CLINICAL STUDY

Associations of TSH levels within the reference range with future blood pressure and lipid concentrations: 11-year follow-up of the HUNT study

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Abstract

Objective: In cross-sectional studies, TSH levels within the reference range have been positively associated with blood pressure and adverse serum lipid levels. In a prospective study, we aimed to determine whether differences in TSH levels within the reference range are associated with future levels of blood pressure and lipids.

Design: We conducted a prospective population-based study.

Methods: In 9709 women and 4644 men without previous thyroid disease who had a baseline TSH level of 0.45–4.5 mU/l, we studied the associations of baseline TSH levels with blood pressure and lipid levels at follow-up 11 years later.

Results: Higher TSH levels at baseline were associated with higher systolic ($P=0.002$ in women) and diastolic ($P=0.03$ in women) blood pressure, non-HDL cholesterol ($P=0.01$ in men) and triglyceride ($P=0.008$ in men) levels and lower HDL cholesterol levels ($P<0.001$ in women and men) at follow-up, but the associations were very modest and not consistent between the sexes. Among people who remained free of thyroid disease, changes in TSH levels during follow-up were associated with concomitant changes in systolic and diastolic blood pressure, non-HDL cholesterol and triglyceride levels (all $P<0.001$), with similar results being observed for women and men. Thus, blood pressure and lipid levels increased among people with an increase in TSH levels and decreased among people with a decrease in TSH levels compared with people with no change in TSH levels.

Conclusions: High TSH levels within the reference range may be associated with modestly higher future levels of blood pressure and adverse serum lipids. TSH levels may co-vary with blood pressure and lipid levels among people with apparently normal thyroid function.

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Introduction

In cross-sectional studies, serum TSH levels in the upper part of the reference range, suggestive of relatively low thyroid function, have been associated with high levels of blood pressure, non-HDL cholesterol and triglycerides and low levels of HDL cholesterol (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Owing to a lack of prospective studies, it is not known whether low thyroid function within the clinically normal range may have long-term effects on blood pressure and lipid levels. In this prospective population-based study, we therefore examined whether TSH levels within the reference range were associated with blood pressure and serum lipid levels after 11 years of follow-up.

Subjects and methods

Study population

In 1995–1997, all inhabitants of the Nord-Trøndelag county who were aged 20 years or above were invited to participate in the second wave of the HUNT study (HUNT 2). In total, 93 898 people were invited, and 65 215 (69%) participated. The study has been described in detail elsewhere (12, 13). Briefly, the participants completed a comprehensive questionnaire that, among a range of health-related topics, included history of thyroid diseases (14), cardiovascular diseases (myocardial infarction, angina pectoris and stroke) and diabetes, use of antihypertensive medication and

smoking habits. Clinical measurements included blood pressure, height and weight. A non-fasting serum sample was drawn and serum lipid levels were measured in all the participants. The population is considered to be iodine sufficient (15).

Serum TSH levels were measured in subsamples of the population, including all women aged 40 years or above, a 50% random sample of men aged 40 years or above and 5% random samples of women and men aged below 40 years. In total, TSH levels were measured in 33 948 participants from these samples. We excluded people aged 70 years or above ($n=8412$), as few of the older participants attended the follow-up examination. We also excluded people with previously known thyroid disease, cardiovascular disease or diabetes (by self-report, $n=3651$), TSH levels outside the reference range of 0.45–4.5 mU/l ($n=1037$) and missing information on blood pressure, serum lipids, smoking habits or BMI ($n=189$), leaving 20 659 participants eligible for the present follow-up study.

In 2006–2008, all adults residing in the Nord-Trøndelag county were invited to participate in the third wave of the HUNT study (HUNT 3) (13), which included the measurement of TSH, blood pressure and lipid levels in all the participants. Among the 20 659 participants in HUNT 2 who were eligible for the present follow-up study, 18 706 still resided in the county, and 14 778 participated in the follow-up examination in HUNT 3. Among them, we included 14 353 individuals whose blood pressure and lipid measurements at follow-up were available.

Baseline examination

In HUNT 2 (1995–1997), blood pressure was measured three times at 1-min intervals using an automated non-invasive blood pressure monitor based on oscillometry (Dinamap 845XT; Critikon, Tampa, FL, USA). The mean values of the second and third measurements of systolic and diastolic blood pressure were used in the analyses. BMI was calculated as weight in kilograms divided by the squared value of height in meters.

Serum TSH levels were analysed at the Hormone Laboratory, Aker University Hospital (Oslo), using a non-competitive immunofluorometric assay (DELFA hTSH Ultra; sensitivity 0.03 mU/l and total analytical variation < 5%) from Wallac Oy (Turku, Finland). The laboratory's reference range for TSH levels was 0.20–4.5 mU/l, but subsequent analyses indicated that 0.50–3.5 mU/l may be a more appropriate reference range for this population (14). In the present study, the TSH reference range was defined as 0.45–4.5 mU/l, as in a recent study by the Thyroid Studies Collaboration (16).

