Association of Serum TSH with High Body Mass Differs between Smokers and Never-Smokers

Bjørn Olav Åsvold, Trine Bjøro, and Lars J. Vatten

Department of Public Health (B.O.A., L.J.V.), Faculty of Medicine, Norwegian University of Science and Technology, N-7489 Trondheim, Norway; Department of Medicine (B.O.A.), St. Olavs Hospital, Trondheim University Hospital, N-7006 Trondheim, Norway; and Department of Medical Biochemistry (T.B.), Rikshospitalet, Oslo University Hospital and University of Oslo, N-0027 Oslo, Norway

Context: Recent studies have suggested that the association of low thyroid function with high body mass is restricted to nonsmokers.

Objective: The aim was to study the association of thyroid function with body mass separately for smokers and never-smokers.

Design and Setting: We conducted a cross-sectional, population-based study.

Subjects: We studied 27,097 individuals older than 40 yr of age who were without previously known thyroid disease.

Main Outcome Measures: We measured mean body mass index (BMI) and odds ratio for obesity (BMI $\geq$30.0 kg/m^2) according to categories of thyroid function, in women and men, and separately for current smokers and never-smokers. We also studied the association with BMI within the reference range of TSH (0.50–3.5 mU/liter).

Results: TSH within the reference range was positively associated with BMI (P for trend $\leq$0.001 in all groups) and with the prevalence of obesity (P for trend $<$0.005 in all groups). Among women, the association did not differ between current smokers and never-smokers, but in men the association was stronger for current smokers. Hypothyroid function was associated with higher BMI and higher prevalence of obesity in women (subclinical and overt hypothyroidism) and men (subclinical hypothyroidism), both in current smokers and in never-smokers.

Conclusion: The association of low thyroid function with high body mass was as least as strong in current smokers as in never-smokers, and our results clearly show that the association is not limited to nonsmokers, as previously suggested. **(*J Clin Endocrinol Metab* 94: 5023–5027, 2009)**

Among their many metabolic effects, thyroid hormones increase the basal metabolic rate; therefore, low thyroid function, even within the clinically normal range, could lead to obesity (1, 2). In support of this hypothesis, several studies of euthyroid people have shown that low levels of free T_4 (2, 3) or high levels of TSH (2, 4, 5) are associated with high body mass index (BMI).

In two recent studies, low thyroid function was associated with high BMI in nonsmokers, but among current smokers, there was no clear association of thyroid function with BMI (3, 4). Therefore, it was suggested that smoking could modify the effects that thyroid hormones appear to have on body mass (3). However, both studies were relatively small, and the different results for smokers and nonsmokers could be due to low precision.

In a Norwegian population study of more than 27,000 individuals, we therefore assessed whether thyroid function is associated with body mass, and in stratified analyses, we studied this association separately for current smokers and never-smokers.

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Abbreviations: BMI, Body mass index; CI, confidence interval; OR, odds ratio.

Subjects and Methods

Study population

Between 1995 and 1997, all inhabitants at least 20 yr old in Nord-Trøndelag County in Norway were invited to participate in the Nord-Trøndelag Health Study (HUNT). A total of 92,936 individuals were invited, and 66,140 (71.2%) attended. The participants were asked to complete a self-administered questionnaire that included a range of health-related questions, including questions about smoking habits and history of thyroid disease (6). Among clinical measurements, standardized measurements of height, weight, blood pressure, and heart rate were included (7).

A nonfasting venous blood sample was drawn from each participant, and serum concentrations of TSH were measured in subsamples of the population. These samples included all women more than 40 yr old and a 50% random sample of men older than 40 yr. In total, TSH was measured in 32,781 individuals (22,662 women and 10,119 men) from these samples. People with TSH below 0.20 mU/liter also had free T_4 and total T_3 measurements, and in people with TSH above 4.0 mU/liter, free T_4 was measured. The Norwegian population is considered to have sufficient iodine intake (8).

Laboratory measurements

Concentrations of TSH, free T_4, and total T_3 were measured at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity, 0.03 mU/liter; total analytical variation, <5%), DELFIA FT_4 (total analytical variation, <7%), and AutoDELFIA T_3 (total analytical variation, <5%), respectively, all from Wallac Oy (Turku, Finland). Reference ranges for TSH in this population have been published previously (6), and the reference range for TSH in this study was defined as 0.50–3.5 mU/liter. The laboratory reference ranges were 8–20 pmol/liter for free T_4, and 1.2–2.7 nmol/liter for total T_3.

