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The Incidence of Ischemic Heart Disease and Mortality in People with Subclinical Hypothyroidism: Reanalysis of the Whickham Survey Cohort

Salman Razvi, Jola U. Weaver, Mark P. Vanderpump, and Simon H. S. Pearce

Department of Endocrinology (S.R., J.U.W.), Gateshead Health National Health Service Foundation Trust, Gateshead NE9 6SX, United Kingdom; Institute of Human Genetics (S.R., J.U.W., S.H.S.P.), Newcastle University, Newcastle upon Tyne NE1 7RU, United Kingdom; and Department of Endocrinology (M.P.V.), Royal Free Hospitals National Health Service Trust, London NW3 2PF, United Kingdom

Context: The Whickham Survey evaluated vascular events over 20 yr in community-dwelling subjects stratified by thyroid function and thyroid autoantibody status. No association between ischemic heart disease (IHD) and a composite autoimmune thyroid disease group, comprising individuals with subclinical hypothyroidism (SCH), with positive thyroid antibodies or those using levothyroxine, was found. This result appears to be at odds with the findings of other cohort studies.

Objective: The objective of the study was to evaluate incident IHD and mortality in participants in relation to their thyroid status.

Outcomes, Design, and Participants: Data were reanalyzed assessing incident IHD events and mortality during 20 yr of follow-up in individuals with endogenous SCH (n = 97; TSH 6.0–15 mIU/liter) *vs.* the euthyroid group (n = 2279), who were IHD free at baseline.

Results: Incident IHD was significantly higher in the SCH group [adjusted hazard ratio 1.76 (95% confidence interval 1.15–2.71); $P = 0.01$]. IHD mortality was also increased in the SCH group [hazard ratio of 1.79 (1.02–3.56); $P = 0.05$]. These findings lost their significance when subsequent treatment with levothyroxine was excluded from the regression model. There was no difference in all-cause mortality between the groups.

Conclusion: In the Whickham Survey, there is an association between incident IHD events and IHD-related mortality with SCH over the 20 yr of follow-up. Furthermore, subsequent treatment of SCH with levothyroxine appears to attenuate IHD-related morbidity and mortality, and this may explain why some other longitudinal studies of SCH have not shown such an association; properly designed controlled trials of treatment of SCH are required to answer this question definitively. **(*J Clin Endocrinol Metab* 95: 0000–0000, 2010)**

Subclinical hypothyroidism (SCH) is prevalent in 5–15% of the population and its frequency increases with age (1, 2). It has been debated for some time whether SCH is associated with ischemic heart disease (IHD) and increased mortality (3–7). The Whickham Survey is a pivotal study that investigated the long-term consequences of thyroid dysfunction and has provided vital data on the demographics of thyroid diseases in the population (8). This study did not find an association between IHD events and a composite autoimmune thyroid disease phenotype, comprising individuals with raised serum TSH and normal thyroid hormones, those with positive thyroid antibody levels but normal thyroid function, and those treated with levothyroxine since the first survey (9). It remains unclear whether there was an association between SCH and IHD-related mortality in this cohort. In addition, there has been

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Abbreviations: ECG, Electrocardiograph; HR, hazard ratio; IHD, ischemic heart disease; SCH, subclinical hypothyroidism.

a misconception in some of the published literature regarding this association (10, 11). We therefore reanalyzed the data to investigate whether such a relationship exists.

Subjects and Methods

Study population

The Whickham Survey is a population-based cross-sectional study of community-dwelling adults in an urban area close to Gateshead/Newcastle in northern England. The full details of the cross-sectional and its 20-yr follow-up studies have been published previously (2, 8, 9). Briefly, a randomly selected group of 2779 individuals were first studied in 1972–1973 and history of medical conditions, demographic details, physical examination, and electrocardiograph (ECG) and biochemical samples for lipids, thyroid function, and thyroid antibodies (antimicrosomal) performed. At the 20-yr follow-up study, cause of death, case-note examination of those who had died, and further examination of the survivors was performed. Participants with known thyroid disease or on medications that could affect thyroid function (n = 60) and IHD (n = 243) at baseline were excluded from this analysis. Furthermore, people with overt hypothyroidism (TSH >15 mIU/liter; n = 13) were also excluded. Details of medical conditions and/or cause of death could not be ascertained at follow-up in 52 individuals, and these were also excluded from this study, leaving data from a total of 2376 individuals who had been followed up for 20 yr.

