Serum TSH within the Reference Range as a Predictor of Future Hypothyroidism and Hyperthyroidism: 11-Year Follow-Up of the HUNT Study in Norway

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Context: Serum TSH in the upper part of the reference range may sometimes be a response to autoimmune thyroiditis in early stage and may therefore predict future hypothyroidism. Conversely, relatively low serum TSH could predict future hyperthyroidism.

Objective: The objective of the study was to assess TSH within the reference range and subsequent risk of hypothyroidism and hyperthyroidism.

Design and Setting: This was a prospective population-based study with linkage to the Norwegian Prescription Database.

Subjects: A total of 10,083 women and 5,023 men without previous thyroid disease who had a baseline TSH of 0.20–4.5 mU/liter and who participated at a follow-up examination 11 yr later.

Main Outcome Measures: Predicted probabilities of developing hypothyroidism or hyperthyroidism during follow-up, by categories of baseline TSH, were estimated.

Results: During 11 yr of follow-up, 3.5% of women and 1.3% of men developed hypothyroidism, and 1.1% of women and 0.6% of men developed hyperthyroidism. In both sexes, the baseline TSH was positively associated with the risk of subsequent hypothyroidism. The risk increased gradually from TSH of 0.50–1.4 mU/liter [women, 1.1%, 95% confidence interval (CI) 0.8–1.4; men, 0.3%, 95% CI 0.1–0.6] to a TSH of 4.0–4.5 mU/liter (women, 31.5%, 95% CI 24.6–39.3; men, 14.7%, 95% CI 7.7–26.2). The risk of hyperthyroidism was higher in women with a baseline TSH of 0.20–0.49 mU/liter (3.9%, 95% CI 1.8–8.4) than in women with a TSH of 0.50–0.99 mU/liter (1.4%, 95% CI 0.9–2.1) or higher (~1.0%).

Conclusion: TSH within the reference range is positively and strongly associated with the risk of future hypothyroidism. TSH at the lower limit of the reference range may be associated with an increased risk of hyperthyroidism. **(*J Clin Endocrinol Metab* 97: 93–99, 2012)**

Autoimmune thyroiditis is the most common cause of hypothyroidism in iodine-sufficient populations. The autoimmune inflammation may be present for years before clinical hypothyroidism may eventually develop (1). As the autoimmune inflammation gradually destroys the thyroid tissue and leads to a decrease in circulating thyroid hormone levels, pituitary secretion of TSH increases. In the early stage of the process, TSH levels may still be within the reference range for the population (1–3), and therefore, high TSH within the reference range may

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Abbreviations: BMI, Body mass index; CI, confidence interval; HUNT, Nord-Trøndelag Health Study; TPO, thyroid peroxidase.

predict increased risk of future hypothyroidism (4–10). Conversely, in the early stage of a process that culminates in hyperthyroidism, TSH could be slightly reduced, and therefore, low TSH within the reference range could predict future hyperthyroidism (6).

Consistent with these suggestions, several studies have shown that TSH in the upper part of the reference range is associated with increased risk of future hypothyroidism (4–10), especially in people with thyroid autoantibodies that indicate autoimmune thyroiditis (7, 8). Conversely, TSH in the lower part of the reference range has been associated with increased risk of reduced TSH levels that are suggestive of hyperthyroidism (6). However, few population-based studies have addressed this topic. In a Norwegian cohort of 15,106 participants who were followed up for 11 yr, we therefore assessed the risk of future hypothyroidism and hyperthyroidism in relation to baseline serum concentrations of TSH.

Subjects and Methods

Study population

In 1995–1997, all inhabitants 20 yr old or older in Nord-Trøndelag County were invited to participate in the second wave of the Nord-Trøndelag Health Study (HUNT). In total, 93,898 people were invited, and 65,215 (69%) participated. The study has been described in detail elsewhere (11, 12). Briefly, the participants completed a comprehensive questionnaire that among a range of health-related topics included history of thyroid diseases. Clinical measurements included height and weight, and a serum sample was drawn from each participant.

