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Thyroid function and cardiovascular disease risk factors in euthyroid adults: a cross-sectional and longitudinal study

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Summary

Objective and design—We explored the cross-sectional and longitudinal associations of thyroid function within the normal range with cardiovascular disease (CVD) risk factors and adiposity measures.

Patients and measurements—A total of 3483 (50·4% women) participants for the cross-sectional CVD study and 1630 (41·2% women) participants for the cross-sectional body composition substudy were drawn from the Framingham Third Generation Exam 1; 2912 participants (50·1% women) for the longitudinal CVD study and 713 participants (35·9% women) for the longitudinal body composition substudy were drawn from the Framingham Third Generation Exams 1–2. Thyroid function was assessed by thyrotropin [thyroid-stimulating hormone (TSH)] and free thyroxine (fT4) concentrations within the reference range at Exam 1. The associations between thyroid function and CVD risk factors were modelled via multivariable-adjusted regression models. Multivariable adjustment included age, sex, current smoking, postmenopausal status and BMI.

Results—Cross-sectionally, higher TSH concentration was associated with increased odds of hypertriglyceridaemia [odds ratio (OR)=1·10], and higher BMI (β = 0·19 kg/m^2), total cholesterol (β = 0·05 mmol/l), triglycerides (β = 0·0006 mmol/l) and subcutaneous adipose tissue (SAT) volume (β = 38·8 cm^3) (all $P < 0·05$). Cross-sectionally, fT4 was inversely associated with

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Disclosure

Alison Pedley is an employee of Merck & Company, Inc.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web site.

metabolic and adiposity-related CVD risk factors, including obesity (OR = 1·17), hypertriglyceridaemia (OR = 1·09), BMI (β = 0·42 kg/m^2), total cholesterol (β = 0·05 mmol/l), triglycerides (β = 0·0002 mmol/l), visceral adipose tissue (VAT) volume (β = −20·7 cm^3) and attenuation (0·17 HU) and VAT/SAT ratio (β = −0·01) (all $P < 0·05$). However, during 6·1 years of follow-up, baseline TSH and fT4 levels were not longitudinally associated with CVD risk factors and adiposity measures.

Conclusions—Thyroid function within the normal range is cross-sectionally, but not longitudinally, associated with CVD risk factors and adiposity measures.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States, accounting for more than 780 000 deaths per year based on the latest report.[1] Thyroid dysfunction is associated with incident CVD and coronary heart disease mortality.[2] In addition, thyroid dysfunction is associated with weight fluctuation as thyroid hormone plays an important role in regulating basal energy expenditure, as well as glucose and lipid metabolism.[3]

Multiple lines of evidence suggest that the concentrations of thyrotropin [thyroid-stimulating hormone (TSH)] and free thyroxine (fT4) within the normal physiological range are associated with clusters of metabolic abnormalities and measures of body fat distribution.[4–7] Specifically, higher TSH and lower fT4 within the reference range have been shown to be associated with unfavourable CVD risk factors and body fat composition.[4,5,7] We have previously shown that a change in TSH among euthyroid participants was associated with weight change after a 3·5-year interval.[6] However, associations between thyroid function with CVD risk and body composition have not been firmly established in euthyroid individuals as prior studies were limited by the cross-sectional setting and lacked comprehensive measures of metabolic and adiposity-related CVD risk factors.

Therefore, we evaluated whether thyroid function within the normal range is cross-sectionally and longitudinally associated with a broad array of CVD risk factors and adiposity measurements. We hypothesized that higher TSH and lower fT4 concentrations within the normal range are associated with more adverse CVD risk and greater indication of body fat accumulation both cross-sectionally and longitudinally.

Methods

Study sample

Participants for this study were drawn from the Third Generation cohort of the Framingham Heart Study who attended two consecutive examinations from 2002 to 2005 for Exam 1 (baseline) and from 2008 to 2011 for Exam 2 (follow-up). Our study population was comprised of whites. The Framingham Heart Study participants were asked to avoid attending a clinic examination when pregnant. The designs of the Framingham Heart Study and selection criteria of the Third Generation cohort have been previously described in detail.[8]

Among 4053 participants with TSH and fT4 data available at Exam 1, we excluded individuals with any of the following reasons: (1) thyroid function parameters outside the reference range of 0·5–5·0 mIU/l for TSH or 12·0–21·9 pmol/l for fT4 or both (n = 437); (2) use of thyroid hormones or antithyroid medications (n = 190); and (3) missing covariates (n = 8), resulting in 3483 individuals (85·9% of eligible) for the cross-sectional design of the CVD study.

For the longitudinal component of this study, there were 3379 participants who attended both examination cycles with TSH and fT4 data available. After excluding individuals with any of the following reasons: (1) thyroid function outside the normal range of TSH or fT4 or both (n = 356); (2) use of thyroid hormones or antithyroid medications at baseline (n = 151); and (3) missing covariates at baseline (n = 6), 2912 participants (86·2% of eligible) were available for the analysis.

