CLINICAL STUDY

Subclinical hyperthyroidism and the risk of cardiovascular events and all-cause mortality: an updated meta-analysis of cohort studies

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Abstract

Objectives: Whether subclinical hyperthyroidism (SCH) results in poor prognosis remains controversial. Our aim was to evaluate the association between SCH and the risk of cardiovascular disease (CVD), cardiovascular mortality, and all-cause mortality by conducting a meta-analysis of cohort studies.

Methods: The PubMed and Embase databases were searched through November 2011 to identify studies that met pre-stated inclusion criteria. Relevant information for analysis was extracted. Either a fixed or a random effects model was used to calculate the overall combined risk estimates.

Results: Seventeen cohort studies were included in this meta-analysis. The overall combined relative risks for individuals with SCH compared with the reference group were 1.19 (95% confidence interval (CI): 1.10 to 1.28) for CVD, 1.52 (95% CI: 1.08 to 2.13) for cardiovascular mortality, and 1.25 (95% CI: 1.00 to 1.55) for all-cause mortality. Subgroup analysis by sample source (community or convenience sample) showed that the significant association for cardiovascular and all-cause mortality only existed when pooling studies from convenience samples. Heterogeneity was observed when pooling studies on the association between SCH and cardiovascular and all-cause mortality. Sensitivity analysis showed omission of each individual study did not significantly change the pooled effects. No evidence of publication bias was observed.

Conclusions: Our findings demonstrated that SCH significantly increased the risk of CVD for the general population and the risk of cardiovascular and all-cause mortality for the individuals with other morbidities.

European Journal of Endocrinology **167** 75–84

Introduction

Subclinical hyperthyroidism (SCH), defined as a serum TSH concentration below the normal range with normal levels of thyroid hormones, affects about 1–2.1% of the general population (1, 2). As a mild form of hyperthyroidism, whether SCH leads to adverse clinical outcomes and should be treated remains controversial. SCH has been found to be associated with a higher risk of atrial fibrillation, hypertension, osteoporosis, and dementia compared with euthyroid subjects in some (3, 4, 5, 6) but not all (7, 8, 9) studies. Similarly, the findings from the cohort studies on the association between SCH and cardiovascular disease (CVD), cardiovascular, and all-cause mortality were also inconsistent (10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27). Lack of randomized clinical trials answering the question whether long-term health outcomes are improved by treatment of SCH made this

issue more elusive. A recent guideline suggested treating SCH in all individuals ≥65 years with other specific comorbidities. However, this recommendation is weak and based on evidence of moderate-to-low quality (28).

Several meta-analyses assessing the relationship between CVD, cardiovascular mortality, and all-cause mortality have been performed previously, providing somewhat conflicting results (29, 30, 31). Because only a small number of studies were available at that time, these meta-analyses had low power to detect this association precisely. Since the latest meta-analysis had been performed (31), the interest of researchers on this issue rose. A total of 11 new large prospective studies (17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27) on this issue have been published. Now data are sufficient to update the meta-analysis to provide more powerful evidence for physicians and policy-makers. With accumulating data, we aimed to evaluate the

association between SCH and the risk of CVD, cardiovascular mortality, and all-cause mortality by conducting a meta-analysis of cohort studies.

Materials and methods

Search strategy

Following the proposed Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (32) guidelines to report the present meta-analysis, we conducted a PubMed and Embase database search without restrictions through November 2011 for relevant studies assessing the association between SCH and CVD or mortality (cardiovascular and all-cause). The following search terms were used: i) subclinical thyroid disease, SCH, thyroid dysfunction, thyroid hormones, and TSH; ii) CVDs, coronary heart disease (CHD), coronary thrombosis, myocardial ischemia, myocardial infarction, coronary stenosis, coronary restenosis, cerebrovascular disorders, death, mortality, and all-cause mortality; iii) cohort studies, prospective studies, and follow-up studies. In addition, we reviewed the reference lists of retrieved papers and recent reviews.

