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

Razvi S, Weaver JU, Vanderpump MP, Pearce SH. The incidence of ischemic heart disease and mortality in people with subclinical hypothyroidism: reanalysis of the Whickham Survey cohort. J Clin Endocrinol Metab [Epub ahead of print February 11, 2010; doi:10.1210/jc.2009-1749]

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 (n = 60) or who had IHD (n = 243) or a serum thyrotropin (TSH) >15 mIU/L (n = 13) and those in whom the cause of death or the cause of medical conditions could not be ascertained (n = 52). Thus, the total cohort who had follow-up for up to 20 years was 2376 individuals.

At baseline, subclinical hypothyroidism (SCH) was defined as a serum TSH of 6.0 to 15.0 mIU/L, with a serum total thyroxine (T_4) of 46 to 174 nmol/L. A first-generation TSH assay was used for the baseline survey, thus making the upper reference limit of TSH 6.0 mIU/L (the 97.5th centile) with negative thyroid antibodies and not on medication affecting thyroid function, rather than 4.5 mIU/L as it is now using sensitive assays. To make the TSH levels comparable to current ranges, the authors used a range of 6.0 to 15.0 mIU/L in the reanalysis. A TSH between 0.3 to 5.9 mIU/L was classified as the euthyroid reference limit. Total serum T_4 levels were not used for this definition because they might be elevated because of some medications such as estrogens. Positive thyroid antibodies were defined as an increase in antimicrosomal antibodies.

At the end of the 20-year follow-up, IHD events were defined by Rose angina questionnaires, ECG changes per the Minnesota code, or hospital admission for IHD, confirmed by ECG or serial cardiac enzymes. Causes of death were ascertained from death certificates.

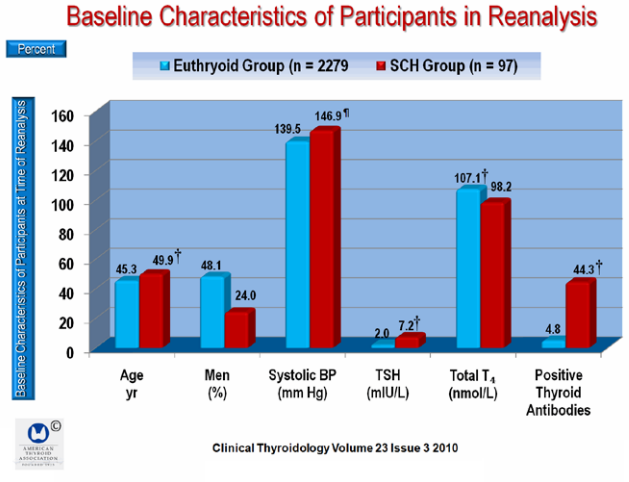

Figure 1. This figure shows the baseline characteristics of participants included in the reanalysis. Some variables may not add up to the total because of missing data. a = reference value (HR = 1.0) for Cox proportional-hazards analysis; significant results are shown in bold type: †P = 0.01, comparing treated with untreated patients in the euthyroid with subclinical hypothyroidism (SCH) group. ¶P = 0.02.

RESULTS

Baseline Characteristics of Participants in the Reanalysis (Figure 1)

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 (Figure 1)

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 (r2 = 0.38, P = 0.03), but not for diastolic blood pressure or serum cholesterol.

Association of Baseline Thyroid Status with Incident IHD Events and Mortality (Figures 2 and 3)

There were 419 IHD fatal and nonfatal events during the follow-up period. There was a positive association between baseline SCH and incident IHD, with an adjusted hazard ratio (HR) of 1.76 (95% confidence interval [CI], 1.15 to 2.71; P = 0.01) after multivariate adjustment (full model). Excluding the use of thyroid hormone during follow-up from the multivariate model (Model B), showed a reduction in the association between SCH and IHD events (HR, 1.53; 95% CI, 0.97 to 2.45; P = 0.07).°

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).

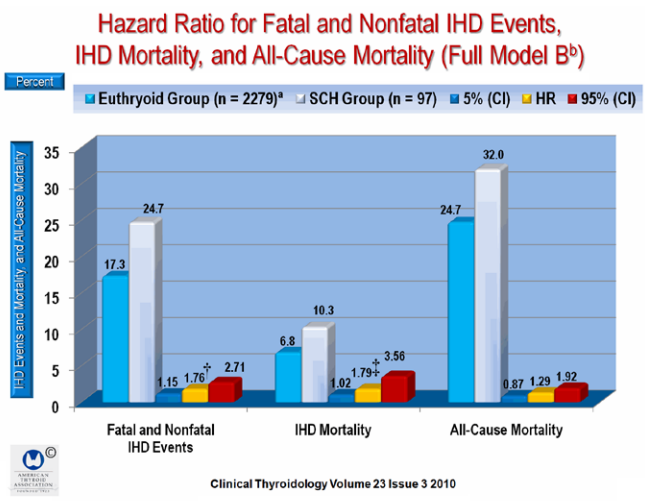

Figure 2. This figure shows the frequency and hazard ratios (HRs) for ischemic heart disease (IHD) events and mortality in participants who are euthyroid as compared with participants with IHD. Reference value (HR = 1.0) for Cox proportional-hazards analysis; significant results are shown in bold type. †P = 0.01. ¶P = 0.02. §P= 0.04. ǂP = 0.05. γP = 0.06. Full Modelb = full model with baseline age, sex, social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, systolic and diastolic blood pressure, serum cholesterol levels, and levothyroxine use during follow-up as a covariate. Model Bc = Model B; as full model, without levothyroxine use during follow-up as a covariate. Model Cd = Model C; as full model, but with the addition of thyroid antibody status at baseline as a covariate.

