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Subclinical Hypothyroidism Is Associated With Increased Risk for All-Cause and Cardiovascular Mortality in Adults

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Objectives This study sought to evaluate the relationship between subclinical hypothyroidism (SCH) and all-cause and cardiovascular disease (CVD) mortality.

Background SCH may increase the risks of hypercholesterolemia and atherosclerosis. The associations between SCH and all-cause or CVD mortality are uncertain, on the basis of the results of previous studies.

Methods A baseline cohort of 115,746 participants without a history of thyroid disease, ≥20 years of age, was recruited in Taiwan. SCH was defined as a serum thyroid-stimulating hormone (TSH) level of 5.0 to 19.96 mIU/l with normal total thyroxine concentrations. Euthyroidism was defined as a serum TSH level of 0.47 to 4.9 mIU/l. Cox proportional hazards regression analysis was used to estimate the relative risks (RRs) of death from all-cause and CVD for adults with SCH during a 10-year follow-up period.

Results There were 3,669 deaths during the follow-up period; 680 deaths were due to CVD. Compared with subjects with euthyroidism, after adjustment for age, sex, body mass index, diabetes, hypertension, dyslipidemia, smoking, alcohol consumption, betel nut chewing, physical activity, income, and education level, the RRs (95% confidence interval) of deaths from all-cause and CVD among subjects with SCH were 1.30 (1.02 to 1.66), and 1.68 (1.02 to 2.76), respectively.

Conclusions Adult Taiwanese with SCH had an increased risk for all-cause mortality and CVD death. (J Am Coll Cardiol 2012;60:730–7) © 2012 by the American College of Cardiology Foundation

Subclinical hypothyroidism (SCH) is defined as an elevated thyroid-stimulating hormone (TSH) level with a normal thyroxine (T4) level. The prevalence of SCH has been reported to be between 4% and 20% (1–4). It varies in populations as a function of sex, age, or ethnic group (1–4). The proposed adverse consequences of SCH include systemic hypothyroid symptoms, psychiatric symptoms, progression to overt hypothyroidism, and hypercholesterolemia (5,6). SCH may impair left ventricular diastolic function, alter endothelial function, increase the C-reactive protein level, and thus increase the risk of atherosclerosis (5). Being associated with hypercholesterolemia and atherosclerosis, screening and treatment for SCH has been suggested to prevent cardiovascular disease (CVD) (7). In their review, Surks et al. (8) concluded that supporting data concerning the associations of SCH with adverse clinical outcomes or benefits of treatment are few. CVD is the leading cause of death in the United States and the second major cause of death in Taiwan (9,10). The associations between SCH and cardiovascular outcomes and/or mortality are uncertain based on the existing literature (11–16). In this study, we determined the impact of SCH on all-cause mortality and cardiovascular death in a large Taiwanese cohort.

Methods

Subjects and measurements. The data were collected from 4 private nationwide MJ Health Screening Centers in Taiwan from 1998 to 1999 as previous reports (17,18). The registered health practitioners in these centers provide a

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multidisciplinary team approach of health assessment for their members. Most of the members undergo health examinations every 3 to 4 years, and approximately 30% of the members will receive the same health check-up every year. A total of 124,456 participants age 20 years and above were recruited into this study. Nine hundred fifty-three participants (0.8%) who had a history of thyroid disease with medication treatment and 3,310 participants (2.6%) with missing TSH or total T4 levels at entry were excluded. SCH was defined as a serum TSH level of 5.0 to 19.96 mIU/l with normal total T4 concentrations (57.9 to 154.4 nmol/l). Euthyroidism was defined as a serum TSH level of 0.47 to 4.9 mIU/l (16). Therefore, participants with serum TSH levels ≥20 mIU/l or <0.47 mIU/l were also excluded (n = 4,447). Finally, 115,746 participants were included for analysis in the study. The population structure (age and sex) in our study was similar to national data of the adults published by the Taiwanese government (19). Deaths were ascertained by computer linkage to the national death registry (death certificates created by the Department of Health, Taiwan) using ID numbers. These death certificates have been validated. The overall agreement rates between the reviewer and coders were above 80% (20). All deaths that occurred between study entry and December 2008 were included. Deaths with the International Classification of Disease, ninth revision (ICD-9) codes 390 to 459 were classified as CVD-related deaths (21). We use all-cause mortality as the primary outcome and CVD death as a secondary outcome.