Study selection

We first performed an initial screening of titles or abstracts. A second screening was based on full-text review. Studies were considered eligible if they met the following criteria: i) the study design was a cohort study (its definition was as follows: exposure is measured at baseline and the occurrence of outcomes is assessed after a certain time span of follow-up); ii) thyroid function was measured at baseline; iii) the outcome of interest was CVD, cardiovascular, or all-cause mortality; and iv) relative risk (RR) or hazard ratio (HR) and the corresponding 95% confidence interval (CI) (or data to calculate them) were reported.

Data extraction

The key exposure variable in this study was the presence or absence of SCH at baseline. Outcomes of interest included major cardiovascular events and cardiovascular and all-cause mortality. Data extraction was performed using a standardized data collection form. The following data were abstracted: first author's name; publication year; country of origin; number, mean age, and sex of the participants; definition of SCH and cardiovascular events, based on the information provided in the primary studies; prevalence of SCH; study design details, including population source (whether the cohort was recruited from the general population or from participants with a specific comorbidity), starting year of the study, and study duration; whether the reported RR or HR was adjusted

for age, gender, or other potential confounders; and losses to follow-up. If a study did not clearly mention any of the above key points, we considered that it had not been performed. Two of us (Yang and Jiang) independently conducted study selection and extracted data. Differences in assessments were resolved by discussion.
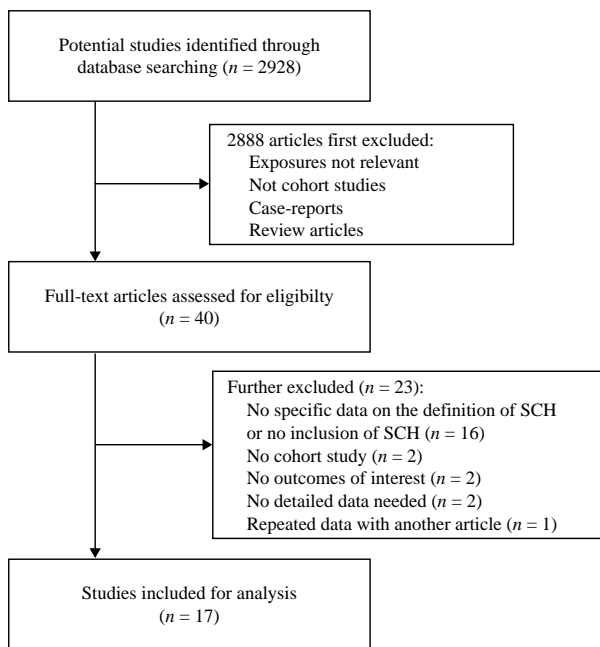
Statistical analyses

The study-specific maximally adjusted RR or HR was used to compute a summary RR and its 95% CI. HRs were directly considered as RRs. Heterogeneity across studies was tested by the Q and I^2 statistic (significance level at $P<0.10$) (33). The combined risk estimates were computed using either fixed effects models or random effects models with the presence of heterogeneity (34). Because characteristics of populations were not consistent between studies, we further conducted a subgroup analysis to explore the potential effect modification of these variables on outcomes. Meta-regression with restricted maximum likelihood estimation was used to explore possible contributors to heterogeneity. We also investigated the influence of a single study on the overall risk estimate by omitting one study in each turn. Potential publication bias was assessed by Egger's test (linear regression method) (35) and Begg's test (rank correlation method) to evaluate publication bias (36). All analyses were performed using STATA version 11.0 (Stata Corp LP, College Station, TX, USA). A P value <0.05 was considered statistically significant, except where otherwise specified.

Results

Literature search

Our search strategy produced 2928 reports. Of these, the majority of reports were excluded after the first screening based on the abstracts or titles, mainly because they were reviews, case reports, case–control studies, or not relevant to our analysis. After the full-text review of 40 papers, 23 studies were excluded for the following reasons: no specific data on the definition of SCH or no inclusion of SCH (37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52), no cohort study (9, 53), no outcomes of interest (6, 54), no detailed data to calculate RRs (21, 55), and repeated data with another study (56). Two studies (10, 11) meeting the inclusion criteria did not provide detailed data to calculate RRs and CIs. We obtained RRs and CIs from the study by Ochs *et al.* (30). Finally, 17 studies (10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27) were included in our meta-analysis. A flow chart showing the study selection is shown in Fig. 1.

