The Influence of Age on the Relationship between Subclinical Hypothyroidism and Ischemic Heart Disease: A Metaanalysis

Salman Razvi, Abdul Shakoor, Mark Vanderpump, Jolanta U. Weaver, and Simon H. S. Pearce

Department of Endocrinology (S.R., A.S., J.U.W.), Queen Elizabeth Hospital, Gateshead, NE9 6SX, United Kingdom; Royal Free Hampstead National Health Service Trust (M.V.), London, NW3 2QG, United Kingdom; School of Clinical Medical Sciences (J.U.W., S.H.S.P.), Newcastle University, Newcastle upon Tyne, NE1 7RU, United Kingdom; and Royal Victoria Infirmary (S.H.S.P.), Newcastle upon Tyne, NE4 6BE, United Kingdom

Context: Subclinical hypothyroidism (SCH) is a common condition that has been associated with ischemic heart disease (IHD) in some, but not all, studies. This may be due to differences in study design and the characteristics of participants.

Objective: Our objective was to investigate whether age and gender influence IHD prevalence, incidence, and mortality in people with SCH.

Data Sources: Computerized (PubMed, EMBASE, and Cochrane Library) and manual searches of the literature to May 2007, published in English, were performed.

Study Selection: Epidemiological studies that quantified thyroid status and IHD events in adults were performed.

Data Extraction: Two authors independently reviewed articles and abstracted data. Results were compared across two groups based on the minimum age of participants studied (younger than 65 yr and 65 yr or older).

Data Synthesis: There were 15 studies included for analysis with 2,531 SCH participants and 26,491 euthyroid individuals. IHD incidence and prevalence were higher in SCH subjects compared with euthyroid participants from studies including those younger than 65 yr, but not studies of subjects aged older than 65 yr [odds ratio (95% confidence interval)]: 1.57 (1.19–2.06) *vs.* 1.01 (0.87–1.18) and 1.68 (1.27–2.23) *vs.* 1.02 (0.85–1.22), respectively. Cardiovascular/all-cause mortality was also elevated in participants from the younger than 65-yr studies, but not from the studies of older people: odds ratio 1.37 (1.04–1.79) *vs.* 0.85 (0.56–1.29). Prevalent IHD was higher in SCH participants of both genders, although this was statistically significant only in women.

Conclusions: SCH is associated with increased IHD (both prevalence and incidence) and cardiovascular mortality only in subjects from younger populations. These data suggest that increased vascular risk may only be present in younger individuals with SCH. (*J Clin Endocrinol Metab* 93: 2998–3007, 2008)

Subclinical hypothyroidism (SCH), defined as an elevated serum TSH level associated with serum thyroid hormone concentrations within the reference range, is found in 4–10% of individuals from Western populations (1–3). Several observa-

tional studies comparing the outcome of SCH individuals with euthyroid subjects have shown divergent results, and it has been debated for some time whether SCH is independently associated with ischemic heart disease (IHD) (4, 5). If the latter were true,

Abbreviations: CI, Confidence interval; IHD, ischemic heart disease; OR, odds ratio; SCH, subclinical hypothyroidism.

this would be an important public health issue for the aging population, in which SCH is most prevalent (1). Differences in reported outcomes from investigations that have compared IHD and/or mortality in people with SCH to that of euthyroid controls are not surprising, given the varied design and settings of the studies. For example, some studies have studied only women (6), others only elderly people (7–12), and others have been conducted in diverse populations (13, 14). A recently published metaanalysis has concluded that SCH individuals are at an increased risk for IHD (15). However, that metaanalysis pooled data from studies with several different designs, including case-control and cohort studies, and outcomes including prevalence, incidence, and mortality, thus making inferences from data sets that were neither uniform nor entirely comparable. Furthermore, additional large and high-quality studies assessing the association between SCH and IHD have since been published (8, 9, 12, 14, 16).

There have been suggestions that age (7, 17) and gender (6, 13, 18) may have an impact on IHD risk in people with SCH, but no quantitative analysis has been performed to investigate this. The purpose of this study was to examine the influence of age and gender on IHD and mortality in SCH. Therefore, we conducted a systematic review and metaanalysis of prospective cross-sectional and longitudinal population-based studies assessing IHD and mortality in SCH with stratification by age and gender.

Subjects and Methods

Study selection

Inclusion criteria

Types of studies. Population-based cross-sectional or longitudinal cohort studies of community living adults were included. We defined population-based studies as those that included participants from the community after screening and whom were not institutionalized, clinic based, or known to have a thyroid disorder. We defined cohort studies as those that selected controls from the same source population as the case participants. Population-based studies (cross-sectional and longitudinal) minimize false-positive results due to selection bias and population stratification.

Types of participants. Only studies that included individuals with mild SCH (TSH levels < 10 mIU/liter) were used for the analysis.

Outcomes. Outcomes were IHD events (prevalent and incident) and cardiovascular mortality. IHD events were defined as those confirmed by self-report, medical records, standardized IHD questionnaires, or investigations, including electrocardiographs and coronary angiograms. Cardiovascular mortality was defined as death due to IHD, cerebrovascular and peripheral vascular diseases confirmed by death certificates or autopsy after evaluation of medical records. When all-cause mortality was reported but not IHD or cardiovascular mortality, then all-cause mortality was included.