Among the Third Generation participants, (1) those who resided in the Greater New England area, (2) women who aged ≥ 40 years and men aged ≥ 35 years and (3) whose body weight < 159 kg were eligible to participate in the multidetector computed tomography (MDCT) substudy Exams 1 (2002–2005) and 2 (2008–2011).[9] In addition, a small subset of participants (n = 12) were enrolled using an identical imaging protocol with slightly different age ranges. For the cross-sectional design of the body composition substudy, 1994 Third Generation participants who attended MDCT substudy Exam 1 were included for the cross-sectional design. After excluding individuals with any of the following reasons: (1) TSH or fT4 or both were missing or outside the reference range (n = 224); (2) use of thyroid hormones or antithyroid medications (n = 116); (3) missing exposures, outcomes or covariates (n = 16); (4) body mass index (BMI) < 17 kg/m^2 (n = 3); (5) history of gastric bypass surgery (n = 4), prevalent cancer (n = 69) or prevalent hard CVD (n = 15) (defined as myocardial infarction, coronary heart disease death, stroke or congestive heart failure) diagnosed on or before Exam 1, 1630 participants (81·7% of eligible) remained in the final analysis.

The study sample for the longitudinal component of the body fat composition substudy was drawn from Third Generation participants (n = 1149) who attended MDCT substudy Exams 1 and 2. We excluded individuals with any of the following reasons: (1) TSH or fT4 or both were missing or outside the normal ranges (n = 124); (2) use of thyroid hormones or antithyroid medications at baseline (n = 67); (3) missing exposures and covariates at baseline, or outcomes at either exam (n = 10); (4) BMI at either exam < 17 kg/m^2 (n = 3); (5) history of gastric bypass surgery (n = 3), prevalent cancer (n = 64) or hard CVD (n = 16) diagnosed on or before Exam 2; (6) death within 1 year after Exam 2 (n = 2); and (7) number of months between either exam and corresponding CT measurements ≥ 7 months (n = 241), resulting in 713 participants (62·1% of eligible).

All study protocols and procedures were approved by the institutional review boards of the Boston University Medical Center and Massachusetts General Hospital. Written informed consent was provided by all the participants.

Plasma thyrotropin and free thyroxine

Blood was obtained after an overnight fast at the first examination cycle to assess TSH and fT4 concentrations. TSH and fT4 were measured on EDTA plasma, using a Roche e411 immunoanalyzer (Roche Diagnostics, Basel, Switzerland). The mean inter- and intra-assay coefficients of variation were 2·6 and 2·3% for TSH and 2·5 and 1·4% for fT4, respectively. Normal range of the thyroid function was defined as a TSH level of 0·5 to 5·0 mIU/l[6] and fT4 level of 12·0–21·9 pmol/l.[10] The average time interval between the blood sampling and the TSH and fT4 analysis for Exam 1 samples was 9·5 years, and the specimens were stored at −80 Celsius until testing.

Cardiovascular disease risk factors

The weight and height of the participants were measured to the nearest pound (0·5 kg) and 0·25 inch (0·6 cm), respectively. BMI was computed as weight in kg divided by height in square metres. Obesity was defined as BMI ≥ 30 kg/m^2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, and hypertension was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg or use of antihypertensive medication. Either high SBP or DBP qualified for hypertension. Fasting plasma glucose and lipids [total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides] were measured. Diabetes was defined as fasting plasma glucose ≥ 7 mmol/l or current use of hypoglycaemic medication. Hypercholesterolaemia was defined as total cholesterol ≥ 6·2 mmol/l or lipid-lowering treatment. Low HDL cholesterol was defined as HDL cholesterol < 1·3 mmol/l for women and < 1·0 mmol/l for men. Hypertriglyceridaemia was defined as triglycerides ≥ 1·7 mmol/l or lipid-lowering treatment. Metabolic syndrome was defined by the Modified National Cholesterol Education Program Adult Treatment Panel III guidelines.[11]

Adiposity measures

Abdominal subcutaneous (SAT) and visceral adipose tissue (VAT) quantity in cm^3 and quality in Hounsfield units (HU) were measured by the radiographic pixel attenuation between −195 and −45 HU with centre attenuation of −120 HU from the eight-slice MDCT scanner (LightSpeed Ultra, General Electric, Milwaukee, WI, USA). State-of-the-art methods via a three-dimensional Workstation tool (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA, USA) were used to trace the abdominal muscular wall to separate SAT and VAT as previously described and validated elsewhere with inter-reader reliability of 0·997 for SAT and 0·992 for VAT.[12] Due to the CT radiographic imaging technique involved in this measurement, adipose tissue quality was referred to as adipose tissue attenuation. The ratio of VAT to SAT was computed as VAT volume divided by SAT volume.

Covariates

Current smokers were specified as individuals who reported smoking at least 1 cigarette per day during the previous year. Postmenopausal status was determined on an individual basis for women whose menstrual cycle has been suspended for at least 1 year.

Statistical analysis

TSH and fT4 were normally distributed. Triglycerides were natural logarithmically transformed due to their skewed distribution. The cross-sectional associations between thyroid function and CVD risk factors were assessed using age- and sex-adjusted Pearson correlations and multivariable-adjusted logistic and linear regression analyses for dichotomous and continuous metabolic risk factors, respectively. The multivariable model was adjusted for age, sex, current smoking and postmenopausal status. BMI was additionally adjusted in the model as a second-level adjustment. We designed our regression models to describe the associations with metabolic and adiposity-related CVD risk factors per 1 mIU/l increment in TSH and 1·3 pmol/l (equal to 0·1 ng/dl) decrement in fT4 based on the range of our data to ease the interpretation of the study results. More specifically, for the dichotomous CVD risk factors, the odds ratios (ORs) described the odds of the risk factor prevalence per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in fT4; for the continuous CVD risk factors, β-coefficients described the associations of the metabolic risk factors per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in fT4.

