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Subclinical Hypothyroidism is Associated with Increased Risk for Cardiovascular and All-cause Mortality in Adults

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Abstract

Aims: The association between subclinical hypothyroidism (SCH) and cardiovascular disease (CVD) death and all-cause mortality is uncertain based on the results of previous studies. We determined the relationship between SCH and cardiovascular and all-cause mortality.

Methods and Results: A baseline cohort of 116,286 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 5.0-19.9 mIU/L with normal thyroxine concentrations. Euthyroidism was defined as a serum TSH level of 0.47-4.9 mIU/L. Cox proportional hazards regression analysis was used to estimate the relative risks (RRs) of deaths from stroke, coronary heart disease (CHD) , CVD, and all-causes for adults with SCH during a 10-year follow-up period. There were 3,679 deaths during the follow-up period; 692 deaths were due to CVD. Compared to subjects with euthyroidism, after adjustment for age, gender, BMI, diabetes, hypertension, dyslipidemia, smoking, alcohol consumption, betel nut chewing, physical activity, income, and education level, the RRs (95% confidence interval) of deaths from stroke, CHD, CVD and all-causes among subjects with SCH were 1.21(0.51-2.95), 2.29 (1.01-5.20), 1.72 (1.06-2.80), and 1.33 (1.05-1.68), respectively. After excluding those who died during the first 3 years of follow-up (only deaths that occurred after > 3 years of follow-up were included), the results were similar.

Conclusion: Adult Taiwanese with SCH had an increased risk for CVD death and all-cause

mortality.

Keywords: subclinical hypothyroidism, mortality, stroke, cardiovascular disease, all-cause mortality

Introduction

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%; the prevalence of SCH varies in populations as a function of gender, 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. concluded that supporting data for the associations of SCH with adverse clinical outcomes or benefits of treatment are few (8). Cardiovascular disease is the leading cause of death in the United States and the second major cause of deaths 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 cardiovascular and all-cause mortality in a large Taiwanese cohort.

Methods

Subjects and measurements

The data were collected from four 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 multidisciplinary team approach of health assessment for their members. Most of the members undergo health examinations every 3-4 years and approximately 30% of the members will receive the same health check-up every year. A total of 124,456 participants $\geq$ 20 years of age were recruited into this study. Nine hundred fifty-three participants who had a history of thyroid disease with medication treatment at entry were excluded. SCH was defined as a thyroid-stimulating hormone (TSH) level of 5.0-19.9 mIU/L with normal thyroxine concentrations (a T4 level of 57.9-154.4 nmol/L). Euthyroidism was defined as a serum TSH level of 0.47-4.9 mIU/L (16). Finally, 116,286 participants were included for analyses in the study. The population structure 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 using ID numbers. All deaths that occurred between study entry and December 2008 were included. Deaths with the International Classification of Disease, ninth revision (ICD-9) codes 390-459 were classified as CVD-related deaths, codes 410-414 were classified as coronary heart disease (CHD)-related deaths, and codes 430-438 were classified as stroke-related deaths (20).

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 (21). Thyroid function (TSH and T4) were also measured (ABBOTT AxSYM, Abbott Park, IL, USA). In brief, trained staff measured height (measured to the nearest 0.1 cm) and weight (measured 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-hour 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 mmHg, and/or a diastolic BP ≥ 90 mmHg, and/or a history of hypertension or taking anti-hypertensive 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 anti-dyslipidemia drugs. The study complies with the Declaration of Helsinki that ethic committee approval for patient recruitment and data analyses was obtained from the MJ Research Foundation Review Committee in Taiwan.

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 three levels, as follows: none-to-mild (exercise < 1 hour per week); moderate (exercise 1-4 hours per week); and vigorous (exercise > 5 hours per week). Income was divided into three levels, as follows: low (< USD 12,500/year); middle (12,500-37,500/year); and high (>37,500/year). Education was also divided into three levels, as follows: low (elementary school and below); middle (junior and senior high school); and high (college/university and above).