Literature search criteria

A search of PubMed, EMBASE, and the Cochrane Library was conducted between June 2006 and May 2007, for all relevant articles in English published from inception till May 2007, using the Medical Subject Heading terms "thyroid diseases" AND "cardiovascular diseases" limited to adult humans. Further studies were identified from references of searched articles and from personal collections of the authors (Fig. 1).
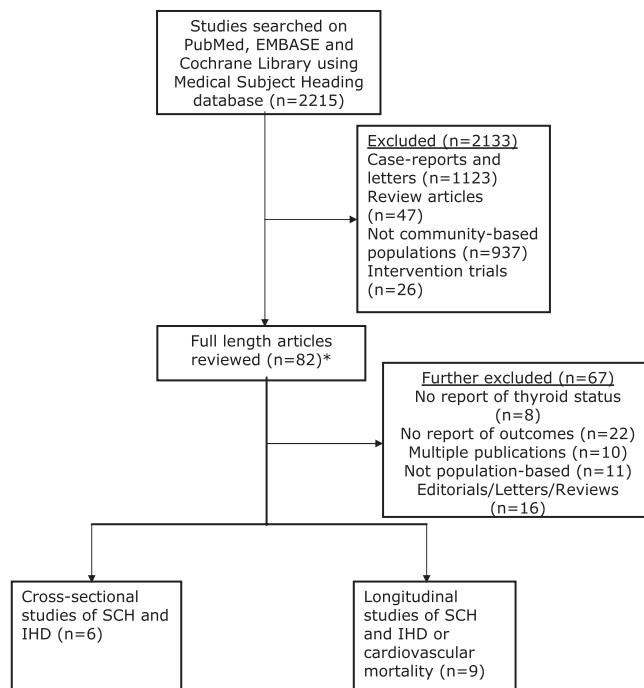

FIG. 1. Flow chart outlining the process of search criteria and study selection. *, Full list on supplemental Appendix 2 (which is published as supplemental data on The Endocrine Society's Journals Online website at http://jcem.endojournals.org).

Evaluation of studies

All studies that were collected were then evaluated against predetermined criteria to assess quality. The criteria were:

1. Unselected community dwelling adults without preset criteria (*e.g.* not from one primary care practice, or health fair, only men or women, or atomic-bomb survivors).

2. Excluded people with conditions or treatments that could affect thyroid function or people with previously treated thyroid disease, in reporting IHD.

3. The primary outcome investigated was the association of thyroid diseases with IHD events and/or mortality.

4. Measured thyroid hormones along with TSH to diagnose SCH.

5. Adjusted (multivariate) analysis for confounding variables.

6. Validated events by confirming by more than one method.

One point was allocated for each criteria and a total score calculated to provide an overview of overall quality (Table 1).

The recommendations of the Metaanalysis Of Observational Studies in Epidemiology Group for reporting metaanalysis of observational studies was used to standardize and report data from each included study (19). Any uncertainty about any item was deliberated and resolved by agreement between the authors.

Data extraction

Two investigators (S.R. and A.S.) both independently extracted outcome data from included studies, and differences were resolved by discussion. When risk estimates [either as odds ratios (ORs) or hazard ratios] were reported after adjustment for variables, then the most fully adjusted multivariate model was included for analysis. For cross-sectional studies that reported only raw event data, unadjusted ORs were calculated. Authors of studies that had not reported data in a useable form for inclusion in the analysis were contacted. Details were received from two of the investigators (6, 10) and were directly extracted for the Whickham survey (20). Additional data were then included for analysis of incident IHD (6), prevalent IHD, and all-cause mortality (10), and incident IHD and IHD mortality (20) (supplemental Table 1, which is

TABLE 1. Quality of cross-sectional and longitudinal population-based studies assessing IHD and mortality in people with SCH compared with euthyroid individuals