For the longitudinal design, we constructed age- and sex-adjusted Pearson correlations and multivariable-adjusted regression analyses to explore the longitudinal associations between thyroid function at baseline with incident CVD risk factors at the follow-up examination (logistic regression) and the changes in CVD risk factors during follow-up (linear regression). Multivariable adjustment for the logistic regression model included age, sex, current smoking, postmenopausal status and baseline metabolic risk factors (baseline SBP and DBP for hypertension, baseline fasting plasma glucose for diabetes mellitus, baseline cholesterol for hypercholesterolaemia, baseline HDL for low HDL and baseline log triglycerides for hypertriglyceridaemia). Baseline BMI was additionally included as a second-level adjustment. For the logistic regression models, participants who had prevalent CVD risk factors at baseline were excluded from the incident analysis in a model-specific manner. For instance, individuals who were diagnosed for hypertension at baseline were excluded from the logistic regression analysis for incident hypertension. The changes in CVD risk factors during follow-up were computed by subtracting baseline values from follow-up values. For the linear regression models, participants using antihypertensive medication at baseline were excluded from the SBP and DBP models. If the participants were on antihypertensive medication at follow-up, 10 mmHg was added to the follow-up value of SBP and 5 mmHg was added to the follow-up value of DBP.[13] For the dichotomous risk factors, the ORs described the odds of the risk factor incidence per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in fT4; for continuous risk factors, β-coefficients described the association of the changes in metabolic risk factors per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in fT4.

A secondary analysis was performed to examine the cross-sectional and longitudinal associations between thyroid function within normal range with adiposity measures, including weight, abdominal fat quantity (fat volume) and quality (fat attenuation), and VAT/SAT ratio at baseline (for the cross-sectional analysis), and also the changes in these parameters between baseline and follow-up (for the longitudinal analysis). Similar to the primary analysis, age- and sex-adjusted Pearson correlations and multivariable-adjusted

regression analyses were used to explore the associations between TSH and fT4 with baseline and changes in adiposity measures. Multivariable adjustment included age, sex, current smoking and postmenopausal status. We also examined whether the cross-sectional associations were independent of adiposity measures by implementing two different covariate-adjusted models, that is with additional adjustment for baseline BMI or respective fat quantity (SAT volume for SAT attenuation and VAT volume for VAT attenuation). For the longitudinal component of this substudy, weight change or the baseline level of respective fat quantity was additionally added as a second-level adjustment.

We further tested for sex interactions between thyroid function with CVD risk factors and adiposity measures based on the multivariable-adjusted model. A two-sided $P < 0{\cdot}05$ was considered statistically significant. All the analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Descriptive characteristics

The characteristics of the cross-sectional CVD risk factor study are shown in Table 1. Characteristics of the study participants at baseline and follow-up are given in Table S1. A total of 2912 participants (50·1% women) were included in this study for the longitudinal design of the CVD risk factors. The average interval between baseline and follow-up examinations was 6·1 ± 0·6 years. The age ranges of the study participants were 19–72 years for the cross-sectional and longitudinal CVD study, 31–72 years for the cross-sectional body composition substudy and 31–70 years for the longitudinal body composition substudy.

Cross-sectional associations between thyroid function and cardiovascular disease risk factors

Age- and sex-adjusted Pearson correlation coefficients between thyroid function with a panel of CVD risk factors are shown in Table 2. Higher TSH was associated with higher levels of total cholesterol ($r = 0{\cdot}04$), HDL cholesterol ($r = 0{\cdot}04$) and triglycerides ($r = 0{\cdot}007$) (all $P < 0{\cdot}05$) (Table 2).

In Table 3, higher TSH was associated with higher odds of prevalent hypercholesterolaemia [OR = 1·09, 95% confidence interval (CI) 1·01–1·18], hypertriglyceridaemia (OR = 1·12, 95% CI 1·03–1·23) and metabolic syndrome (OR = 1·12, 95% CI 1·01–1·23). After further adjusting for BMI, only the association between TSH with hypertriglyceridaemia remained significant (OR = 1·10, 95% CI 1·00–1·21). Similar patterns were observed with lower fT4 level and dichotomous CVD risk factors (Table 3).

For the continuous CVD risk parameters, a 1 mIU/l increment in TSH was associated with an increase of 0·19 kg/m^2 (95% CI 0·00–0·38) of BMI, 0·05 mmol/l (95% CI 0·02–0·08) of total cholesterol and 0·0007 mmol/l (95% CI 0·0005–0·0009) of log triglycerides (Table 4). Similar observations were found for lower fT4 concentrations. All of these associations between TSH and fT4 with CVD risk factors remained significant even after further adjustment of BMI ($P < 0{\cdot}05$).

Longitudinal associations between thyroid function and cardiovascular disease risk factors

Baseline TSH concentrations were not associated with incident CVD risk factors at the follow-up examination or longitudinal changes in CVD risk factors during follow-up (all $P \geq 0{\cdot}08$, Tables 5–6). Similarly, decrement in baseline fT4 was not associated with incident or changes in CVD risk factors (all $P \geq 0{\cdot}16$, Tables 5–6). The only notable exception was fT4 with HDL cholesterol change, in which a 1·3 pmol/l decrement in baseline concentrations of fT4 was associated with a 0·008 mmol/l (95% CI −0·015–0·0003) decrease in HDL cholesterol change.

