CLINICAL STUDY

Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese–Brazilian thyroid study

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Abstract

Objective: The currently available data concerning the influence of subclinical thyroid disease (STD) on morbidity and mortality are conflicting. Our objective was to investigate the relationships between STD and cardiometabolic profile and cardiovascular disease at baseline, as well as with all-cause and cardiovascular mortality in a 7.5-year follow-up.

Design: Prospective, observational study.

Methods: An overall of 1110 Japanese–Brazilians aged above 30 years, free of thyroid disease, and not taking thyroid medication at baseline were studied. In a cross-sectional analysis, we investigated the prevalence of STD and its relationship with cardiometabolic profile and cardiovascular disease. All-cause and cardiovascular mortality rates were assessed for participants followed for up to 7.5 years. Association between STD and mortality was drawn using multivariate analysis, adjusting for potential confounders.

Results: A total of 913 (82.3%) participants had euthyroidism, 99 (8.7%) had subclinical hypothyroidism, and 69 (6.2%) had subclinical hyperthyroidism. At baseline, no association was found between STD and cardiometabolic profile or cardiovascular disease. Multivariate-adjusted hazard ratios (HRs (95% confidence interval)) for all-cause mortality were significantly higher for individuals with both subclinical hyperthyroidism (HR, 3.0 (1.5–5.9); $n=14$) and subclinical hypothyroidism (HR, 2.3 (1.2–4.4); $n=13$) than for euthyroid subjects. Cardiovascular mortality was significantly associated with subclinical hyperthyroidism (HR, 3.3 (1.4–7.5); $n=8$), but not with subclinical hypothyroidism (HR, 1.6 (0.6–4.2); $n=5$).

Conclusion: In the Japanese–Brazilian population, subclinical hyperthyroidism is an independent risk factor for all-cause and cardiovascular mortality, while subclinical hypothyroidism is associated with all-cause mortality.

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Introduction

Subclinical thyroid disease (STD) is characterized by abnormal serum thyrotropin (TSH) levels in the presence of free thyroxine (FT₄) and total or free triiodothyronine (FT₃) within their reference ranges (1–3). Epidemiological studies have reported a considerable prevalence of unsuspected STD in the general population (4–6), and clinicians have more frequently diagnosed this condition in their daily clinical practice. The main question that a clinician faces is whether a patient with STD requires treatment or whether an observational strategy could be safely followed (7); however, opinions diverge regarding the clinical significance of STD (8). Both subclinical hypothyroidism (SCHypo) (9–15) and subclinical hyperthyroidism

(SCHyper) (16–20) have been associated with cardiovascular abnormalities; but there are no prospectively validated trials, and treatment remains nonevidence based (21–22).

One frequently raised question concerns the impact of STD on life expectancy, but findings emerging from epidemiological studies are very controversial on this matter (23–29).

In this study, we estimated the prevalence of STD in an entire Japanese–Brazilian population and assessed its associations with cardiometabolic profile and cardiovascular disease in individuals with unrecognized thyroid dysfunction. We also investigated the relationship between STD at baseline and all-cause and cardiovascular mortality in a 7.5-year follow-up.

Methods

Study population and design

A survey was conducted in a nonmixed Japanese–Brazilian population living in Bauru (Human Development Index 0.825; Source: www.ipeadata.gov.br), State of São Paulo, Brazil, which aimed to estimate the prevalence of diabetes and associated diseases in this community. A detailed description of this survey was reported previously (30). In summary, the entire population of ≥ 30 years of age ($n = 1751$) was invited, and 1330 (76%) individuals agreed to participate (Fig. 1). Reasons for nonparticipation (421 individuals, 24.0%) were refusal (64.6%), change of address (13.5%), and death (21.9%).

In the cross-sectional phase conducted in 1999–2000, the prevalence of thyroid dysfunction and the associations of STD with cardiometabolic profile or cardiovascular disease were assessed. Individuals were followed from 1999 to 2007 in order to investigate the influence of STD on all-cause and cardiovascular mortality.

Study procedures

Socio-demographic, cultural, lifestyle, and health data were obtained by standardized questionnaires and

trained interviewers. A specific thyroid questionnaire that included family and personal history of thyroid disease was applied by experts in thyroid diseases.

