

Small Differences in Thyroid Function May Be Important for Body Mass Index and the Occurrence of Obesity in the Population

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Context: Increasing prevalence of overweight in the population is a major concern globally; and in the United States, nearly one third of adults were classified as obese at the end of the 20th century. Few data have been presented regarding an association between variations in thyroid function seen in the general population and body weight.

Objective: The aim of this study was to investigate the association between thyroid function and body mass index (BMI) or obesity in a normal population.

Design: A cross-sectional population study (The DanThyr Study) was conducted.

Participants: In all, 4649 participants were investigated, and 4082 were eligible for these analyses after exclusion of subjects with previous or present overt thyroid dysfunction.

Main Outcome Measures: The study examined the association between category of serum TSH or serum thyroid hormones and BMI or

obesity in multivariate models, adjusting for possible confounding.

Results: We found a positive association between BMI and category of serum TSH ($P < 0.001$) and a negative association between BMI and category of serum free T_4 ($P < 0.001$). No association was found between BMI and serum free T_3 levels. The difference in BMI between the groups with the highest and lowest serum TSH levels was 1.9 kg/m^2 , corresponding to a difference in body weight of 5.5 kg among women. Similarly, the category of serum TSH correlated positively with weight gain during 5 yr ($P = 0.04$), but no statistically significant association was found with weight gain during 6 months ($P = 0.17$). There was an association between obesity ($\text{BMI} > 30 \text{ kg}/\text{m}^2$) and serum TSH levels ($P = 0.001$).

Conclusions: Our results suggest that thyroid function (also within the normal range) could be one of several factors acting in concert to determine body weight in a population. Even slightly elevated serum TSH levels are associated with an increase in the occurrence of obesity. (*J Clin Endocrinol Metab* 90: 4019–4024, 2005)

VARIATIONS IN THYROID function are seen between individuals also within the normal range, documented by relatively small individual variation in serum levels of thyroid hormones and TSH between measurements in the same individual compared with variations between individuals (1). Such differences in individual thyroid function are caused by a combination of genetic and environmental factors (2). Likewise, considerable differences may be seen in thyroid function between populations when estimated by median serum TSH levels. Such variations are probably caused by a number of primarily environmental factors, of which iodine intake level seems to be of major importance (3, 4). The optimal level for thyroid hormones and TSH in serum to attain physical and mental well being has not been established, but the trend these years is to narrow the range of serum TSH, regarded as optimal. Det-

perimental effects on the cardiovascular system have been reported for suppressed and particularly elevated serum levels of TSH, and follow-up studies have shown an increase in risk of development of overt thyroid dysfunction in subjects with high normal serum TSH levels (5–8).

Even small differences in thyroid function with TSH variation within the normal laboratory range for patients on T_4 substitution therapy are associated with measurable differences in resting energy expenditure (REE), but the impact on body mass index (BMI) remains unsettled (9). A prolonged decrease in REE might well lead to increased body weight in the current environment of food plenty and physical inactivity in many industrialized countries. However, the association between small differences in thyroid hormone levels, as seen in the general population without thyroid dysfunction, and body weight or BMI has only been described in few previous studies. In a recent study of old participants, an association was found between serum TSH and BMI, but also subjects with overt thyroid dysfunction were included (10). In a study of elderly subjects, a possible association between mild hypothyroidism and BMI was found among women (11), however with the opposite tendency among men. In

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Abbreviations: BMI, Body mass index; REE, resting energy expenditure; TPO Ab, thyroid peroxidase antibodies.

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another recent study, no association was identified (5). In recent intervention studies, no effect was found on BMI of T₄ supplementation to patients with mild hypothyroidism (12, 13).

The possible implications of these slight differences in thyroid function (without reaching overt thyroid dysfunction) for the risk of gaining weight and developing overweight or obesity have high actuality with the present worldwide epidemic of obesity and complications associated with obesity. Overweight is a major threat to public health, with the prevalence of obesity now exceeding 30% in the United States (14). Lifestyle is undoubtedly of major importance for weight gain in the population, but the interaction with other factors is far from elucidated in detail (15). We used data from a large, cross-sectional, population-based study to evaluate a possible association between thyroid hormone levels and BMI and weight changes.