Serum TSH was measured in subsamples of the population, including all women 40 yr of age or older, in a 50% random sample of men 40 yr of age or older and in a 5% random sample of women and men below 40 yr of age. In total, TSH was measured in 33,948 participants from these samples. If TSH was above 4.0 mU/liter, serum free T_4 and thyroid peroxidase (TPO) antibodies were also measured. Among 33,948 participants with TSH measurement, we excluded people with current or previous thyroid disease (by self-report, n = 2,880), TSH outside the laboratory's reference range of 0.20–4.5 mU/liter (n = 1,331), free T_4 below the laboratory's lower reference limit of 8.0 pmol/liter (n = 7), and missing information on self-reported thyroid disease (n = 727). Among older participants, few attended the follow-up examination, and we therefore excluded participants aged 70 yr or older at baseline (n = 6,797), leaving 22,206 participants eligible for the present follow-up study.

In 2006–2008, all adults residing in Nord-Trøndelag County were invited to participate in the third wave of the HUNT Study, which included measurement of serum TSH in all participants. Among 22,206 participants with TSH measurement from the baseline examination at second wave of the HUNT Study, 19,845 still resided in the county, and a total of 15,532 participated in the follow-up examination at third wave of the HUNT Study. Among them, we included 15,106 individuals whose TSH measurements at follow-up were available.

Thyroid function

At baseline, serum concentrations of TSH and free T_4 were analyzed at the Hormone Laboratory, Aker University Hospital (Oslo, Norway) using DELFIA hTSH Ultra (total analytical variation, < 5%; sensitivity, 0.03 mU/liter) and DELFIA FT4 (total analytical variation, <7%), respectively (both from Wallac Oy, Turku, Finland). TPO antibodies were measured with a luminoimmunoassay from B.R.A.H.M.S. Diagnostica GmbH (Berlin, Germany). For TSH, the laboratory's reference range was 0.2–4.5 mU/liter, but subsequent analyses indicated that 0.5–3.5 mU/liter is a more appropriate reference range for this population (11). The laboratory's reference ranges were 8–20 pmol/liter for free T_4 and less than 200 U/ml for TPO antibodies.

At follow-up, serum concentrations of TSH were measured in all participants, and free T_4 was measured if TSH was below 0.10 mU/liter or above 3.00 mU/liter. Serum TSH (total analytical variation, < 5%; sensitivity, 0.01 mU/liter) and free T_4 (total analytical variation, < 5%; reference range, 9.0–19.0 pmol/liter) were analyzed at Levanger Hospital, Nord-Trøndelag Hospital Trust, using chemiluminescent microparticle immunoassays on an Architect ci8200 from Abbott, with reagents from Architect iSystem (Abbott Ireland, Longford, Ireland; and Abbott Laboratories, Abbott Park, IL). The methods for TSH measurements at baseline and at follow-up were compared in blood samples from 94 individuals, showing that the two methods yielded nearly identical results.

In a questionnaire at the follow-up examination, the participants were asked if they had ever had hypothyroidism or hyperthyroidism, and 88% of the participants returned this questionnaire. 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 noninstitutionalized inhabitants in Norway since January 2004. From that database, we obtained individual information on prescriptions of levothyroxine and thionamides.

Hypothyroidism at follow-up was defined as prescription of levothyroxine between January 2004 and the date of the follow-up examination (between October 2006 and June 2008) or biochemical hypothyroidism at the follow-up examination, as indicated by TSH above 4.50 mU/liter combined with free T_4 below 9.0 pmol/liter. Prescription of levothyroxine was considered as evidence of hypothyroidism only if levothyroxine was dispensed on at least three occasions or if levothyroxine was dispensed during the last 6 months before the follow-up examination. Prescription of levothyroxine or biochemical hypothyroidism at follow-up was not considered as evidence of hypothyroidism in participants with hyperthyroidism during the follow-up period. Hyperthyroidism during the follow-up period was defined as any prescription of thionamides registered in the prescription database between January 2004 and the follow-up examination or self-report of hyperthyroidism at follow-up or TSH below 0.10 mU/liter combined with free T_4 above 19.0 pmol/liter at follow-up in people without a history of hypothyroidism.

Statistical analysis

We categorized the participants according to serum TSH at baseline (0.20–0.49, 0.50–1.4, 1.5–1.9, 2.0–2.4, 2.5–2.9, 3.0–3.4, 3.5–3.9, and 4.0–4.5 mU/liter). We used logistic regression analysis to estimate odds ratios [with 95% confidence intervals

(CI)] of hypothyroidism at follow-up by categories of baseline TSH, separately for women and men. As reference category, we used TSH of 0.50–1.4 mU/liter, which is considered to be the lowest part of the reference range in this population (11). From the logistic regression analysis, we also estimated predicted probabilities (with 95% CI) as a measure of the absolute risk of developing hypothyroidism during the follow-up period. We assessed trends across the TSH reference range by P_{trend}, using TSH as a continuous variable.