Thyroid status and ascertainment of events

At baseline, SCH was defined as serum TSH between 6.0 and 15.0 mIU/liter with normal total T_4 levels (46–174 nmol/liter). The baseline survey used a first-generation TSH assay that overestimated TSH levels (12). Hence, the normal range of TSH was up to 6.0 (the 97.5th centile in the cohort with negative thyroid antibodies and not on medications affecting thyroid function) rather than 4.5 mIU/liter as it would be today using ultrasensitive TSH assays. Therefore, to make the range of TSH levels in SCH individuals comparable with the current range of 4.5–10.0 mIU/liter, we used a range of 6.0–15.0 mIU/liter in the reanalysis. All individuals with TSH levels between 0.3 and 5.9 mIU/liter were classed as being euthyroid; total T_4 levels were not used for this categorization because they might be elevated due to some medications (such as estrogens). Positive thyroid antibodies were defined as increased titers of antimicrosomal antibodies. Details of all the laboratory methodology have been previously described (2). At the end of the follow-up period of 20 yr, the status of participants was determined. IHD events were defined by Rose angina questionnaires, ECG changes as per the Minnesota code, or hospital admission for IHD events that were confirmed by ECG or serial cardiac enzymes. For deceased patients, cause of death was ascertained by examining death certificates and coding them as per criteria of the *International Classification of Diseases*, ninth revision, and other medical conditions were determined by examining hospital and primary care records.

Statistical analysis

Baseline characteristics of the analyzed sample were compared stratified by thyroid status, using unpaired *t* test or χ^2 test for continuous and categorical variables, respectively. Variables that were not normally distributed were log transformed before analysis. Baseline vascular risk factors that were significantly different between the two thyroid groups were further analyzed by linear regression after adjusting for confounding variables (age, gender, weight, smoking, and relevant medications) to investigate whether thyroid function was independently associated with those risk factors. Analysis of IHD events and mortality as hazard ratios (HR) in the euthyroid and SCH groups at baseline was performed by multivariable Cox-regression analysis after adjusting for IHD risk factors and thyroid hormone use during follow-up (full model). These IHD risk factors were age, gender, social class (class 1–6, as a surrogate marker of socioeconomic status and educational level based on occupation), body weight in kilograms, systolic and diastolic blood pressure in millimeters of mercury, serum total cholesterol in millimoles per liter, smoking (current smoker, ex-smoker, or never-smoker), and cerebrovascular disease and diabetes mellitus (both as categoricals). The analyses were repeated after excluding the variable of thyroid hormone use during follow-up (model B). Finally, thyroid antibody status scored as positive or negative at baseline was added to the equation (model C). The Cox-regression model was stratified by gender initially. However, because there was no heterogeneity between sexes (*P* for interaction = 0.15) with respect to thyroid status, both men and women were analyzed as a whole for greater statistical power. Similarly, there was no interaction between any outcome and age (less than or greater than 65 yr) (*P* for interaction >0.2). In addition, a further analysis restricted to SCH participants at baseline was performed investigating the above outcomes after adjusting for baseline variables and stratified for thyroid hormone treatment during follow-up (categorical as yes/no) was performed. SPSS 10.0 (Chicago, IL) was used to perform all analyses.

Results

In this reanalysis, after exclusion of individuals with known thyroid disease or IHD and on medications that could affect thyroid function, the majority of participants at baseline were euthyroid (95.9%; mean age 45.3 yr, range 18–92). The prevalence of SCH was 4.1% (mean age 49.9 yr, range 18–87) and was higher in women, older individuals, nonsmokers, and those with positive thyroid antibodies (Table 1). As expected, serum TSH levels were higher and thyroxine concentrations lower in the SCH group compared with euthyroid individuals. Forty-five participants (three men and 42 women: 25 euthyroid and 20 SCH at baseline) had been treated with levothyroxine over the 20-yr follow-up period.