Subjects and Methods

We analyzed data from a Danish population study conducted in 1997–1998 before the initiation of an iodization program in Denmark (The Danish Centre for Prevention of Thyroid Diseases Study). A random sample of the population in two Danish cities within certain age groups was drawn from the civil registration system, in which all subjects living in Denmark are registered. The cohort was sampled in Aalborg with moderate iodine deficiency and Copenhagen with mild iodine deficiency, reflected by median iodine concentrations of 45 and 61 µg/liter in casual urine specimens in the two regions, respectively. For this classification of iodine status, subjects taking individual iodine supplementation were excluded.

The sample was drawn among women in the age groups 18–22, 25–30, 40–45, and 60–65 yr to represent women before childbearing age, within childbearing age, after childbearing age but premenopausal, and postmenopausal women. A group of men in the age group 60–65 yr were included for comparison between genders. A preponderance of women was chosen for the study due to the expected higher prevalence of thyroid abnormalities among women. This was done to increase the statistical power of the study at the lowest cost. Likewise, the group of men was chosen in the age group with the highest expected prevalence of thyroid abnormalities.

People were invited by letter; and in cases of no response, reminders were sent. People were informed that the purpose of the study was an investigation of the occurrence of thyroid diseases. In all, 9274 persons were addressed, and 4649 (50.1%) participated in the full study. Among the participants, there was a slight overrepresentation of subjects with known thyroid disease compared with nonparticipants (16). However, for the analyses presented in this study, all participants with known thyroid disease were excluded, and the slight selection bias does not impose bias to these analyses. The cohort has previously been described in detail (16, 17).

All participants answered questionnaires regarding previous diseases, lifestyle, and education. Questions were also asked about self-estimated weight 6 months and 5 yr earlier. These self-reported weights were obviously not precise; but for comparisons with thyroid function, this results only in nondifferentiated misclassification. The consequence of the measurement error is thus large dispersion of the estimates with a tendency to underestimate the association but no bias. A specially designed food frequency questionnaire, focusing on potential sources of iodine, and few questions regarding recent changes in diet were also included, but energy intake was not estimated for all participants. In a personal interview with a physician, information about previous thyroid disease and present medication was obtained; and in case of doubt regarding medical history of thyroid disease, medical records were traced.

Tobacco smoking was initially categorized in four groups: never smokers, ex-smokers, light smokers (1–19 cigarettes per day), and heavy smokers (20 or more cigarettes per day). For the final analyses, only two categories were used: present smokers, or nonsmokers, because no dif-

ferences regarding the association with BMI were found between never smokers and ex-smokers or between light smokers and heavy smokers. Alcohol consumption was also evaluated with four categories, but was finally used in two categories: low consumption (maximum seven drinks/wk), and moderate to high consumption (eight drinks or more/wk). These simplifications were made to reduce the number of parameters in the models.

Educational level was used with five categories: basic school and no vocational education, basic school with vocational education, extended school with no or short further education, extended school with medium to long further education, and still under education. Physical activity in leisure time was evaluated in four groups, but condensed into three categories: less than 2 h of physical activity per week, 2–4 h of easy physical activity per week, and more than 4 h of easy physical activity per week or more than 2 h of strenuous physical activity per week.

Height was measured, without shoes, using a stadiometer; and weight was measured, with normal indoor clothes and without shoes, with SECA analog person medical scales. BMI was computed as weight in kilograms divided by the square of the height in meters. Thus, BMI is slightly overestimated for all participants compared with values without clothing.