Study, yr (reference no.)	Type of participants studied	Primary objective of main study	Participants on medications affecting thyroid function excluded?	Hormones measured to diagnose thyroid status	Instruments used to define outcomes	Completeness of observation (persons in whom outcome ascertained/persons recruited)	Covariates assessed	Total quality score (maximum possible of 6)
Tunbridge et al., 1977 (34)	Men and women ≥ 18 yr	To assess IHD events in thyroid diseases	Yes	TSH and FT4	Self-report, ECG, questionnaire	2779/2779 for prevalent IHD	Age and gender	6
Vanderpump et al., 1996 (20)	Men and women ≥ 18 yr	To assess IHD events and mortality in thyroid diseases	Yes	TSH and FT4	ECGs, death certificates, autopsy reports, and medical records	2672/2779 for incident IHD and IHD mortality	Age, gender, BMI, BP, DM, social status, smoking, TC, triglycerides	6
Hak et al., 2000 (6)	Community living women ≥ 55 yr	To assess occurrence and risk factors for chronic diseases in men and women ≥55 yr	Yes	TSH FT4 only if TSH abnormal	Self-report, ECGs, and medical records	994/1055 for prevalent IHD and 1036/1055 for incident IHD	Age, BMI, TC, HDL, BP, smoking	5
Parle et al., 2001 (21)	Men and women ≥ 60 yr from one primary care practice	To assess mortality in thyroid diseases	Yes	TSH FT4 only if TSH abnormal	Death certificates	1190/1191 for all-cause and circulatory mortality	Age and gender	4
Gussekloo et al., 2004 (7)	Men and women ≥ 85 yr	Mortality	Yes (in subgroup analysis)	TSH and FT4	Self-report and ECG	558/558 for all-cause mortality	Gender, number of diseases, CRP, albumin	6
Imaizumi et al., 2004 (13)	Adult men and women surviving atomic bomb	To assess IHD events and mortality in SCH	Yes	TSH and FT4	Self-report, ECG, and information from GPs	2550/2550 for prevalent IHD and nonneoplastic disease mortality	Age, systolic BP, BMI, TC, smoking, ESR and DM	5
Walsh et al., 2005 (14)	Men and women 17–89 yr	To assess risk factors for common diseases in a series of health surveys	No (self-reported thyroid disease and goitre adjusted in analysis)	TSH and FT4	Self-report, questionnaire, clinical records, or ECG	2064/2108 for prevalent IHD. 1890/2108 for incident IHD and CV mortality	Age, gender, BMI, BP, DM, social status, smoking, exercise, TC, triglycerides, self-reported thyroid disease, goitre	5
Rodondi et al., 2005 (9)	Men and women aged 70–79 yr	To study change in body composition in older people and its association with other diseases	No (for patients on thyroxine treatment, adjustment made in analysis)	TSH FT4 only if TSH was ≤ 0.1 or ≥ 7.0 mIU/liter	Self-report, ECG, medical records, and death certificates	2730/2730 for prevalent and incident IHD, and CV mortality	Age, gender, race, smoking, DM, prevalent CVD, health status, BP, TC, creatinine, education, income, thyroid hormone, and ACE inhibitor use	5
van den Beld et al., 2005 (10)	Independent men 73–94 yr	To assess determinants of chronic diseases in men and women	Yes	TSH, FT4, and FT3	Validated survey	386/403 for prevalent IHD, 387/403 for all-cause mortality	Age	4
Cappola et al., 2006 (8)	Men and women ≥ 65 yr	To assess risk factors for IHD events and mortality	Yes	TSH FT4 only if TSH abnormal	Self-report, ECG, medical records, death certificates, and autopsy reports	3233/3233 for prevalent and incident IHD, and CV mortality	Age, gender, race, smoking, DM, BMI, medications, lipids, CRP	6

(Continued)

TABLE 1. Continued

Study, yr (reference no.)	Type of participants studied	Primary objective of main study	Participants on medications affecting thyroid function excluded?	Hormones measured to diagnose thyroid status	Instruments used to define outcomes	Completeness of observation (persons in whom outcome ascertained/persons recruited)	Covariates assessed	Total quality score (maximum possible of 6)
Lindeman et al., 2003 (11)	Men and women ≥ 65 yr	To study health and health-related issues in equal number of elderly Hispanic and non-Hispanic white persons	No	TSH FT4 only if TSH > 4.6 mIU/liter	Self-report and ECG	755/883 for prevalent IHD	None	3
Kvetny et al., 2004 (18)	Men and women aged 20–69 yr from one primary care practice	To assess association of IHD with thyroid disease	Yes	TSH FT4 only if TSH abnormal	Questionnaire and medical records	1212/1212 for prevalent CVD	None	4
Volzke et al., 2004 (27)	Men and women aged 45–79 yr	Carotid intima-media thickness	Yes	TSH FT4 measured but not used in thyroid stratification	Self-report	2086/2086 for prevalent IHD	None	2
Wilson et al., 2006 (12)	Men and women ≥ 65 yr from 20 primary care practices	To assess association between socioeconomic status and thyroid disease	Yes	TSH and FT4	Self-report and medical records	5872/5872 for prevalent vascular diseases	None	4
Takashima et al., 2007 (16)	Men and women aged 30–79 yr	IHD events	Yes	TSH FT4 only if TSH abnormal	Self-report	3607/3607 for prevalent IHD	None	4

ACE, Angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CV, cerebrovascular; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiograph; ESR, erythrocyte sedimentation rate; FT4, free T_4; GP, general practitioner; HDLc, high-density lipoprotein cholesterol; TC, total cholesterol.

published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org).

Data for cardiovascular (circulatory) disease mortality was available from four studies (8, 9, 14, 21). In the other studies, nonneoplastic disease mortality (13) or all-cause mortality (7, 10) was used to abstract data on fatal events. In studies in which risk of events was reported as hazard ratio (7–9, 13, 14, 20), this was included as OR because the two are similar when the event rate is low (22). For one study (21) that reported risk as standardized mortality ratio, published ORs previously derived from raw data were used (15).

Other data extracted for each group were: number of participants, age at baseline, number of men and women, length of follow-up for longitudinal studies, adjusted risk estimates for outcome data, and type of adjustment factors. In those articles that reported outcomes from the same study population (9, 11, 14, 23–31), the article that most closely matched our inclusion criteria was included. All available case data were analyzed for every participant for whom the outcome was obtained (32).