Serum levels of total cholesterol, HDL cholesterol and triglycerides were analysed at Levanger Hospital, Nord-Trøndelag Hospital Trust, using enzymatic colorimetric methods on a Hitachi 911 Autoanalyzer (Hitachi) with reagents obtained from Boehringer Mannheim

(Mannheim, Germany). As a measure of the cholesterol content of atherogenic lipoproteins, we calculated non-HDL cholesterol levels as the difference between total and HDL cholesterol levels.

Follow-up examination

In HUNT 3 (2006–2008), blood pressure was measured three times using a Dinamap 845XT, and the mean values of the second and third measurements were used in the analyses. In 12% of the participants, blood pressure was only measured two times, and for these individuals, we used the second measurement in the analyses.

The participants were asked if they had ever had hypothyroidism or hyperthyroidism. A non-fasting serum sample was drawn, and serum TSH levels (sensitivity 0.01 mU/l and total analytical variation < 5%) were measured in all the participants. The methods for TSH measurements at baseline and at follow-up were compared for serum samples obtained from 94 individuals, showing that the two methods yielded nearly identical results. If serum TSH levels were higher than 3.00 mU/l, free thyroxine (reference range 9.0–19.0 pmol/l) and TPO antibody (reference range < 5.61 U/ml) levels were also measured. The analyses were performed at Levanger Hospital using chemiluminescent microparticle immunoassays with reagents obtained from Architect iSystem (Abbott Ireland (Longford, Ireland) and Abbott Laboratories).

Serum total cholesterol levels were measured using an enzymatic cholesterol esterase method, HDL cholesterol levels were measured using an accelerator selective detergent method, and triglyceride levels were measured using a glycerol phosphate oxidase method, all with reagents obtained from Abbott. Triglyceride measurements were not performed during the last 4 months of follow-up examinations and were, therefore, available in only 80% of the participants.

Linkage to the Norwegian Prescription Database

The unique 11-digit identity number of every Norwegian citizen enabled linkage to the Norwegian Prescription Database (www.norpd.no), which includes information on virtually all prescriptions to non-institutionalised inhabitants in Norway since January 2004. From this database, we obtained individual information on prescriptions of thyroid hormone (ATC code H03A), thionamides (ATC code H03B) and antihypertensive (ATC codes C02-C03 and C07-C09) and lipid-lowering (ATC code C10) medication.

Statistical analysis

We used a linear regression analysis to study the associations of TSH levels at baseline with blood

pressure and lipid levels at follow-up. Thus, we estimated the mean differences (with 95% CI) in systolic and diastolic blood pressure, non-HDL and HDL cholesterol and triglyceride levels at follow-up per 1 mU/l higher TSH level at baseline. Triglyceride levels were log-transformed due to a non-normal distribution. We adjusted for age and smoking status (never, former and current smokers) at baseline. In additional analyses, we also adjusted for baseline BMI (in quintiles) to assess whether adiposity could either confound or mediate the associations (17, 18, 19). Furthermore, we compared mean blood pressure and lipid levels at follow-up between categories of TSH levels at baseline (0.45–1.4, 1.5–2.4, 2.5–3.4 and 3.5–4.5 mU/l). We used the lowest TSH category (0.45–1.4 mU/l) as the reference and adjusted for age, smoking status and BMI at baseline.

To evaluate whether antihypertensive or lipid-lowering treatment could influence the results, we repeated the analyses after excluding participants taking such medication at follow-up. We also examined whether baseline TSH levels were associated with the use of antihypertensive or lipid-lowering medication at follow-up, as defined by any prescription of such medication between January 2004 and the date of the follow-up examination (between October 2006 and June 2008). We used a logistic regression analysis to adjust for age, smoking status and BMI at baseline.

To evaluate whether loss to follow-up or thyroid treatment could influence the results, we examined whether the cross-sectional associations of TSH levels with blood pressure and lipid levels at baseline (1, 2) differed between the entire baseline study population and participants who attended the follow-up examination without known thyroid disease. Known thyroid disease was defined as having any prescription of thyroid hormone or thionamides between January 2004 and the date of the follow-up examination or having self-reported hyperthyroidism at follow-up. We used a linear regression analysis to adjust for age, smoking status and BMI at baseline.

Co-variation of TSH levels with blood pressure and lipid levels could explain why TSH has been associated with blood pressure and lipid levels in cross-sectional studies. Among people who remained free of thyroid disease, we therefore examined whether the change in TSH levels was associated with changes in blood pressure and lipid levels during follow-up. First, we used a linear regression analysis to estimate the mean change in blood pressure and lipid levels per 1 mU/l increase in TSH levels during follow-up. Second, we categorised the participants by the change in TSH levels during follow-up (TSH increase >0.50 mU/l, TSH decrease >0.50 mU/l or TSH change $\leq$ 0.50 mU/l) and compared mean changes in blood pressure and lipid levels between the categories, using people with no change in TSH levels (TSH change $\leq$ 0.50 mU/l) as the reference. We excluded participants with known thyroid

disease or TSH levels outside the reference range of 0.45–4.50 mU/l at follow-up, and we adjusted for age and smoking status at baseline and the baseline value of blood pressure or lipid variable under study. In additional analyses, we adjusted for BMI at baseline and weight change (in quintiles) during follow-up (19) to assess whether adiposity could either confound or mediate the associations. As some people with TSH levels in the upper part of the reference range may have early-stage hypothyroidism (20), we also examined whether the associations changed after the exclusion of participants with TSH levels >3.00 mU/l at follow-up combined with free thyroxine levels <9.0 pmol/l or TPO antibody levels $\geq$ 5.61 U/ml. Furthermore, we repeated the analyses after excluding participants taking antihypertensive or lipid-lowering medication at follow-up to evaluate whether such treatment could influence the results. To examine whether the adjustment for baseline blood pressure or lipid levels could have inflated the estimates, we repeated the analyses without such an adjustment.