Blood samples were obtained and stored at –20 C and analyzed later, ensuring that samples for analyses were mixed with respect to season, age, sex, and city. Serum TSH, free T₄ and free T₃ were analyzed with LUMitest (BRAHMS, Berlin, Germany). The functional sensitivity of the TSH assay was 0.01 mU/liter. A normal range of serum TSH of 0.4–3.6 mU/liter was defined as the 2.5th and the 97.5th percentiles after exclusion of participants with known thyroid disease, serum thyroid peroxidase antibodies (TPO Ab) more than 60 kU/liter, or thyroid enlargement or thyroid nodules at ultrasonography (3). Participants were divided into five groups according to serum TSH levels: a group with serum TSH less than 0.4 mU/liter but normal free T₄ and a group with serum TSH more than 3.6 but normal free T₃ and free T₄ level. The intermediate TSH values were arbitrarily divided as 0.4–0.99, 1.0–1.99, and 2.0–3.6 mU/liter, ensuring sufficient representation in all groups. Normal ranges for free T₄ and free T₃ were defined as 2.5th and 97.5th percentiles after exclusion of participants with serum TSH outside the reference interval or with known thyroid disease. These intervals were 9.8–20.4 pmol/liter for free T₄ and 3.6–6.9 pmol/liter for free T₃. Serum free T₄ values were divided in five groups with sufficient representation: less than 11.5, 11.5–12.99, 13.0–15.99, 16.0–18.0, and more than 18.0 nmol/liter. In the same way, free T₃ values were categorized as less than 4.0, 4.0–4.99, 5.0–5.49, 5.5–6.0, and more than 6.0 nmol/liter.

Serum TPO Ab levels were analyzed with a RIA with a functional sensitivity of 30 kU/liter (Dyntest; BRAHMS). Urine iodine concentration was analyzed with the Ce/As method after alkaline ashing, as previously described (17).

The study was approved by the regional Ethics Committee in Copenhagen and Northern Jutland, and all participants gave written informed consent.

Statistics

Data processing was done with SPSS version 10.0 software (SPSS Scandinavia, Holte, Denmark). Analyses were performed in linear models (ANOVA) and logistic regression analyses to consider confounding from other factors with a possible association with thyroid function as well as BMI. First, a full model with all factors with potential confounding was constructed. Initially serum free T₄, serum free T₃, and serum TSH were tested as continuous covariates with significant associations with BMI for free T₄ and TSH ($P < 0.001$); but for an informational presentation, further analyses were performed with categorical variables. These variables were included in the models as fixed factors.

In the generation of a statistical model, all factors without significant association with BMI were excluded. To identify possible confounders, the association between the remaining factors and serum TSH categories was tested. Only region of inhabitancy, sex, age, and tobacco smoking showed significant associations with TSH category. The remaining factors were removed from the model stepwise according to F values. As expected, the exclusion of factors without association with TSH did not influence the association between TSH category and BMI, and these factors were not included in the final model. The same procedure was followed for the construction of the linear models regarding serum T₄

and for the logistic regression models, leaving the same factors to be included as confounders in the final models. The level of significance was set to 5%.

For evaluation of the factors in the statistical models, data are presented in tables with *P* values and partial r^2 values. The partial r^2 values represent the sum of squares (type III) compared with the total sum of squares and is an estimate of the fraction of the variation in the dependent variable accounted for by the variation in the independent variable.

First-order interactions between serum TSH and the other significant factors in the model were tested, but no significant interactions were found. This included sex and the region of inhabitancy indicating similar associations between TSH and BMI in the two investigated regions and among men and women.

Results

In all, 4649 subjects participated. All subjects with previous ($n = 151$) or present ($n = 77$) treatment for thyroid disease, subjects with overt hypothyroidism [TSH > 3.6 mU/liter and free $T_4 < 9.8$ pmol/liter ($n = 16$)] or overt hyperthyroidism [TSH < 0.4 mU/liter and free $T_4 > 20.4$ or free $T_3 > 6.9$ ($n = 26$)], and pregnant women ($n = 60$) and women with a pregnancy within 12 months from the investigation ($n = 78$) were excluded. Of the 4241 eligible subjects, a further 159 were excluded due to missing values for one or more factors in the analyses, leaving 4082 subjects to be included in the final analyses.

A multivariate model including all factors with a significant association with BMI is shown in Table 1. Factors that were also tested in the model but found not to be significantly associated with BMI were: physical activity at work, use of oral contraceptives, use of iodine supplementation, milk consumption, time of the day for the investigation, and number of childbirths. As expected, BMI was higher among participants with diabetes; among those with little physical activity in leisure time; among nonsmokers, alcohol consumers, and participants with low educational levels; during winter and springtime; in the older age groups; and among men. r^2 for the full model was 0.22.