Analyses of thyroid function with adiposity measures

We further tested the cross-sectional associations between thyroid function with adiposity measures. A 1 mIU/l increment in TSH concentration was associated with higher levels of SAT volume (β = 117·5 cm^3, 95% CI 44·1–190·9) and SAT attenuation (β = −0·32 HU, 95% CI −0·59–0·04) (Table 4). Among these, only the associations between TSH with SAT volume (β = 38·8 cm^3, 95% CI 5·3–72·4) remained significant after further adjustment of BMI. The relations of lower fT4 with adiposity measures were not materially different. Notably, the associations with fT4 and VAT volume (β = −20·7 cm^3, 95% CI −39·9–1·5) and VAT/SAT ratio (β = −0·01, 95% CI −0·02–0·00) persisted even after additionally adjusting for BMI. Longitudinally, baseline TSH and fT4 were generally not associated with changes in body fat distribution during follow-up (Table 6).

Sex interaction

Cross-sectionally, there were no significant sex interactions in the associations between thyroid function and CVD risk factors and adiposity measures (all $P > 0{\cdot}06$), except for TSH with triglycerides ($P = 0{\cdot}001$) and fT4 with HDL cholesterol ($P = 0{\cdot}03$), where the magnitude of associations was stronger in men compared with women. For the longitudinal aspect of the CVD risk factors and adiposity study, we did not found evidence of sex interaction (all $P > 0{\cdot}06$), except baseline TSH and fasting plasma glucose change ($P = 0{\cdot}03$), where the associations were more pronounced in men (β = −0·07 mmol/l, $P = 0{\cdot}04$), as compared to women (β = −0·02 mmol/l, $P = 0{\cdot}40$).

Discussion

Principle findings

In this cohort of biochemically euthyroid individuals, we identified cross-sectional associations between thyroid function, as assessed by TSH and fT4 concentrations within the reference range, with a panel of CVD risk factors, primarily with markers of lipid and glucose metabolism and measures of body fat distribution. In particular, higher TSH and lower fT4 levels were associated with more adverse CVD risk factors and greater indication of body fat accumulation. However, during 6·1 years of follow-up, baseline TSH and fT4 were not longitudinally associated with incident and changes in CVD risk factors or changes in body fat composition.

In the context of the current literature

A substantial body of literature reported that higher TSH or lower fT4 concentrations within the normal range are cross-sectionally associated with more adverse CVD risk factors[5,14,15] and body fat measurements (i.e. greater body weight, BMI, waist circumference, abdominal SAT and subcutaneous fat/preperitoneal fat layer ratio).[6,14–21] For instance, a population-based study of 2703 euthyroid participants reported in an age- and sex-adjusted model that TSH and fT4 were associated with markers of lipid and glucose metabolism, in which higher TSH was associated with higher triglycerides, apolipoprotein A1 and homeostasis model assessment for insulin resistance (all $P < 0{\cdot}05$).[14] Similar trends with thyroid function and metabolic and adiposity-related CVD risk factors were reported in another cross-sectional study of 2771 euthyroid Hispanic participants.[15] Nevertheless, conflicting studies also exist, in which these studies did not identify significant cross-sectional associations between TSH with fasting plasma glucose,[14,22,23] HOMA-IR,[4,7,23] total cholesterol,[14] low-density lipoprotein cholesterol,[14] HDL cholesterol,[23] triglycerides,[22] BMI[7,19,20,24] and body weight,[7] or fT4 with BMI,[7,16,24] body weight[7] and waist circumference.[16]

Prior studies explored the cross-sectional and longitudinal associations between thyroid function within the normal range and CVD risk factors; however, data on the longitudinal associations are more limited, as compared to the studies based on cross-sectional design. Similar to our findings, a recent study of an older population from 70 to 79 years of age identified an association between higher TSH and prevalent metabolic syndrome (OR 1·18, $P = 0{\cdot}002$), but not with incident metabolic syndrome (OR 1·00, $P = 0{\cdot}92$).[25] For the longitudinal relations of the body fat measurements, previous studies have reported lack of associations between thyroid function within the normal range and changes in adiposity measures, such as body weight,[26] BMI,[27] waist circumference[27] and waist-to-hip ratio.[26,27] A large population-based Danish study reported no significant association between baseline fT4 and weight change during 11 years of follow-up.[26] Our findings were consistent with these prior findings. Importantly, our study extends the existing literature by exploring the longitudinal associations of thyroid function with CVD risk factors in euthyroid population. We incorporated more comprehensive measures of CVD risk factors and more precise measures of body fat distribution, including abdominal fat quantity and quality, as well as ratio of VAT and SAT volume.

Potential mechanisms

There are several potential explanations for our significant cross-sectional findings but negative longitudinal findings. First, the absence of a longitudinal association between thyroid function with metabolic and adiposity-related CVD risk factors may suggest that changes in CVD risk profiles or body fat distribution within the euthyroid range may precede changes in thyroid function rather than the other way round. Specifically, more adverse CVD risk factors or excessive fat accumulation could have led to altered secretion of thyroid hormones by affecting the endocrine system that contributes to the regulation of the hypothalamic–pituitary–adrenal axis.[5] This is supported by weight loss studies that demonstrated decreased TSH concentration after weight loss among obese participants with normal TSH range.[28,29] Gene expression experiments have demonstrated that thyroid gene expression (i.e. expression of the TSH receptor and thyroid hormone receptor genes) in SAT

and VAT was reduced in obese participants, as compared to the control group. Additionally, an increase in gene expression and a decrease in TSH concentration were observed after subsequent weight loss.[30,31] Taken together, these findings suggest that changes in CVD risk profiles or body fat distribution may affect changes in thyroid function in euthyroid adults. However, weak or no longitudinal association between baseline BMI and change in TSH within the normal reference range[26,27] may rule out the possibility of reverse causation and support that the basis of the associations between thyroid function within normal range and CVD risk factors is multifactorial.