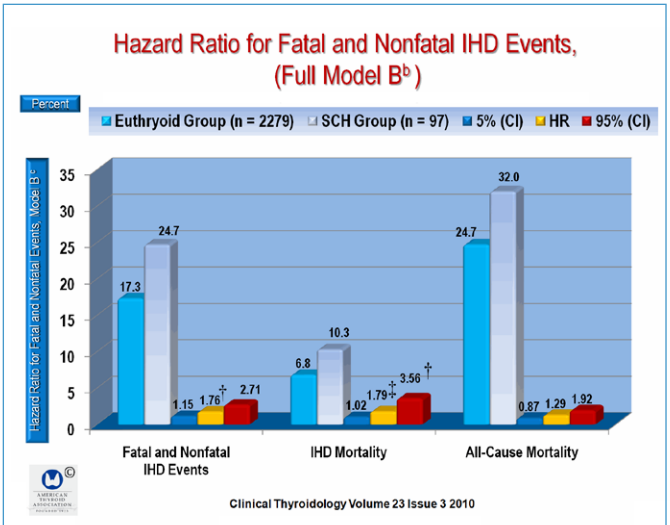

Figure 3. Frequency and hazard ratios for IHD events and mortality in treated and untreated participants with SCH over 20 years of follow-up. (See Figure 2 for explanations of symbols.)

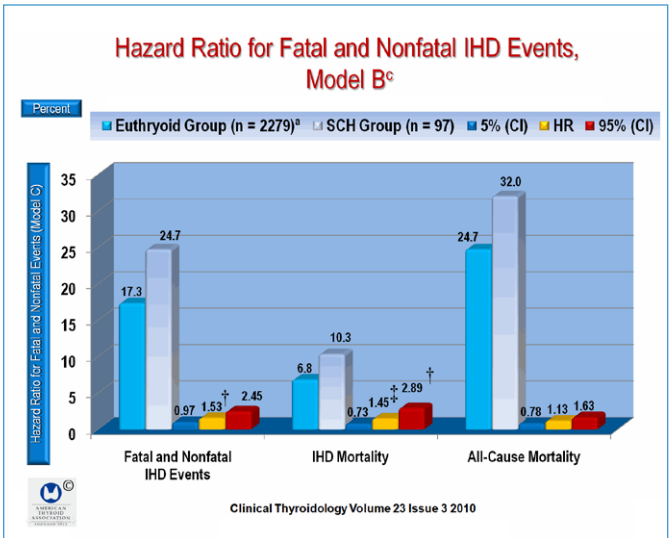

Figure 4. Hazard ratio for fatal and nonfatal IHD events (Model B^C, see Figure 2 legend for P values.)

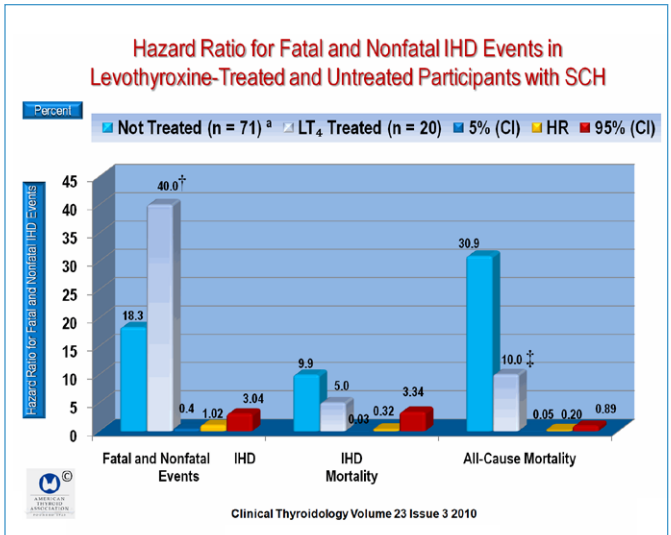

Figure 5. Hazard ratio comparing patients treated with levothyroxine (LT_4) with the untreated group. Age, sex, and total serum cholesterol adjusted. Model further adjusted for baseline social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, and systolic and diastolic blood pressure as covariates. (See Figure 2 for P values.)

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.

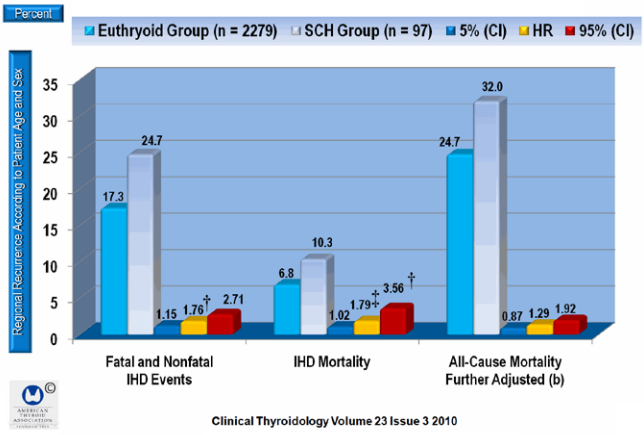

Figure 6. Frequency and hazard ratios for IHD events and mortality in treated and untreated SCH. ¶P = 0.03. b Model further adjusted for baseline social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, and systolic and diastolic blood pressure as covariates.

COMMENTARY

Subclinical hypothyroidism (SCH) is defined as serum free T_4 and free triiodothyronine (T_3) 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

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