Potential studies identified through database searching (*n* = 2928)

2888 articles first excluded:
Exposures not relevant
Not cohort studies
Case-reports
Review articles

Full-text articles assessed for eligibilty (*n* = 40)

Further excluded (*n* = 23):
No specific data on the definition of SCH or no inclusion of SCH (*n* = 16)
No cohort study (*n* = 2)
No outcomes of interest (*n* = 2)
No detailed data needed (*n* = 2)
Repeated data with another article (*n* = 1)

Studies included for analysis (*n* = 17)

Figure 1 Flow chart of study selection illustrating literature search for cohort studies.

Study characteristics and quality assessment

The characteristics of 17 cohort studies were summarized in Table 1. These studies were published between 2001 and 2011. Most studies were conducted in Europe. The mean length of the follow-up ranged from 2 to 20 years. In most studies, participants were recruited from communities, whereas in five studies, participants were recruited from convenience samples (15, 16, 18, 25, 27). Eight studies used the second-generation method for TSH assay (10, 11, 15, 16, 18, 23, 24, 26) and nine studies used the third-generation method (12, 13, 14, 17, 19, 20, 22, 25, 27). Most studies had a TSH cut-off value of 0.25–0.5 mU/l with normal free thyroxine (FT_4) level. Two studies defined SCH as low TSH levels without a reported T_4 measurement (14, 18). The prevalence of SCH ranged from 1.4 to 14.7%. Seven studies (10, 11, 15, 16, 18, 23, 26) repeatedly measured thyroid functions over the follow-up and the others made single baseline measurements. The definition of cardiovascular events varied greatly across all studies. In most studies, it referred to a combined end point including various kinds of heart diseases and one study even included cerebrovascular disease (24). Three studies limited CVD to CHD (12, 13, 22). CHD was defined as acute myocardial infarction, angina pectoris, and other ischemic heart disease. All outcome assessments were from medical records and hospital databases. Most studies adjusted for a group of conventional risk factors for CVD, including age, BMI, blood pressure, diabetes, cholesterol, smoking, etc. Two studies adjusted for only age and sex (10) or sex and education (11). One study made no adjustments (16). Subjects with thyroid

medications were excluded from ten studies (10, 13, 15, 17, 19, 20, 22, 23, 25, 26) and included in four studies (11, 14, 18, 24), while two studies (18, 24) did not specifically refer to this issue. One study (12) included subjects with self-reported thyroid disease but adjustment was made in the calculation of RRs. Losses to follow-up were lower than 5% in all except one study (11) in which the loss was 13%. The Newcastle–Ottawa Scale (57) was adopted in our quality assessment. As shown in Table 2, the full score was 9 and all studies scored 6 or higher.

SCH and risk of CVD

Eleven eligible studies on the association between SCH and CVD were pooled. Two studies were from convenience samples (18, 27). The RRs for the association varied from 0.91 to 1.98 across studies. Most studies failed to show a significantly positive relationship between SCH and CVD except one study (23). However, as shown in Fig. 2A, the summary RR from the fixed effects model was 1.19 (95% CI: 1.10 to 1.28) with no evidence of heterogeneity ($P = 0.48$, $I^2 = 0.0\%$). For combining studies from the community sample, the summary RR was 1.30 (95% CI: 1.16 to 1.47; $P = 0.00$). Atrial fibrillation and stroke are other important outcomes of SCH, but a sub-analysis was restricted because only two studies specifically refer to atrial fibrillation (13) and stroke (24) as an end point respectively.

SCH and risk of cardiovascular mortality

The RRs of 12 eligible studies on the association between SCH and cardiovascular mortality were combined with three studies from convenience samples (15, 16, 25). The summary RR for cardiovascular mortality was 1.52 (95% CI: 1.08 to 2.13) with a moderate degree of heterogeneity ($P = 0.084$, $I^2 = 38.5\%$) (Fig. 2B). Sub-analysis by sample source showed that the summary RR was 1.26 (95% CI: 0.94 to 1.68) when restricting to studies from community samples and 3.21 (95% CI: 1.66 to 6.21) when restricting to those from convenience samples.