Statistical analyses

Because of substantial qualitative and quantitative heterogeneity across studies, all analyses were performed using the random effects model because this assumes that all studies are heterogeneous and, thus, provide a more conservative risk estimate. Adjusted risk estimates of effect were calculated by the generic inverse variance method. IHD events (both prevalence and incidence) and mortality were expressed as ORs. For studies that reported only unadjusted dichotomous outcome data, risk estimates were calculated by the DerSimonian and Laird method (33). Heterogeneity was tested by the χ^2 test for degree of significance (in which $P < 0.1$ was considered indicative of statistically significant heterogeneity) and I^2 test for magnitude of the heterogeneity (a value $> 50\%$ being indicative of substantial heterogeneity). Each contributing study was weighted so that larger studies with more precise estimates contributed more to the pooled result than smaller studies. The statistical package Revman 4.2 (Nordic Cochrane Centre, Copenhagen, Denmark) was used for analyses and generating figures. Publication bias was assessed by funnel plot, in which the OR was plotted on a logarithmic scale against its SE for each study. The term "significant" refers to statistical significance throughout this manuscript.

A priori, two subgroup analyses were planned. To test the hypotheses that age and gender have varying effects on cardiovascular disease in people with SCH, we analyzed data from population-based trials categorized by age, using the minimum age of participants recruited of younger than 65 yr or 65 yr and older, and also divided by gender. The age of 65 yr was chosen because the majority of trials that recruited older people had used this cutoff (8, 11, 12). Age-stratified data on outcomes were not available for any study, and, therefore, analysis was not performed.

Post hoc, further subgroup and sensitivity analyses were conducted based on individual quality criteria, the level of TSH ("mild" SCH with TSH < 10 mIU/liter), length of follow-up, after exclusion of studies with unpublished data and those without multivariate adjustment.

Results

Selection and characteristics of studies

The search criteria identified 2215 studies (Fig. 1). Irrelevant articles (n = 2133) were excluded after their title and abstracts were studied. Full text of the remaining articles and their reference list were reviewed and assessed against the inclusion criteria (supplemental appendix 2, which is published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). Finally, 15 studies (nine longitudinal) were included in the metaanalyses for IHD and mortality (6–14, 16, 18, 20, 21, 27, 34).

Qualitative analysis

The characteristics of the studies included for metaanalysis are summarized in Table 2. The mean age of SCH participants (considering age at baseline in longitudinal studies) was 60 and 74 yr in those studies including participants with a minimum age of younger than 65 yr and those including only people aged 65 yr or older, respectively. The studies were performed in different geographical areas, including the United States, United Kingdom, The Netherlands, Australia, Japan, Denmark, and Germany. The sample sizes of participants with SCH ranged from six to 496, whereas euthyroid individuals ranged from 353-5538. Overall, the studies were well powered, with 11 of 15 containing data from more than 1000 participants. The minimum age for inclusion in a study varied from 18–85 yr across different studies. There were 12 studies that recruited both men and women, whereas two studies recruited exclusively from one gender (Table 2). The upper limit of normal TSH concentration above which SCH was defined also varied from 2.8–6.0 mIU/liter, as did the degree of thyroid failure, with a mean TSH ranging from 3.7–8.9 mIU/liter in SCH groups. It is pertinent to point out that studies have been conducted across different time periods, and, thus, different serum TSH assays have been used. For example, two older studies used a less sensitive TSH RIA (13, 34), whereas the rest of the studies have used third-generation chemiluminescent TSH assays. In the longitudinal cohort studies, follow-up periods ranged from 4–20 yr.

The quality parameters of the various studies are outlined in Table 1. The primary analysis was IHD events or mortality in all but two studies. In one study it was the relationship of thyroid dysfunction with socioeconomic status (12), whereas in another it was its relation with carotid intima-media thickness (27). The quality of outcome measurements was good with the majority of studies using standard definitions of outcomes, although the instruments varied widely. Most studies validated outcomes by different means, with 12 studies using two or more methods to confirm primary outcomes and only two studies using exclusively participant-reported data to define outcomes (16, 27).

There were 10 studies designed to assess long-term outcomes of common diseases and not primarily to assess the associations of thyroid disease with IHD or cardiovascular events (6–11, 13, 14, 16, 27). However, four studies were designed with the primary intention to assess the relationship between thyroid diseases and cardiovascular events or mortality (18, 20, 21, 34). All studies characterized participant's thyroid status based on a single measurement, thus a proportion of these individuals may have had transient TSH abnormality. Thus, the majority of studies were comparable in having vascular events as the primary endpoint and using standard criteria to define thyroid status and outcome measurements.