Body weight and height were measured while individuals were wearing light clothing without shoes. Waist circumference was measured at the level of the umbilicus while standing and during slight expiration. Blood pressure was taken three times with an automatic device (Omron model HEM-712C, Omron Health Care, Bannockburn, IL, USA). The mean of the last two measurements was used to express systolic and diastolic blood pressure values. A standard 12-lead electrocardiogram (ECG) was obtained in the resting state by the standard procedure and was analyzed by two cardiologists. A Doppler probe (Imbracios 8 MHz) was used to determine the ankle–brachial pressure index for both extremities.

Fasting blood samples were taken and a 75-g oral glucose tolerance test was performed. Samples were processed for immediate analyses in the local laboratory or were stored at -80°C . Plasma glucose was measured by the glucose oxidase method, while the total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides were enzymatically evaluated with an automatic analyzer. Low-density lipoprotein cholesterol (LDL-c) was calculated according to the Friedewald equation (31). Insulin concentration was determined by a MAB-based immunofluorometric assay (AutoDelphia, PerkinElmer Life Sciences Inc., Norton, OH, USA). Insulin resistance was calculated by the homeostasis model assessment ($\text{HOMA-IR} = \text{fasting insulin } (\mu\text{U/ml}) / 22.5 \times \text{fasting glycemia } (\text{mmol/l})$).

Urinary iodine concentration (UIC) was measured in early-morning urine samples by a colorimetric method (32), with a detection limit of $10 \mu\text{g/l}$ and the normal range between 100 and $299 \mu\text{g/l}$.

TSH levels were measured in duplicate by a sensitive immunofluorometric assay (Wallac–Delfia, PerkinElmer, Turku, Finland) with a reference range of 0.45–4.5 mU/l and functional sensitivity of 0.05 mU/l. Serum FT_4 was measured using a competitive immunoassay (Wallac–Delfia), wherein the normal reference range was 0.7–1.5 ng/dl.

Date and cause of death were collected from death certificates between the start of the screening (November 1999) and June 2007. For individuals ($n = 3$) who moved out of the study area and for whom we were not able to have access to the death certificate, we asked families about the occurrence of death and its date and cause. In June 2007, the ascertainment of mortality was 100%. Cardiovascular death was defined as death from any cardiovascular or cerebrovascular event. All-cause mortality was defined as all deaths from any natural cause.

This study was approved by the ethics committee of Escola Paulista de Medicina, Federal University of São Paulo, and written informed consent was obtained from all participants.

Figure 1 Study flow diagram.

Definitions

Euthyroidism was defined as serum TSH and FT₄ within the normal reference ranges; SCHyper as TSH below 0.45 mU/l with normal FT₄ level; overt hyperthyroidism as TSH below 0.1 mU/l with high FT₄ level; SCHypo as TSH above 4.5 mU/l with normal FT₄ level; and overt hypothyroidism as TSH above 4.5 mU/l with low FT₄ level or a TSH concentration above 20 mU/l (21).

Hypertension was defined as a blood pressure $\geq 140/90$ mmHg or as the use of antihypertensive medication; diabetes was defined according to the American Diabetes Association criteria; and dyslipidemia was defined by the presence of any lipid abnormality (total cholesterol levels ≥ 200 mg/dl or triglycerides ≥ 150 mg/dl or LDL-c > 130 mg/dl).

The presence of cardiovascular disease at baseline was defined by a medical history of myocardial infarction confirmed by a physician and by major ECG abnormalities of old infarction (Q waves) or by previous angioplasty or any heart revascularization procedure, or coronary insufficiency diagnosed previously by catheterization, or stroke. Peripheral arterial disease was defined by any ankle–brachial pressure index < 0.9 (33).

Statistical analysis

Prevalence rates were calculated by point and confidence interval (CI). The data were described through absolute (*n*) or relative (%) frequencies, mean with s.d., and 95% CI. Differences in means of the baseline characteristics according to thyroid status categories were assessed by ANOVA (Tukey's test for multiple comparisons if $P < 0.05$) or nonparametric ANOVA (Kruskal–Wallis test), followed by the Mann–Whitney *U* test. Frequencies were compared by the χ^2 test or the Fisher test when one of the absolute frequencies was below five. Variables without a normal distribution were subjected to logarithmic transformations before statistical analysis.

