Reanalysis of the Whickham Survey shows an association of subclinical hypothyroidism and ischemic heart disease


SUMMARY

BACKGROUND
It is widely known that over a 20-year period the Whickham Survey has not found an association between ischemic heart disease (IHD) and autoimmune thyroid disease in community-dwelling subjects with positive antibodies or those using levothyroxine, which appears to be at odds with other studies. As a result, the authors performed this study to evaluate the incident rate of IHD and mortality in participants of the Whickham study in relation to their thyroid status.

METHODS
The Whickham Survey is a population-based cross-sectional study of community-dwelling adults in an urban area in northern England. The study cohort comprised a randomly selected group of 2779 individuals who were first studied from 1972 through 1973, during which a history of medical conditions was elicited, a physical examination was performed, and an electrocardiograph (ECG) and blood samples for lipids, thyroid function, and thyroid antimicrosomal antibodies were obtained. At a 20-year follow-up study, the causes of death were ascertained and further examination of survivors was performed. Excluded from the analysis were participants who had thyroid disease at baseline or were on medications that could affect thyroid function.

RESULTS
Baseline Characteristics of Participants in the Reanalysis

![Figure 1](image)

In the reanalysis, at baseline the majority of participants were euthyroid (95.9%; mean age, 45.3 years; range, 18 to 92). The prevalence of SCH was 4.1% (mean age, 49.9 years; range, 18 to 87) and was higher in women, older individuals, nonsmokers, and those with positive thyroid antibodies (Figure 1). Serum TSH levels were higher in the SCH group as compared with euthyroid individuals. Over the 20-year follow-up period, 45 participants (3 men and 42 women, 25 euthyroid and 20 with SCH at baseline) had been treated with levothyroxine.

Association between Thyroid Status and IHD Risk Factors at Baseline

Systolic and diastolic blood pressure and total cholesterol levels were higher in the SCH group as compared with the euthyroid group (P<0.001 for blood pressure and P = 0.02 for cholesterol). Multiple-linear-regression analysis, after adjusting for other IHD risk factors including age, sex, weight, smoking, and relevant medications, showed that SCH was significantly associated only with higher systolic blood pressure (r^2 = 0.38, P = 0.03), but not for diastolic blood pressure or serum cholesterol.
Over the 20-years of follow-up, there were 165 deaths due to IHD. The mortality rate of IHD was higher in the SCH participants than in the euthyroid individuals, with an adjusted HR of 1.79 (95% CI, 1.02 to 3.56; P = 0.05) in the full model (Figures 2 and 3). However, when thyroid hormone use was excluded from the multivariate analysis (Model B), there was a reduction in the association between SCH and IHD (HR, 1.45; 95% CI, 0.73 to 2.89; P = 0.28) (Figures 2 and 3).

There were a total of 595 deaths in the entire cohort, and all-cause mortality was not significantly different in the SCH and euthyroid groups, with an adjusted HR of 1.29 (95% CI, 0.87 to 1.92) (full model). Thus, withdrawal of thyroid hormone use did not change the results. Adding thyroid antibody status to the full multivariate model (Model C) did not significantly change the results (Figure 2).
Association of Mortality and IHD Events in SCH
Participants Stratified by Thyroid Hormone Therapy
(Figures 3 to 6)

During the 20-year follow-up, levothyroxine therapy was started in 20 of the 91 individuals with SCH at baseline. At follow-up there were 24 deaths in the SCH group. All-cause mortality was significantly lower in the SCH group treated with levothyroxine as compared with untreated individuals with SCH (HR, 0.20; 95% CI, 0.05 to 0.89; P = 0.03) after adjusting for age, sex, and cholesterol levels, and further adjustment for other IHD risk factors did not change the results (HR, 0.22; 95% CI, 0.06 to 0.91; P = 0.02) (Figure 3). Also, IHD mortality and IHD events were not significantly different in the treated groups as compared with the untreated group (HR, 0.32; 95% CI, 0.03 to 3.34; and HR, 1.02; 95% CI, 0.40 to 3.05, respectively).

CONCLUSION

The initial report of the 20-year follow-up of the Whickham Survey cohort did not find an association between IHD events and a composite of people with either SCH or positive thyroid antibody levels or individuals taking levothyroxine, regardless of their TSH levels. The current analysis shows an association of IHD and IHD-related mortality in people with SCH.

COMMENTARY

Subclinical hypothyroidism (SCH) is defined as serum free T4 and free triiodothyronine (T3) levels within their respective reference ranges in the presence of abnormal serum TSH levels. SCH is being diagnosed more frequently in clinical practice in young and middle-aged people as well as in the elderly; still, the incidence of SCH varies widely, from 4 to 10%, largely because of the variability in TSH cutoffs used to diagnose SCH (1). Moreover, the clinical relevance of SCH continues to be debated, although it can have effects on the cardiovascular system and bone and other organs and systems (1). The treatment of SCH and population screening are even more controversial, despite the potential risk of progression to overt disease, as there is no consensus on the upper TSH reference range and at what TSH cutoff, if any, treatment should be contemplated. Thus, whether SCH plays a major role in IHD remains a matter of debate, with some finding that SCH is an independent risk factor for atherosclerosis and myocardial infarction in elderly patients (2-5), while others do not find this association.

The current reanalysis of the Whickham Survey found an association between subclinical hypothyroidism and ischemic heart disease. In addition to the main findings that link SCH with IHD and IHD-related mortality, a subgroup analysis also suggests improvement in mortality among individuals with SCH who were treated with levothyroxine over an extended period as compared with those with SCH who were not treated. Moreover, this reanalysis found that the risk for IHD events was not related to baseline antibody status. The authors of the study opine that one obvious explanation for the apparent discord between this and the previous analysis was the inclusion of individuals with hypothyroidism who were treated with levothyroxine, which may have diluted the observed risk for IHD events.

Several, but not all, studies have found that older adults with serum TSH levels ≥10.0 mIU/L have a moderately increased risk of heart failure and alterations in cardiac function that do not occur in older adults with TSH levels <10.0 mIU/L, suggesting that levothyroxine therapy might ameliorate the adverse effects in patients with SCH who had TSH levels >10 mIU/L (3,4).

Razvi et al. mention several limitations of their study; all individuals were classified as either euthyroid or as having SCH on the basis of a single blood test, which, if anything, may have diluted the evidence for an association between SCH and IHD by including some euthyroid individuals with transient TSH elevations in the SCH group. Moreover, some individuals with SCH may have been progressed to overt hypothyroidism by their primary physicians or at the 20-year follow-up survey, thus increasing their vascular risk during the period without levothyroxine therapy. Also the lower TSH reference limit of 0.6 mIU/L may not be identical to the reference ranges in current sensitive TSH assays. Although the finding that levothyroxine reduced mortality rates of IHD, the authors suggest that the total number of events is small and should thus be interpreted with caution until a randomized, controlled trial is available. Of these concerns, perhaps the most important is that the diagnosis of subclinical hypothyroidism is severely limited by a single set of thyroid-function tests and the biologic variation in thyroid testing from visit to visit (6).

— Ernest L. Mazzaferri, MD, MACP
References