Figure 1 shows the average BMI in groups of participants with different levels of TSH. As shown, a significant, positive association was found between actual serum TSH category and BMI. Values of BMI were calculated in a model including only factors with a significant association with BMI as well as with TSH as expression of thyroid

function. These factors were age, sex, and tobacco smoking. Inclusion of further factors in the model (from Table 1) did not affect the association between serum TSH and BMI. For a woman with a height of 1.66 m (average in this study), the observed difference in BMI between the group with serum TSH more than 3.6 mU/liter (median, 4.5 mU/liter) and the group with serum TSH less than 0.4 mU/liter (median, 0.28 mU/liter) corresponds to a difference in body weight of 5.5 kg. For the group with serum TSH of 1–1.99 mU/liter, the difference in BMI corresponds to 4.0 kg when compared with the group with the highest TSH values but still with serum free T_4 levels within the reference range.

The association between category of TSH and BMI were also tested after exclusion of subjects with possible mild (subclinical) thyroid dysfunction. Including only subjects with serum TSH in the range of 0.4–3.6 mU/liter in the calculations (TSH category 2, 3, and 4 in Fig. 1), *P* was 0.003 after adjustment for possible confounding as mentioned above.

Similar linear models were constructed with weight gain during the past 6 months and during the past 5 yr as dependent variables; and as shown in Fig. 1, significant associations were found between actual serum TSH levels and weight changes during the past 5 yr.

The association between serum free T_4 or free T_3 and BMI was analyzed in similar models. Higher values of serum free T_4 were associated with lower BMI, whereas there was no association between serum free T_3 and BMI as depicted in Fig. 2. No significant associations were found between free T_4 or free T_3 levels and weight changes. Likewise, no association was found between serum levels of TPO Ab and BMI or weight changes (data not shown).

The association between serum TSH levels and obesity (BMI > 30 kg/m²) was analyzed with logistic regression analysis. Again, adjustment was done for age, sex, and tobacco smoking. A significant association was found with increasing odds ratios for obesity with increasing serum TSH (Table 2). For the group with serum TSH above 3.6 mU/liter, a significantly increased odds ratio for obesity of 2.1 was found, compared with the group with serum TSH of 1.0–1.99 mU/liter.

TABLE 1. Factors with significant association with BMI in a Danish population study

Factor	<i>P</i>	Partial r^2 (%)	Difference in BMI ^a	BMI positively associated with	SE of BMI difference
Age	<0.001	8.3	3.2	Old age	0.25
Recent changes in diet ^b	<0.001	2.7	2.1	No changes	0.23
Educational level	<0.001	1.9	1.8	Low education	0.22
Physical activity ^c	<0.001	1.2	1.4	Low activity	0.21
Tobacco smoking	<0.001	1.1	0.9	Nonsmoking	0.14
TSH level	<0.001	0.8	1.9	High TSH	0.45
Diagnosed diabetes	<0.001	0.6	1.9	Diabetes	0.39
Gender	<0.001	0.4 ^d	0.9	Male gender	0.22
Region of inhabitancy	<0.001	0.3	0.5	Eastern region	0.13
Season	0.007	0.3	0.7	Winter	0.20
Alcohol consumption	0.002	0.2	0.5	High consumption	0.15

Data are from a multivariate model including 4082 subjects without previous or present overt thyroid dysfunction. r^2 describes the part of the variation in BMI attributable to variations in each factor.

^a Difference in BMI (kg/m²) between highest and lowest group within the variable [= the difference in regression coefficient (B)].

^b Self-reported changes in diet within 3 yr, categorized in three groups. More changes were associated with low BMI.

^c Only physical activity in leisure time.

^d The estimate for gender will be underestimated compared to the general population because fewer men than women were included, but this bias bears no influence on the thyroid-BMI association.