In the longitudinal analysis, survival curves according to thyroid status across the 7.5 years of follow-up were estimated using Kaplan–Meier analysis with the log-rank test. They were constructed considering the death as 'event' and contrary cases as 'not event' (censorship), which were predicted by the baseline thyroid status. Living individuals who did not complete the 7.5 years of follow-up by June 30, 2007 were censored for survival at 7.5 years. A Cox regression model of proportional risks in bivariate analysis was used to determine the crude hazard ratios (HRs). Multivariate analysis was used to account for potential confounders of the mortality rate. Relevant confounders were selected by their significant association with mortality (age, sex, presence of hypertension, diabetes mellitus, and cardiovascular disease), which were determined by the χ^2 test or the Fisher test when frequencies were compared, and by the Student *t*-test or

the Mann–Whitney test (for variables without normal distribution). Risk factors classically associated with mortality were also considered (total cholesterol, smoking status, and waist circumference), totaling a maximum of eight risk factors (maximum of one risk factor for every ten deaths). In cases of variables with co-linear inter-relationships, such as diabetes and fasting or 2-h plasma glucose levels, hypertension and systolic blood pressure, and total cholesterol and LDL-c, only one was considered. Models were first adjusted for age and sex, and afterwards for the relevant confounders. A Cox regression model of proportional risks in bivariate analysis was used to determine multiple HRs with 95% CI to express the adjusted relative risk of dying for individuals classified as having STD relative to euthyroid individuals. All statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc., Cary, NC, USA). The assumed level of significance was at $P < 0.05$ (two-tailed).

Results

From the 1330 individuals who agreed to participate in this cohort, we excluded those who self-reported thyroid disease or taking thyroid medications ($n = 47$), and those who reported to be using amiodarone, lithium, or corticosteroids ($n = 6$). Furthermore, we excluded 167 participants for whom ECG and ankle–brachial pressure indices were not available. Thus, 1110 individuals were considered for the present analysis (Fig. 1). There was no difference in demographic characteristics between included ($n = 1110$) and excluded ($n = 220$) individuals.

Cross-sectional analysis

Prevalence rates for each thyroid status category are presented in Table 1. The median UIC was 210 $\mu\text{g/l}$, with no statistical difference among the thyroid status categories (Table 2). Euthyroidism, overt, and SCHyper

Table 1 Demographic characteristics and thyroid status in Japanese–Brazilians.

Demographic characteristics	
Total participants (<i>n</i>)	1110
Women, <i>n</i> (%)	591 (53.2)
Mean age, years (s.d.)	56.9 (12.5)
Age distribution, <i>n</i> (%)	
30–39 years	96 (8.6)
40–49 years	229 (20.6)
50–59 years	311 (28.3)
60–69 years	285 (25.7)
> 70 years	189 (17.0)
Thyroid status, prevalence rates, % (95% CI)	
Euthyroidism, <i>n</i> = 913	82.3 (80.8–84.9)
Overt hyperthyroidism, <i>n</i> = 20	1.8 (1.0–2.6)
Subclinical hyperthyroidism, <i>n</i> = 69	6.2 (4.8–7.5)
Overt hypothyroidism, <i>n</i> = 9	0.8 (0.3–1.3)
Subclinical hypothyroidism, <i>n</i> = 99	8.9 (7.0–10.1)

CI, confidence interval.

Table 2 Baseline characteristics according to thyroid status. Data are presented as mean $\pm$ s.d., unless noted otherwise.