Association between thyroid status and IHD risk factors at baseline

Systolic and diastolic blood pressure levels were higher in the SCH group, as were total cholesterol levels (Table 1). Multiple linear regression analysis, after adjusting for other IHD risk factors as outlined in *Subjects and Methods*, showed that SCH was significantly associated only with higher systolic blood pressure ($r^2 = 0.38$, $df = 6$, standard-

TABLE 1. Baseline characteristics of participants included in reanalysis[a]

	Euthyroid (n = 2279)	SCH (n = 97)	*P* value
Age (yr)	45.3 ± 15.8	49.9 ± 17.9	<0.01
Males	1096 (48.1)	23 (24)	<0.01
Social class			
Class 1	120 (5.3)	4 (4)	0.88
Class 2	401 (18)	15 (16)	
Class 3	1278 (57)	61 (65)	
Class 4	326 (15)	11 (12)	
Class 5	124 (6)	3 (3)	
Mean weight (kg)	69.3 ± 45.5	67.4 ± 12.7	0.67
Blood pressure (mm Hg)			
Systolic	139.5 ± 24.7	146.9 ± 26.4	<0.01
Diastolic	85.4 ± 13.7	88.8 ± 13.3	0.02
Serum TSH (mIU/liter)	2.0 (0.3–5.9)	7.2 (6.0–15.0)	<0.01
Total T_4 (nmol/liter)	107.1 ± 24.2	98.2 ± 22.9	<0.01
Positive thyroid antibodies	109 (4.8)	43 (44.3)	<0.01
Total cholesterol (mmol/liter)	5.9 ± 1.2	6.2 ± 1.3	0.02
History of CVD	36 (2)	1 (1)	0.81
History of DM	6 (0.3)	0 (0)	0.42
Smoking status			
Never	823 (37)	49 (51)	0.02
Past	352 (16)	18 (19)	
Current	1078 (48)	29 (30)	

Values are reported as mean ± SD, median (range), or number (%). To convert total cholesterol from millimoles per liter to milligrams per deciliter, multiply by 38.6. To convert total T_4 from nanomoles per liter to nanograms per deciliter multiply by 12.8. CVD, Cerebrovascular disease; DM, diabetes mellitus.

[a] Some variables may not add up to the total due to missing data.

ized β-coefficient = 0.03, $P = 0.03$) but not diastolic blood pressure or serum cholesterol levels (data not shown).

Association between thyroid status at baseline and incident IHD events and mortality (Table 2)

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

There were 165 deaths due to IHD in the cohort over the subsequent 20 yr of follow-up. IHD mortality was higher in the SCH participants than in the euthyroid individuals with adjusted HR of 1.79 (1.02–3.56; $P = 0.05$), in the full model (Fig. 1). However, when subsequent thyroid hormone use was excluded from the multivariate model (model B), this association was lost [HR of 1.45 (0.73–2.89); $P = 0.28$]. Other causes of mortality (due to cerebrovascular disease, trauma, infection, and malignancy) were similar in both groups.

There were a total of 595 deaths in the entire cohort, and all-cause mortality was not different in the SCH group compared with euthyroid participants, with an adjusted HR of 1.29 (0.87–1.92) (full model); the exclusion of subsequent thyroid hormone use did not change the results fundamentally. The addition of thyroid antibody status to the full multivariate model (model C) did not change the above results for any outcome significantly (Table 2).