Anthropometric index and laboratory assays. The anthropometric characteristics, blood pressure (BP), plasma glucose, total cholesterol (TCHOL), high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured and described as in a previous report (22). Thyroid function (TSH and total T4) were also measured (Abbott AxSYM, Abbott Park, Illinois). The coefficients of variation were 3.6% to 4.3% at level 2.837 to 3.419 mIU/l and 8.1% to 8.8% at level 15.32 to 19.727 mIU/l for the precision of TSH assay, and were 2.8% to 3.6% at level 101.65 to 108.85 nmol/l for that of total T4. In brief, trained staff measured height (to the nearest 0.1 cm) and weight (to the nearest 0.1 kg). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). The BP was measured in the right arm using a standard mercury sphygmomanometer with an appropriately sized cuff while participants were in a seated position. Blood was drawn with minimal trauma from an antecubital vein in the morning after a 12-h overnight fast. Diabetes was defined as a fasting glucose ≥7.0 mmol/l and/or a history of diabetes and taking oral hypoglycemic agents or insulin. Hypertension was defined as a systolic BP ≥140 mm Hg, and/or a diastolic BP ≥90 mm Hg, and/or a history of hypertension or taking antihypertensive drugs. Dyslipidemia was defined as a TCHOL ≥5.18 mmol/l and/or triglycerides ≥1.70 mmol/l and/or HDL-C <1.04 mmol/l in men, and <1.30 mmol/l in women and/or a history of dyslipidemia and taking antidyslipidemia drugs. The history of diabetes, hypertension, or dyslipidemia was collected by patient self-reported questionnaire. For example, patients who reported physician-diagnosed diabetes and took antidiabetes medication were classified as "history of diabetes." The study complies with the Declaration of Helsinki in that ethic committee approval for patient recruitment and data analyses was obtained from the MJ Research Foundation Review Committee in Taiwan.

Abbreviations and Acronyms

BMI = body mass index
BP = blood pressure
CHD = coronary heart disease
CI = confidence interval
CVD = cardiovascular disease
HDL-C = high-density lipoprotein cholesterol
IHD = ischemic heart disease
RR = relative risk
SCH = subclinical hypothyroidism
T4 = thyroxine
TCHOL = total cholesterol
TSH = thyroid-stimulating hormone

Questionnaire. Cigarette smoking, alcohol consumption, betel nut chewing, and physical activity histories were recorded for each subject from a questionnaire. Current, former, or never users were defined as those subjects who reported current use, any prior use, or never use of betel nuts, respectively, in the baseline survey. Physical activity was divided into 3 levels: none-to-mild (exercise <1 h per week); moderate (exercise 1 to 4 h per week); and vigorous (exercise >5 h per week). Income was divided into 3 levels: low (<$12,500 [USD]/year); middle ($12,500 to $37,500/year); and high (>$37,500/year). Education was also divided into 3 levels: low (elementary school and below); middle (junior and senior high school); and high (college/university and above). All participants (n = 115,746) have complete data for age, sex, BMI, total T4, TSH, BP, fasting glucose, lipid profile, disease status, mortality status, and survival time. Although some lifestyle and socioeconomic factors were missing, 83.3% of participants (n = 96,383) had all covariates measured.

Statistical analysis. The data were presented as the mean and standard deviation for continuous variables. The Student *t* test for unpaired data was used for the comparison of mean values between 2 groups. Proportions and categorical variables were tested by the chi-square test. The characteristics of subjects with SCH or euthyroidism are shown in Table 1. Cox proportional hazards regression analyses adjusted for potential confounders were used to estimate the relative risks (RRs) for death from all causes and from CVD. We adjusted the covariates according to the traditional CVD risk factors or nontraditional risk factors, or on the basis of their relationship with either SCH (predictor) or death (outcome) in univariate analysis ($p < 0.05$). For example, age and sex are strongly associated with mortality, so we adjusted these 2 covariates in our Cox proportional hazards regression analyses (model 1). Lifestyle and socioeconomic status such as smoking, alcohol drinking, physical activity, income level, and education level are traditional cardiovascular risk factors for mortality, so we adjusted these