Second, it is feasible that the differences in the exclusion criteria for the study sample between the cross-sectional and longitudinal designs may have contributed to the observed discrepancies in our cross-sectional findings, as compared to the longitudinal results. Explicitly, we excluded informative individuals with diabetes, hypertension, hypercholesterolaemia, low HDL, hypertriglyceridaemia or metabolic syndrome at baseline in our longitudinal analysis. Consequently, individuals with extreme values for a specific variable were excluded when examining the change in this variable/incidence; in turn, it may have affected the study results.

Third, it is plausible that the discrepancies between our cross-sectional and longitudinal findings may have been affected by the regression towards the mean bias by the random variations in the repeated outcome variable.[32] We may have detected extreme values of the CVD risk factors for the cross-sectional component of our study, whereas the follow-up outcome values may have not been as extreme as the baseline CVD risk factors due to this statistical phenomenon.

Finally, we may not have comprehensively captured the associations between thyroid function within the normal range and CVD risk factors and adiposity measures as we only incorporated two-time point measurements (baseline and follow-up) of the outcome variables. Consequently, our data might have been insufficient to detect the fluctuation of the changes in metabolic and adiposity-related CVD risk factors during follow-up.

Implications

Our data suggest that identifying variation in TSH and fT4 within the normal range may contribute limited information to the future development of CVD risk or unfavourable changes in body fat distribution. Confirmation of our study findings is warranted in other euthyroid study samples with prolonged and more frequent follow-up periods.

Strengths and limitations

The strengths of our study include a comprehensive list of CVD risk factor profile information and body fat measures that were directly assessed on site by physicians and field experts at baseline and follow-up. We had baseline and follow-up values for the CVD risk factors and body fat measurements for a mean of 6·1 years apart; thus, we were able to assess the changes in these outcome variables. A limitation of this study was the lack of TSH and fT4 at the follow-up examination. We cannot rule out that some participants may have developed thyroid abnormalities in the intervening years. Information on prior thyroid illness was not available. Accordingly, inclusion of those participants may have affected the

results of our study. This study was based on a prospective observational study design, which precludes the causal inference of thyroid function with metabolic and adiposity-related CVD risk factors in euthyroid adults. Our study population was comprised of whites, and thus, the study findings cannot be generalized to other ethnic groups. In our study, participants with lipid-lowering treatment were classified as having hypercholesterolaemia and hypertriglyceridaemia. We may have misclassified some of our participants as lipid-lowering medications, as statin may also be prescribed to individuals with high CVD risk.[33] However, the likelihood of misclassifying participants as hypercholesterolaemia and hypertriglyceridaemia is low given that the data were collected in 2002–2005. In addition, statins have a modest effect on triglycerides,[34] which may be considered as a confounder for the association between thyroid function and metabolic and adiposity-related CVD risk factors.

Conclusions

Thyroid function characterized as higher TSH and lower fT4 concentrations within the reference range is cross-sectionally, but not longitudinally, associated with adverse CVD risk factors and a greater accumulation of body fat. Our findings suggest that thyroid function as assessed by TSH and fT4 may have limited utility in CVD risk stratification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the cardiovascular disease risk factors study sample[*] for the cross-sectional design

Characteristics	Women (*n* = 1756)	Men (*n* = 1727)	Overall participants (*n* = 3483)
Age, years	39·6 (8·8)	40·2 (8·8)	39·9 (8·8)
Weight, kg	69·1 (15·9)	88·1 (15·8)	78·5 (18·5)
Body mass index, kg/m^2	25·6 (5·8)	27·9 (4·7)	26·7 (5·4)
Waist circumference, cm	88 (15)	98 (13)	93 (15)
SAT[†], cm^3	2893 (1522)	2582 (1267)	2710 (1386)
VAT[†], cm^3	1083 (706)	1979 (878)	1610 (924)
VAT/SAT Ratio[†]	0·4 (0·1)	0·8 (0·3)	0·6 (0·3)
SAT[†], HU	−102 (5·6)	−100 (4·7)	−101 (5·2)
VAT[†], HU	−92 (4·3)	−96 (4·5)	−94 (4·8)
TSH, mIU/l	2·1 (1·0)	1·9 (0·9)	2·0 (0·9)
Free thyroxine, pmol/l	14·8 (1·5)	15·4 (1·8)	15·1 (1·8)
Systolic blood pressure, mmHg	113 (14)	121 (13)	117 (14)
Diastolic blood pressure, mmHg	72 (9·1)	78 (9·3)	75 (9·7)
Fasting plasma glucose, mmol/l	5·1 (1·0)	5·5 (1·0)	5·3 (1·0)
Total cholesterol, mmol/l	4·8 (0·9)	5·0 (1·0)	4·9 (0·9)
HDL cholesterol, mmol/l	1·6 (0·4)	1·2 (0·3)	1·4 (0·4)
Triglycerides[‡], mmol/l	0·89 (0·68–1·28)	1·22 (0·82–1·83)	1·03 (0·73–1·55)
Obesity[§], %	18·4% (323)	25·2% (436)	21·8% (759)
Smoking status, %			
Former[¶]	28·4% (499)	22·0% (380)	25·2% (879)
Current[**]	16·2% (284)	18·5% (319)	17·3% (603)
Never[††]	55·4% (973)	59·5% (1028)	57·5% (2001)
Postmenopausal status, %	13·2% (231)	–	–
Hormone replacement therapy, %	4·2% (72)	–	–

Data on means (standard deviations) or proportions (counts) are shown.