	Euthyroidism (n=913)	Overt hyperthyroidism (n=20)	Subclinical hyperthyroidism (n=69)	Overt hypothyroidism (n=9)	Subclinical hypothyroidism (n=99)
Women, n (%)	469 (51.4)	10 (50.0)	42 (60.9)	7 (77.8)*	63 (63.6)*
Men, n (%)	444 (48.6)	10 (50.0)	27 (39.1)	2 (22.2)	36 (36.4)
Mean age, years (s.d.)	56.4 (12.4)	56 (12.2)	61.4 (12.5) [†]	65.1 (13.4)	58.5 (12.3)
Age distribution, n (%)					
30–39 years	79 (8.7)	2 (10.0)	5 (7.2)	–	10 (10.1)
40–49 years	205 (22.5)	4 (20.0)	8 (11.6)	1 (11.1)	11 (11.1)
50–59 years	259 (28.4)	5 (25.0)	13 (18.8)	2 (22.2)	32 (32.3)
60–69 years	224 (24.5)	7 (35.0)	24 (34.8)	3 (33.3)	27 (27.3)
≥ 70 years	146 (16.0)	2 (10.0)	19 (27.5)	3 (33.3)	19 (19.2)
Characteristics					
BMI ^a (kg/m ²)	25.1 (3.9)	24.1 (2.6)	24.5 (4.2)	23.6 (2.0)	24.5 (3.7)
Waist circumference ^a (cm)	84.5 (10.6)	83.2 (8.8)	83.9 (9.9)	79.6 (4.9)	82.5 (9.8)
Current smoker, n (%)	120 (13.2)	2 (10.0)	5 (7.2)	–	10 (10.1)
Past smoker, n (%)	173 (19.1)	9 (45.0)*	12 (17.4)	2 (22.2)	12 (12.1)
Hypertension, n (%)	342 (37.5)	6 (30.0)	32 (46.4)	4 (44.4)	43 (43.4)
Diabetes, n (%)	328 (35.9)	11 (55.0)	30 (43.5)	2 (22.2)	35 (35.4)
PAD, n (%)	117 (12.8)	3 (15.0)	10 (14.5)	2 (22.2)	10 (10.1)
CVD, n (%)	120 (13.1)	5 (25.0)	13 (18.8)	3 (33.3)	15 (15.2)
Statin usage, n (%)	13 (1.4)	–	1 (1.4)	1 (11.1)*	5 (5.1)*
Systolic BP (mmHg)	132.8 $\pm$ 24.4	127.5 $\pm$ 18.7	135.5 $\pm$ 26.3	130.1 $\pm$ 32.4	133.5 $\pm$ 25.2
Diastolic BP ^a (mmHg)	79.4 $\pm$ 13.3	72.4 $\pm$ 12.8	78.8 $\pm$ 12.8	76.2 $\pm$ 11.4	78.2 $\pm$ 14.2
UIC (μ g/l)	204 $\pm$ 103	184 $\pm$ 99	207 $\pm$ 113	235 $\pm$ 68	221 $\pm$ 113
TSH (mU/l)	1.62 $\pm$ 0.94	0.1 $\pm$ 0.11 [§]	0.22 $\pm$ 0.1 [§]	64.7 $\pm$ 77.3 [§]	7.1 $\pm$ 2.82 [§]
Free T ₄ (ng/dl)	1.07 $\pm$ 0.17	3.2 $\pm$ 2.74 [§]	1.12 $\pm$ 0.18 [§]	0.53 $\pm$ 0.22 [§]	1.01 $\pm$ 0.2 [†]
Fasting glucose (mg/dl)	124.4 $\pm$ (33.5)	137.0 $\pm$ (57.6)	127.9 $\pm$ (40.1)	113.2 $\pm$ (8.3)	122.6 $\pm$ (29.8)
Two-hour glucose (mg/dl)	166.5 $\pm$ 76.9	184.3 $\pm$ 98.8	184.4 $\pm$ 87.2	135.3 $\pm$ 42.4	161.6 $\pm$ 87.9
Fasting insulin (pmol/l)	63.2 $\pm$ 49.5	48.8 $\pm$ 32.3	66.0 $\pm$ 46.7	82.6 $\pm$ 117.7	63.9 $\pm$ 55.3
HOMA-IR ^a	2.8 $\pm$ 2.6	2.5 $\pm$ 2.1	3.0 $\pm$ 2.7	3.2 $\pm$ 2.7	2.8 $\pm$ 2.6
Total cholesterol (mg/dl)	215.0 $\pm$ 41.1	193.2 $\pm$ 53.7 [†]	207.4 $\pm$ 31.7	240.8 $\pm$ 49.9*	214.4 $\pm$ 47.6
LDL-c (mg/dl)	131.2 $\pm$ 37.3	119.6 $\pm$ 44.9	125.9 $\pm$ 31.9	158.1 $\pm$ 40.4*	126.0 $\pm$ 43.7
HDL-c (mg/dl)	50.8 $\pm$ 10.9	46.8 $\pm$ (9.5)	48.9 $\pm$ (7.2)	55.3 $\pm$ (10.5)	50.6 $\pm$ (12.9)
Triglycerides (mg/dl)	232.3 $\pm$ 189.5	224.4 $\pm$ 137.1	209.0 $\pm$ 118.5	172.8 $\pm$ 112.9	250.7 $\pm$ 197.9