Statistical analysis

The data were presented as the means and standard deviation for continuous variables. Student's *t*-test for unpaired data was used for the comparison of mean values between two groups. Proportions and categorical variables were tested by the χ^2 test and the two-tailed Fisher's exact method when appropriate. Cox proportional hazards regression analyses adjusted for potential confounders were used to estimate the RRs for death from stroke, CHD, CVD, and all-causes. Survival curves adjusted for other covariates (age, gender, BMI, diabetes, hypertension, dyslipidemia, alcohol drinking, smoking, betel nut chewing, physical activity status, income, and education level) were drawn for SCH status (22,23). These

statistical analyses were performed using the PC version of SPSS statistical software (17th version; SPSS, Inc., Chicago, IL, USA).

Results

There were 3,679 deaths during the 10 years of follow-up; 692 deaths were due to CVD. At the baseline survey, there were 1,895 (1.6%) subjects with SCH and 114,391 (98.4%) subjects with euthyroidism. As shown in **Table 1**, subjects with SCH were older and had higher BMI, BP, and fasting glucose, TCHOL, HDL-C, and triglycerides levels than subjects with euthyroidism. As shown in **Table 2**, participants who died due to CVD were older and had higher BMIs, BPs, and fasting glucose, TCHOL, and triglycerides levels, and lower HDL-C levels than survivors. Participants who died due to any cause of death were also older and had higher BPs, and fasting glucose, TCHOL, and triglycerides levels, and lower HDL-C levels than survivors.

Using Cox proportional hazards regression analyses with adjustment for potential confounders, the RRs for stroke, CHD, CVD, and all-cause mortality were higher among subjects with SCH than among subjects with euthyroidism (**models 1-3 in Table 3**). The adjusted RRs (95% confidence interval, CI) for stroke, CHD, CVD, and all-cause mortality were 1.21(0.50-2.95), 2.29 (1.01-5.20), 1.72 (1.06-2.80), and 1.33 (1.05~1.68) in subjects with SCH, respectively (**model 3 in Table 3 and Figure 1**).

To clarify the effects of potential diseases on mortality, we excluded subjects who died during the first 3 years of follow-up. After excluding study subjects who died during the first 3 years of follow-up, compared with subjects with euthyroidism, the adjusted RRs for stroke,

CHD, CVD, and all-cause deaths for subjects with SCH are shown in **Table 3**. The adjusted RRs (95% CI) for stroke, CHD, CVD, and all-cause mortality were 1.31 (0.48-3.54), 2.46 (1.00-6.05), 1.75 (1.00-3.04), and 1.41 (1.08-1.83), respectively.

Discussion

In this study, the prevalence of SCH was approximately 1.6%, which is lower than in other countries (1-3). It has been reported that serum TSH levels increase with age and in women[3]. In agreement with that finding, our cohort revealed that patients with SCH were older and were more likely females than euthyroid patients.

It has been reported that serum TSH concentrations are positively associated with increasing BMI (24,25). However, some literature has reported no difference in BMI between SCH and euthyroid subjects (25,26). Our data revealed that subjects with SCH had higher BMI than euthyroid subjects.

A previous study reported a positive correlation between serum TSH levels and TCHOL, low-density lipoprotein cholesterol (LDL-C), and triglycerides levels, whereas HDL-C decreased consistently with increasing TSH (27). The Colorado study and a study in a Hispanic population showed that euthyroid patients had a lower TCHOL level than patients with SCH (2). A study in Japan revealed that the TCHOL and HDL-C levels were higher in male subjects with SCH (28). In SCH patients, serum TCHOL and LDL-C levels reduced after T_4 therapy (27). Our data revealed that patients with SCH had increased TCHOL, triglycerides, and HDL-C levels than euthyroid subjects.

Several studies have reported a positive correlation between TSH and systolic and/or diastolic BP (29,30). In the Busselton thyroid study, mean systolic BP, diastolic BP, and the

prevalence of hypertension did not differ between euthyoid or SCH patients (31). Duan et al. have reported that SCH is an independent predictor of increased SBP and pulse pressure in females (32). In our study, patients with SCH had a higher SBP, DBP, and prevalence of hypertension.

Compared to euthyroid patients, the SCH patients in our cohort had increased fasting glucose levels and a higher prevalence of diabetes. In a review of the literature, the risk for metabolic syndrome is not increased in SCH patients (26,28). The level of fasting glucose and the percentage of abnormal fasting glucose levels did not differ between the SCH and euthyroid subjects (26,28).