[*] Data are limited to participants who had TSH level of 0·5–5·0 mIU/l and free thyroxine level of 12·0–21·9 pmol/l.

[†] For the cross-sectional design of the body composition substudy, 1630 participants (672 women and 958 men) were included.

[‡] Values are shown as medians (25th, 75th percentiles) due to the skewed distribution.

[§] Defined as body mass index ≥ 30 kg/m^2.

[¶] Defined as not a current smoker but previously smoked ≥ 1 cigarette/day for at least a year.

[**] Defined as ≥ 1 cigarette/day within the previous year.

[††] Neither a former nor a current smoker.

HDL, high-density lipoprotein; HU, Hounsfield unit; SAT, subcutaneous adipose tissue; TSH, thyrotropin; VAT, visceral adipose tissue.

Table 2

Age- and sex-adjusted Pearson correlation coefficients between baseline TSH and free thyroxine concentrations with cardiovascular disease risk factors at baseline and changes during the follow-up

Parameters	TSH	Free thyroxine
Values at baseline		
Body mass index	0·02	0·05†
Systolic blood pressure	0·003	−0·03
Diastolic blood pressure	0·01	−0·04*
Fasting plasma glucose	0·01	−0·03
Total cholesterol	0·04*	0·04*
HDL cholesterol	0·04*	0·09‡
Triglycerides§	0·07‡	0·02
Changes in the parameters¶		
Body mass index	−0·04	−0·03
Systolic blood pressure	−0·02	−0·02
Diastolic blood pressure	0·002	0·007
Fasting plasma glucose	−0·04*	−0·01
Total cholesterol	−0·005	−0·005
HDL cholesterol	−0·008	−0·01
Triglycerides§	−0·04*	−0·02

*$P < 0·05$.

†$P < 0·01$.

‡$P < 0·001$.

§Natural logarithmically transformed to enhance the normalization of the skewed distributions.

¶Baseline values were subtracted from the follow-up values.

HDL, high-density lipoprotein; TSH, thyrotropin.

Table 3

Cross-sectional associations between TSH and free thyroxine levels with selected dichotomous cardiovascular disease risk factors

Parameters	N-Case/Total N* (%)	Model†	TSH	*P*-Value	Free thyroxine	*P*-Value
Obesity	629/2912 (21·6%)	MV	1·09 (1·00–1·19)	0·06	1·17 (1·10–1·25)	<·0001
Hypertension	563/3478 (16·2%)	MV	1·04 (0·93–1·15)	0·51	1·00 (0·93–1·07)	0·96
		MV+BMI	1·00 (0·90–1·12)	0·96	0·93 (0·86–1·01)	0·07
Diabetes	97/3481 (2·8%)	MV	0·98 (0·77–1·23)	0·84	1·05 (0·89–1·23)	0·58
		MV+BMI	0·94 (0·74–1·19)	0·61	0·96 (0·81–1·13)	0·63
Hypercholesterolaemia	1388/3483 (39·9%)	MV	1·09 (1·01–1·18)	0·04	1·08 (1·02–1·14)	0·01
		MV+BMI	1·08 (0·99–1·17)	0·07	1·06 (1·00–1·12)	0·052
Low HDL cholesterol	905/3482 (26·0%)	MV	1·05 (0·97–1·15)	0·21	1·03 (0·97–1·09)	0·37
		MV+BMI	1·03 (0·95–1·13)	0·48	0·98 (0·92–1·04)	0·52
Hypertriglyceridaemia	851/3482 (24·4%)	MV	1·12 (1·03–1·23)	0·01	1·13 (1·06–1·21)	0·0001
		MV+BMI	1·10 (1·00–1·21)	0·045	1·09 (1·02–1·16)	0·01
Metabolic syndrome	727/3469 (21·0%)	MV	1·12 (1·01–1·23)	0·02	1·11 (1·04–1·19)	0·002
		MV+BMI	1·07 (0·95–1·20)	0·25	1·00 (0·93–1·08)	0·95

Data are shown as odds ratios (95% confidence intervals). The results show the odds of the each risk factor prevalence per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in free thyroxine.

BMI, body mass index; HDL, high-density lipoprotein; MV, multivariable; TSH, thyrotropin.

*The number of new cases of a cardiovascular disease risk factor at follow-up divided by the number of persons at risk for the risk factor.

†MV model was adjusted for age, sex, current smoking and postmenopausal status (women only). MV+BMI model was additionally adjusted for BMI.