BMI, body mass index; PAD, peripheral arterial disease; CVD, cardiovascular disease; BP, blood pressure; UIC, urinary iodine concentration; TSH, thyrotropin; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol. * $P < 0.05$; [†] $P < 0.01$; [‡] $P < 0.001$; [§] $P < 0.0001$.

^aValues were log-transformed for statistical analysis.

were found in 82.3, 1.8, and 6.2% of the participants respectively, with no significant difference in sex distribution (Table 2). On the other hand, unsuspected overt and SCHypo were identified in 0.8 and 8.9% of the participants respectively, both significantly more frequent in women ($P = 0.04$). The mean age was similar among the groups, except for the SCHyper group, in which age was significantly higher relative to the euthyroid group. As noted in Table 2, the expected significant differences in TSH and FT₄ levels were observed between euthyroid individuals and those with STD.

There were no statistically significant differences among the groups concerning body mass index, waist circumference, smoking status, systolic or diastolic blood pressure, fasting or 2-h plasma glucose, fasting serum insulin, HOMA-IR, HDL-c, or triglyceride levels (Table 2). Mean total cholesterol ($P = 0.03$) and LDL-c ($P = 0.02$) levels were significantly increased in overt hypothyroid subjects, but not in SCHypo subjects in comparison to euthyroid individuals. However, the proportion of individuals undergoing statin therapy

was significantly higher in both overt hypothyroid and SCHypo groups than in the euthyroid group ($P < 0.05$). The OR for statin use, adjusted for age and sex, was significantly higher in SCHypo individuals (3.4 (95% CI, 1.2–9.8)) than in the euthyroid individuals. Since statin use could be masking a potential association between serum levels of lipids and SCHypo, the analysis was repeated excluding this condition, but the results did not change.

The overall proportions of diabetes, hypertension, peripheral arterial disease, and cardiovascular disease were not statistically different among the groups (Table 2).

Longitudinal analysis

During the 7.5 years of follow-up, 83 (7.5%) deaths were recorded in this population. Four events of death by nonnatural causes (one by suicide and three by trauma) were censored, and three deaths by unknown causes were censored just for the cardiovascular death analyses. The deaths by unknown causes occurred in

the euthyroid ($n=2$) and in the SCHyper ($n=1$) group. Deaths mainly occurred as a result of cardiovascular causes (51.3%), cancer (22.3%), or infectious disease (14.5%). Table 3 shows the main differences between living and dead individuals. Among the dead subjects, 50 (65.8%) had been categorized as euthyroid, 14 (17.7%) as SCHyper, and 13 (16.5%) as SCHypo. No death was notified among individuals who were classified as having overt thyroid disease. At baseline, serum FT₄ levels were significantly higher ($P=0.018$) among dead individuals than among those who were alive at the end of the follow-up, but no differences in TSH levels were found between the groups.

Table 4 shows the relationship between STD and mortality. All-cause mortality was significantly higher in SCHyper (20.3%) and SCHypo (13.1%) individuals than in euthyroid (5.7%) individuals ($P<0.0001$). Kaplan–Meier analysis (Fig. 2) with the log-rank test

reveals higher overall mortality for both SCHyper ($P<0.0001$) and SCHypo ($P=0.0035$) groups in comparison to the euthyroid group. Cardiovascular mortality was significantly associated with SCHyper ($P<0.0001$). These differences emerged after 4 years of the follow-up. Cox regression analysis (Table 4) revealed that these significant associations were preserved even after adjusting for age, sex, and multiple potential confounders.