Our study revealed that patients with SCH differed from euthyroid subjects with respect to smoking, alcohol consumption, betel nut chewing, income, and education. Compared to survivor, participants who died were older, more frequently male, had higher BMIs, BPs, and fasting glucose, TCHOL, and triglycerides levels, and a lower HDL-C level. The prevalence of smoking, alcohol consumption, betel nut chewing, low income, and low education was less in survivors. To analyze the association between SCH and mortality, we adjusted those factors to avoid possible confounding.

Being associated with hypercholesterolemia, atherosclerosis, impaired left ventricular diastolic function, and endothelial dysfunction, SCH will theoretically increase cardiovascular risk (4-6). However, studies concerning the association between SCH and CHD events and

mortality have disparate results (11-16). Factors such as TSH cut-off, CVD definition, characteristics of study subjects, severity of SCH, and thyroxine regimen may confound the study results (12). Several studies concluded that SCH may be an independent risk for CHD or increased risk of mortality in patients with cardiac disease (11), while other studies have reported that SCH is not associated with an increased risk for CHD, stroke, peripheral arterial disease, or cardiovascular-related or total mortality (12,13). Völzke et al. concluded that the current evidence for the association of SCH with mortality is weak (14). In a recent meta-analysis study with individual participant data analysis, Rodondi et al. concluded that SCH is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels (particularly in those with a TSH concentration of 10 mIU/L or greater), but not all-cause mortality(16). Our data revealed that SCH was associated with increased risk for CVD and all-cause mortality. To reduce confounding, we excluded subjects who died during the first 3 year of follow-up and adjusted potential risk factors for mortality. The association between SCH and CVD /all-cause mortality persisted after further adjustment for demographic factors (age, gender), metabolic factors (BMI, diabetes, hypertension, and dyslipidemia), health-related behaviors (smoking, alcohol consumption, betel nut chewing, and physical activity status), and socioeconomic factors (income and education level). The association between SCH and CHD mortality was significant only after adjusting all factors. The association between SCH and stroke mortality was not statistically significant.

Some reports suggested that treating SCH by thyroxine 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. The Whickham survey did not find an association between ischemic heart disease (IHD) events with raised serum TSH (33). It was reported that SCH increased IHD events (prevalence and incidence) and cardiovascular mortality only in subjects from younger population (34). Razvi et al. re-analyzed the Whickham survey data and reported the association between incident IHD events and IHD-related mortality(35). They concluded that the association between SCH and IHD events/mortality may be attenuated by treatment of SCH with levothyroxine (35).

The association between SCH and mortality in Asians has seldom been discussed. Although we demonstrated that SCH was associated with an increased risk for CVD and all-cause mortality, there were several limitations in our study. First, measurement of serum total T4 could be influenced by non-thyroidal conditions such as alteration in thyroxine binding globulin or in women taking oral contraceptives. We didn't measure free T4 in our patients. Some may argue that measuring total T4, not free T4, could lead to misclassification of thyroid function status. However, thyroid function test measured with both serum TSH level and T4 level were also used in previous literatures (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 of 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 thyroxine regimen in SCH patients may affect the mortality. We did not know if the patients with SCH were treated by thyroxine or not during the follow-up period. In conclusion, we have found that old age and female gender increase the prevalence of SCH. Patients with SCH had higher BMIs, and increased frequency of hyperlipidemia, diabetes, and hypertension compared to euthyroid subjects. Furthermore, SCH is independently associated with an increased risk for CVD and all-cause mortality after adjusting for the above confounders. Adult Taiwanese with SCH had an increased risk for cardiovascular and all-cause mortality.

Disclosure

The authors declared no conflicts of interest.

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Table 1. Baseline characteristics according to status of subclinical hypothyroidism and euthyroidism

	Subclinical hypothyroidism (n=1,895)	Euthyroidism (n=114,391)	*P* value
Age (years)[1]	47.2±14.1	42.9±13.8	<0.001
Male (n, %)[2]	529 (27.9%)	54,759 (47.9%)	<0.001
Height (cm)[1]	159.2±7.8	162.2±8.5	0.922
Body weight (kg)[1]	59.6±11.2	61.0±11.5	<0.001
BMI (kg/m^2)[1]	23.5±3.7	23.1±3.5	<0.001
Systolic BP (mmHg)[1]	124.2±23.0	120.4±20.5	<0.001
Diastolic BP (mmHg)[1]	74.8±12.8	73.4±12.7	<0.001
Fasting glucose (mmol/L)[1]	5.62±1.60	5.48±1.29	<0.001
TCHOL (mmol/L)[1]	5.37±1.04	5.21±1.00	<0.001
Triglycerides (mmol/L)[1]	1.55±1.14	1.40±1.19	<0.001
HDL-C (mmol/L)[1]	1.29±0.42	1.26±0.40	0.008
TSH (mIU/L)	7.19±2.60	1.56±0.79	<0.001
T4 (nmol/L)	91.5±20.3	99.5±20.1	<0.001
Diabetes (n, %)[2]	124 (6.5%)	5442 (4.8%)	<0.001