We analysed women and men separately. In the analyses of blood pressure, we excluded participants who reported current or previous use of antihypertensive medication at baseline (by self-report). All data analyses were conducted using Stata version 12.1 for Windows (Stata Corporation, College Station, TX, USA).

The study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate, and all the participants gave their informed consent. The HUNT study is a collaborative effort of the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority and the Norwegian Institute of Public Health.

Results

The characteristics of the participants are given in Table 1. Median time between the baseline and follow-up examinations was 11.1 years (range 9.4–12.8 years).

Associations of TSH levels at baseline with blood pressure and lipid levels at follow-up

In women, there was a modest positive association of TSH levels at baseline with blood pressure at follow-up, but not in men (Table 2). Thus, a 1 mU/l higher TSH level among women at baseline was associated with 0.8 mmHg higher systolic blood pressure ($P=0.002$) and 0.3 mmHg higher diastolic blood pressure ($P=0.03$) at follow-up. In men, a 1 mU/l higher baseline TSH level was associated with a 0.05 mmol/l higher non-HDL cholesterol level at follow-up ($P=0.01$), but there was no association of TSH levels at baseline with non-HDL cholesterol levels at follow-up in women. However, a 1 mU/l higher baseline TSH level

Table 1 Characteristics^a, by sex, displayed separately for people who were included in the analyses and people without follow-up information.

	Women		Men	
	Included in the analyses (n=9709)	No follow-up information (n=3970)	Included in the analyses (n=4644)	No follow-up information (n=2336)
At baseline				
TSH (mU/l; median (IQR))	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.5 (1.1–2.0)	1.5 (1.1–2.0)
Age (years; median (IQR))	51 (45–58)	52 (45–62)	51 (45–57)	51 (44–61)
Never/former/current smokers (%)	46.5/23.6/29.9	36.3/19.6/44.1	38.8/34.4/26.8	27.5/29.6/42.9
Systolic blood pressure ^b (mmHg)	132.3 (19.2)	135.9 (21.8)	136.9 (16.4)	140.4 (18.5)
Diastolic blood pressure ^b (mmHg)	78.8 (10.6)	80.4 (11.8)	82.8 (10.2)	84.5 (11.5)
Non-HDL cholesterol (mmol/l)	4.56 (1.23)	4.79 (1.34)	4.80 (1.11)	4.82 (1.14)
HDL cholesterol (mmol/l)	1.55 (0.40)	1.51 (0.42)	1.27 (0.34)	1.25 (0.36)
Triglycerides (mmol/l; median (IQR))	1.30 (0.93–1.85)	1.42 (1.01–2.06)	1.71 (1.21–2.46)	1.78 (1.25–2.58)
BMI (kg/m ²)	26.2 (4.1)	26.7 (4.8)	26.6 (3.2)	26.8 (3.7)
Current or previous use of anti-hypertensive medication (%)	9.9	14.2	8.6	10.8
At follow-up				
TSH (mU/l; median (IQR))	1.46 (1.04–2.01)		1.51 (1.11–2.03)	
Systolic blood pressure ^b (mmHg)	134.0 (19.5)		136.6 (17.7)	
Diastolic blood pressure ^b (mmHg)	72.8 (10.8)		78.9 (10.6)	
Non-HDL cholesterol (mmol/l)	4.48 (1.07)		4.34 (1.05)	
HDL cholesterol (mmol/l)	1.50 (0.37)		1.24 (0.31)	
Triglycerides (mmol/l; median (IQR))	1.4 (1.0–1.9)		1.6 (1.2–2.3)	
BMI (kg/m ²)	27.4 (4.6)		27.6 (3.6)	
Known thyroid disease (%)	4.5		1.7	
Use of antihypertensive medication (%)	35.0		35.8	
Use of lipid-lowering medication (%)	19.8		20.0	

IQR, interquartile range.

^aGiven as mean (s.d.) unless otherwise noted.^bAmong people who did not report current or previous use of antihypertensive medication at baseline.

was associated with a 0.02 mmol/l lower HDL cholesterol level at follow-up in both women and men ($P < 0.001$). In men, a 1 mU/l higher baseline TSH level was associated with 3% higher triglyceride levels at follow-up ($P = 0.008$), but there was no association of baseline TSH levels with triglyceride levels at follow-up in women.

We adjusted for BMI at baseline to assess whether adiposity could either confound or mediate the associations. After adjustment for BMI, the associations of baseline TSH levels with blood pressure and non-HDL cholesterol levels at follow-up were not substantially changed, but the associations of baseline TSH levels with HDL cholesterol and triglyceride levels at follow-up were attenuated by ~40% (Table 2).