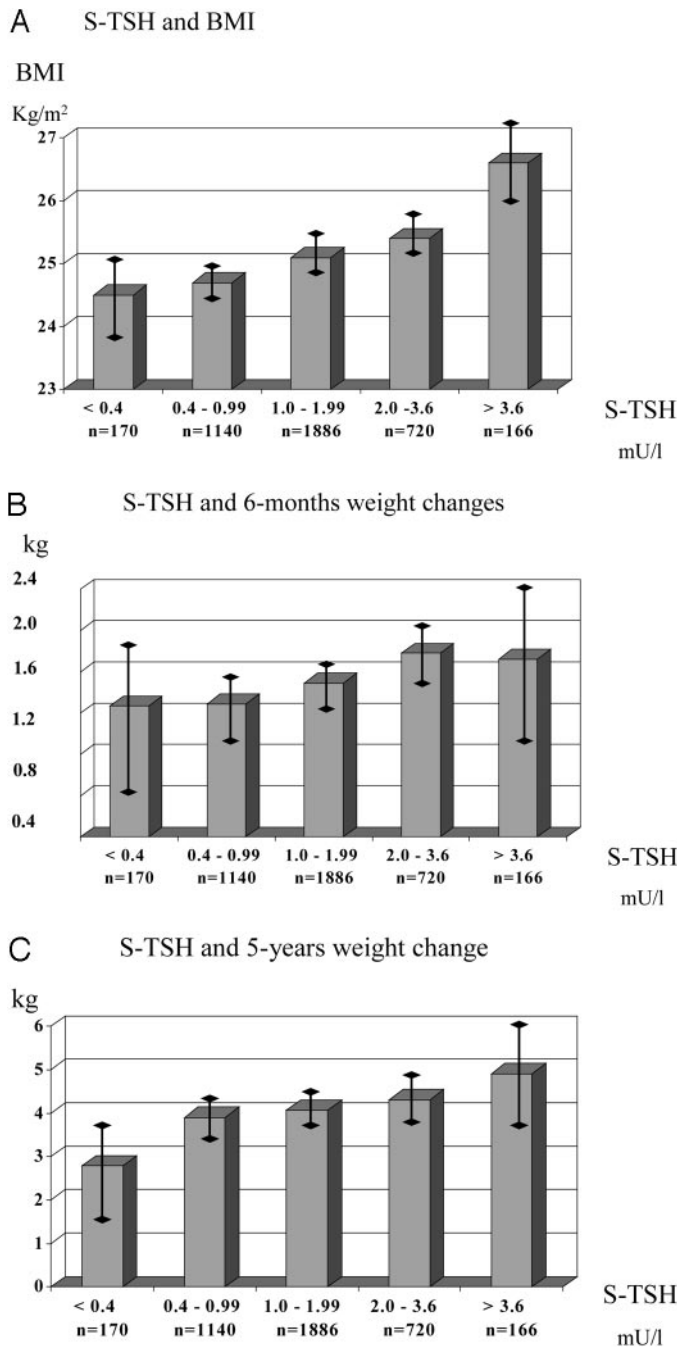


FIG. 1. The association between serum TSH (S-TSH) and BMI or weight changes in a Danish population comprising 4082 subjects randomly sampled within specific age groups. Subjects with thyroid dysfunction were excluded. Adjustments were made for age, sex, and tobacco smoking in multivariate models. Weight changes were computed as present weight minus self-reported weight 6 months or 5 yr earlier. Bars, Means; lines, 95% confidence interval for means. *P* was less than 0.001 for TSH and BMI, 0.17 for TSH and 6-month weight changes (*P* for trend, 0.019), and 0.04 for TSH and 5-yr weight changes (*P* for trend, 0.004)

Discussion

We demonstrate a clear association between thyroid function and BMI in our study population, an association also seen within the normal range of both serum TSH and free T₄.