covariates in our model 2. Our previous study found that betel nut chewing is associated with increased risk of CVD and all-cause mortality in Taiwan, so we also adjusted this covariate in model 2 (17). Hypertension, diabetes, and dyslipidemia are chronic diseases associated with increased CVD and all-cause mortality, so we further adjusted these covariates in model 3. Participants with missing covariate data were excluded in the Cox proportional hazards regression analyses. Among these models, there was no interaction ($p > 0.05$) between SCH and other variables, including sex, age (<65 or ≥65 years), or prevalent CVD diseases for predicting the risk of all-cause and CVD mortality. The unadjusted Kaplan-Meier survival curves of all-cause and CVD for SCH and euthyroid subjects are shown in Figures 1A and 1B. Competing risk approached by cumulative incidence competing risk estimate were done in Table 2. Stratified analysis by age and TSH level at entry for the association between SCH and risk of all-cause and CVD mortality is summarized in Table 3. All analyses were performed with the SAS statistical package for Windows (version 9.1, SAS, Cary, North Carolina).

Results

There were 3,669 deaths during the 10 years of follow-up; 680 deaths were due to CVD. At the baseline survey, there were 1,841 (1.6%) subjects with SCH and 113,905 (98.4%) subjects with euthyroidism. As shown in Table 1, subjects with SCH were older and had higher BMIs, BP, and fasting glucose, TCHOL, HDL-C, and triglycerides levels than subjects with euthyroidism. SCH subjects also differed from euthyroid subjects with respect to smoking, alcohol consumption, betel nut chewing, income, and education.

Participants who died during the follow-up period were older, more frequently male, and had higher BMIs, BP, and fasting glucose, TCHOL, and triglycerides levels, and lower HDL-C levels than survivors (data not shown). The prevalence of smoking, alcohol consumption, betel nut chewing, low income, and low education was less in survivors (data not shown). To analyze the association between SCH and mortality, we adjusted those factors to avoid possible confounding.

Using Cox proportional hazards regression analyses with adjustment for potential confounders and competing risk approach by cumulative incidence competing risk estimate, the RRs for all-cause mortality and CVD deaths were higher among subjects with SCH than among subjects with euthyroidism (Table 2). However, the proportional hazards assumption was not held ($p < 0.05$). The Kaplan-Meier survival curves revealed a more significant difference in survival between SCH and euthyroid subjects after 5 years (Figs. 1A and 1B). Therefore, we added 1 interaction term of survival time and SCH status in the Cox proportional hazard model, and survival time was categorized into <5 years and ≥5 years. The actual number of deaths and CVD deaths in the 2 groups, before and after 5 years follow-up, were 1,565 and 2,104 for all-cause death and 306 and 374 for CVD deaths, respectively. Compared with euthyroid subjects, the adjusted RRs (95% confidence interval [CI]) for all-cause mortality among <5 years, ≥5 years, and overall survival time were 1.08 (0.71 to 1.64), 1.53 (1.13 to 2.06), and 1.30 (1.02 to 1.66) in subjects with SCH, respectively (model 3 in Table 2). The adjusted RRs (95% CI) for CVD deaths among <5 years, ≥5 years, and overall survival time were 1.40 (0.64 to 3.05), 1.76 (0.90 to 3.41), and 1.68 (1.02 to 2.76) in subjects with SCH, respectively (model 3 in Table 2).