We also examined the associations of TSH categories at baseline with blood pressure and lipid levels at follow-up. This categorical analysis showed similar associations as the analysis using TSH as a continuous variable. In addition, the categorical analysis showed a 0.1 mmol/l higher non-HDL cholesterol level at follow-up among women with high baseline TSH levels (3.5–4.5 mU/l) compared with women with low TSH levels (0.45–1.4 mU/l) ($P = 0.04$; Table 3).

To evaluate whether the use of antihypertensive or lipid-lowering medication could influence the results, we repeated the analyses after excluding participants taking such medication at follow-up, but this exclusion

did not substantially change the estimates (data not shown). Furthermore, we examined whether TSH levels at baseline were associated with the use of such medication at follow-up, but found no evidence for any association with the use of either antihypertensive or lipid-lowering medication at follow-up (Table 4).

Cross-sectional associations of TSH levels with blood pressure and lipid levels at baseline

To evaluate whether loss to follow-up or thyroid treatment could influence the results, we compared associations of TSH levels with blood pressure and lipid levels at baseline between the total study population and participants without known thyroid disease who attended the follow-up examination, but found no substantial differences in results between the groups (Table 5).

Associations of the change in TSH levels with changes in blood pressure and lipid levels during follow-up

We also examined whether TSH levels co-varied with blood pressure and lipid levels during follow-up. Among people who remained free of thyroid disease, the change in TSH levels during follow-up was associated with concomitant changes in all blood pressure and lipid

Table 2 Associations of TSH levels at baseline with blood pressure and lipid levels^a at follow-up: mean differences in blood pressure and lipid levels at follow-up per 1 mU/l higher baseline TSH level, by sex.

	Women		Men	
	n	Difference (95% CI), adjusted for age and smoking	n	Difference (95% CI), adjusted for age and smoking
Systolic blood pressure ^b (mmHg)	8730	0.8 (0.3, 1.3)	4240	0.3 (−0.4, 1.1)
Diastolic blood pressure ^b (mmHg)	8730	0.3 (0.0, 0.6)	4240	−0.3 (−0.8, 0.1)
Non-HDL cholesterol (mmol/l)	9709	0.021 (−0.006, 0.049)	4644	0.052 (0.010, 0.094)
HDL cholesterol (mmol/l)	9709	−0.018 (−0.027, −0.008)	4644	−0.024 (−0.037, −0.012)
Triglycerides (%)	7767	1.3 (−0.1, 2.6)	3775	3.1 (0.8, 5.4)
				0.2 (−0.6, 0.9)
				−0.4 (−0.9, 0.0)
				0.055 (0.013, 0.097)
				−0.016 (−0.028, −0.004)
				1.8 (−0.4, 4.0)

^aMeasured in non-fasting serum samples.^bAmong people who did not report current or previous use of antihypertensive medication at baseline.

measures except for HDL cholesterol (Table 6). Thus, a 1 mU/l increase in TSH levels was associated with ~2 mmHg increase in systolic blood pressure, 1–2 mmHg increase in diastolic blood pressure and 0.1 mmol/l increases in non-HDL cholesterol and triglyceride levels, with similar results being observed for women and men (all $P < 0.001$). We adjusted for baseline BMI and weight change during follow-up to assess whether adiposity could either confound or mediate these associations. However, the associations were attenuated by only 10–20% after such an adjustment, except for the co-variation of TSH levels with triglyceride levels in women, which was attenuated by nearly 40% (Table 6). In separate analyses, we adjusted for season of serum sampling, time from the last meal to clinical examination and serum sampling, arm circumference, smoking habits at follow-up and development of cardiovascular disease during follow-up (by self-report), but the estimates remained essentially unchanged after these adjustments (data not shown).

As some people with TSH levels in the upper part of the reference range may have early-stage hypothyroidism, we repeated the analyses after excluding participants with TSH levels higher than 3.00 mU/l at follow-up combined with TPO antibodies or low free thyroxine levels, but this exclusion did not substantially influence the estimates (data not shown). Also, the exclusion of participants taking antihypertensive or lipid-lowering medication at follow-up did not materially change the results (data not shown). To examine whether the adjustment for baseline blood pressure or lipid levels could have inflated the estimates, we repeated the analyses without such an adjustment, but the associations were either similar or stronger without this adjustment (data not shown).

Among people who remained free of thyroid disease, we also compared changes in blood pressure and lipid levels between people with an increase, a decrease or no change in TSH levels during follow-up. In brief, systolic and diastolic blood pressure, non-HDL cholesterol and triglyceride levels increased among people with an increase in TSH levels and decreased among people with a decrease in TSH levels compared with people with no change in TSH levels (Table 7).

Discussion

In this 11-year follow-up study of 14 353 individuals with serum TSH levels within the reference range, higher TSH levels at baseline were associated with higher levels of blood pressure and adverse serum lipids at follow-up, but the associations were modest and not consistent between women and men. These findings suggest that differences in normal thyroid function may be associated with differences in future blood pressure

Table 3 Associations of TSH categories at baseline with blood pressure and lipid levels^a at follow-up, by sex. For each category of baseline TSH, the table shows the mean differences^b (95% CI) in blood pressure and lipid levels at follow-up compared with subjects with baseline TSH in the range 0.45–1.4 mU/l.