SCH and risk of all-cause mortality

Twelve studies were pooled to calculate the overall RR for all-cause mortality with three studies from convenience samples (15, 16, 25). A borderline significant association was observed when combining all studies (RR: 1.25 (95% CI: 1.00 to 1.55); $P = 0.05$) with the presence of heterogeneity ($P = 0.03$, $I^2 = 48.0\%$) (Fig. 2C). Significant difference between SCH and the reference group disappeared when combining studies from community samples (RR: 1.13 (95% CI: 0.91 to 1.41); $P = 0.26$) but existed when pooling those

Table 1 Characteristics of 17 cohort studies.

Reference	Location/ initial year	Duration (years)	Sample size/ mean age (years)	TSH cut-off value (mU/l) (percentage of SCH)	Outcomes	Adjustment for covariates
(10)	UK/1988	8.2	1191 adults/70.4	<0.5 (5.9)	CVD Cardiovascular mortality All-cause mortality	Age and sex
(16)	Germany/NR	2	93 adults/77	<0.1 (14.7)	Cardiovascular mortality All-cause mortality	NR
(11)	The Nether-lands/1997	3.7	558 adults/85	<0.3 (3)	CVD Cardiovascular mortality All-cause mortality	Sex and education
(12)	Australia/1981	20	1926 adults/49.8	<0.4 (1.8)	CVD Cardiovascular mortality	Age, sex, BMI, smoking, diabetes, TC, TG, BP, anti-hypertensive therapy, exercise, thyroid disease
(13)	USA/1989	12.5	3233 adults/72.7	<0.44 (1.5)	CVD Cardiovascular mortality All-cause mortality	Age, sex, CVD and atrial fibrillation at baseline, CRP, smoking, diabetes, LDL-C, lipid-lowering and thyroid medications during follow-up, race, hypertension, BMI
(14)	USA/1986	11.9	487 adults/71.7	<0.5 (4.1)	CVD Cardiovascular mortality All-cause mortality	Age, weight, baseline use of estrogen
(15)	Italy/2000	2.7	3121 adults/61.1	<0.3 (3.1)	Cardiovascular mortality All-cause mortality	Age, sex, CHD, levels of TSH, FT$_4$, FT$_3$
(17)	USA/1989	12	3044 adults/72.6	<0.1 (1.4)	Heart failure	Age, sex, race, CVD and atrial fibrillation at baseline, alcohol use, smoking, diabetes, hypertension, BMI, LDL-C, HDL-C, creatinine
(18)	UK/1993	4.5	17 684 adults/60.5	<0.4 (NR)	CVD	Age, sex, history of hyper-thyroidism and CVD, socio-economic status, diabetes, age × sex interaction
(22)	UK/1993	10.6	11 554 adults/58.1	<0.4 (1.87)	CVD All-cause mortality	Age, sex, smoking, diabetes, WHR, systolic BP, LDL-C, HDL-C
(19)	Germany/1997	8.5	3651 adults/49.0	<0.25 (6.7)	Cardiovascular mortality All-cause mortality	Age, sex, smoking, hyper-tension, stroke, MI, diabetes, BMI, TC, fibrinogen
(20)	Brazil/1999	7.5	1110 adults/56.9	<0.45 (6.2)	Cardiovascular mortality All-cause mortality	Age, sex, hypertension, dia-betes, CVD, TC, smoking, waist circumference
(23)	UK/1993	5.6	NR/66.5[a]	<0.4 (NR)	CVD	Age × sex interaction, history of CVD, cerebrovascular disease and renal failure, socioeco-nomic status, diabetes
(24)	Denmark/1998	5	605 adults/68	<0.4 (2.8)	CVD Cardiovascular mortality All-cause mortality	Age, sex, hypertension, dia-betes, current smoking
(25)	Italy/2000	2.5	1026 adults/67.7	<0.3 (2.2)	Cardiovascular mortality All-cause mortality	Age, sex, smoking, CHD, history of percutaneous angioplasty, coronary artery bypass, left ventricular ejection fraction, CRP, creatinine, TG
(26)	The Nether-lands/1995	10.7	1219 adults/75.5	<0.3 (2.8)	Cardiovascular mortality All-cause mortality	Age, sex, alcohol use, smoking, physical activity, TC, number of chronic diseases, BMI, mean BP, heart rate