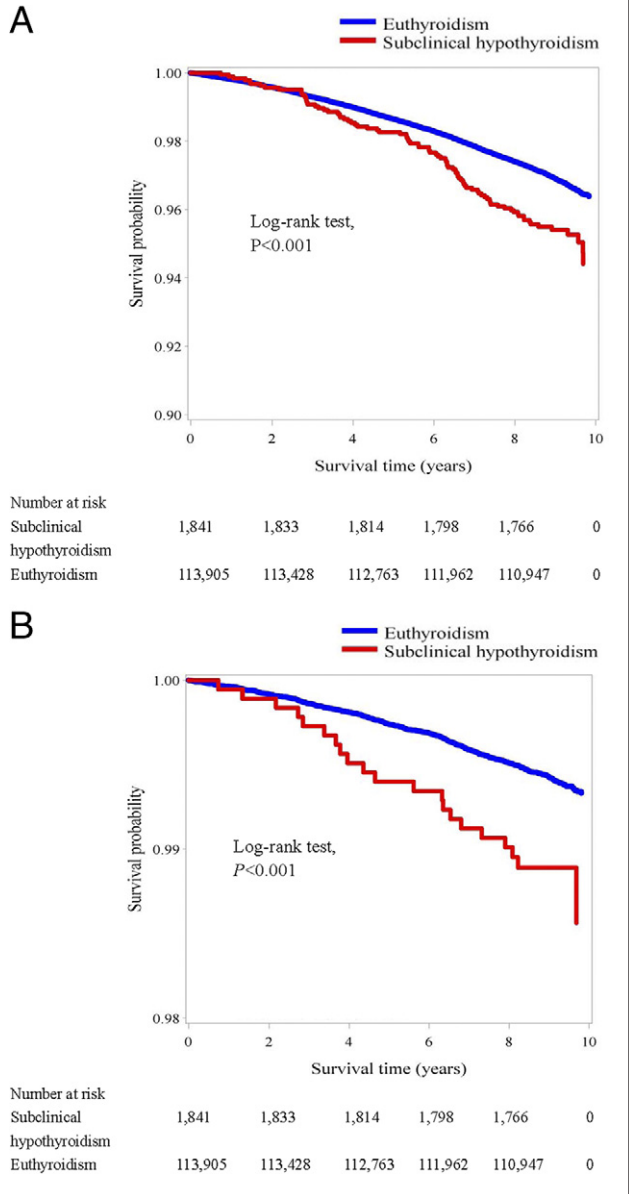

Figure 1 **Kaplan-Meier Survival Curves for Subjects With SCH Versus Subjects With Euthyroidism**

(A) All-cause mortality and **(B)** cardiovascular disease (CVD)-related mortality. The all-cause and CVD mortality are significantly different (the log-rank test $p < 0.001$) between both subject groups. SCH = subclinical hypothyroidism.

Table 1 Baseline Characteristics According to Status of SCH and Euthyroidism

	Subclinical Hypothyroidism (n = 1,841)	Euthyroidism (n = 113,905)	p Value
Age, yrs	47.1 ± 14.1	42.9 ± 13.9	<0.001
Male	512 (27.8%)	54,471 (47.8%)	<0.001
Height, cm	159.2 ± 7.9	162.2 ± 8.5	<0.001
Body weight, kg	59.6 ± 11.2	61.0 ± 11.5	<0.001
BMI, kg/m^2	23.5 ± 3.7	23.1 ± 3.5	<0.001
Systolic BP, mm Hg	124.2 ± 23.0	120.4 ± 20.6	<0.001
Diastolic BP, mm Hg	74.7 ± 12.8	73.4 ± 12.7	<0.001
Fasting glucose, mmol/l	5.62 ± 1.62	5.48 ± 1.29	<0.001
TCHOL, mmol/l	5.36 ± 1.04	5.21 ± 1.00	<0.001
Triglycerides, mmol/l	1.54 ± 1.13	1.41 ± 1.19	<0.001
HDL-C, mmol/l	1.29 ± 0.41	1.26 ± 0.40	<0.001
TSH, mIU/l	7.07 ± 2.44	1.56 ± 0.79	<0.001
T4, nmol/l	93.1 ± 17.3	99.9 ± 19.1	<0.001
Diabetes	122 (6.6%)	5,430 (4.8%)	<0.001
Hypertension	516 (28.0%)	22,728 (20.0%)	<0.001
Smoking (n = 110,386)			<0.001
Never	1,411 (81.1%)	77,045 (70.9%)	
Former	100 (5.7%)	7,148 (6.6%)	
Current	230 (13.2%)	24,452 (22.5%)	
Alcohol consumption (n = 106,136)			<0.001
Never	1,360 (82.7%)	82,023 (78.5%)	
Former	60 (3.6%)	3,612 (3.5%)	
Current	225 (13.7%)	18,856 (18.0%)	
Betel nut chewing (n = 109,332)			<0.001
Never	1,615 (93.8%)	96,312 (89.5%)	
Former	44 (2.6%)	5,380 (5.0%)	
Current	63 (3.7%)	5,918 (5.5%)	
Physical activity (n = 109,003)			0.252
None/mild	872 (50.7%)	53,639 (50.0%)	
Moderate	577 (33.5%)	37,828 (35.3%)	
Vigorous	271 (15.8%)	15,816 (14.7%)	
Income (n = 108,593)			<0.001
Low	1,035 (61.6%)	51,278 (48.0%)	
Middle	568 (33.8%)	48,833 (45.7%)	
High	76 (4.5%)	6,803 (6.4%)	
Education (n = 112,286)			<0.001
Low	634 (35.7%)	25,355 (22.9%)	
Middle	645 (36.3%)	40,270 (36.4%)	
High	497 (28.5%)	44,885 (40.7%)	

The Student *t* test was used for comparing mean values of continuous variables between groups; data are shown as the mean ± SD; log transformation was used for normal distribution. The Pearson chi-square test was used for categorical data; and data are shown as n (%).

BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; SCH = subclinical hypothyroidism; TCHOL = total cholesterol; TSH = thyroid-stimulating hormone.

Although there was no interaction ($p > 0.05$) between SCH and age, we found that SCH increased the risks of all-cause and CVD mortality in older subjects (Table 3). The risks categorized by different TSH levels at entry are also shown in the table.

Discussion

Factors influencing the prevalence of SCH include TSH cutoff to define SCH, the race, sex, and age distribution of the population, pre-existing presence of autoimmune thyroid disorders, and iodine intake (5). The prevalence of SCH in this study was approximately 1.6%, which is lower than in other countries (1–3,23,24). In a community of Southern Taiwan, the prevalence of SCH in the elderly was reported to be 1.5% in women and 1.7% in men (25). The prevalence of SCH in our cohort was compatible with that study. In general, prevalence of SCH increased with age and was higher in women (1,3). As in those reports, our SCH subjects were older and more likely to be women than were euthyroid subjects. Taiwan used to be an area of iodine deficiency. The prevalence of endemic goiter was reduced markedly after an island-wide salt iodination campaign starting in 1967 (26). Lacking thyroid autoantibody data, the status of thyroid autoimmunity in our population is

Table 2 RR (95% CI) of SCH for All-Cause and CVD Mortality in Several Different Models

	Mortality	
	All-Cause	CVD
Model 1		
Survival <5 yrs	1.19 (0.84–1.70)	1.67 (0.78–3.57)
Survival ≥5 yrs	1.38 (1.05–1.80)*	1.69 (0.87–3.29)
Overall	1.24 (1.00–1.53)*	1.66 (1.01–2.73)*
Model 2		
Survival <5 yrs	1.07 (0.70–1.62)	1.36 (0.63–2.96)
Survival ≥5 yrs	1.51 (1.12–2.04)†	1.73 (0.89–3.36)
Overall	1.29 (1.02–1.65)*	1.66 (1.01–2.73)*
Model 3		
Survival <5 yrs	1.08 (0.71–1.64)	1.40 (0.64–3.05)
Survival ≥5 yrs	1.53 (1.13–2.06)†	1.76 (0.90–3.41)
Overall	1.30 (1.02–1.66)*	1.68 (1.02–2.76)*

CVD mortality was determined with a competing risk approach by cumulative incidence competing risk estimate with adjustment for non-CVD mortality. The models used Cox proportional hazards regression analyses adjusted for potential confounders: model 1 adjusted for age and sex; model 2 included the confounders in model 1 plus BMI, smoking, alcohol consumption, betel nut chewing, physical activity status, income, and education level; and model 3 included the confounders in model 2 plus diabetes, hypertension, and dyslipidemia. *$p < 0.05$; †$p < 0.01$.

CI = confidence interval; CVD = cardiovascular disease; RR = relative risk; other abbreviations as in Table 1.

unclear. The cause of the low prevalence of SCH in Taiwanese remains to be investigated.

It has been reported that serum TSH concentrations are positively associated with increasing BMI (27,28). However, some of the literature has reported no difference in BMI between SCH and euthyroid subjects (11,13,29,30). Imaizumi et al. (24) noted the correlation of SCH and higher BMI in women but not in men. Our data revealed that subjects with SCH had higher BMI than euthyroid subjects.

The Colorado study revealed an increasing trend of TCHOL, triglyceride, and low-density lipoprotein cholesterol levels as thyroid function declined (2). Some studies reported that TCHOL and low-density lipoprotein cholesterol levels were positively correlated with serum TSH (31,32). Compared with euthyroid subjects, male SCH subjects may have higher TCHOL levels (11,29), higher triglyceride levels (11), or higher HDL-C levels (30). As in previous studies, our data revealed that patients with SCH had increased TCHOL, triglycerides, and HDL-C levels compared with euthyroid subjects.