	TSH mean (95% CI)			
	Baseline	1.5–2.4 mU/l	2.5–3.4 mU/l	3.5–4.5 mU/l
Systolic blood pressure ^c (mmHg)				
Women	133.5	0.9 (0.0, 1.8)	0.8 (–0.6, 2.1)	1.0 (–1.1, 3.0)
Men	136.2	0.7 (–0.4, 1.8)	0.9 (–0.9, 2.8)	–0.5 (–3.7, 2.8)
Diastolic blood pressure ^c (mmHg)				
Women	72.8	0.0 (–0.5, 0.5)	–0.2 (–0.9, 0.6)	1.1 (0.0, 2.3)
Men	78.8	0.3 (–0.3, 1.0)	–0.4 (–1.5, 0.8)	–2.0 (–3.9, 0.0)
Non-HDL cholesterol (mmol/l)				
Women	4.473	0.009 (–0.038, 0.056)	–0.010 (–0.081, 0.060)	0.118 (0.007, 0.229)
Men	4.307	0.033 (–0.031, 0.098)	0.109 (0.002, 0.215)	0.208 (0.021, 0.396)
HDL cholesterol (mmol/l)				
Women	1.511	–0.017 (–0.033, –0.002)	–0.024 (–0.047, 0.000)	–0.023 (–0.060, 0.014)
Men	1.251	–0.017 (–0.035, 0.002)	–0.031 (–0.061, 0.000)	–0.056 (–0.110, –0.002)
Triglycerides (%)				
Women	1.43 ^d	–0.2 (–2.4, 2.0)	–1.0 (–4.3, 2.4)	4.2 (–1.1, 9.8)
Men	1.61 ^d	1.7 (–1.7, 5.2)	3.9 (–1.7, 9.9)	6.7 (–3.3, 17.6)

^aMeasured in non-fasting serum samples.^bAdjusted for age, smoking status and BMI at baseline.^cAmong participants who did not report current or previous use of antihypertensive medication at baseline.^dGeometric mean.

and lipid levels, but the strength of the associations suggests that the findings may not be clinically relevant.

The strengths of this study include the large sample size and the population-based prospective design with long-term follow-up. Information obtained at the follow-up examination was supplemented with data obtained from the Norwegian Prescription Database, and the information about the use of thyroid, antihypertensive and lipid-lowering medication at follow-up is, therefore, likely to be accurate. A limitation of the study is that follow-up information was lacking for ~30% of the participants who were eligible at baseline. However, the associations of TSH levels with blood pressure and lipid levels at baseline were similar in the total study population and in participants without known thyroid disease who attended the follow-up examination. This observation weakens the possibility that loss to follow-up, or thyroid treatment during follow-up, may have biased the results. Moreover, there was no association of TSH levels at baseline with the use of antihypertensive or lipid-lowering medication at

follow-up, and the exclusion of participants taking such medication did not materially change the estimates. The use of antihypertensive and lipid-lowering medication is, therefore, not likely to have substantially influenced the results. Serum TSH levels measured at a standardised time of day might have been a better marker of thyroid function, because TSH levels tend to be higher in the early morning than later in the day (21). The potential influence of recent food intake on blood pressure and lipid levels does not appear to have biased the results, because the estimates remained essentially unchanged after statistical adjustment for time from the last meal to blood pressure measurement and serum sampling.

Few previous studies have assessed whether differences in TSH levels within the reference range are associated with future blood pressure and lipid levels. However, a study of 10 048 individuals found no association of TSH levels at baseline with the development of hypertension during 5 years of follow-up (7). Also, a 6-year follow-up study of 1032 individuals

Table 4 ORs for the use of antihypertensive or lipid-lowering medication at follow-up per 1 mU/l higher TSH level at baseline, by sex.

	Women				Men			
	Total no.	No. on medication	OR (95% CI), adjusted for age and smoking	OR (95% CI), adjusted for age, smoking and BMI	Total no.	No. on medication	OR (95% CI), adjusted for age and smoking	OR (95% CI), adjusted for age, smoking and BMI
Antihypertensive medication ^a	8730	2509	1.05 (0.99, 1.12)	1.02 (0.96, 1.09)	4240	1287	0.98 (0.89, 1.07)	0.94 (0.85, 1.04)
Lipid-lowering medication	9709	1921	1.03 (0.96, 1.10)	1.01 (0.95, 1.08)	4644	929	0.97 (0.88, 1.08)	0.94 (0.85, 1.05)

OR, odds ratio.

^aAmong people who did not report current or previous use of antihypertensive medication at baseline.

Table 5 Cross-sectional associations of TSH levels with blood pressure and lipid levels^a at baseline: mean differences^b (with 95% CI) in blood pressure and lipid levels per 1 mU/l higher TSH level, by sex, in the total baseline population and among participants without known thyroid disease who attended the follow-up examination.