Hypertension (n, %)[2]	533 (28.1%)	22,783 (19.9%)	<0.001
Smoking[2]			<0.001
Never	1450(81.1%)	77,387(70.9%)	
Former	104(5.8%)	7,173(6.6%)	
Current	235(13.1%)	24,561(22.5%)	
Alcohol consumption[2]			<0.001
Never	1,397(82.7%)	82,409(78.5%)	
Former	61(3.6%)	3,616(3.4%)	
Current	232(13.7%)	18,939(18.0%)	
Betel nut chewing[2]			<0.001
Never	1,658(93.9%)	96,760(89.5%)	
Former	44(2.5%)	5,393(5.0%)	
Current	64(3.6%)	5,930(5.5%)	
Physical activity[2]			0.239
None/mild	894(50.5%)	53,850(50.0%)	
Moderate	596(33.7%)	38,049(35.3%)	
Vigorous	280(15.8%)	15,858(14.7%)	
Income[2]			<0.001
Low	1,057(61.3%)	51,362(47.8%)	

Middle	590(34.2%)	49,117(45.7%)	
High	77(4.5%)	6,889(6.4%)	
Education[2]			<0.001
Low	657(36.0%)	25,369(22.9%)	
Middle	656(35.9%)	40,349(36.4%)	
High	513(28.1%)	45,268(40.8%)	

[1]Student t-test was used for comparing mean values of continuous variables between groups; data were shown as the mean ± SD

[2]Pearson chi-square test was used for categorical data; data were shown as percentage

Abbreviations: BMI, body mass index; BP, blood pressure; TCHOL, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone

Table 2. Baseline characteristics according to survival status and causes of death

	Survivors (n=112,607)	CVD Deaths (n=692)[1]	All-cause Deaths (n=3,679)[2]
Age (years)[3]	42.3±13.5	64.7±11.9‡	61.5±13.1‡
Male (n, %)[4]	53,015 (47.1%)	441 (63.7%)‡	2,273 (61.8%)‡
Height (cm)[3]	162.2±8.5	160.1±8.6‡	160.4±8.4‡
Body weight (kg)[3]	61.0±11.5	62.1±11.4*	61.3±11.1‡
BMI (kg/m^2)[3]	23.1±3.5	24.1±3.6‡	23.8±3.6
Systolic BP (mmHg)[3]	120.0±20.2	143.7±26.9‡	136.0±26.4‡
Diastolic BP (mmHg)[3]	73.2±12.6	81.3±15.4‡	78.0±14.4‡
Fasting glucose (mmol/L)[3]	5.45±1.21	6.45±2.57‡	6.37±2.68‡
TCHOL (mmol/L)[3]	5.20±0.99	5.64±1.17‡	5.41±1.17‡
Triglycerides (mmol/L)[3]	1.40±1.17	1.91±1.55‡	1.74±1.55‡
HDL-C (mmol/L)[3]	1.26±0.40	1.14±0.45‡	1.19±0.45‡
TSH (mIU/L)	1.65±1.10	1.70±1.25	1.71±1.30†
T4 (nmol/L)	99.3±20.0	101.1±22.3*	101.9±24.3‡
Smoking[4]			
Never	76,896 (71.5%)	353 (55.2%)‡	1,941 (56.6%)‡
Former	6,832 (6.4%)	101 (15.8%)	445 (13.0%)