Association of mortality and IHD events in SCH participants stratified by thyroid hormone treatment

Over the 20 yr of follow-up, 20 of the 91 participants with SCH at baseline were commenced on treatment with levothyroxine therapy (no follow-up data were available for six SCH participants). Women and those with higher serum cholesterol levels at baseline were more likely to be treated; age, other chronic conditions (hypertension, diabetes mellitus, and cerebrovascular disease), smoking history, and serum TSH levels were not significantly different between the two groups. At follow-up, there were 24

TABLE 2. Frequency and HRs for IHD events and mortality in euthyroid and subclinical hypothyroid participants

	Number of events (%)		HRs (5–95% confidence intervals)		
	Euthyroid (n = 2279)[a]	SCH (n = 97)	Full model[b]	Model B[c]	Model C[d]
Fatal and nonfatal IHD events	395 (17.3)	24 (24.7)	**1.76 (1.15–2.71)** ***P* = 0.01**	1.53 (0.97–2.45) $P = 0.07$	**1.66 (1.02–2.72)** ***P* = 0.04**
IHD mortality	155 (6.8)	10 (10.3)	**1.79 (1.02–3.56)** ***P* = 0.05**	1.45 (0.73–2.89) $P = 0.28$	**1.71 (1.00–3.69)** ***P* = 0.06**
All-cause mortality	564 (24.7)	31 (32.0)	1.29 (0.87–1.92) $P = 0.21$	1.13 (0.78–1.63) $P = 0.51$	1.34 (0.89–1.98) $P = 0.16$

[a] Reference value (HR = 1.0) for Cox proportional hazards analysis; significant results are shown in *bold* typeface.

[b] Full model; with baseline age, gender, 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 covariates.

[c] Model B; as full model but without levothyroxine use during follow-up as a covariate.

[d] Model C; as full model but with the addition of thyroid antibody status at baseline as a covariate.

