mU/L, especially in younger individuals, may still be beneficial; analysis from the UK General Practice Research Database indicated that in individuals under the age of 70, levothyroxine treatment at TSH levels between 5 and 10 mU/L reduced the future risk of ischemic heart disease events (HR = 0.61; 95% CI, 0.39–0.95) (81). This is in keeping with our observed differences in the odds of adverse cardiovascular outcomes within even the population range.

We have identified that variation in thyroid hormone parameters within the population reference range resulted in increased odds of adverse outcomes, but this should not be used as justification for treating at-risk individuals with thyroid hormone parameters within the reference range (pregnancy aside). In particular, data do not support levothyroxine treatment with TSH levels within the reference range for low mood. The potential benefits of treating individuals within the normal population range would only be modest, and over-replacement with levothyroxine is associated with osteoporosis and atrial fibrillation (29).

In summary, this review has highlighted that modest variations in thyroid hormone levels are associated with increased odds of developing a wide range of adverse health outcomes. Prospective clinical trials in subclinical hypothyroidism, which recognize the complexities of thyroid hormone replacement, are therefore urgently required. In particular, adequately powered prospective, randomized, controlled, double-blinded long-term interventional trials will be required to fully identify the benefits and risks of treatment as well as to determine appropriate TSH thresholds for intervention in different patient groups.

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