	Women		Men	
	Total baseline population (n=13 679)	No known thyroid disease at follow-up (n=9269)	Total baseline population (n=6980)	No known thyroid disease at follow-up (n=4563)
Systolic blood pressure ^c (mmHg)	1.2 (0.8, 1.6)	1.6 (1.1, 2.1)	1.5 (0.9, 2.0)	1.5 (0.8, 2.2)
Diastolic blood pressure ^c (mmHg)	0.7 (0.4, 0.9)	0.9 (0.6, 1.2)	1.1 (0.8, 1.5)	0.8 (0.4, 1.2)
Non-HDL cholesterol (mmol/l)	0.046 (0.022, 0.070)	0.042 (0.012, 0.072)	0.083 (0.048, 0.117)	0.098 (0.054, 0.143)
HDL cholesterol (mmol/l)	−0.006 (−0.014, 0.003)	0.000 (−0.010, 0.011)	−0.012 (−0.023, −0.001)	−0.013 (−0.026, 0.001)
Triglycerides (%)	1.6 (0.6, 2.6)	1.5 (0.3, 2.8)	4.3 (2.6, 6.0)	4.9 (2.7, 7.0)

^aMeasured in non-fasting serum samples.^bAdjusted for age, smoking status and BMI at baseline.^cAmong participants who did not report current or previous use of antihypertensive medication at baseline.

found no association of TSH levels with subsequent development of the metabolic syndrome, of which hypertension, high triglyceride levels and low HDL cholesterol levels account for some of the components (22). In contrast, the results of large cross-sectional studies have suggested that TSH levels within the reference range may be positively associated with blood pressure and adverse lipid levels (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Such a discrepancy between cross-sectional and prospective results may occur if TSH levels co-vary with blood pressure and lipid levels. In support of this possibility, we observed that blood pressure and lipid levels increased among people with an increase in TSH levels during follow-up, but decreased among people with a decrease in TSH levels. Similar to these results, an increase in TSH levels was positively associated with an increase in blood pressure, cholesterol and triglyceride levels in a 3-year follow-up study of almost 6000 individuals (23).

Changes in thyroid function during follow-up may underlie this co-variation of TSH levels with blood pressure and lipid levels, because an increase in TSH levels may indicate a decline in thyroid function, and low thyroid function may be accompanied by high blood pressure, cholesterol and triglyceride levels (1, 2, 24, 25). Alternatively, changes in thyroid function, blood pressure and lipid levels may have common causes. Adiposity is one plausible example, because leptin from adipose tissue may stimulate TSH secretion (18), and adiposity is often accompanied by high blood pressure and lipid levels (26, 27). In our study, however, the strength of the co-variation of TSH levels with blood pressure and lipid levels was only moderately attenuated after adjustment for adiposity, as indicated by BMI and weight change.

In some people, an increase in TSH levels within the reference range may indicate early-stage hypothyroidism (20). For two reasons, however, it seems unlikely

Table 6 Mean changes^a in blood pressure and lipid levels^b during follow-up per 1 mU/l increase in TSH levels during follow-up among people who remained free of thyroid disease during follow-up^c, by sex, with and without adjustment for baseline BMI and weight change during follow-up.

	Women			Men		
	n	Change (95% CI), without adjustment for BMI and weight change	Change (95% CI), with adjustment for BMI and weight change	n	Change (95% CI), without adjustment for BMI and weight change	Change (95% CI), with adjustment for BMI and weight change
Systolic blood pressure ^d (mmHg)	7689	2.1 (1.5, 2.7)	1.8 (1.1, 2.4)	3913	2.5 (1.6, 3.3)	2.2 (1.4, 3.1)
Diastolic blood pressure ^d (mmHg)	7689	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)	3913	1.8 (1.3, 2.3)	1.6 (1.1, 2.1)
Non-HDL cholesterol (mmol/l)	8537	0.091 (0.057, 0.124)	0.072 (0.039, 0.106)	4283	0.122 (0.073, 0.171)	0.102 (0.054, 0.151)
HDL cholesterol (mmol/l)	8537	−0.003 (−0.012, 0.006)	0.006 (−0.003, 0.014)	4283	−0.007 (−0.018, 0.004)	−0.001 (−0.011, 0.010)
Triglycerides (mmol/l)	6824	0.081 (0.052, 0.109)	0.050 (0.022, 0.077)	3481	0.137 (0.080, 0.193)	0.108 (0.053, 0.162)

^aAdjusted for age and smoking at baseline and for the baseline value of the blood pressure or lipid variable under study.^bMeasured in non-fasting serum samples.^cDefined as having TSH levels in the range of 0.45–4.50 mU/l and no known thyroid disease at follow-up.^dAmong participants who did not report current or previous use of antihypertensive medication at baseline.

Table 7 Mean changes^a in blood pressure and lipid levels^b during follow-up in people with TSH decrease > 0.50 mU/l^c or TSH increase > 0.50 mU/l^d during follow-up compared with people with TSH change ≤ 0.50 mU/l^e among people who remained free of thyroid disease^f.