In people with a baseline TSH above 4.0 mU/liter, baseline levels of TPO antibodies were measured. In this subgroup, we could therefore assess the risk of hypothyroidism separately for people with (44 women and 14 men) and without (64 women and 36 men) TPO antibodies, using TPO antibody concentration of 200 U/ml as cutoff point.

The prevalence of hypothyroidism increases with age (11), adiposity may increase serum TSH (13), and smoking may increase the risk of hyperthyroidism (14) but reduce the risk of autoimmune hypothyroidism (15). We therefore assessed the association of baseline TSH with the risk of hypothyroidism by age (<50 or ≥ 50 yr of age), smoking habits (current smokers or not), and body mass index (BMI; weight in kilograms divided by the squared value of height in meters; <25.0 or ≥ 25.0 kg/m^2) at baseline. We used likelihood-ratio tests (with *P* values for interaction) to examine whether the association of baseline TSH with future hypothyroidism differed by categories of age, smoking, and BMI.

In an additional analysis of the association of baseline TSH with the risk of future hypothyroidism, we extended the definition of hypothyroidism and included people with subclinical hypothyroidism at follow-up, defined as TSH above 4.50 mU/liter combined with free T_4 of 9.0 pmol/liter or higher in people without a history of hypothyroidism or hyperthyroidism.

Among the 88% who returned the follow-up questionnaire with items on thyroid diseases (8892 women and 4357 men), we estimated the association of baseline TSH with the risk of hyperthyroidism during the follow-up period. We particularly wanted to assess the risk of hyperthyroidism related to TSH in the lower part of the reference range and therefore used other categories of baseline TSH (0.20–0.49, 0.50–0.99, 1.00–1.4, 1.5–1.9, and 2.0–4.5) than in the analyses of hypothyroidism.

All results were adjusted for age. Stata version 10.1 for Windows (Stata Corp., College Station, TX) was used for the statistical analyses.

The study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate, and all participants gave their informed consent. The HUNT Study is a collaborative effort of HUNT Research Center (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

Baseline characteristics are shown in Table 1. Serum TSH, age, and BMI at baseline did not differ substantially between those who participated and those who did not participate at the follow-up examination, but smokers were less likely to attend the follow-up examination.

Median follow-up was 11.1 yr (range 9.4–12.8 yr). Three hundred fifty-five (3.5%) of 10,083 women and 63 (1.3%) of 5,023 men developed hypothyroidism during the follow-up period, as indicated by prescription of levothyroxine (349 women and 63 men) or hypothyroidism detected at the follow-up examination (six women and no men). Among the 88% who returned the questionnaire with items on thyroid diseases, 96 women (1.1%) and 24 men (0.6%) developed hyperthyroidism during the follow-up period, as indicated by prescription of thionamides (11 women and two men), by self-report (79 women and 20 men), or by hyperthyroidism detected at the follow-up examination (six women and two men).

In women, the risk of future hypothyroidism increased gradually with higher baseline levels of TSH ($P_{trend} < 0.001$; Table 2 and Fig. 1). Compared with women with a baseline TSH of 0.50–1.4 mU/liter (1.1%, 95% CI 0.8–1.4), the risk of hypothyroidism at follow-up was approximately 2-fold higher (2.3%, 95% CI 1.8–3.0) in women with a TSH of 1.5–1.9 mU/liter, 8-fold higher (8.2%, 95% CI 6.4–10.3) in women with TSH of 2.5–2.9 mU/liter, and

TABLE 1. Baseline characteristics for 22,206 participants with baseline TSH measurements, by sex, displayed separately for people with (n = 15,106) and without (n = 7,100) information on thyroid function at follow-up

Characteristic	Information on thyroid function at follow-up	No information on thyroid function at follow-up
Women		
Participants, n	10,083	4,352
TSH (mU/liter), median (IQR)	1.5 (1.1–2.1)	1.5 (1.1–2.1)
Age (yr), median (IQR)	51 (45–58)	53 (46–63)
Never/former/current smokers (%)	46.6/23.7/29.8	36.3/20.3/43.4
BMI (kg/m^2), mean (SD)	26.3 (4.2)	26.9 (4.9)
Men		
Participants, n	5,023	2,748
TSH (mU/liter), median (IQR)	1.5 (1.1–2.0)	1.5 (1.1–2.0)
Age (yr), median (IQR)	51 (45–58)	52 (45–63)
Never/former/current smokers (%)	37.6/36.0/26.4	26.1/31.6/42.3
BMI (kg/m^2), mean (SD)	26.7 (3.2)	27.0 (3.8)