Statistical analysis

Among 32,781 individuals with TSH measurements, we excluded people with previously known thyroid disease (n = 2,831) or missing information on height, weight, or smoking status (n = 996). In addition, we excluded those who died within the first 5 yr after data collection (n = 1,857, identified by data linkage to the National Registry) to reduce a possible bias from effects that serious nonthyroidal disease could have on thyroid function tests or on BMI. Thus, 27,097 individuals (18,317 women and 8,780 men) were eligible for analysis in this study.

The participants were placed in seven categories according to thyroid function: one category of biochemically overt hyperthyroid function (defined as TSH <0.20 mU/liter combined with free T_4 >20.0 pmol/liter and/or total T_3 >2.7 nmol/liter); one category of probable subclinical hyperthyroid function (TSH 0.20–0.49 mU/liter, or TSH <0.20 mU/liter, and neither free T_4 nor total T_3 above the reference range); three categories of TSH within the clinical reference range (0.50–1.4, 1.5–2.4, and 2.5–3.5 mU/liter); one category of probable subclinical hypothyroid function (TSH 3.6–4.0 mU/liter, or TSH > 4.0 mU/liter and free T_4 ≥8.0 pmol/liter); and one category of biochemically overt hypothyroid function (TSH >4.0 mU/liter and free T_4 <8.0 pmol/liter).

BMI was calculated as weight (in kilograms) divided by the squared value of height (in meters), and obesity was defined as BMI ≥30.0 kg/m^2.

In a linear regression analysis, we calculated mean BMI [with 95% confidence intervals (CIs)] within each of the seven categories of thyroid function. We compared mean BMI in the hyperthyroid or hypothyroid groups with mean BMI in people with TSH in the lower third of the reference range (0.50–1.4 mU/liter).

Within the reference range of TSH, we estimated partial regression coefficients that express mean difference in BMI per unit difference in TSH and tested whether this association displayed a linear trend (expressed as *P* values for trend). These assessments were done using both log-transformed and nontransformed BMI values, but the results were nearly identical, and we therefore present the nontransformed results.

In a logistic regression analysis, we calculated odds ratios (OR; with 95% CIs) of obesity for each category of thyroid function, using people with TSH levels of 0.50–1.4 mU/liter as the reference group. Using TSH as a continuous variable, we tested whether TSH within the reference range was linearly associated with the prevalence of obesity (expressed as *P* values for trend).

We analyzed women and men separately because the prevalence of thyroid dysfunction substantially differs by sex. All results were age-adjusted. The overall results were adjusted for smoking status (never, former, and current smokers; former smokers were subdivided by years since smoking cessation), and in a stratified analysis, we assessed the association of thyroid function with BMI separately for never-smokers and current smokers. We also examined whether the associations of thyroid function with body mass differed between current smokers and never-smokers (expressed as *P* values for interaction).

In supplementary analyses, we also adjusted for physical activity, heart rate, month of serum collection, and average number of cigarettes smoked per day, but the results were not substantially altered after these adjustments. Also, the results remained essentially similar after the exclusion of participants with known cardiovascular disease, diabetes, serious renal failure, or cancer.

For men with overt hyperthyroidism (n = 4) or overt hypothyroidism (n = 21), the low number of participants precluded meaningful estimates. Their results were therefore omitted.

All statistical analyses were conducted using SPSS statistical software, version 14.0, for Windows (SPSS Inc., Chicago, IL).

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 the Faculty of Medicine, the Norwegian University of Science and Technology; the Norwegian Institute of Public Health; and Nord-Trøndelag County Council.

Results

TSH within the reference range (0.50–3.5 mU/liter) was positively associated with BMI in both sexes, both overall and separately, for never-smokers and current smokers (*P* for trend ≤0.001 for all groups). Overall, BMI was 0.41 kg/m^2 (95% CI, 0.31–0.51 kg/m^2) higher per unit higher TSH in women, and 0.48 kg/m^2 (95% CI, 0.36–0.59 kg/m^2) higher per unit higher TSH in men, after adjustment for age and smoking status. The stratified analysis showed that BMI in never-smoking women was 0.38 kg/m^2 (95% CI, 0.24–0.52 kg/m^2) higher per unit higher TSH, compared with 0.50 kg/m^2 (95% CI, 0.31–0.69 kg/m^2) in current smokers.

Among men, BMI was 0.32 kg/m^2 (95% CI, 0.12–0.51 kg/m^2) higher per unit higher TSH in never-smokers, and 0.81 kg/m^2 (95% CI, 0.59–1.03 kg/m^2) higher in current smokers. In other words, the association of TSH with BMI was similar for current smokers and never-smokers in women (P for interaction = 0.69), whereas in men, the association was in fact stronger among current smokers (P for interaction = 0.003).