Discussion

In this study, we found a strong relationship between SCHyper and all-cause and cardiovascular mortality, while SCHypo was significantly associated with all-cause mortality. These significant associations with mortality emerged after 4 years of follow-up.

Table 3 Thyroid status, demographic characteristics, and biological variables according to vital status at the end of the follow-up. Data are presented as mean $\pm$ s.d., unless noted otherwise.

Variable	Alive ($n=1031$)	Dead ($n=79$)	P value
Euthyroidism	861 (83.5)	52 (65.8)	<0.0001
Overt hyperthyroidism	20 (1.9)	—	
SCHyper	55 (5.3)	14 (17.7)	
Overt hypothyroidism	9 (0.9)	—	
SCHypo	86 (8.3)	13 (16.5)	
Men, n (%)	472 (45.8)	47 (59.5)	0.02
Women, n (%)	559 (54.2)	32 (40.5)	
Mean age, years	56.1 $\pm$ 12.2	67.7 $\pm$ 11.3	<0.0001
Distribution of age, n (%)			
30–39 years	95 (9.2)	1 (1.3)	<0.0001
40–49 years	225 (21.8)	4 (5.1)	
50–59 years	297 (28.8)	14 (17.7)	
60–69 years	264 (25.6)	21 (26.6)	
≥ 70 years	150 (14.5)	39 (49.4)	
Survival time, years	7.3 $\pm$ 0.3	4.1 $\pm$ 2.0	<0.0001
BMI ^a (kg/m ²)	25.1 $\pm$ 3.8	24.1 $\pm$ 4.3	0.03
Waist circumference ^a (cm)	84.2 $\pm$ 10.3	84.7 $\pm$ 11.3	0.8
Current smoker, n (%)	125 (12.2)	12 (15.2)	0.72
Past smoker, n (%)	193 (18.8)	15 (19.0)	
Hypertension, n (%)	379 (36.8)	48 (60.8)	<0.0001
Diabetes, n (%)	366 (35.5)	40 (50.6)	0.007
PAD, n (%)	129 (12.5)	13 (16.5)	0.31
CVD, (%)	133 (12.9)	23 (29.1)	<0.0001
Statin usage, n (%)	19 (1.8)	1 (1.3)	1.0
Systolic BP (mmHg)	132.0 $\pm$ 24.0	145.3 $\pm$ 27.4	<0.0001
Diastolic BP (mmHg)	79.0 $\pm$ 13.3	80.6 $\pm$ 14.2	0.47
UIC (μ g/dl)	20.7 $\pm$ 10.5	19.7 $\pm$ 9.0	0.56
TSH (mU/l)	2.5 $\pm$ 9.2	2.4 $\pm$ 2.8	0.86
Free T ₄ (ng/dl)	1.1 $\pm$ 0.5	1.13 $\pm$ 0.2	0.018
Fasting glucose (mg/dl)	124.3 $\pm$ 33.9	127.1 $\pm$ 36.9	0.63
Two-hour glucose (mg/dl)	165.5 $\pm$ 78.2	189.3 $\pm$ 85.1	0.006
Fasting insulin (pmol/l)	61.7 $\pm$ 49.3	52.7 $\pm$ 36.8	0.09
HOMA-IR ^a	2.8 $\pm$ 2.6	2.4 $\pm$ 2.1	0.11
Total cholesterol (mg/dl)	214.8 $\pm$ 40.9	207.3 $\pm$ 50.8	0.02
LDL-c (mg/dl)	130.9 $\pm$ 37.9	124.3 $\pm$ 36.6	0.1
HDL-c (mg/dl)	50.8 $\pm$ 10.9	48.2 $\pm$ 10.1	0.04
Triglycerides (mg/dl)	233.7 $\pm$ 189.8	208.1 $\pm$ 109.7	0.6

SCHyper, subclinical hyperthyroidism; SCHypo, subclinical hypothyroidism; BMI, body mass index; PAD, peripheral arterial disease; CVD, cardiovascular disease; BP, blood pressure; UIC, urinary iodine concentration; TSH, thyrotropin; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol.

^aValues were log-transformed for statistical analysis.

Table 4 Hazard ratios (95% confidence interval (CI)) for 7.5-year mortality due to all and cardiovascular causes among 1110 Japanese–Brazilians.