Current	23,751 (22.1%)	185 (29.0%)	1045 (30.5%)
Alcohol consumption[4]			
Never	81,601 (78.9%)	396(66.1%)‡	2,205 (67.4%)‡
Former	3,326 (3.2%)	74 (12.4%)	351 (10.7%)
Current	18,452 (17.8%)	129 (21.5%)	716 (21.9%)
Betel nut chewing[4]			
Never	95,508 (89.7%)	544 (85.0%)‡	2,910 (85.7%)‡
Former	5,200 (4.9%)	50 (7.8%)	237 (7.0%)
Current	5,745 (5.4%)	46 (7.2%)	249 (7.3%)
Physical activity[4]			
None/mild	53,285 (50.2%)	261 (41.%)‡	1,459 (43.5%)‡
Moderate	37,592 (35.4%)	196 (31.1%)	1053 (31.4%)
Vigorous	15,296 (14.4%)	173 (27.5%)	842 (25.1%)
Income[4]			
Low	49,993(47.3%)	491(77.2%)‡	2,426(72.0%)‡
Middle	48,873(46.2%)	131(20.6%)	834(24.8%)
High	6,857(6.5%)	14(2.2%)	109(3.2%)
Education[4]			
Low	24,053 (22.0%)	382 (58.2%)‡	1973 (56.2%)‡

Middle	40,016 (36.6%)	175 (26.6%)	989 (28.2%)
High	45,235 (41.4%)	100 (15.2%)	546 (15.6%)

Statistical analysis was performed for comparing variables [1]between survivors and CVD deaths, and [2]between survivors and all-cause deaths using [3]Student t-test for continuous variables and [4]Pearson chi-square test for categorical data

Data are presented as the means ± SD or percentage; $^{*}p < 0.05$; $^{\dagger}p < 0.01$; $^{\ddagger}p < 0.001$

Abbreviations: BMI, body mass index; BP, blood pressure; TCHOL, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TSH, thyroid-stimulating hormone; CVD, cardiovascular disease

Table 3. Relative risks (95% confidence interval) of subclinical hypothyroidism for CHD, stroke, CVD and all-cause mortality in several different models using Cox proportional hazards regression analyses adjusted for potential confounders

	Mortality	Model 1	Model 2	Model 3
Euthyroidism	All-cause	1.00 (reference)	1.00 (reference)	1.00 (reference)
Subclinical				
Hypothyroidism	All-cause	1.27(1.03,1.56)*	1.3(1.03,1.66)*	1.33(1.05,1.68)*
1998/1999-2008				
2001/2002-2008[6]	All-cause	1.34(1.07,1.69)*	1.39(1.07,1.81)*	1.41(1.08,1.83)*
Euthyroidism	CVD	1.00 (reference)	1.00 (reference)	1.00 (reference)
Subclinical				
Hypothyroidism	CVD	1.56(1.02,2.39)*	1.70(1.05,2.76)*	1.72(1.06,2.80)*
1998/1999-2008				
2001/2002-2008[6]	CVD	1.69(1.04,2.74)*	1.76(1.01,3.07)*	1.75(1.00,3.04)*
Euthyroidism	CHD	1.00 (reference)	1.00 (reference)	1.00 (reference)
Subclinical				
Hypothyroidism	CHD	1.87(0.88,3.97)	2.25(0.99,5.11)	2.29(1.01,5.20)*
1998/1999-2008				
2001/2002-2008[6]	CHD	1.72(0.70,4.20)	2.40(0.98,5.91)	2.46(1.00,6.05)*

Euthyroidism	Stroke	1.00 (reference)	1.00 (reference)	1.00 (reference)
Subclinical				
Hypothyroidism	Stroke	0.99(0.44,2.22)	1.20(0.49,2.91)	1.21(0.501,2.95)
1998/1999-2008				
2001/2002-2008[6]	Stroke	1.09(0.45,2.66)	1.29(0.48,3.50)	1.31(0.48,3.54)

*p <0.05; †p <0.01; ‡p <0.001

Model 1: adjusted for age, and gender

Model 2: adjusted for age, gender, BMI, smoking, alcohol consumption, betel nut chewing, physical activity status, income, and education level