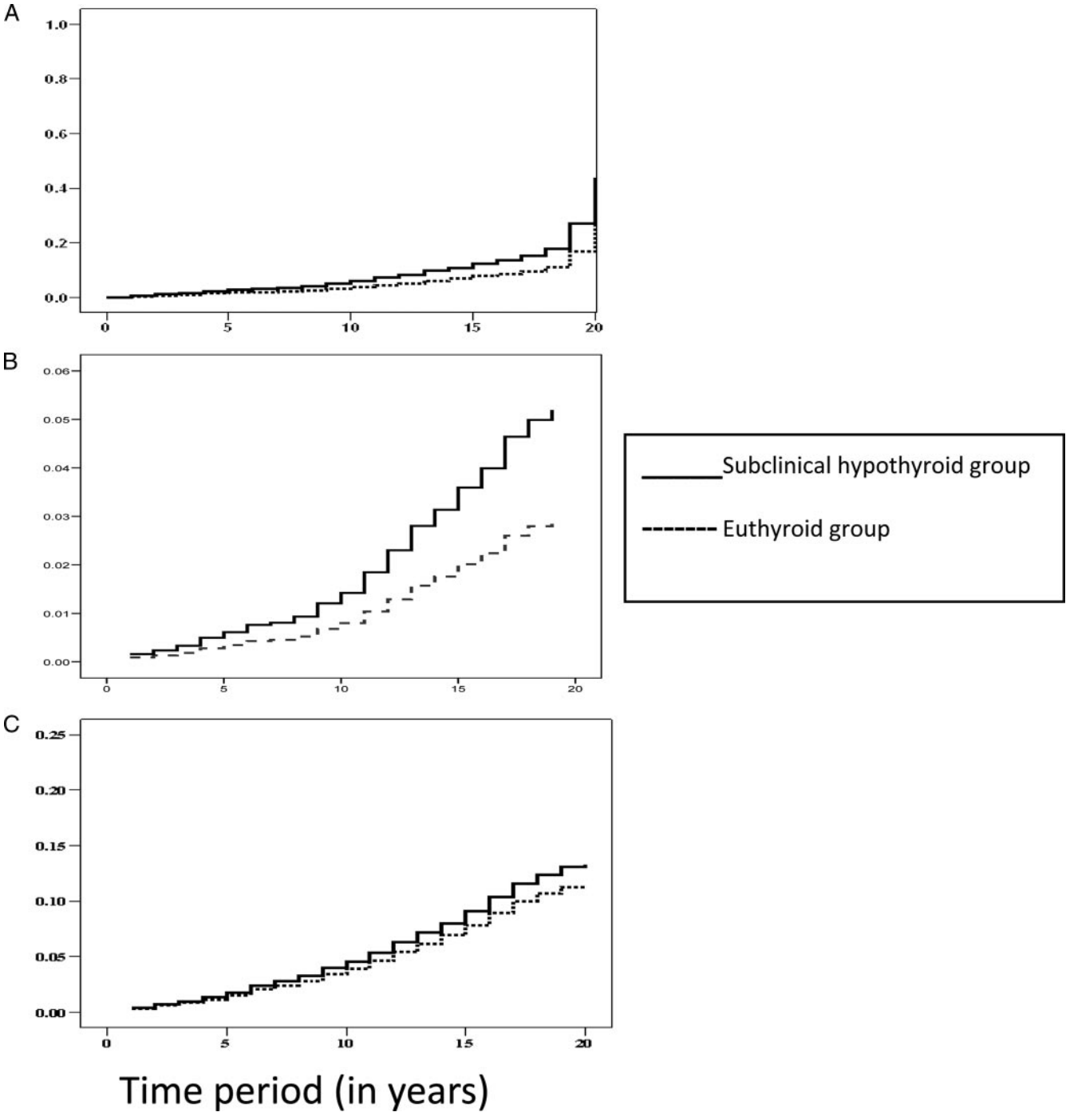

FIG. 1. The *P* values are derived from assessing the HRs for each group based on thyroid function at baseline and adjusted for age, gender, social class, weight, cerebrovascular disease, diabetes mellitus, smoking, systolic and diastolic blood pressure, total cholesterol levels, and thyroid hormone use during follow-up. Hazard plots for fatal and nonfatal IHD events (A), IHD mortality (B), and all-cause mortality (C) in the Whickham cohort over 20 yr are stratified by thyroid status at baseline.

deaths in the whole SCH group. All-cause mortality was significantly lower in the levothyroxine-treated SCH group compared with untreated SCH individuals [HR of 0.20 (0.05–0.89); $P = 0.03$], after adjusting for age, gender, and cholesterol levels (Table 3). Further adjustment for other IHD risk factors did not change the results with a HR of 0.22 (0.06–0.81; $P = 0.02$). IHD mortality and IHD events were not significantly different in the treated group *vs.* the untreated group [HR 0.32 (0.03–3.34) and 1.02 (0.40–3.04), respectively].

Discussion

The initial report of the 20-yr follow-up study of the Whickham Survey cohort did not find an association be-

TABLE 3. Frequency and HRs for IHD events and mortality in treated and untreated subclinical hypothyroid participants over 20 yr of follow-up

	Number of events (%)		HRs (5–95% confidence intervals)	
	Not treated (n = 71)[a]	Thyroid hormone treated (n = 20)	Age, gender, and total serum cholesterol adjusted	Further adjusted[b]
Fatal and nonfatal IHD events	13 (18.3)	8 (40)	1.02 (0.4–3.04) $P = 0.65$	0.99 (0.33–2.95) $P = 0.98$
IHD mortality	7 (9.9)	1 (5)	0.32 (0.03–3.34 $P = 0.31$	0.36 (0.03–3.86) $P = 0.39$
All-cause mortality	22 (30.9)	2 (10)	**0.20 (0.05–0.89) $P = 0.03$**	**0.22 (0.06–0.81) $P = 0.02$**

[a] Reference value (HR = 1.0) for Cox proportional hazards analysis; significant results are shown in *bold* typeface.

[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.

tween IHD events and a composite of thyroid phenotypes including people with either SCH or positive thyroid antibody levels or on levothyroxine treatment, irrespective of their serum TSH levels (9). In the current analysis, we show that there is an association of IHD and IHD-related mortality in people with SCH. This is in keeping with the results of several other studies that have assessed this association (3, 4, 7). Furthermore, our subgroup analysis of SCH participants comparing thyroxine-treated and untreated participants, although not a randomized controlled trial, is the first data to suggest improvement in mortality with treatment over an extended period of follow-up, as far as we are aware. Interestingly, in the Cardiovascular Health Study, the risk of heart failure was considerably lower and at similar levels to that of euthyroid individuals in thyroxine-treated SCH individuals (13). In addition, our reanalysis of the data after including people with SCH alone has shown that the risk of IHD events was not related to antibody status at baseline. One obvious explanation for the apparent discrepant findings of this analysis is that the inclusion of treated overtly hypothyroid individuals in the original follow-up study may have diluted the observed risk of IHD events.