Compared with BMI of women with TSH of 0.50–1.4 mU/liter (26.8 kg/m^2), BMI was higher in women with subclinical (27.7 kg/m^2; $P < 0.001$) or overt hypothyroidism (28.0 kg/m^2; $P = 0.002$). In men with subclinical hypothyroidism, BMI was also higher (27.6 kg/m^2; $P < 0.001$), compared with men with TSH of 0.50–1.4 mU/liter (26.6 kg/m^2). These differences were present in both never-smokers and current smokers and did not differ by smoking status (P for interaction = 0.76 in women and P for interaction = 0.22 in men). There was no significant association of hyperthyroid function with BMI (Fig. 1).

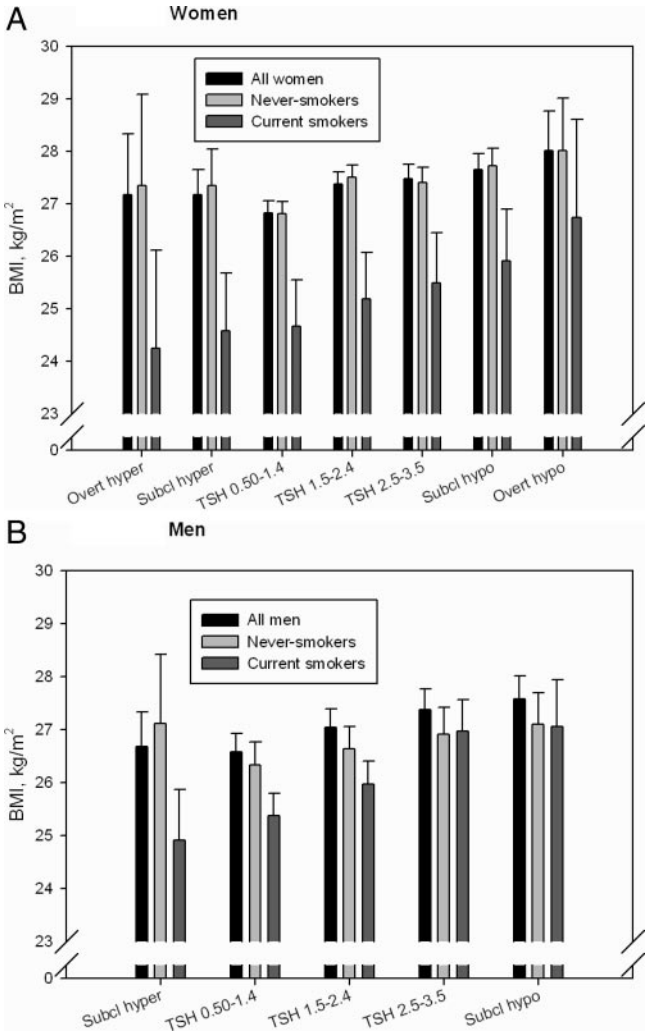

FIG. 1. Mean BMI (with upper limit of 95% CI) by categories of thyroid function, in women (A) and men (B), both overall (age- and smoking-adjusted) and in strata of never-smokers and current smokers (age-adjusted).

TSH within the reference range was positively associated with obesity in both sexes, both overall and within strata of never-smokers and current smokers (P for trend <0.005 in all groups) (Table 1). Compared with women with TSH in the lower third of the reference range (0.5–1.4 mU/liter), obesity was 30% more common (OR, 1.30) among women with TSH in the upper third (2.5–3.5 mU/liter), with no substantial difference between never-smokers and current smokers. Among men with TSH of 2.5–3.5 mU/liter, the prevalence of obesity was about 50% higher (OR, 1.53) than for men with TSH of 0.50–1.4 mU/liter. The association appeared to be stronger for current smokers (OR, 2.57) than for never-smokers (OR, 1.47), but the difference between smokers and never-smokers was not statistically significant (P for interaction = 0.10).

Compared with women with TSH of 0.50–1.4 mU/liter, the prevalence of obesity was higher in women with subclinical (OR, 1.54) or overt hypothyroidism (OR, 1.66). The associations appeared to be stronger among current smokers (OR of 2.32 for subclinical and OR of 2.79 for overt hypothyroid function) than among never-smokers (OR of 1.50 for both subtypes of hypothyroid function), but the difference between smokers and never-smokers was not statistically significant (P for interaction = 0.09). In men with subclinical hypothyroidism, obesity was about twice as common as in men with TSH of 0.50–1.4 mU/liter, both in the population as a whole (OR, 1.83), and separately, among never-smokers (OR, 2.00) and current smokers (OR, 2.23) (Table 1).