	Euthyroidism (n=913)	Subclinical hyperthyroidism (n=69)	Subclinical hypothyroidism (n=99)
All-cause mortality, n (%)	52 (5.7)	14 (20.3)	13 (13.1)
Crude	1	4.0 (2.2–7.2)	2.2 (1.2–4.3)
Model 1	1	3.4 (1.9–6.3)	2.2 (1.2–4.1)
Model 2	1	3.0 (1.5–5.9)	2.3 (1.2–4.4)
Cardiovascular mortality, n (%)	26 (2.8)	8 (11.6)	5 (5.1)
Crude	1	4.5 (2.1–10.0)	1.8 (0.7–4.6)
Model 1	1	3.7 (1.6–8.4)	1.7 (0.6–4.3)
Model 2	1	3.3 (1.4–7.5)	1.6 (0.6–4.2)

CI, confidence interval. Data are given as hazard ratio (95% CI). Model 1, adjusted for age and sex. Model 2, adjusted for Model 1 plus hypertension, diabetes mellitus, cardiovascular disease, total cholesterol, smoking status, and waist circumference.

Despite differences in the population characteristics, these results are similar to those found by Parle *et al.* (23) and Gussekloo *et al.* (25), by having a significant association between mortality and SCHyper, and because increased levels of FT₄ were also associated with increased all-cause mortality. However, we could not confirm Gussekloo's findings of lower mortality among octogenarians with increased TSH levels because our small number of individuals and events limited our power to detect significant associations in that age group. Such a strong association was also reported in a recent meta-analysis (34), in which SCHyper was associated with a significant increase in the relative likelihood of death from all causes, whereas another meta-analysis found only a modest association (35). On the other hand, our findings disagree with previous studies (28, 29), which found no association between SCHyper and mortality. These studies were larger and had a greater follow-up than the current cohort. Therefore, both had a lower prevalence of SCHyper, and in one (28), analysis of death was based on only three events, limiting the power to detect an effect of SCHyper on mortality.

In the present report, SCHypo was significantly associated with death by all causes, but not with cardiovascular mortality. However, as can be noted in Table 4, the point estimates for association between SCHypo and cardiovascular mortality ranged from 1.6 to 1.8 in the different models, but with very large CIs. The small number of cardiovascular deaths (five events) probably limited our ability to detect an association between SCHypo and cardiovascular mortality, and these HRs might have been significant with a larger number of outcomes.

These data partially agree with a Japanese study (24), although in such a study, the association between SCHypo and mortality disappeared by the 10-year mark. Despite our shorter follow-up, we do not have any evidence of a similar outcome in our population, as the association between STD and mortality became more pronounced throughout the study (Fig. 2). In addition, comparisons between these cohorts should be done with

caution, given that they have been exposed to different iodine intake, and because such a study (24) was highly selective in that it only included survivors of the atomic bomb. Our findings also agree with two recent meta-analyses (34, 35), but differ from others (36, 37) and from recent observational studies (28, 29); however, in one of them (29) the mean age of the population (72.7 years) was higher than that of our population. This difference is of particular importance since it has been suggested (38) that SCHypo is associated with mortality in only relatively younger populations (≤ 65 years).

In this cohort, mortality was associated with some metabolic and clinical variables (Table 3); however, the causal role of STD for mortality remained significant, even after a multivariate analysis adjusted for all variables significantly related to mortality and for those classically known to have an association with mortality. Findings regarding the relationship between STD and mortality are very discrepant, mainly because confounders known to affect prognosis have not been carefully considered in many studies (37).

The prevalence rates for STD in this population confirm previous epidemiological studies reporting an elevated prevalence of unsuspected STD in the general population (4–6). The prevalence of SCHypo in this study was similar to that reported previously (4–6), while the rate of SCHyper was higher than that reported for iodine-sufficient Western (4–6, 29) and Japanese populations (39, 40). The reason for this difference is not clear; however, similar findings were found in another Brazilian population study (41). It has been reported that 5 years of excessive iodine intake (1998–2003) may have increased the prevalence of hyperthyroidism in Brazil (42), but only 17.5% of the Japanese–Brazilians had an increased UIC, and no difference in UIC was found among the thyroid categories. This population could be studied during a time when iodine supply was shifted from a mildly deficient to a sufficient or more than sufficient supply, but unfortunately no data for iodine status exist before the time of the study. There is a possibility of selection bias in having included