IHD prevalence in SCH

There were 12 studies that assessed the prevalence of IHD in SCH (n = 2,399) compared with euthyroid (n = 24,868) people (6, 8–14, 16, 18, 27, 34). The mean age of subjects in the SCH group was 66 yr compared with 65 yr in the euthyroid group, with 63 and 53% of women in each respective group. Metaanalysis, using data that had been adjusted for covari-

TABLE 2. Characteristics of cross-sectional and longitudinal population-based studies assessing IHD and mortality in people with SCH compared with euthyroid individuals

Study, yr (reference)	Country	Study design	No. (at baseline)		% Women		Mean age (yr)		Normal TSH range (mIU/liter)	Mean TSH level (mIU/liter)		Outcomes measured	Follow-up period (yr)
			SCH	Eu	SCH	Eu	SCH	Eu		SCH	Eu		
Tunbridge et al., 1977 (34)	UK	Cross-sectional	132	2460	74	51	52	47	0.3–6.0	8.9	2.1	Prevalent IHD	N/Ap
Vanderpump et al., 1996 (20)	UK	Longitudinal	76	1841	73	52	65	62	0.3–6.0	8.9	2.1	Incident IHD, All-cause and IHD mortality	20
Hak et al., 2000 (6)	The Netherlands	Cross-sectional and longitudinal	124, 107	931, 850	100	100	69	69		N/A	N/A		
Parle et al., 2001 (21)	UK	longitudinal	94	1026	84	54	69	70	0.5–5.0	N/A	N/A	All-cause and circulatory mortality	10
Gussekloo et al., 2004 (7)	The Netherlands	Cross-sectional and longitudinal	30	472	N/A	N/A	85	85	0.3–4.8	N/A	N/A	All-cause and CVD mortality	4
Imaizumi et al., 2004 (13)	Japan	Cross-sectional and longitudinal	257	2293	63	61	62	58	0.6–5.0	6.9	2.8	Prevalent IHD, All-cause and nonneoplastic disease mortality	10
Walsh et al., 2005 (14)	Australia	Cross-sectional and longitudinal	119	1906	69	48	58	49	0.4–4.0	6.3	1.4	Prevalent IHD, Incident IHD and IHD mortality	20
Rodondi et al., 2005 (9)	USA	Cross-sectional and longitudinal	338	2392	55	50	75	75	0.1–4.4	N/A	N/A	Prevalent CVD and CHF, Incident IHD, All-cause and CVD mortality	4
van den Beld et al., 2005 (10)	The Netherlands	Cross-sectional and longitudinal	6	353	0	0	N/A	N/A	0.4–4.3	N/A	N/A	Prevalent IHD	4
Cappola et al., 2006 (8)	USA	Cross-sectional and longitudinal	496	2639	65	59	73	73	0.45–4.5	6.7	2.2	All-cause mortality, Prevalent IHD, Incident IHD, All-cause and IHD mortality	412.5
Lindeman et al., 2003 (11)	USA	Cross-sectional	112	643	66	44	76	74	0.6–4.6	N/A	N/A	Prevalent IHD	N/Ap
Kvetny et al., 2004 (18)	Denmark	Cross-sectional	249	963	58	45	42	43	0.6–2.8	3.7	1.7	Prevalent CVD	N/Ap
Volzke et al., 2004 (27)	Germany	Cross-sectional	29	1745	69	45	59	62	0.3–3.0	N/A	N/A	Prevalent IHD	N/Ap
Wilson et al., 2006 (12)	UK	Cross-sectional	168	5538	64	50	74	73	0.4–5.5	6.8	1.6	Prevalent vascular disease	N/Ap
Takashima et al., 2007 (16)	Japan	Cross-sectional	377	3130	46	54	69	64	0.4–3.8	8.3	1.7	Prevalent IHD	N/Ap

CHF, Congestive heart failure; CVD, cardiovascular disease; Eu, euthyroid; N/A, not available; N/Ap, not applicable; UK, United Kingdom; USA, United States of America.
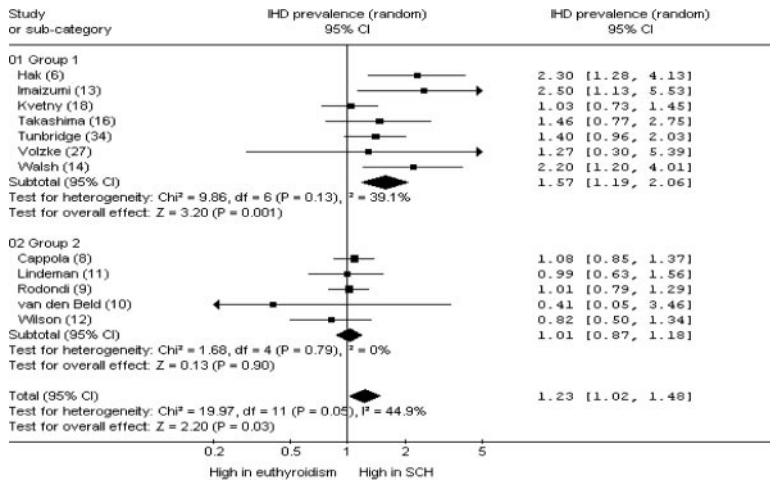
FIG. 2. Forest plot of IHD prevalence in cross-sectional studies of SCH and euthyroid controls. Group 1 studies are those that included participants younger than 65 yr of age, whereas group 2 studies are those that only included participants 65 yr or older. Although the overall prevalence of IHD was higher in SCH participants, the studies were heterogeneous, with an I² of 44.9% (*P* = 0.05). Dividing the studies according to age group substantially reduced the heterogeneity in both of the groups and shows that the increased IHD prevalence is confined to the group 1 studies.