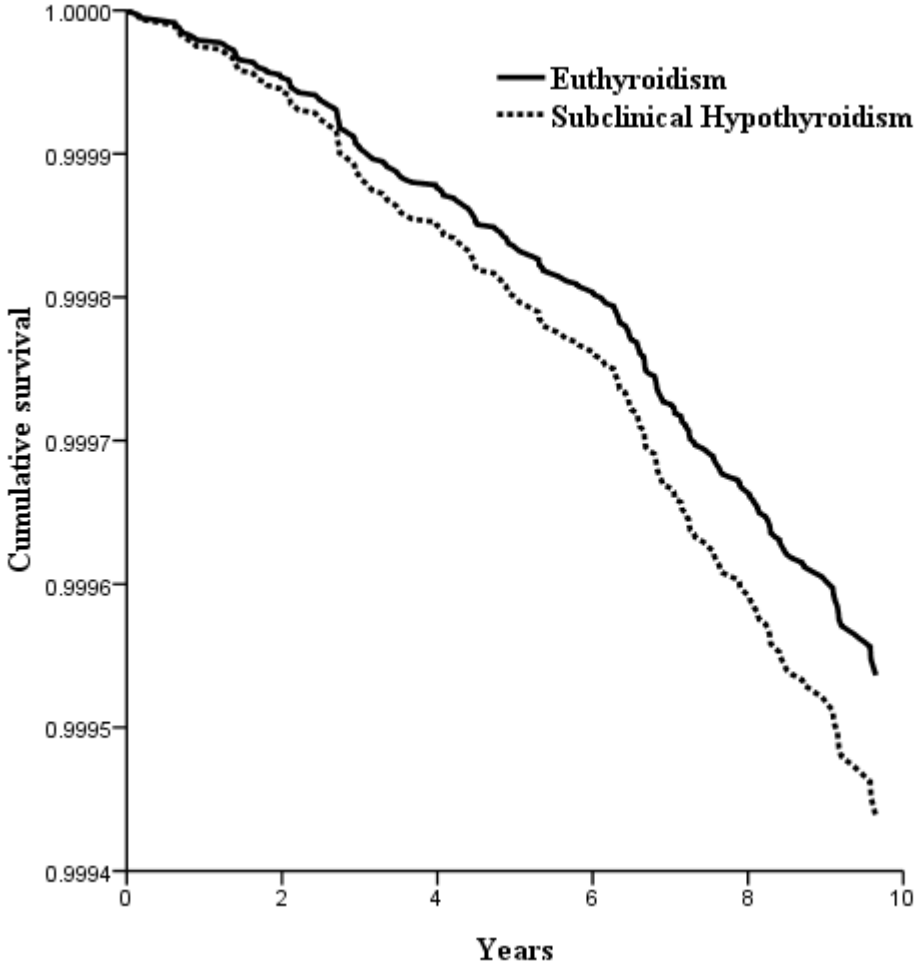
Model 3: adjusted for age, gender, BMI, diabetes, hypertension, dyslipidemia, smoking, alcohol consumption, betel nut chewing, physical activity status, income, and education level

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease

Figure Legend.

Figure 1. Survival curves for subclinical hypothyroidism adjusted for other covariates. Using Cox proportional hazards regression analyses adjusted for age, gender, body mass index, diabetes, hypertension, dyslipidemia, alcohol consumption, smoking, physical activity status, income, and education level, (a) the adjusted relative risk (RR, 95% confidence interval) for (a) stroke-related mortality, (b) CHD-related mortality, (c) CVD-related mortality, and (d) all-cause mortality among individuals with subclinical hypothyroidism was 1.21 (0.51-2.95), 2.29 (1.01-5.20), 1.72 (1.06-2.80), and 1.33 (1.05-1.68), respectively, compared with those who were euthyroidism.