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Table 4

Cross-sectional associations between TSH and free thyroxine levels with continuous cardiovascular disease risk factors and adiposity measures

Parameters	Model†	TSH	*P*-Value	Free thyroxine	*P*-Value
Cardiovascular risk factors					
Body mass index, kg/m^2	MV	0·19 (0·00–0·38)	0·048	0·42 (0·29–0·55)	<·0001
Systolic blood pressure, mmHg	MV	0·33 (−0·14–0·80)	0·17	0·40 (0·07–0·72)	0·02
	MV+BMI	0·18 (−0·27–0·62)	0·44	0·06 (−0·25–0·37)	0·69
Diastolic blood pressure, mmHg	MV	0·32 (−0·01–0·65)	0·06	0·21 (−0·02–0·44)	0·08
	MV+BMI	0·23 (−0·09–0·55)	0·16	0·00 (−0·22–0·22)	0·98
Fasting plasma glucose, mmol/l	MV	0·03 (−0·001–0·07)	0·054	0·01 (−0·01–0·03)	0·42
	MV+BMI	0·02 (−0·01–0·06)	0·16	−0·01 (−0·04–0·01)	0·32
Total cholesterol, mmol/l	MV	0·05 (0·02–0·08)	0·002	0·05 (0·03–0·08)	<·0001
	MV+BMI	0·05 (0·02–0·08)	0·003	0·05 (0·02–0·07)	<·0001
HDL cholesterol, mmol/l	MV	−0·001 (−0·014–0·013)	0·92	−0·004 (−0·013–0·005)	0·41
	MV+BMI	0·004 (−0·009–0·017)	0·58	0·005 (−0·004–0·014)	0·24
Triglycerides *, mmol/l	MV	0·0007 (0·0005–0·0009)	<·0001	0·0005 (0·0002–0·0006)	<·0001
	MV+BMI	0·0006 (0·0003–0·0008)	<·0001	0·0002 (0·0001–0·0005)	0·0003
Adiposity measures					
SAT, cm^3	MV	117·5 (44·1–190·9)	0·002	110·1 (60·3–159·8)	<·0001
	MV+BMI	38·8 (5·3–72·4)	0·02	−2·6 (−25·6–20·4)	0·82
VAT, cm^3	MV	34·6 (−7·7–76·9)	0·11	34·1 (5·4–62·9)	0·02
	MV+BMI	−3·5 (−31·6–24·6)	0·81	−20·7 (−39·9–1·5)	0·04
VAT/SAT Ratio	MV	−0·01 (−0·02–0·01)	0·33	−0·01 (−0·02–0·00)	0·01
	MV+BMI	−0·01 (−0·02–0·01)	0·48	−0·01 (−0·02–0·00)	0·048
SAT, HU	MV	−0·32 (−0·59–0·04)	0·02	−0·12 (−0·31–0·07)	0·21
	MV+BMI	−0·19 (−0·44–0·06)	0·14	0·07 (−0·10–0·24)	0·44
	MV+Fat Volume	−0·08 (−0·31–0·15)	0·51	0·11 (−0·05–0·26)	0·18
VAT, HU	MV	−0·19 (−0·43–0·05)	0·12	−0·04 (−0·20–0·12)	0·64
	MV+BMI	−0·05 (−0·25–0·16)	0·66	0·17 (0·03–0·31)	0·02
	MV+Fat Volume	−0·04 (−0·20–0·11)	0·59	0·11 (−0·00–0·21)	0·06

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Data are shown as estimated β-coefficients (95% confidence intervals). The results show association of each risk factor per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in free thyroxine.

BMI, body mass index; HDL, high-density lipoprotein; HU, Hounsfield units; MV, multivariable; SAT, subcutaneous adipose tissue; TSH, thyrotropin; VAT, visceral adipose tissue.

*Natural logarithmically transformed to enhance the normalization of the skewed distributions.

†MV model was adjusted for age, sex, current smoking and postmenopausal status (women only). MV+BMI model was additionally adjusted for BMI. MV+ Fat volume model was additionally adjusted for SAT volume (for SAT attenuation) or VAT volume (for VAT attenuation).

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Table 5

Longitudinal associations between baseline TSH and free thyroxine levels with incident cardiovascular disease risk factors

Parameters	N-Event/N-Risk* (%)	Model†	TSH	*P*-Value	Free thyroxine	*P*-Value
Obesity	279/2282 (12·2%)	MV	0·95 (0·79–1·14)	0·58	1·03 (0·92–1·16)	0·61
Hypertension	265/2450 (10·8%)	MV	0·94 (0·80–1·11)	0·48	1·03 (0·92–1·15)	0·59
		MV+BMI	0·94 (0·80–1·11)	0·48	1·01 (0·90–1·13)	0·90
Diabetes	68/2829 (2·4%)	MV	1·11 (0·85–1·47)	0·44	1·03 (0·85–1·26)	0·74
		MV+BMI	1·07 (0·81–1·41)	0·64	0·98 (0·80–1·20)	0·84
Hypercholesterolaemia	372/1736 (21·4%)	MV	1·11 (0·97–1·28)	0·13	0·99 (0·90–1·09)	0·80
		MV+BMI	1·11 (0·97–1·27)	0·13	0·98 (0·89–1·09)	0·76
Low HDL cholesterol	119/2168 (5·5%)	MV	1·04 (0·84–1·29)	0·70	0·98 (0·85–1·14)	0·84
		MV+BMI	1·03 (0·83–1·27)	0·81	0·97 (0·83–1·12)	0·65
Hypertriglyceridaemia	357/2206 (16·2%)	MV	1·07 (0·93–1·23)	0·33	1·06 (0·96–1·16)	0·25
		MV+BMI	1·06 (0·92–1·22)	0·42	1·04 (0·95–1·14)	0·41
Metabolic syndrome	266/2298 (11·6%)	MV	1·14 (0·99–1·31)	0·08	1·02 (0·92–1·13)	0·69
		MV+BMI	1·14 (0·98–1·33)	0·09	0·97 (0·87–1·07)	0·52

Data are shown as odds ratios (95% confidence intervals). The results show the odds of the each risk factor incidence per 1 mIU/l increment in TSH and 1·3 pmol/l (= 0·1 ng/dl) decrement in free thyroxine.