ates, showed that prevalent IHD was higher in the SCH group [OR 1.23 (95% confidence interval (CI) 1.02–1.48); *P* = 0.03]. However, there was modest evidence of statistical heterogeneity (Fig. 2). Subgroup analysis by age showed that IHD was more prevalent in SCH individuals compared with euthyroid subjects in the studies that included people who were younger than 65 yr of age [OR 1.57 (95% CI 1.19–2.06); *P* = 0.001] (6, 13, 14, 16, 18, 27, 34). However, this was not found in studies that involved only subjects older than 65 yr [OR 1.01 (95% CI 0.87–1.18); *P* = 0.9] (8–12). The significant statistical heterogeneity found in the whole data set was not found when either of the two subgroups was analyzed separately (Fig. 2). The relative background risk of prevalent IHD events was about three times higher in older than 65-yr studies (2,442 of 12,624 = 0.19) than in younger than 65-yr studies (828 of 14,643 = 0.06).
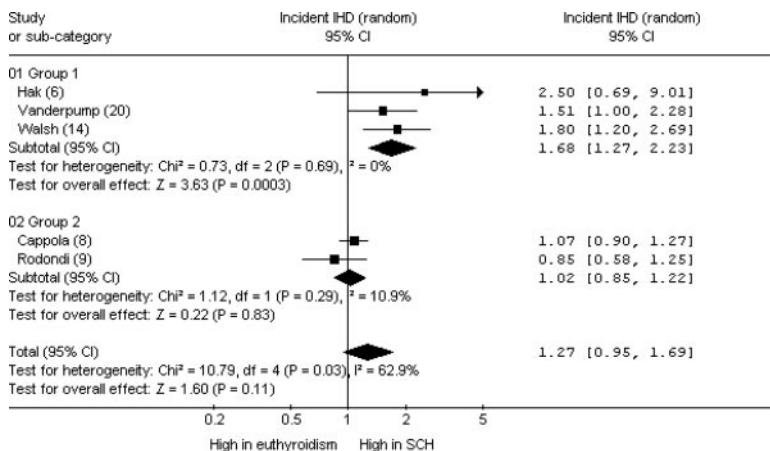

FIG. 3. Forest plot of IHD incidence in longitudinal studies of SCH and euthyroid controls. Group 1 studies are those that included participants younger than 65 yr of age, whereas group 2 studies are those that only included participants 65 yr or older. The overall incidence of IHD was not significantly higher in SCH participants, but the studies were heterogeneous, with an I² of 62.9% (*P* = 0.03). Dividing the studies according to age group substantially reduced the heterogeneity in both of the groups and shows that the increased IHD incidence is confined to the group 1 studies.

Five studies reported prevalent IHD separately for women (n = 4313) and men (n = 3166) (6, 11, 13, 18, 34). Prevalent IHD was higher in SCH women *vs.* euthyroid female participants [OR 1.71 (95% CI 1.26–2.34); *P* < 0.001], with no significant heterogeneity. Prevalent IHD was elevated in SCH men compared with euthyroid males to a similar degree as observed in SCH women, although there were fewer male participants, and the difference was not significant [OR 1.66 (95% CI 0.71–3.88); *P* = 0.24] (supplemental Fig. 1, which is published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem. endojournals.org). IHD events were twice as prevalent in men (308 of 3142 = 0.1) than women (230 of 4248 = 0.05).

Incidence of IHD in SCH

Metaanalysis was performed using data from five longitudinal studies that encompassed 954 SCH participants (67% women, mean age 65.2 yr) and 8673 euthyroid individuals (57% women, mean age 62.4 yr), followed for a median length of 8.6 yr (6, 8, 9, 14, 20). Overall, there was no difference in incident IHD in SCH individuals compared with euthyroid participants [OR 1.27 (95% CI 0.95–1.69); *P* = 0.11] (Fig. 3). However, there was evidence of substantial heterogeneity among these studies. When the three studies in the group including individuals younger than 65 yr (6, 14, 20) (n = 273 for SCH participants *vs.* 4443 for euthyroid) were analyzed, the risk of incident IHD was significantly increased [OR 1.68 (95% CI 1.27–2.23); *P* < 0.001]. This compares with an OR of 1.02 (95% CI 0.85–1.22; *P* = 0.83) in the two studies that included only individuals older than 65 yr (8, 9) (n = 834 for SCH participants *vs.* 5031 for euthyroid). There was no longer evidence for heterogeneity when studies from groups divided by age were analyzed separately. The background risk of incident IHD events was similar in both groups.

It was not meaningful to calculate incident IHD separately by gender because results were only available for two studies (6, 20).