TABLE 2. Age-adjusted odds ratios and predicted probabilities (with 95% CI) of hypothyroidism at follow-up, by baseline TSH, in women and men[a]

TSH, mU/liter	Total, n	Hypothyroid, n	Odds ratio	(95% CI)	Probability (%)	(95% CI)
Women						
0.20–0.49	177	1	—		—	
0.50–1.4	4531	48	1.0	(Reference)	1.1	(0.8–1.4)
1.5–1.9	2418	57	2.3	(1.5–3.3)	2.3	(1.8–3.0)
2.0–2.4	1396	49	3.4	(2.3–5.1)	3.5	(2.7–4.6)
2.5–2.9	759	62	8.4	(5.7–12.3)	8.2	(6.4–10.3)
3.0–3.4	395	49	13.3	(8.8–20.1)	12.3	(9.5–16.0)
3.5–3.9	254	41	18.5	(11.9–28.7)	16.4	(12.3–21.5)
4.0–4.5	153	48	43.4	(27.8–67.7)	31.5	(24.6–39.3)
Men						
0.20–0.49	73	0	—		—	
0.50–1.4	2343	7	1.0	(Reference)	0.3	(0.1–0.6)
1.5–1.9	1303	10	2.6	(1.0–6.8)	0.8	(0.4–1.4)
2.0–2.4	682	10	4.9	(1.9–13.0)	1.4	(0.8–2.7)
2.5–2.9	328	6	6.1	(2.0–18.3)	1.8	(0.8–3.9)
3.0–3.4	157	13	29.2	(11.4–74.4)	8.0	(4.7–13.4)
3.5–3.9	79	8	36.3	(12.8–102.9)	9.7	(4.9–18.4)
4.0–4.5	58	9	57.9	(20.6–162.4)	14.7	(7.7–26.2)

[a] Hypothyroidism defined as prescription of levothyroxine, or TSH above 4.50 mU/liter combined with free T_4 below 9.0 pmol/liter, in people without a history of hyperthyroidism.

30-fold higher (31.5%, 95% CI 24.6–39.3) in women with TSH of 4.0–4.5 mU/liter.

In men, there was a similar association of baseline TSH with future hypothyroidism ($P_{trend} < 0.001$), but at any given level of TSH, the risk of hypothyroidism was lower in men than in women (Table 2 and Fig. 1). Thus, the risk of hypothyroidism at follow-up ranged from 0.3% (95% CI 0.1–0.6) in men with TSH of 0.50–1.4 mU/liter to 14.7% (95% CI 7.7–26.2) in men with a TSH of 4.0–4.5 mU/liter.

In people with a baseline TSH of 4.1–4.5 mU/liter, baseline levels of TPO antibodies were measured, and we assessed whether this variable could improve the prediction of hypothyroidism at follow-up. Thus, the risk of hypothyroidism was higher in people with TPO antibodies (women, 43.3%, 95% CI 29.5–58.1; men, 21.5%, 95% CI 7.1–49.6) compared with people without TPO antibodies at baseline (women, 20.3%, 95% CI 12.1–31.9; men, 12.9%, 95% CI 5.4–27.8).

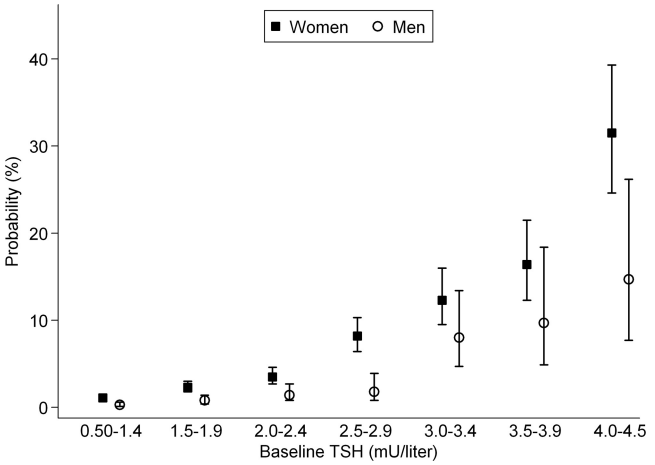

FIG. 1. Age-adjusted predicted probabilities (%, with 95% CI) of hypothyroidism at follow-up, by baseline TSH (mU/liter), in women and men. Hypothyroidism was defined as prescription of levothyroxine, or TSH above 4.50 mU/liter combined with free T_4 below 9.0 pmol/liter, in people without a history of hyperthyroidism.