	Women		Men	
	Change (95% CI), without adjustment for BMI and weight change	Change (95% CI), with adjustment for BMI and weight change	Change (95% CI), without adjustment for BMI and weight change	Change (95% CI), with adjustment for BMI and weight change
Systolic blood pressure ^g (mmHg)				
TSH decrease	-1.7 (-2.7, -0.7)	-1.5 (-2.5, -0.5)	-1.7 (-3.2, -0.2)	-1.6 (-3.1, -0.2)
TSH increase	1.8 (0.8, 2.9)	1.4 (0.4, 2.5)	1.8 (0.5, 3.1)	1.5 (0.2, 2.8)
Diastolic blood pressure ^g (mmHg)				
TSH decrease	-1.5 (-2.1, -0.9)	-1.4 (-2.0, -0.8)	-1.7 (-2.6, -0.9)	-1.6 (-2.5, -0.8)
TSH increase	0.8 (0.2, 1.4)	0.6 (0.0, 1.2)	1.1 (0.3, 1.9)	0.9 (0.1, 1.6)
Non-HDL cholesterol (mmol/l)				
TSH decrease	-0.123 (-0.178, -0.069)	-0.110 (-0.165, -0.056)	-0.089 (-0.171, -0.007)	-0.072 (-0.153, 0.009)
TSH increase	0.054 (-0.003, 0.111)	0.033 (-0.023, 0.090)	0.115 (0.041, 0.190)	0.103 (0.029, 0.176)
HDL cholesterol (mmol/l)				
TSH decrease	0.001 (-0.013, 0.015)	-0.004 (-0.018, 0.010)	0.006 (-0.012, 0.024)	0.004 (-0.014, 0.021)
TSH increase	-0.016 (-0.030, -0.001)	-0.005 (-0.019, 0.010)	-0.007 (-0.024, 0.009)	0.001 (-0.015, 0.017)
Triglycerides (mmol/l)				
TSH decrease	-0.104 (-0.151, -0.056)	-0.085 (-0.130, -0.039)	-0.080 (-0.174, 0.014)	-0.063 (-0.155, 0.028)
TSH increase	0.070 (0.022, 0.118)	0.033 (-0.013, 0.080)	0.146 (0.062, 0.230)	0.111 (0.029, 0.193)

^aAdjusted for age and smoking at baseline and for the baseline value of the blood pressure or lipid variable under study.^bMeasured in non-fasting serum samples.^cA total of 1516 women and 603 men in the analyses of cholesterol levels, 1352 women and 549 men in the analyses of blood pressure levels, and 1181 women and 482 men in the analysis of triglyceride levels.^dA total of 1378 women and 767 men in the analyses of cholesterol levels, 1226 women and 693 men in the analyses of blood pressure levels, and 1134 women and 635 men in the analysis of triglyceride levels.^eA total of 5643 women and 2913 men in the analyses of cholesterol levels, 5111 women and 2671 men in the analyses of blood pressure levels, and 4509 women and 2364 men in the analysis of triglyceride levels.^fDefined as having TSH levels in the range of 0.45–4.50 mU/l and no known thyroid disease at follow-up.^gAmong participants who did not report current or previous use of antihypertensive medication at baseline.

that the development of hypothyroidism could explain the co-variation of TSH levels with blood pressure and lipid levels that we observed. First, the co-variation was equally strong in women and men, even though hypothyroidism develops more often in women than in men (20). Second, the strength of the co-variation was not attenuated when we excluded participants with TSH levels higher than 3.0 mU/l at follow-up who had biochemical signs of hypothyroidism (TPO antibodies or low free thyroxine levels).

In summary, the results of this large prospective study suggest that high TSH levels within the reference range may be associated with higher future levels of blood pressure and adverse serum lipids, but the associations are modest and not consistent between the sexes. Among people with apparently normal thyroid function, changes in TSH levels are associated with concomitant changes in blood pressure, non-HDL cholesterol and triglyceride levels, suggesting a co-variation between these factors that warrants further study.

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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References