Cardiovascular mortality in SCH

Eight longitudinal studies assessed mortality in 1,417 people with SCH and compared it with that of 13,302 euthyroid participants (7–10, 13, 14, 20, 21). The SCH group consisted of 64% women (mean age 68 yr) compared with 53% women with a mean age of 65 yr in the euthyroid participants. The median follow-up period was 10 yr. Metaanalysis of the studies that assessed cardiovascular mortality (or all-cause mortality in which cardiovascular-specific mortality was not available) showed that there

was no overall increased risk in SCH individuals [OR 1.09 (95% CI 0.84–1.41); $P = 0.52$]. However, there was evidence of heterogeneity in these studies (Fig. 4). Splitting the entire data set by age in studies including individuals younger than 65 yr, SCH participants had an increased risk of cardiovascular mortality compared with euthyroid individuals [OR 1.37 (95% CI 1.04–1.79); $P = 0.02$] (13, 14, 20, 21), whereas no such risk was evident in the studies with subjects older than 65 yr only [OR 0.85 (95% CI 0.56–1.29); $P = 0.44$] (7–10). There was evidence of statistical heterogeneity within the four studies in the older than 65-yr group, which remained when a small study with wide CIs (10) was excluded but disappeared completely when the study with the youngest age group (8) was excluded from analysis. No statistical heterogeneity was found among the younger than 65-yr studies (Fig. 4).

The background risk of cardiovascular mortality was similar in both age group studies. When studies that reported cardiovascular mortality alone were considered (n = 5) (8, 9, 14, 20, 21), there was no substantial change in the result obtained.

We did not calculate gender-specific mortality differences because data were available from just two studies (13, 20).

Sensitivity and *post hoc* subgroup analysis

Study quality

When studies stratified by minimum age (<65 yr and >65 yr) were analyzed, based on individual quality scores, the results remained essentially unchanged, apart from IHD/all-cause mortality that was nonsignificantly increased in younger than the 65-yr group that excluded participants on medications affecting thyroid function (supplemental Table 2).

Different measure of effect size

There was no appreciable difference in results of IHD outcomes when relative risk was used as a measure of risk ratio.

Incident IHD and cardiovascular mortality in TSH up to 10 mIU/liter group

There was no significant association between prevalent IHD and SCH in people with TSH less than 10 mIU/liter in studies including individuals younger than 65 yr (14, 18, 34) with OR of 1.31 (95% CI 0.92–1.88), although incident IHD events were higher in this group (9, 14, 20), with OR of 1.89 (95% CI 1.38–2.57). These results were obtained from a relatively small number of participants (n = 433 for SCH and 5359 for euthyroidism) and, therefore, need to be interpreted with caution. No analysis could be performed for prevalent and incident IHD events in the group of studies that included only subjects older than 65 yr due to nonavailability of data, nor for mortality in SCH groups due to availability of data for only one study in each group (9, 20).

Duration of follow-up

In the younger than 65-yr longitudinal studies group that had a follow-up period of more than 10 yr, incident IHD was increased with an OR of 1.65 (95% CI 1.24–2.20), with no heterogeneity between studies (8, 14, 20). Cardiovascular mortality was also increased with an OR of 1.37 (95% CI 1.04–1.79) (8, 13, 14, 21). Interestingly, mortality was decreased in the older than 65-yr group studies that had follow-up data for less than 10 yr [OR 0.67 (95% CI 0.48–0.92)] (7, 9, 10). No analysis could be performed for younger than 65-yr group studies with a follow-up period of less than 10 yr (6) or the older than 65-yr studies group with a follow-up period of more than 10 yr (8) due to only one study being available for each, respectively.

Publication bias

There was little evidence of publication bias in the studies reporting primary outcomes, but this was difficult to interpret due to the small number of studies included.

Unpublished data

We reanalyzed the data after excluding information from unpublished sources (supplemental Table 2). In the younger than 65-yr studies, the results for prevalent and incident IHD remained unchanged, but incident cardiovascular mortality became nonsignificant [OR 1.51 (95% CI 0.86–2.67); $P = 0.15$] in the SCH group.

Discussion

This metaanalysis, which has involved only observational studies of unselected community dwelling subjects, shows that SCH is associated with prevalent and incident IHD, as well as IHD mortality only in the studies that included participants younger than 65 yr of age. Importantly, studies stratified by age show little heterogeneity when either group is analyzed separately but become significantly heterogeneous when the two age
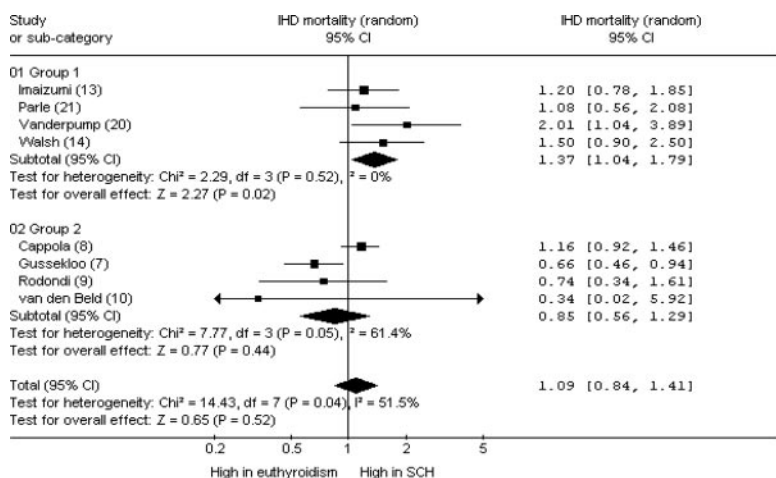