The relationship between SCH and IHD has been controversial, and not all studies have shown a positive association (3–7). The inconsistency in results may be due to differences in the populations as well as the duration of follow-up of the various studies. Metaanalyses of IHD events and SCH have shown that such an association probably exists (14), especially in younger cohorts (15). There have been suggestions that any possible increase in vascular risk in SCH may be mediated via conventional risk factors and that these factors improve with levothyroxine treatment (16). It is also possible that emerging or nonconventional risk factors may be responsible; endothelial dysfunction (17) and elevated C-reactive protein levels (18) have been shown to be associated with SCH in some studies. The other possible reason for increased IHD risk might be that the risk factors exert their effect at the outset and that any change over the subsequent years does not influence outcomes.

The strengths of this study include the long duration of follow-up, the rigorous methods of assessing outcomes, and the low number of individuals who were lost to follow-up. Furthermore, this study also tried to probe the reasons that people with SCH have an increased IHD risk. It is interesting to note that a cohort study from Australia, with participant numbers and follow-up period similar to the Whickham study, showed a similar result (4).

The limitations of this study were that all individuals were classed as either euthyroid or with SCH based on one blood test. Thus, some individuals with transient TSH elevation may have been labeled as SCH. If anything, this factor may actually have diluted the evidence for association that we have found between SCH and IHD by including some euthyroid individuals with transient TSH elevation in the SCH group. Furthermore, some individuals with SCH may have progressed to overt hypothyroidism before being detected by their primary care practitioners or at the 20 yr follow-up survey, thereby increasing their vascular risk for the time period without treatment. However, some of these patients would have commenced T_4 treatment once diagnosed (via primary care practitioners). Although we tried to account for most variables affecting vascular risk in our multivariate analysis, we may not have accounted for all and other, currently unmeasured, risk factors may have a role. For instance, the use of antihypertensive medication during follow-up or the timing of treatment with T_4 has not been assessed in this analysis. In addition, as mentioned previously, due to serum TSH being measured by a first-generation assay, the lower cutoff of 6.0 mIU/liter used in this study may not be identical with similar levels using current assays. An ad-

ditional minor consideration is that it is possible one or two individuals with central hypothyroidism were misclassified as euthyroid at follow-up due to reliance solely on TSH in defining the euthyroid state. Similarly, individuals with subclinical hyperthyroidism were not identified due to the inability of the first-generation serum TSH assay to detect TSH levels lower than 0.3mIU/liter. Therefore, individuals with subclinical hyperthyroidism were grouped with euthyroid individuals and may have inflated the apparent vascular risk of the latter (19).

The role of treatment of SCH in reducing IHD or IHD-related mortality has not been studied so far. There is some evidence that certain IHD risk factors may improve with levothyroxine treatment (20–23). Based on the results of this analysis, it would appear that treatment of SCH may be associated with reduced mortality as well as IHD events. However, there is a potential for bias in our retrospective observational analysis (*i.e.* SCH patients who were treated may have been more health conscious leading to a healthy user bias). In addition, the total number of events in each group of SCH participants (treated and nontreated) are small. Therefore, these results need to be interpreted with caution until a randomized controlled trial is available to provide level 1 evidence to inform this question.

In conclusion, this reanalysis of the Whickham Survey cohort has found an association of SCH with IHD and IHD-related mortality. The prevalent conventional risk factors at baseline, apart from systolic blood pressure, do not explain this association. The original analysis of the 20 yr follow-up of the Whickham Survey cohort had included individuals with normal thyroid function and/or positive antibodies, as well as treated hypothyroid individuals in a composite autoimmune thyroid disease group, but did not find this association. The results of this reanalysis are consistent with several other long-term cohort studies that have investigated this association.