The putative associations between SCH and hypertension are not well established. Certain studies reported higher systolic BP, diastolic BP, or prevalence of hypertension in SCH subjects (11,33,34), whereas others demonstrated no association of SCH and hypertension (13,24,29,30,35). Duan et al. (23) reported SCH as an independent predictor of increased SBP and pulse pressure in females. In this study, subjects with SCH had a higher systolic BP, diastolic BP, and prevalence of hypertension than euthyroid subjects.

Previous studies revealed that the level of fasting glucose (29,30) and hemoglobin A_{1C} (30), or prevalence of diabetes mellitus (11,13,24) did not differ between the SCH and euthyroid subjects. In contrast to those reports, our study found higher fasting glucose and higher prevalence of diabetes in SCH versus euthyroid subjects.

The cardiovascular system is a specific target of thyroid hormone. As a novel vasodilator, triiodothyronine (T3) directly affects the vascular smooth muscle cells that promote relaxation (5,36). Being associated with hypercholesterolemia, impaired cardiac contractility and diastolic function, increased systemic vascular resistance, decreased endothelial-derived endothelial factors, and increased C-reactive protein and homocysteine levels, SCH will theoretically increase cardiovascular risk (4–6,37). However, studies concerning the association between SCH and CVD have disparate results (11–16,24,38–44). SCH has been associated with increased prevalence of coronary heart disease (CHD) (11,38–40) or incident ischemic heart disease (IHD) (41). Imaizumi et al. (24) reported that SCH was associated with IHD in men but not in women. Hak et al. (42) reported SCH as a strong indicator of risk for atherosclerosis and myocardial infarction in elderly women. By contrast, several studies reported no association between SCH and CHD (13,43), IHD (44), or CVD (13,24). Rodondi et al. (12) reported that SCH is associated with an increased risk of congestive heart failure among older adults with a TSH level of 7.0 mIU/l, but not with other cardiovascular events. Factors such as TSH cutoff, CVD definition, characteristics of study subjects, severity of SCH, and T4 regimen may confound the study results.

The associations of SCH with all-cause or CVD mortality were controversial in previous studies. Several studies reported no association of SCH with death from CVD (11–13), IHD (44), or all-cause mortality (12,13,44). In the Whickham Survey, SCH was associated with IHD-related mortality over the 20 years of follow-up (41). In a cohort of atomic bomb survivors from Nagasaki, increased mortality from all causes in years 3 to 6 were apparent in men with

Table 3 RR (95% CI) of SCH for All-Cause and CVD Mortality Stratified by Age and by TSH Levels at Entry

	Mortality	
	All-Cause	CVD
Age, yrs		
<65 (n = 105,948)	1.08 (0.75–1.56)	1.22 (0.50–2.98)
≥65 (n = 9,798)	1.53 (1.11–2.11)*	2.02 (1.10–3.70)*
p value for interaction	0.093	0.276
TSH, mIU/l		
0.47–4.99 (n = 113,905)	1.00 (Reference)	1.00 (Reference)
5–9.99 (n = 1,635)	1.38 (1.08–1.78)*	1.80 (1.07–3.01)*
10–19.96 (n = 206)	0.68 (0.26–1.81)	0.91 (0.13–6.44)
p value for trend	0.107	0.080

Age was stratified as <65 and ≥65 years, and TSH levels were stratified as 5 to 9.99 and 10 to 19.96 mIU/l using Cox proportional hazards regression analyses adjusted for age, sex, BMI, diabetes, hypertension, dyslipidemia, smoking, alcohol consumption, betel nut chewing, physical activity status, income, and education level. The reference group consisted of participants with euthyroidism. *$p < 0.05$.

Abbreviations as in Tables 1 and 2.

SCH, but not in women (24). A mildly altered thyroid status had been reported to be associated with an increased risk of mortality in patients with cardiac disease (45). Haentjens et al. (46) reported an increased RR of all-cause mortality in SCH patients with comorbid conditions. The Leiden 85-Plus Study observed that elderly subjects with increasing levels of TSH had lower mortality rates (47). Recent meta-analysis studies concerning the association between SCH and mortality had varied conclusions. Völzke et al. (14) concluded that the current evidence for the association of SCH with mortality is weak. Ochs et al. (15) reported a modest increased risk for CHD and mortality in SCH. Rodondi et al. (16) concluded that SCH is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, but not all-cause mortality. Our study revealed a significant association between SCH and all-cause and CVD mortality in subjects with TSH levels that ranged from 5 to 9.9 mIU/l. With relatively small numbers, the results became unstable in subjects with higher TSH. Razvi et al. (48) reported that SCH increased IHD events and cardiovascular mortality only in younger subjects. Rodondi et al. (16) reported that SCH significantly increased CHD mortality and total mortality in subjects age 65 to 79 years, but not in other age groups. Our data revealed that SCH was associated with increased risk for all-cause and CVD mortality, especially in older subjects.