Discussion

In this population study of 27,097 people without previously known thyroid disease, low thyroid function was associated with high body mass, and the association was present for women and men, both among current smokers and never-smokers. Thus, our results show that the association of low thyroid function with high body mass is not limited to nonsmokers, as previously suggested (3).

Our findings differ from those of two other studies in which low thyroid function, expressed as either high TSH (4) or low free T_4 (3) levels, was associated with high BMI among nonsmokers, but not in smokers. Our study is substantially larger and allows higher precision of the estimates, both overall and in stratified analyses of smokers and never-smokers.

Two hypotheses have been proposed to explain the relation of thyroid function with body mass. First, it has been suggested that adipose tissue may influence thyroid function, possibly through effects of leptin and other adipokines (9). In support of this hypothesis, it has been observed that weight reduction in obese individuals may be

TABLE 1. OR with 95% CI of obesity (BMI ≥30.0 kg/m^2) by thyroid function in women and men, both overall and in strata of never-smokers and current smokers

	Total population				Never-smokers				Current smokers			
	Persons	Cases	OR[a]	95% CI	Persons	Cases	OR[b]	95% CI	Persons	Cases	OR[b]	95% CI
Women												
Overt hyperthyroidism	56	7	0.64	0.29–1.43	25	4	0.65	0.22–1.93	24	2	0.67	0.16–2.88
Subclinical hyperthyroidism	376	81	1.25	0.96–1.61	167	41	1.16	0.81–1.68	143	21	1.21	0.75–1.95
TSH												
0.50–1.4 mU/liter	7426	1309	1.0	(Reference)	3271	693	1.0	(Reference)	2680	326	1.0	(Reference)
1.5–2.4 mU/liter	6640	1558	1.32	1.21–1.43	3647	981	1.36	1.22–1.53	1612	258	1.36	1.14–1.62
2.5–3.5 mU/liter	2329	569	1.30	1.16–1.46	1408	366	1.26	1.09–1.46	408	67	1.39	1.04–1.86
Subclinical hypothyroidism	1353	378	1.54	1.34–1.76	844	251	1.50	1.27–1.78	218	53	2.32	1.66–3.24
Overt hypothyroidism	137	41	1.66	1.14–2.42	78	24	1.50	0.92–2.45	24	7	2.79	1.14–6.79
Men												
Overt hyperthyroidism	4	0			3	0			1	0		
Subclinical hyperthyroidism	137	23	1.31	0.82–2.07	26	5	1.64	0.60–4.45	57	5	0.79	0.31–2.01
TSH												
0.50–1.4 mU/liter	3862	518	1.0	(Reference)	1032	128	1.0	(Reference)	1407	149	1.0	(Reference)
1.5–2.4 mU/liter	3319	564	1.33	1.17–1.52	1162	176	1.26	0.98–1.61	872	127	1.47	1.14–1.90
2.5–3.5 mU/liter	986	187	1.53	1.26–1.84	355	62	1.47	1.05–2.05	190	42	2.57	1.75–3.79
Subclinical hypothyroidism	451	95	1.83	1.43–2.35	179	40	2.00	1.33–2.99	67	13	2.23	1.18–4.21
Overt hypothyroidism	21	1			7	0			4	0		

[a] Adjusted for age and smoking status.

[b] Adjusted for age.

followed by reduced thyroid function (10, 11), and that weight gain in patients with anorexia nervosa may be associated with subsequent increase in thyroid function (12). The second hypothesis suggests that low thyroid function may lead to obesity, possibly mediated by lower basal metabolic rate (2). In support of this, clinical studies have shown that T_4 treatment of hypothyroidism may lead to weight reduction (13, 14), and it has been observed that treatment of hyperthyroidism may lead to weight gain (15). Also, the results of some cross-sectional population studies suggest that both low free T_4 (2, 3) and high TSH levels (2, 4, 5) are associated with higher BMI. Within their specific contexts, both hypotheses may be reasonable, but in the general population it seems more plausible to interpret associations between thyroid function and body mass as effects of thyroid hormones, rather than suggesting an influence of body mass on thyroid function (2).

In conclusion, we found that the association of low thyroid function with high body mass was at least as strong in current smokers as in never-smokers, and our results clearly show that the association is not limited to nonsmokers, as previously suggested.

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Address all correspondence and requests for reprints to: Bjørn Olav Åsvold, Department of Public Health, Faculty of Medicine, Norwegian University of Science and Technology, N-7489 Trondheim, Norway. E-mail: bjorn.o.asvold@ntnu.no.

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