FIG. 4. Forest plot of cardiovascular mortality in longitudinal studies of people with SCH and euthyroid controls. Group 1 studies are those that included participants younger than 65 yr of age, whereas group 2 studies are those that only included participants 65 yr or older. The overall incidence of mortality was not significantly higher in SCH participants, but the studies were heterogeneous, with an I^2 of 51.5% ($P = 0.04$). Dividing the studies according to age group substantially reduced the heterogeneity of group 1 and shows that the increased IHD/cardiovascular mortality is confined to the group 1 studies.

groups are combined. Thus, age appears to be a key variable in explaining the differences of the reported outcome of SCH in the various published studies.

The striking effect of age on vascular risk that we observe in subjects with SCH may be explained in a variety of ways. First, it is possible that at a younger age, SCH has a more severe pathophysiological effect, resulting in accelerated vascular disease, perhaps through dyslipidemia, endothelial dysfunction, or a direct effect on the myocardium in a proportion of susceptible individuals. As populations age, subjects that are relatively resistant to the adverse vascular effects of SCH may survive, leading to an attenuation of this effect in older age. Differential effects of other vascular risk factors during aging are well recognized, *e.g.* being overweight does not appear to carry the same health implications in advanced age (35). An alternative explanation is that SCH is contributing equally to vascular risk at all ages, but in the more elderly cohorts, there is a relatively larger component from conventional, non-SCH, vascular risk factors and that the effects of SCH are relatively masked by the larger contribution from other risk factors. The existing studies may simply not have enough power to detect a relatively small contribution to vascular risk in this age group. Another possibility is that "medicalization" of people with SCH encourages them to report more IHD symptoms or access more investigation. The final possibility is that our findings represent a false-positive result due to stochastic factors. We feel this latter is extremely unlikely, given that the effect of age is reproduced in different data sets and for the related outcomes of prevalent IHD, incident IHD and IHD mortality.

The broad results obtained by this investigation are similar to three other metaanalyses that have examined the association of IHD with SCH (15, 36, 37). However, this metaanalysis has used stringent selection criteria, reduced bias by two authors independently extracting data, and included additional published and unpublished data. The age-dependent outcome of SCH has been commented on previously but never investigated systematically (17, 38, 39). In this metaanalysis we have explored various subgroups of study design and participant demographics to investigate the reason for the differences in results among the various original studies. This has led to robust confirmation of the hypothesis that the age of the cohort studied has an important bearing on the relative influence of SCH on IHD prevalence, incidence, and outcome. From our analysis the prevalence of IHD appears to be similar in both men and women with SCH; however, this achieves statistical significance only in women probably due to a greater power to detect this association.

Our metaanalysis of the literature has several limitations. It was limited to studies reported in English. We also excluded several case-control, hospital-based, and nursing home studies to limit bias. The greatest proviso is the heterogeneous nature of the different studies, which we have tried to reduce by using a random effects model, and performing subgroup and sensitivity analyses. Still, it cannot be said with any degree of certainty that all variation between the different studies analyzed has been explained. Combining all the individual patient data from all the different studies and performing *a priori* subgroup analyses could go some way further toward this goal. The iodine status of participants in the different studies is unknown, but all studies

analyzed were performed in iodine-replete areas. All studies classified participants into different thyroid status categories based on measurement of thyroid function at only one time point. Thus, a proportion of the participants may have had transient TSH elevation (*e.g.* after nonthyroidal illness) to account for abnormal results. The most extreme example of this was the Leiden 85-Plus study (7), in which 11 of 21 elderly participants with SCH at baseline were euthyroid at 3 yr. It should be emphasized that the association, that we report, between SCH and IHD in younger individuals does not imply a causal relationship. This can best be investigated by prospective interventional trials.

Currently, the indications for therapy of SCH in the general population are unclear. However, there is some evidence that adverse vascular risk factors may be ameliorated by L-T$_4$ treatment (40–44). In contrast, the effect of L-T$_4$ therapy on symptoms and well-being in SCH remains ill defined (40, 43, 45–49). If therapy of SCH is to be considered on prognostic grounds, the finding that SCH is a more marked vascular risk factor in younger patients may have substantial implications. Several individual studies have demonstrated that SCH in advanced age may not be associated with an adverse prognosis (7–10). Thus, there may be an age or risk threshold, which remains to be defined, above which SCH should no longer be considered for treatment on prognostic grounds alone. Only well-powered prospective randomized studies with age-stratified groups, and vascular events as the primary endpoint rather than surrogate markers, will give clear answers to this complex question.

In conclusion, this study shows that SCH is associated with increased IHD risk in younger age groups. Well-designed randomized controlled trials of treatment of SCH are needed to investigate if this risk can be alleviated, but any such trial needs to consider the age of the participants.

Acknowledgments

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