- 1 Åsvold BO, Bjørø T, Nilsen TI & Vatten LJ. Association between blood pressure and serum thyroid-stimulating hormone concentration within the reference range: a population-based study. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 841–845. (doi:10.1210/jc.2006-2208)
- 2 Åsvold BO, Vatten LJ, Nilsen TI & Bjørø T. The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT study. *European Journal of Endocrinology* 2007 **156** 181–186. (doi:10.1530/eje.1.02333)
- 3 Boekholdt SM, Titan SM, Wiersinga WM, Chatterjee K, Basart DC, Luben R, Wareham NJ & Khaw KT. Initial thyroid status and cardiovascular risk factors: the EPIC-Norfolk prospective population study. *Clinical Endocrinology* 2010 **72** 404–410. (doi:10.1111/j.1365-2265.2009.03640.x)
- 4 Garduno-Garcia Jde J, Alvirde-Garcia U, Lopez-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM *et al.* TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *European Journal of Endocrinology* 2010 **163** 273–278. (doi:10.1530/EJE-10-0312)
- 5 Iqbal A, Figenschau Y & Jorde R. Blood pressure in relation to serum thyrotropin: the Tromsø study. *Journal of Human Hypertension* 2006 **20** 932–936. (doi:10.1038/sj.jhh.1002091)
- 6 Ittermann T, Thamm M, Wallaschofski H, Rettig R & Volzke H. Serum thyroid-stimulating hormone levels are associated with blood pressure in children and adolescents. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 828–834. (doi:10.1210/jc.2011-2768)
- 7 Ittermann T, Tiller D, Meisinger C, Agger C, Nauck M, Rettig R, Hofman A, Franco O, Joergensen T, Linneberg A *et al.* High serum TSH levels are associated with current but not with incident hypertension. *Thyroid* 2013 in press. (doi:10.1089/thy.2012.0626)
- 8 Lee YK, Kim JE, Oh HJ, Park KS, Kim SK, Park SW, Kim MJ & Cho YW. Serum TSH level in healthy Koreans and the association of TSH with serum lipid concentration and metabolic syndrome. *Korean Journal of Internal Medicine* 2011 **26** 432–439. (doi:10.3904/kjim.2011.26.4.432)
- 9 Volzke H, Alte D, Dorr M, Wallaschofski H, John U, Felix SB & Rettig R. The association between subclinical hyperthyroidism and blood pressure in a population-based study. *Journal of Hypertension* 2006 **24** 1947–1953. (doi:10.1097/01.jhh.0000244942.57417.8e)
- 10 Wang CY, Chang TC & Chen MF. Associations between subclinical thyroid disease and metabolic syndrome. *Endocrine Journal* 2012 **59** 911–917. (doi:10.1507/endocrj.EJ12-0076)
- 11 Wang F, Tan Y, Wang C, Zhang X, Zhao Y, Song X, Zhang B, Guan Q, Xu J, Zhang J *et al.* Thyroid-stimulating hormone levels within the reference range are associated with serum lipid profiles independent of thyroid hormones. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2724–2731. (doi:10.1210/jc.2012-1133)
- 12 Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, Vatten LJ & Lund-Larsen PG. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods, and participation. *Norsk Epidemiologi* 2003 **13** 19–32.
- 13 Krokstad S, Langhammer A, Hveem K, Holmen T, Midthjell K, Stene T, Bratberg G, Heggland J & Holmen J. Cohort profile: the HUNT study, Norway. *International Journal of Epidemiology* 2013 in press. (doi:10.1093/ije/dys095)
- 14 Bjørø T, Holmen J, Krüger Ø, Midthjell K, Hunstad K, Schreiner T, Sandnes L & Brochmann H. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trøndelag (HUNT). *European Journal of Endocrinology* 2000 **143** 639–647. (doi:10.1530/eje.0.1430639)
- 15 Kapelrud H, Frey H & Theodorsen L. Excretion of iodine in the urine. A study from 6 different Norwegian districts in 1985. *Tidsskrift for Den Norske Lægeforening* 1987 **107** 1320–1321, 1317.
- 16 Collet TH, Gussekloo J, Bauer DC, den Elzen WP, Cappola AR, Balmer P, Iervasi G, Åsvold BO, Sgarbi JA, Volzke H *et al.* Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Archives of Internal Medicine* 2012 **172** 799–809. (doi:10.1001/archinternmed.2012.402)
- 17 Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L & Jorgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4019–4024. (doi:10.1210/jc.2004-2225)
- 18 Reinehr T. Obesity and thyroid function. *Molecular and Cellular Endocrinology* 2010 **316** 165–171. (doi:10.1016/j.mce.2009.06.005)
- 19 Svare A, Nilsen TI, Bjørø T, Åsvold BO & Langhammer A. Serum TSH related to measures of body mass: longitudinal data from the HUNT study, Norway. *Clinical Endocrinology* 2011 **74** 769–775. (doi:10.1111/j.1365-2265.2011.04009.x)
- 20 Åsvold BO, Vatten LJ, Midthjell K & Bjørø T. Serum TSH within the reference range as a predictor of future hypothyroidism and hyperthyroidism: 11-year follow-up of the HUNT study in Norway. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 93–99. (doi:10.1210/jc.2011-1724)

- 21 Surks MI, Goswami G & Daniels GH. The thyrotropin reference range should remain unchanged. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 5489–5496. (doi:10.1210/jc.2005-0170)
- 22 Waring AC, Rodondi N, Harrison S, Kanaya AM, Simonsick EM, Miljkovic I, Satterfield S, Newman AB & Bauer DC. Thyroid function and prevalent and incident metabolic syndrome in older adults: the Health, Ageing and Body Composition Study. *Clinical Endocrinology* 2012 **76** 911–918. (doi:10.1111/j.1365-2265.2011.04328.x)
- 23 Park SB, Choi HC & Joo NS. The relation of thyroid function to components of the metabolic syndrome in Korean men and women. *Journal of Korean Medical Science* 2011 **26** 540–545. (doi:10.3346/jkms.2011.26.4.540)
- 24 Canaris GJ, Manowitz NR, Mayor G & Ridgway EC. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine* 2000 **160** 526–534. (doi:10.1001/archinte.160.4.526)
- 25 Cappola AR & Ladenson PW. Hypothyroidism and atherosclerosis. *Journal of Clinical Endocrinology and Metabolism* 2003 **88** 2438–2444. (doi:10.1210/jc.2003-030398)
- 26 Droyvold WB, Midthjell K, Nilsen TI & Holmen J. Change in body mass index and its impact on blood pressure: a prospective population study. *International Journal of Obesity* 2005 **29** 650–655. (doi:10.1038/sj.ijo.0802944)
- 27 Lavie CJ, Milani RV & Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *Journal of the American College of Cardiology* 2009 **53** 1925–1932. (doi:10.1016/j.jacc.2008.12.068)

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