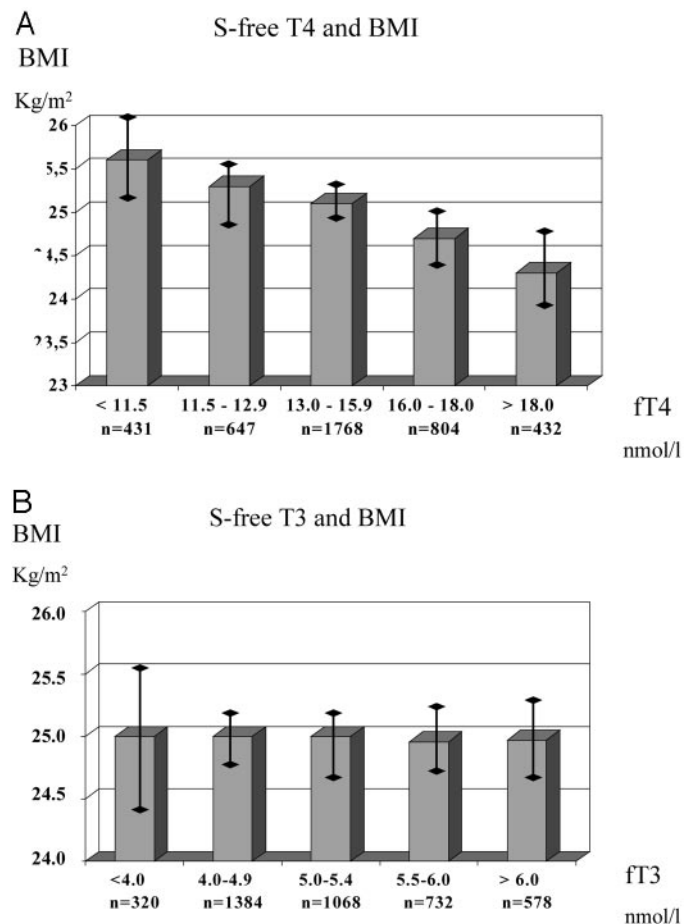


FIG. 2. The association between serum levels of thyroid hormones and present BMI in Danish population comprising 4082 subjects randomly sampled within specific age groups. Subjects with thyroid dysfunction were excluded. Adjustments were made for age, sex, and tobacco smoking in multivariate models. Bars, Means; lines, 95% confidence interval for means. *P* was less than 0.001 for serum free (f)T₄ and BMI and 1.0 for serum fT₃ and BMI.

Furthermore, thyroid function correlated to weight increases over 5 yr. Thyroid function accounts, in our model, for 1% of the variation in BMI between individuals, which seems to be modest, but thyroid function had approximately the same impact on BMI as tobacco smoking and physical activity. A difference in BMI of 1.9 kg/m² (corresponding to 5.5 kg) between the group of participants with the highest and lowest TSH levels, but no overt thyroid dysfunction, may be of importance for these individuals, and the difference

TABLE 2. The association between serum TSH levels and obesity in a population of 4082 Danes

Serum TSH (mU/liter)	Odds ratio for BMI > 30 kg/m ²	95% Confidence interval
<0.4	0.67	0.40–1.11
0.4–0.99	1.06	0.85–1.32
1.0–1.99	Reference	
2.0–3.6	1.20	0.94–1.55
>3.6	2.13	1.44–3.14

Data are from a logistic regression analysis adjusting for age, sex, region of inhabitancy, and tobacco smoking. *P* = 0.001 for association between serum TSH category and obesity.

in BMI associated with thyroid function is similar to the difference between diabetic and nondiabetic participants of our study. A larger proportion of the variation in BMI was explained by age and educational level; educational level probably being a marker of lifestyle in general, including dietary habits and physical activity. Thus, estimates concerning education and lifestyle should be regarded with some reservation, because their individual importance may not be precisely estimated.

These observational data do not prove any causal association, but there are plausible biological explanations and other studies pointing in the same direction. A relationship has been found between body weight and thyroid disease; the study was, however, based on self-reported thyroid dysfunction, and data were from a highly selected cohort of weight-conscious women (18). In a cohort of 85-yr-old subjects, an association was found between thyroid function and BMI, but data were not adjusted for possible confounding, and the association may be caused by subjects with overt thyroid dysfunction because they were also included (10). An association between REE and serum free T_4 was found in euthyroid young males (19), and 2% of the variation in energy expenditure has been attributed to variations in serum T_3 (20). A cross-sectional study found a higher BMI among women with subclinical hypothyroidism of borderline statistical significance, but the opposite association was found among men (11). A major study of subclinical hypothyroidism found no such association (5), but multivariate statistics were not used for this association. There is an established association between overt thyroid dysfunction and weight changes, because weight loss is a relatively constant phenomenon in hyperthyroidism (21).

The thyroid hormone-induced increase in thermogenesis is explained, among other things, by an increased need for ATP due to increased activity in most cells and reduced efficiency of ATP synthesis (22), but the specific mechanism has not been settled (19). Increases are observed for obligatory, as well as facultative, thermogenesis (23).