Figure 1(a)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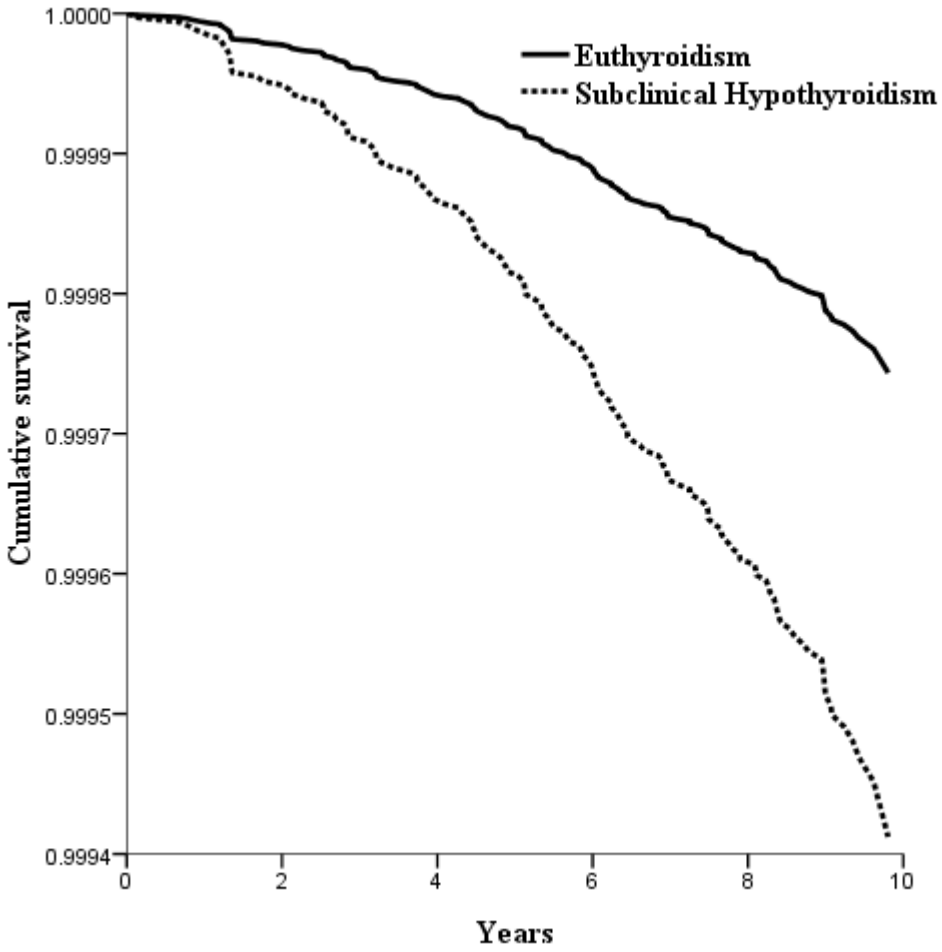
0.9998
0.9997
0.9996
0.9995
0.9994
Cumulative survival
0
2
4
6
8
10
Years
Euthyroidism
Subclinical Hypothyroidism

Figure 1(b)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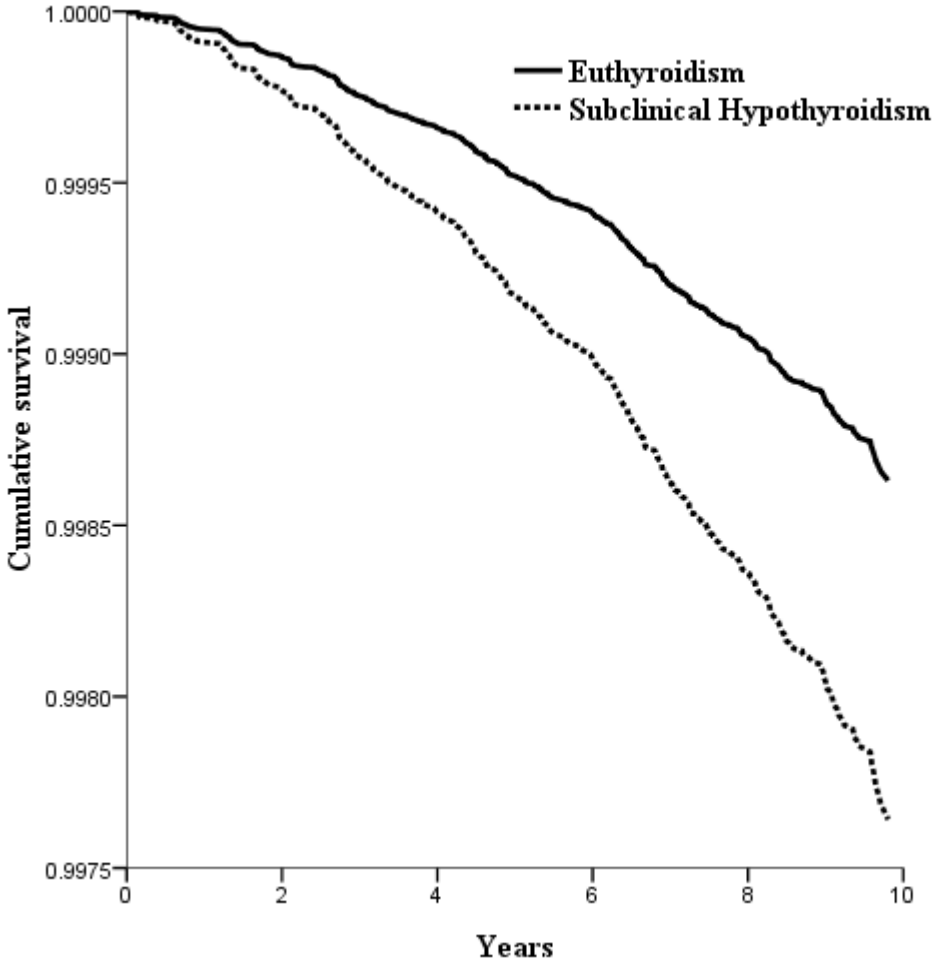
0.9999
0.9998
0.9997
0.9996
0.9995
0.9994
Cumulative survival
0
2
4
6
8
10
Years
Euthyroidism
Subclinical Hypothyroidism