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Address all correspondence and requests for reprints to: Dr. Salman Razvi, Consultant Endocrinologist and Honorary Senior Lecturer, Newcastle University, Queen Elizabeth Hospital, Gateshead NE9 6SX, United Kingdom. E-mail: salman.razvi@ghnt.nhs.uk.

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References

1. **Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE** 2002 Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 87:489–499
2. **Tunbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Grimley Evans J, Young E, Bird T, Smith PA** 1977 The spectrum of thyroid disease in a community: the Whickham Survey. Clin Endocrinol (Oxf) 7:481–493
3. **Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC** 2000 Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 132:270–278
4. **Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V** 2005 Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. Arch Intern Med 165: 2467–2472
5. **Cappola AR, Fried LP, Arnold AM, Danese MD, Kuller LH, Burke GL, Tracy RP, Ladenson PW** 2006 Thyroid status, cardiovascular risk, and mortality in older adults. JAMA 295:1033–1041
6. **Rodondi N, Newman AB, Vittinghoff E, de Rekeneire N, Satterfield S, Harris TB, Bauer DC** 2005 Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. Arch Intern Med 165:2460–2466
7. **Imaizumi M, Akahoshi M, Ichimaru S, Nakashima E, Hida A, Soda M, Usa T, Ashizawa K, Yokoyama N, Maeda R, Nagataki S, Eguchi K** 2004 Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. J Clin Endocrinol Metab 89:3365–3370
8. **Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, Young ET** 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 43:55–68
9. **Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Rodgers H, Tunbridge F, Young ET** 1996 The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. Thyroid 6:155–160
10. **Helfand M; U.S. Preventive Services Task Force** 2004 Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 140:128–141
11. **Kvetny J, Heldgaard PE, Bladbjerg EM, Gram J** 2004 Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. Clin Endocrinol (Oxf) 61:232–238
12. **Nicoloff JT, Spencer CA** 1990 The use and misuse of the sensitive thyrotropin assays. J Clin Endocrinol Metab 71:553–558
13. **Rodondi N, Bauer DC, Cappola AR, Cornuz J, Robbins J, Fried LP, Ladenson PW, Vittinghoff E, Gottdiener JS, Newman AB** 2008 Subclinical thyroid dysfunction, cardiac function, and the risk of heart failure. The Cardiovascular Health study. J Am Coll Cardiol 52: 1152–1159
14. **Rodondi N, Aujesky D, Vittinghoff E, Cornuz J, Bauer DC** 2006 Subclinical hypothyroidism and the risk of coronary heart disease: a meta-analysis. Am J Med 119:541–551
15. **Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH** 2008 The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a meta-analysis. J Clin Endocrinol Metab 93:2998–3007
16. **Biondi B, Cooper DS** 2008 The clinical significance of subclinical thyroid dysfunction. Endocr Rev 29:76–131
17. **Taddei S, Caraccio N, Virdis A, Dardano A, Versari D, Ghiadoni L, Salvetti A, Ferrannini E, Monzani F** 2003 Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: benefi-

cial effect of levothyroxine therapy. J Clin Endocrinol Metab 88:3731–3737

18. **Christ-Crain M, Meier C, Guglielmetti M, Huber PR, Riesen W, Staub JJ, Müller B** 2003 Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. Atherosclerosis 166:379–386
19. **Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B** 2008 Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. Eur J Endocrinol 159:329–341
20. **Caraccio N, Ferrannini E, Monzani F** 2002 Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. J Clin Endocrinol Metab 87:1533–1538
21. **Monzani F, Carracio N, Kozàkowà M, Dardano A, Vittone F, Virdis A, Taddei S, Palombo C, Ferrannini E** 2004 Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. J Clin Endocrinol Metab 89:2099–2106
22. **Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog R, Müller B** 2001 TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). J Clin Endocrinol Metab 86:4860–4866
23. **Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU** 2007 The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. J Clin Endocrinol Metab 92:1715–1723