Table 1 Continued

Reference	Location/ initial year	Duration (years)	Sample size/ mean age (years)	TSH cut-off value (mU/l) (percentage of SCH)	Outcomes	Adjustment for covariates
(27)	UK/1992	NR	2306 adults/64.5	<0.45 (2.4)	CVD	Age, sex, hypertension, stroke, diabetes, cerebrovascular disease, greater serum creatinine

WHR, waist–hip ratio; TC, total cholesterol; TG, triglyceride; CHD, coronary heart disease; CVD, cardiovascular disease; BP, blood pressure; MI, myocardial infarction; CRP, C-reactive protein; FT$_4$, free thyroxine; FT$_3$, free triiodothyronine; NR, not reported.
[a]Mean age in SCH.

from convenience samples (RR: 1.84 (95% CI: 1.05 to 3.25); $P=0.03$).

Exploration of the sources of heterogeneity

Given that a certain degree of heterogeneity among studies was observed when combining studies on the relationship of SCH to cardiovascular and all-cause mortality, exploratory univariate meta-regression was performed with age (<65 or ≥65 years old), sample source (community or convenience), publication year, length of follow-up (<10 or ≥10 years), ethnicity (Caucasian or non-Caucasian), and sample size (<1000 or ≥1000 participants) as the potential sources of between-study heterogeneity. Sample source was a key contributor to the heterogeneity ($P=0.045$) among studies on the association between SCH and cardiovascular mortality. None of the abovementioned variables were identified as a potentially important source of between-study heterogeneity in combining RRs for total mortality. Stratified analysis by assessment of thyroid function (repeated or not) and mean age barely changed the results among studies from community samples (shown in Table 3).

Sensitivity analysis

Omission of the study by Flynn *et al.* (18) had moderate influence on the combined RRs of SCH for risk of CVD, changing the summary RR to 1.29 (95% CI: 1.15 to 1.44). No evidence of any individual study having excessive influence on the pooled effect in combining risk estimates of SCH for cardiovascular mortality or all-cause mortality was observed.
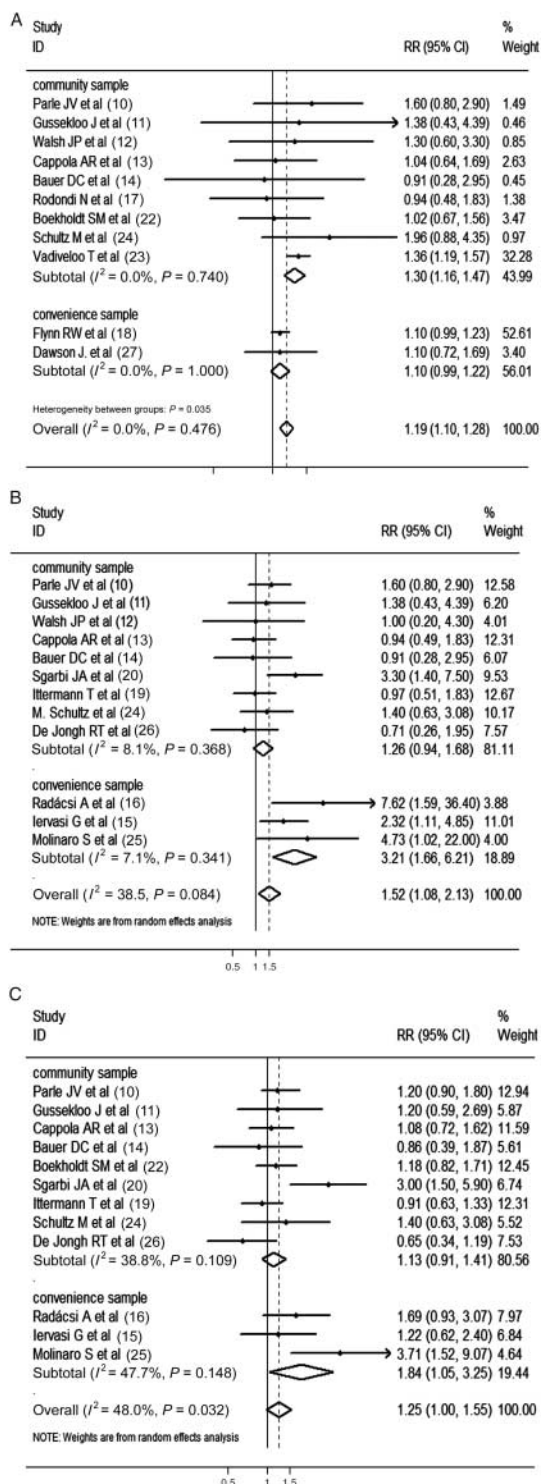
Publication bias