Figure 1(c)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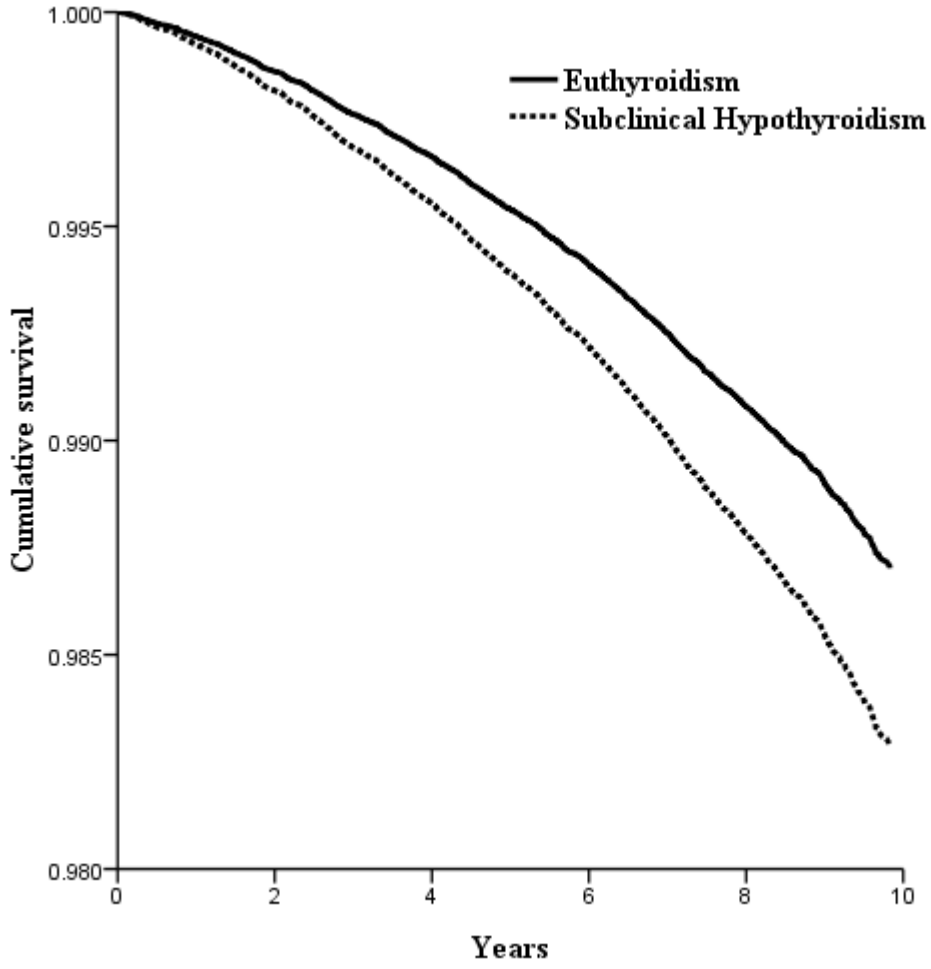
0.9990
0.9985
0.9980
0.9975
Cumulative survival
0
2
4
6
8
10
Years
Euthyroidism
Subclinical Hypothyroidism

Figure 1(d)


1.000
0.995
0.990
0.985
0.980
Cumulative survival
0
2
4
6
8
10
Years
Euthyroidism
Subclinical Hypothyroidism