Some reports suggested that treating SCH by T4 replacement may reduce symptoms of hypothyroidism, prevent progression to overt hypothyroidism, improve quality of life, and potentially decrease CVD events and mortality (4–6). However, this remains to be proven in randomized controlled studies. In the Whickham Survey, treatment of SCH with levothyroxine attenuated IHD-related morbidity and mortality (41). Cooper et al. (49,50) reported significant improvement in symptoms of hypothyroidism and suggested a therapeutic trial for SCH patients with symptoms consistent with mild hypothyroidism, hypercholesterolemia, or a goiter. On the other hand, Kong et al. (51) did not find any significant improvement in their patients with mild SCH. Conflicting results in studies could be caused by the differing nature and number of patients recruited, study design, dose of T4 therapy, and small sample size. In their review, Surks et al. (8) concluded that data addressing associations of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment were insufficient or absent. In the United States, a consensus statement of 3 societies recommended against routine treatment of SCH patients with serum TSH levels of 4.5 to 10 mIU/l, but recommended treatment for patients with TSH levels >10 mIU/l (7).

Study limitations. Although we have demonstrated that SCH is associated with an increased risk for all-cause and CVD mortality, there are several limitations in our study. First, measurement of serum total T4 could be influenced by nonthyroidal conditions, such as alteration in thyroxine-binding globulin or the use of oral contraceptives. We did not measure free T4 levels in our patients. Some may argue that measuring total T4, not free T4, could lead to misclassification of thyroid function status. However, thyroid function tests that measured both serum TSH level and total T4 level were also used in previous reports (16). Second, SCH is most often caused by chronic lymphocytic thyroiditis (5). The presence or absence of thyroid autoantibodies may influence the progression of SCH to overt hypothyroidism (6). We did not have data on thyroid autoantibodies or thyroid sonography. The prevalence of autoimmune thyroid disorders in our participants was not clear. Third, conditions such as subacute, painless, postpartum thyroiditis or withdrawal of thyroid hormone therapy in euthyroid patients may cause transient SCH (5). In our study, the serum TSH and T4 levels and other laboratory data were checked when subjects were recruited. We did not have follow-up thyroid function data to confirm the persistence of SCH. The changes of other covariates during the follow-up period were also not clear. Fourth, the T4 regimen in SCH patients may affect the mortality. We did not know whether or not the patients with SCH were treated by T4 during the follow-up period. However, it is a common limitation in these types of analyses (11–13,24). Spontaneous normalization of SCH and T4 regimen for SCH may bias the association between SCH and mortality toward the null. Our study demonstrated a positive association between SCH and mortality; lack of follow-up thyroid function data or medication history does not jeopardize the value of our observation. Fifth, deaths were ascertained by computer linkage to the national death registry using ID numbers. Possible inherent limitations of using ICD-9 codes may exist, but have been minimized as in our previous studies (17,18). Sixth, some participants had missing data in lifestyle and socioeconomic variables. The missing rate was 16.7%, indicating that potential selection bias might exist. There exists a slight difference in distributions of age, sex, and SCH status between individuals with and without missing data. This kind of missing error might be random as long as there is a nondifferential relationship in age, sex, and SCH status with all-cause and CVD mortality. Thus, the biased results in the effect may be toward the null, a lesser threat to validity. Seventh, this study is observational in nature. Even with adjustment for age, sex, traditional CVD risk factors, and nontraditional risk factors, as in our analysis, the possibility of residual confounding remained.

Conclusions

We have found that old age and female sex increase the prevalence of SCH. Patients with SCH had higher BMIs and increased frequency of hyperlipidemia, diabetes, and hypertension compared with euthyroid subjects. Furthermore, SCH is independently associated with an increased risk for all-cause and CVD mortality after adjusting for the aforementioned confounders. Adult Taiwanese with

SCH had an increased risk for all-cause and cardiovascular mortality.

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