The Begg's funnel plot did not show any substantial asymmetry. Egger's regression test also indicated little evidence of publication bias ($P=0.31$–0.84 for all associations).

Discussion

There is an ongoing debate on whether SCH results in an increased risk of cardiovascular events and mortality. In the present meta-analysis, we explored the association between SCH and CVD, cardiovascular,

Table 2 Quality assessment of eligible studies.

Studies	1	2	3	4	5A	5B	6	7	8
(10)	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
(16)	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes
(11)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
(12)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(13)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(14)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(15)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(17)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(18)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(22)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(19)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(20)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(23)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
(24)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(25)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(26)	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(27)	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No

1, exposed cohort truly representative; 2, controls drawn from the same community; 3, ascertainment of exposure; 4, outcome of interest not present at the beginning; 5A, cohorts controlled for age; 5B, cohorts controlled for other factor(s); 6, quality of outcome assessment; 7, follow-up long enough for outcomes to occur; 8, complete accounting for cohorts.

Figure 2 (A) Forest plot showing overall and subgroup analyses on the association between SCH and risk of CVD. (B) Forest plot showing overall and subgroup analysis on the association between SCH and risk of cardiovascular mortality. (C) Forest plot showing overall and subgroup analysis on the association between SCH and risk of all-cause mortality. CI, confidence interval; RR, relative risk.

and all-cause mortality by pooling cohort studies. To our knowledge, this is the most comprehensive meta-analysis on this issue to date. Contrary to the results of two previous meta-analyses (29, 30), our study provided statistical evidence that SCH was significantly associated with an increased risk of CVD. Results from the sub-analysis combining community-based studies suggested that the general population with SCH was at a 31% increased risk of CVD. Nearly all studies made adjustments for conventional cardiovascular risk factors, including age, BMI, blood pressure, diabetes, cholesterol, and smoking, suggesting that SCH is probably an independent risk factor for CVD. The mean length of follow-up in primary studies ranged from 2 to 20 years. Such a large interval between the two diseases provides further support. Moreover, a causal relationship between SCH and CVD was plausible from a biological point of view. SCH has been found to be associated with some cardiovascular risk factors, including atrial fibrillation (3), hypertension (4), increased factor X activity (58), and levels of plasma von Willebrand factor (59), fibrinogen, and D-dimer (60). These abnormalities predisposed individuals with SCH to increased CVD risk.

As shown in our subgroup analysis, a significant association between SCH and cardiovascular and all-cause mortality was only found among sick individuals. However, given the relatively small number of studies in each subgroup, this result should be interpreted with caution and needs to be confirmed by further studies. A previous meta-analysis (31) pooling seven studies showed that SCH was significantly associated with all-cause mortality, the result of which appeared to be inconsistent with ours. However, two studies conducted among convenience samples (15, 16) were also included in this analysis, and the significant association disappeared after excluding these two studies, which was similar to our result. Though the adverse effects of SCH on the cardiovascular, skeletal, and nervous system have been documented by some studies (3, 4, 5, 6), we speculated that these deleterious effects were not powerful enough to result in a higher rate of mortality in the general population. On the contrary, sick individuals were less tolerant to the harmful effects of SCH.