In women, the association of baseline TSH with hypothyroidism at follow-up did not substantially differ by age ($P_{interaction} = 0.99$), smoking ($P_{interaction} = 0.08$), or BMI ($P_{interaction} = 0.07$) at baseline (Table 3). The low number of hypothyroid men precluded similar stratified analyses in men.

At follow-up, participants with subclinical hypothyroidism (115 women and 39 men) tended to have relatively low free T_4 levels (median, 11.4 pmol/liter in women and 11.8 pmol/liter in men). In an additional analysis, we extended the definition of hypothyroidism at follow-up to include subclinical hypothyroidism. Using the extended definition, the probability of hypothyroidism at follow-up related to baseline TSH above 2 mU/liter was moderately higher than in the original analysis (Table 4).

The risk of hyperthyroidism was higher in women with baseline TSH of 0.20–0.49 mU/liter (3.9%, 95% CI 1.8–8.4) than in women with TSH of 0.50–0.99 mU/liter (1.4%, 95% CI 0.9–2.1) or higher (~1.0%) ($P_{trend} = 0.05$). The low number of hyperthyroid men precluded precise estimates of the association of baseline TSH with the risk of hyperthyroidism in men (Table 5).

Discussion

In this longitudinal population-based study, serum TSH within the reference range was positively and strongly as-

TABLE 3. Age-adjusted predicted probabilities (with 95% CI) of hypothyroidism[a] at follow-up according to categories of baseline TSH in women, by age, smoking, and BMI at baseline[b]

TSH (mU/liter)	Hypothyroid, n/total	Probability (%)	(95% CI)	Hypothyroid, n/total	Probability (%)	(95% CI)
		20–49 yr of age			50–69 yr of age	
0.20–0.49	0/74	—		1/103	—	
0.50–1.4	28/2160	1.3	(0.9–1.9)	20/2371	0.8	(0.5–1.3)
1.5–1.9	25/1020	2.4	(1.7–3.6)	32/1398	2.3	(1.6–3.2)
2.0–2.4	23/575	4.0	(2.7–5.9)	26/821	3.2	(2.2–4.6)
2.5–2.9	24/305	7.8	(5.3–11.4)	38/454	8.3	(6.1–11.3)
3.0–3.4	23/164	13.9	(9.4–20.1)	26/231	11.2	(7.7–15.9)
3.5–3.9	13/83	15.7	(9.3–25.1)	28/171	16.4	(11.6–22.7)
4.0–4.5	21/56	37.3	(25.7–50.6)	27/97	27.8	(19.8–37.5)
		Nonsmokers			Smokers	
0.20–0.49	1/104	—		0/72	—	
0.50–1.4	31/2812	1.1	(0.8–1.6)	17/1704	1.0	(0.6–1.6)
1.5–1.9	32/1758	1.8	(1.3–2.6)	25/654	3.8	(2.5–5.5)
2.0–2.4	34/1113	3.0	(2.2–4.2)	15/279	5.3	(3.2–8.7)
2.5–2.9	41/609	6.7	(5.0–9.0)	21/146	14.5	(9.6–21.2)
3.0–3.4	33/322	10.2	(7.4–14.0)	16/73	21.8	(13.7–32.7)
3.5–3.9	34/222	15.4	(11.2–20.8)	7/32	21.7	(10.7–39.2)
4.0–4.5	35/121	28.9	(21.5–37.7)	13/31	40.5	(24.8–58.3)
		BMI <25.0 kg/m^2			BMI ≥ 25.0 kg/m^2	
0.20–0.49	0/77	—		1/100	—	
0.50–1.4	21/2067	1.0	(0.6–1.5)	27/2456	1.1	(0.7–1.6)
1.5–1.9	17/967	1.7	(1.1–2.7)	40/1446	2.7	(2.0–3.7)
2.0–2.4	22/546	3.9	(2.5–5.8)	27/849	3.2	(2.2–4.6)
2.5–2.9	24/263	8.7	(5.8–12.7)	38/495	7.7	(5.7–10.5)
3.0–3.4	19/148	12.3	(8.0–18.6)	30/247	12.3	(8.7–17.0)
3.5–3.9	15/82	18.2	(11.2–28.1)	26/172	15.3	(10.6–21.5)
4.0–4.5	19/52	35.4	(23.6–49.3)	29/101	29.2	(21.1–38.9)