Figure 2 Kaplan–Meier survival curves for all (A) and cardiovascular (B) causes of death in Japanese–Brazilians according to thyroid status. SCHyper, subclinical hyperthyroidism; SCHypo, subclinical hypothyroidism. * (A) Log-rank test; all causes of death, $P < 0.0001$ for SCHyper versus euthyroidism and $P = 0.0035$ for SCHypo versus euthyroidism. † (B) Log-rank test; cardiovascular death, $P < 0.0001$ for SCHyper versus euthyroidism and $P = 0.23$ for SCHypo versus euthyroidism.

some individuals with nonthyroidal illness (43), but it is not very likely to be of significance in this study, since FT_4 levels were significantly higher in individuals with SCHyper than in euthyroid subjects (Table 2), which is consistent with mild thyroid hormone excess. Finally, the use of slimming pills, a common practice in Brazil (44), could have affected the prevalence of SCHyper in our population, but participants did not report such use.

No consistent association of STD with cardiometabolic risk factors was found at baseline in this study

(Table 2). These findings agree with some previous large population-based studies (4, 29, 45, 46), but differ from others (5, 6, 28). In two of these studies (6, 28), the difference disappeared after adjusting for other relevant risk factors, such as age, sex, and statin use. A meta-analysis (47) found a significant decrease in total serum cholesterol levels following $L-T_4$ therapy, but most of the selected studies had a nonrandomized design. In contrast, a systematic review (48) found only marginal evidence indicating an association between thyroid hormone replacement and improvement in lipid profile. Recently, a randomized, double-blind, and crossover study of $L-T_4$ and placebo (49) found that SCHypo treated with $L-T_4$ improved total cholesterol and LDL-c levels. Thus, there are no homogeneous data concerning the effects of SCHypo on serum lipid levels.

We found no association of STD with cardiovascular disease or with peripheral arterial disease at baseline in this study, which is similar to some studies (28, 29, 50). A modest association of SCHypo with an increased risk of coronary heart disease at baseline and at follow-up has been found in different studies and meta-analyses (28, 35, 36, 45, 51), but the estimated risk was close to 1.0 when only higher quality studies were pooled (35). A recent analysis suggested that SCHypo may be associated with increased cardiovascular risk only in middle-aged (< 65 years old) individuals (38). Unfortunately, the small number of events eliminates the ability to perform meaningful analysis according to age in the present study.

The major strength of our study lies in our inclusion of an entire population. In addition, participants were examined by thyroid experts, and individuals who self-reported thyroid diseases or were taking thyroid medications were excluded from the analysis; life status was obtained for all participants, and mortality risk was adjusted for multiple confounders.

This study also has several limitations, including the fact that our data are based only on a baseline set of thyroid tests. Thus, we cannot exclude the possibility of influence determined by the progression from subclinical to overt thyroid dysfunction on the risk of mortality; however, this limitation is common to all previously published studies. We also had a relatively small number of cardiovascular deaths, decreasing the power of the analysis and our ability to detect an association with SCHypo. Another limitation is the lack of analysis stratified according to age, sex, and TSH levels due to the small numbers of events. In addition, we are unable to exclude the possibility of overt thyrotoxicosis in some of our SCHyper individuals, since T_3 and FT_3 serum levels were not determined in this study. Furthermore, cause of death was only based on death certificates without additional validation by hospital records for those who died in the hospital. Finally, we cannot guarantee the generalizability of the findings due to our selected population of Japanese–Brazilians.

In summary, SCHyper is an independent risk factor for all-cause and cardiovascular mortality, whereas SCHypo is associated with increased all-cause mortality among Japanese–Brazilians. These findings suggest that further preventive strategies of treatment are necessary in order to reduce mortality associated with STD in the general population; however, to demonstrate some therapeutic benefit, large, well-designed, randomized, and placebo-controlled trials of STD treatment will be needed. Thus, while the treatment of STD persists as a nonevidence-based program, the choice between treating and not treating patients with persistent endogenous STD remains dependent on the best clinical judgment.

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.

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