The cause of SCH includes Graves' disease, toxic multinodular goiter, solitary autonomously functioning nodules, various forms of thyroiditis, central hypo-thyroidism, and nonthyroidal illness (28). The state of SCH may be transient, especially when the cause is thyroiditis or nonthyroidal illness. It is important to assess thyroid function repeatedly over the course of study to exclude transient SCH. Therefore, a subgroup analysis was performed to evaluate the modification effect of assessment times of thyroid function on the outcome. As shown in Table 3, no significant influence was observed. All included studies did not provide detailed information on the cause of primary SCH,

Table 3 Stratified analysis of the association of SCH with CVD and mortality. Stratified analysis was performed among studies from community samples. Random effects model was used in combining RRs.

Stratified factors	Summary RR (95% CI)	P for Q test	I^2 (%)	Studies (*n*)
SCH and risk of CVD				
Mean age (years)				
≥65	1.33 (1.18 to 1.51)	0.71	0.0	7
<65	1.07 (0.73 to 1.56)	0.62	0.0	2
Assessment of thyroid function				
Single at baseline	1.10 (0.85 to 1.41)	0.76	0.0	6
Repeated	1.37 (1.20 to 1.57)	0.90	0.0	3
SCH and risk of cardiovascular mortality				
Mean age (years)				
≥65	1.17 (0.83 to 1.64)	0.74	0.0	6
<65	1.53 (0.63 to 3.71)	0.07	63.2	3
Assessment of thyroid function				
Single at baseline	1.26 (0.84 to 1.90)	0.23	27.6	6
Repeated	1.28 (0.79 to 2.10)	0.41	0.0	3
SCH and risk of all-cause mortality				
Mean age (years)				
≥65	1.07 (0.87 to 1.33)	0.60	0.0	6
<65	1.37 (0.79 to 2.39)	0.01	77.7	3
Assessment of thyroid function				
Single at baseline	1.21 (0.90 to 1.62)	0.08	49.6	6
Repeated	1.02 (0.70 to 1.49)	0.23	31.9	3

which hindered us from performing a sub-analysis. Further observational and interventional studies are warranted to explore the effects of various causes of primary SCH on the clinical outcomes. The availability of only two studies (16, 17) that had TSH cut-off values of <0.1 mU/l to define SCH made it impossible to perform a suitable sub-analysis. Exclusion of these two studies did not significantly influence the results.

Heterogeneity across studies is often a concern in meta-analysis. It was not surprising that a certain degree of heterogeneity was observed among studies on SCH and mortality given the between-study variation, such as comorbidities, age, length of follow-up, sample source, etc. For this reason, meta-regression was adopted and only the sample source was identified as a potential contributor to heterogeneity in combining RRs for cardiovascular mortality. Because the meta-regression was performed on summary data, and not on data from individual study participants, and <15 studies were included in our single analysis, this result should be interpreted with caution (61).

Some potential limitations should be considered in the current meta-analysis. First, various definitions of SCH were used between studies. The absence of uniform diagnostic criteria increased the likelihood of misclassification bias, thereby wrongly estimating the strength of the association. A second limitation was the heterogeneity among studies for the association between SCH and the risk of mortality. Thirdly, we cannot exclude the possibility of publication bias even though it was not

observed by Egger's and Begg's test. Application of modified Egger's linear regression test proposed by Harbord *et al.* (62) may be the first choice in such a meta-analysis but its use was impeded by the availability of data from the primary papers. Finally, most of the included studies were performed in Europe and America, so it was difficult to say how well the findings can be extrapolated to Asian populations.

Despite these limitations, our analysis possessed several strengths. A major strength of our study was that all the included original studies used a cohort design, which was more powerful to detect a causal relationship than a cross-sectional one. Secondly, most studies adjusted for important confounders, including age, smoking, diabetes, etc. Thirdly, the quality of all included studies was evaluated as good by the Newcastle–Ottawa Scale.

In summary, our data demonstrated that SCH was associated with an increased risk of CVD for general individuals and with an increased risk of mortality only for sick individuals. Certainly, these results should not be translated into aggressive intervention of SCH. It was reported that treatment with antithyroid drugs for 6 months reduced the average heart rate and ventricular thickness in subjects with SCH (63). The relatively short follow-up and small sample size in this study did not allow evaluation of whether intervention reduced cardiovascular events and mortality. Therefore, well-designed clinical trials are warranted to address these questions.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

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