Administration of thyroid hormones has been suggested in the treatment of obesity, however with little success, due to side effects if doses were adjusted to achieve a clinically significant weight loss within the study period (21). In an experimental situation with variation in the dose of T_4 administered to hypothyroid patients, considerable variations in REE were found between states of euthyroidism and mild (subclinical) hyperthyroidism or hypothyroidism (9). The possible implications of such variations in energy expenditure for weight control in the long run have not been settled but may well lead to the differences in body mass found in the present study. Intervention studies with T_4 administration to patients with mild hypothyroidism did not identify any significant changes in BMI. The time-span of the studies of 6–8 wk (13) or 6 months (12) may, however, be too short for changes in body weight to appear with the minor changes in thyroid function.

It could be speculated that the association between serum TSH and body weight observed in the present study is caused by signals from adipose tissue. Leptin produced by adipocytes has important influences on central regulation of thyroid function through stimulation of TRH. This seems to be important for down-regulation of thyroid function in states of energy deficits,

but the importance for modulation of thyroid function under more physiological conditions is uncertain (24–26).

A positive correlation has been found between serum leptin and serum TSH in several studies (26), which corresponds to the positive association between BMI and TSH found in our study. However, if the mechanism behind our findings was a leptin-induced increase in TSH secretion via hypothalamic effects, it would be expected that this higher TSH would lead to an increase in thyroid secretion and in serum free T_4 (24, 25). We found the opposite, a decrease in serum free T_4 with the increase in BMI. This pattern supports that alterations in thyroid function with normal pituitary feedback regulation (low free T_4 associated with high TSH) is the primary event, and alterations in BMI via alterations in energy expenditure the secondary event. The increase in BMI and fat mass may then lead to an increase in serum leptin, and a positive correlation between serum TSH and serum leptin would be expected.

In our study, serum T_3 was not associated with BMI, and an increase in T_3/T_4 ratio in serum was observed with increasing BMI. This might support the concept of primary alterations in thyroid function and secondary changes in BMI. In progressive thyroid failure, there will initially be an increase in serum TSH, which is then followed by a decrease in serum free T_4 . Serum T_3 will remain normal until severe hypothyroidism develops (27).

Hypothetically, factors secreted or stimulated by adipose tissue, with a detrimental effect directly on the thyroid, might be the cause of our observations. This is biologically less likely because it would lead to a vicious spiral. Estrogen metabolites could, however, be such a factor because 2-methoxyestradiol has been shown to have detrimental effects on thyroid cells in culture (28). Inflammatory cytokines released by visceral fat have been suggested to inhibit the hypothalamic-pituitary-thyroid axis (29). This should result in negative associations between BMI and serum TSH as well as serum T_4 , whereas we found a positive association between TSH and BMI.

Our data support that small variations in thyroid function still within the normal laboratory range of free T_4 may contribute to the regulation of body weight in a population. Though this has not previously been demonstrated epidemiologically, it has been suggested that thyroid hormones may be a significant determinant of sleeping energy expenditure also in subjects without overt thyroid dysfunction (20). In a population where physical activity has been gradually diminished, even a relatively small contribution to energy expenditure mediated through thyroid hormones may be enough to accomplish increases in BMI.

The suggestion that the differences in thyroid function are primary and weight differences secondary was also supported by a study among grossly obese subjects undergoing surgery to reduce body weight. Free T_3 levels were positively correlated with BMI, but substantial reductions in fat mass after surgery did not cause changes in thyroid function (30). Studies of subjects undergoing heavy weight reduction do not show homogenous results, however. Weight reduction has been found associated with reduction in both serum TSH and T_3 levels (31, 32), reduction in serum TSH levels alone (33, 34), reduction in T_3 levels alone (35), or no change in thyroid function tests (36). These alterations may, however, be influenced by the catabolic state associated with heavy

weight reduction, and no associations were found with serum T₄ levels. Controversy also exists regarding thyroid function in obese subjects compared with controls; some found no differences (37, 38), but also higher serum TSH and T₃ levels have been found in obesity (39).

In conclusion, we suggest that differences in thyroid function, within what is considered the normal range, are associated with differences in BMI, caused by longstanding minor alterations in energy expenditure. This is more pronounced when mild hypo- or hyperthyroidism is present. The prevalences of such abnormalities in thyroid function are high and may be influenced by environmental factors (4). Because small abnormalities in thyroid function are common, thyroid function may importantly influence the prevalence of obesity in a population.

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