[a] Defined as prescription of levothyroxine, or TSH above 4.50 mU/liter combined with free T_4 below 9.0 pmol/liter, in people without a history of hyperthyroidism.

[b] Due to missing information on smoking or BMI, 31 and 15 women were excluded from the analyses by smoking and BMI, respectively.

sociated with the risk of future hypothyroidism. The risk increased gradually from TSH of 0.50–1.4 mU/liter to TSH of 4.0–4.5 mU/liter. The association of TSH with future hypothyroidism was essentially similar in women and men, but at any given TSH level, the absolute risk of hypothyroidism was higher in women than in men. The risk of hyperthyroidism was higher in women with TSH of 0.20–0.49 mU/liter than in women with higher TSH levels.

The Norwegian population is considered to be iodine sufficient (16), with autoimmune thyroiditis being the most common cause of hypothyroidism. People with autoimmune thyroiditis, as indicated by thyroid autoantibodies in serum, often have serum TSH in the upper part of the reference range (3, 11, 17). These relatively high TSH levels are probably a response to slightly reduced thyroid hormone levels in the early stage of autoimmune thyroid destruction. Thus, in some individuals, TSH in the upper part of the reference range may be a marker for mild hypothyroid disease (1, 3).

The results of previous population-based studies have also indicated an increased risk of future hypothyroidism in people with high serum TSH within the reference range, in particular if TSH is above approximately 2.0 mU/liter (6, 7) or 2.5 mU/liter (8). Conversely, TSH levels below 1.0 mU/liter have been associated with an increased risk of subnormal TSH levels (6), suggestive of hyperthyroidism, although studies of individuals with TSH of 0.1–0.4 mU/liter indicate that the absolute risk of overt hyperthyroidism is low (18, 19). Compared with previous studies, our study population was larger and yielded higher precision in the risk estimates across the TSH reference range in both women and men.

The risk of hypothyroidism is particularly high among people with high TSH combined with thyroid autoantibodies (7, 8), and it is likely that information on baseline serum levels of TPO antibodies and free T_4 would have enabled a better prediction of future hypothyroidism. Also, serum TSH may be transiently reduced or elevated (20, 21), and repeated measurements of TSH at baseline might have yielded better prediction of future thyroid dysfunction.

Hypothyroidism at follow-up was indicated by the physicians' prescription of levothyroxine, and we do not know the participants' thyroid function at the initiation of levothyroxine treatment. Therefore, the proportion of participants with subclinical rather than overt hypothyroidism at the initiation of levothyroxine treatment is not

TABLE 4. Age-adjusted odds ratios and predicted probabilities (with 95% CI) of overt or subclinical hypothyroidism at follow-up, by baseline TSH, in women and men[a]

TSH, mU/liter	Total, n	Hypothyroid, n	Odds ratio	(95% CI)	Probability (%)	(95% CI)
Women						
0.20–0.49	177	1	—		—	
0.50–1.4	4531	54	1.0	(Reference)	1.2	(0.9–1.5)
1.5–1.9	2418	68	2.4	(1.7–3.5)	2.8	(2.2–3.5)
2.0–2.4	1396	72	4.6	(3.2–6.5)	5.1	(4.1–6.4)
2.5–2.9	759	74	9.1	(6.3–13.0)	9.7	(7.8–12.1)
3.0–3.4	395	72	18.6	(12.8–27.0)	18.1	(14.6–22.2)
3.5–3.9	254	65	29.6	(20.0–43.8)	26.1	(21.0–31.9)
4.0–4.5	153	64	61.0	(40.1–92.9)	42.1	(34.5–50.1)
Men						
0.20–0.49	73	0	—		—	
0.50–1.4	2343	10	1.0	(Reference)	0.4	(0.2–0.8)
1.5–1.9	1303	14	2.5	(1.1–5.7)	1.1	(0.6–1.8)
2.0–2.4	682	15	5.2	(2.3–11.6)	2.2	(1.3–3.6)
2.5–2.9	328	14	10.2	(4.5–23.3)	4.2	(2.5–7.0)
3.0–3.4	157	19	31.0	(14.1–68.1)	11.7	(7.5–17.7)
3.5–3.9	79	17	62.5	(27.4–142.2)	21.1	(13.5–31.4)
4.0–4.5	58	13	64.8	(26.9–156.0)	21.7	(12.9–34.0)