BMI, body mass index; HDL, high-density lipoprotein; MV, multivariable; TSH, thyrotropin.

*The number of new cases of a cardiovascular disease risk factor at follow-up divided by the number of persons at risk for the risk factor.

†MV model was adjusted for age, sex, current smoking, postmenopausal status (women only) and baseline continuous variable (baseline systolic blood pressure and diastolic blood pressure for hypertension, baseline fasting plasma glucose for diabetes, baseline cholesterol for hypercholesterolaemia, baseline high-density lipoprotein cholesterol for low high-density lipoprotein, baseline log triglycerides for hypertriglycerides. MV+BMI model was additionally adjusted for BMI.

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Table 6

Longitudinal associations between baseline TSH and free thyroxine levels with changes in selected cardiovascular disease risk factors and adiposity measures

Parameters	Model†	TSH	*P*-Value	Free thyroxine	*P*-Value
Δ in Cardiovascular risk factors					
Body mass index, kg/m^2	MV	−0·07 (−0·17–0·03)	0·17	0·03 (−0·10–0·04)	0·40
Systolic blood pressure, mmHg	MV	−0·08 (−0·52–0·36)	0·72	0·06 (−0·24–0·37)	0·67
	MV+BMI	−0·14 (−0·58–0·29)	0·52	−0·07 (−0·36–0·23)	0·67
Diastolic blood pressure, mmHg	MV	0·18 (−0·13–0·49)	0·26	0·14 (−0·08–0·35)	0·20
	MV+BMI	0·14 (−0·17–0·45)	0·37	0·05 (−0·16–0·26)	0·63
Fasting plasma glucose, mmol/l	MV	−0·03 (−0·06–0·01)	0·13	−0·003 (−0·03–0·02)	0·80
	MV+BMI	−0·03 (−0·06–0·004)	0·09	−0·01 (−0·03–0·01)	0·38
Total cholesterol, mmol/l	MV	0·004 (−0·026–0·034)	0·80	−0·002 (−0·023–0·018)	0·83
	MV+BMI	0·007 (−0·023–0·037)	0·64	0·004 (−0·017–0·024)	0·72
HDL cholesterol, mmol/l	MV	−0·006 (−0·017–0·005)	0·30	−0·008 (−0·015–0·0003)	0·04
	MV+BMI	−0·004 (−0·015–0·006)	0·42	−0·005 (−0·013–0·002)	0·16
Triglycerides *, mmol/l	MV	0·00 (−0·0001–0·0002)	0·84	0·0001 (0·00–0·0002)	0·24
	MV+BMI	0·00 (−0·0001–0·0002)	0·85	0·00 (−0·0001–0·0002)	0·38
Δ in Adiposity measures					
SAT, cm^3	MV	−77·9 (−128·2–27·6)	0·003	2·63 (−31·2–36·4)	0·88
	MV+Δ in Weight	−34·0 (−68·7–0·6)	0·054	12·54 (−10·6–35·7)	0·29
VAT, cm^3	MV	−15·3 (−61·8–31·2)	0·52	−6·7 (−37·9–24·6)	0·68
	MV+Δ in Weight	18·6 (−15·2–52·3)	0·28	0·9 (−21·7–23·6)	0·94
VAT/SAT Ratio	MV	0·01 (−0·03–0·05)	0·56	−0·01 (−0·03–0·02)	0·66
	MV+Δ in Weight	0·01 (−0·03–0·05)	0·61	−0·01 (−0·03–0·02)	0·64
SAT, HU	MV	0·17 (−0·06–0·40)	0·14	0·00 (−0·15–0·16)	0·95
	MV+Δ in Weight	0·02 (−0·17–0·20)	0·86	−0·03 (−0·16–0·09)	0·61
	MV+Fat Volume	0·20 (−0·03–0·43)	0·09	0·02 (−0·13–0·18)	0·77
VAT, HU	MV	0·16 (−0·17–0·49)	0·35	−0·18 (−0·40–0·05)	0·12
	MV+Δ in Weight	−0·03 (−0·31–0·24)	0·82	−0·22 (−0·40–0·03)	0·02
	MV+Fat Volume	0·14 (−0·16–0·45)	0·36	−0·13 (−0·33–0·07)	0·21

Data are shown as estimated β-coefficients (95% confidence intervals). The results show associations of each risk factor change per 1 mIU/l increment in TSH and 1·3 pmol/l (=0·1 ng/dl) decrement in free thyroxine.

BMI, body mass index; HDL, high-density lipoprotein; HU, Hounsfield units; MV, multivariable; SAT, subcutaneous adipose tissue; TSH, thyrotropin; VAT, visceral adipose tissue.

*Natural logarithmically transformed to enhance the normalization of the skewed distributions.

†MV model was adjusted for age, sex, current smoking and postmenopausal status (women only). MV+BMI model was additionally adjusted for BMI. If participants were on antihypertensive medication at follow-up, 10 mmHg was added to the follow-up systolic blood pressure and 5 mmHg was added to the follow-up diastolic blood pressure. MV+ Δ in weight model was additionally adjusted for weight change. MV+ Fat volume model was additionally adjusted for baseline SAT volume (for SAT attenuation) or baseline VAT volume (for VAT attenuation).