[a] Hypothyroidism defined as prescription of levothyroxine, or TSH above 4.50 mU/liter, in people without a history of hyperthyroidism.

known. In a few participants, hypothyroidism is likely to be caused by thyroidectomy or radioiodine treatment for thyroid cancer or nontoxic goiter or by radiation therapy for nonthyroidal cancer. We did not have individual information on these diagnoses, but based on information from the Norwegian Cancer Registry, we estimated that approximately eight of the 15,106 participants were diagnosed with thyroid cancer during follow-up. Hyperthyroidism treated before 2004 was identified by self-report only, which may be less reliable than the information in the prescription database. However, among the 13 participants who were prescribed thionamides between 2004 and the follow-up examination and also returned the follow-up questionnaire with items on thyroid diseases, 12 reported hyperthyroidism at the follow-up examination. This suggests that self-report was a sensitive tool to detect hyperthyroidism during follow-up.

For one third of the participants who were eligible at baseline, we had no follow-up information on thyroid function, and we cannot exclude the possibility that the association of TSH with the risk of thyroid dysfunction may differ between those who attended and those who did not attend the follow-up examination. Smokers were less likely to participate at the follow-up examination; however, this may not have materially influenced the results because the association of TSH with subsequent hypothyroidism did not substantially differ between smokers and nonsmokers.

It has been suggested that the upper limit of the reference range for TSH should be lowered, in part based on the

TABLE 5. Age-adjusted odds ratios and predicted probabilities (with 95% CI) of developing hyperthyroidism during the follow-up period, by categories of baseline TSH, in women and men[a]

TSH, mU/liter	Total, n	Hyperthyroid, n	Odds ratio	(95% CI)	Probability (%)	(95% CI)
Women						
0.20–0.49	154	6	2.9	(1.2–7.3)	3.9	(1.8–8.4)
0.50–0.99	1560	22	1.0	(Reference)	1.4	(0.9–2.1)
1.00–1.4	2427	24	0.7	(0.4–1.2)	1.0	(0.7–1.4)
1.5–1.9	2119	18	0.6	(0.3–1.1)	0.8	(0.5–1.3)
2.0–4.5	2632	26	0.7	(0.4–1.3)	1.0	(0.7–1.4)
Men						
0.20–0.49	56	0	—		—	
0.50–0.99	727	5	1.0	(Reference)	0.7	(0.3–1.6)
1.00–1.4	1302	5	0.5	(0.2–1.9)	0.4	(0.1–0.9)
1.5–1.9	1139	8	1.0	(0.3–3.0)	0.7	(0.3–1.3)
2.0–4.5	1133	6	0.7	(0.2–2.3)	0.5	(0.2–1.1)

[a] Hyperthyroidism defined as prescription of thionamides, self-reported hyperthyroidism, or TSH below 0.10 mU/liter combined with free T_4 above 19.0 pmol/liter in people without a history of hypothyroidism.

observation that people with TSH in the upper part of the reference range are at increased risk of hypothyroidism (21). Our results indicate, however, that most people with TSH between 2.5 and 4.5 mU/liter do not develop hypothyroidism during 11 yr of follow-up. Furthermore, the association of TSH with the risk of hypothyroidism appears to be gradual across the reference range, with no cutoff point that distinctly separates TSH levels that are associated with increased risk of hypothyroidism from TSH levels that are not. Nonetheless, a substantial proportion of people with TSH in the uppermost part of the reference range developed hypothyroidism, which gives support to the suggestion that follow-up of thyroid function in these individuals may be appropriate (3, 8, 20).

In summary, this longitudinal population-based study shows that serum TSH concentrations within the reference range are positively and strongly associated with the risk of developing hypothyroidism during 11 yr of follow-up in both women and men. Conversely, TSH at the lower limit of the reference range may be associated with an increased risk of hyperthyroidism.

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