

Relations of Thyroid Function to Body Weight

Cross-sectional and Longitudinal Observations in a Community-Based Sample

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Background: Overt hypothyroidism and hyperthyroidism may be associated with weight gain and loss. We assessed whether variations in thyroid function within the reference (physiologic) range are associated with body weight.

Methods: Framingham Offspring Study participants (n=2407) who attended 2 consecutive routine examinations, were not receiving thyroid hormone therapy, and had baseline serum thyrotropin (TSH) concentrations of 0.5 to 5.0 mIU/L and follow-up concentrations of 0.5 to 10.0 mIU/L were included in this study. Baseline TSH concentrations were related to body weight and body weight change during 3.5 years of follow-up.

Results: At baseline, adjusted mean weight increased progressively from 64.5 to 70.2 kg in the lowest to highest TSH concentration quartiles in women ($P < .001$ for trend), and from 82.8 (lowest quartile) to 85.6 kg (highest quartile)

in men ($P = .007$ for trend). During 3.5 years of follow-up, mean (SD) body weight increased by 1.5 (5.6) kg in women and 1.0 (5.0) kg in men. Baseline TSH concentrations were not associated with weight change during follow-up. However, an increase in TSH concentration at follow-up was positively associated with weight gain in women (0.5-2.3 kg across increasing quartiles of TSH concentration change; $P < .001$ for trend) and men (0.4-1.3 kg across quartiles of TSH concentration change; $P = .007$ for trend).

Conclusions: Thyroid function (as assessed by serum TSH concentration) within the reference range is associated with body weight in both sexes. Our findings raise the possibility that modest increases in serum TSH concentrations within the reference range may be associated with weight gain.

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OBESITY IS ASSOCIATED WITH an increased risk for diabetes,¹⁻³ vascular disease,⁴ all-cause mortality,⁵ and cancer.⁶ The prevalence of obesity has increased substantially in the United States,^{7,8} suggesting a need to understand risk factors for weight gain. There are multiple known predictors of obesity and weight gain, including a low level of physical activity,⁹ increased caloric intake,¹⁰ parity,¹¹ smoking cessation,¹¹ inflammation,¹² depression,¹³ and genetic factors.¹⁴ In addition, metabolic factors are associated with body weight, including biomarkers of adiposity

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(adipocytokines)¹⁵ and a lower resting metabolic rate.¹⁶ In this context, it is noteworthy that thyroid dysfunction is well recognized as a cause of weight change. Weight loss is a frequent manifestation of hyperthyroidism, and hyperthyroid patients who are treated adequately gain nearly 4 kg/y.¹⁷ Conversely, weight gain is a common com-

plaint in patients with hypothyroidism, and treatment with thyroid hormone is associated with modest weight loss.¹⁸

However, trials of subclinical hypothyroidism have not resulted in significant weight loss,^{18,19} raising the question of whether body weight varies with variation in thyroid function within the reference (physiologic) range. Some studies have related thyroid function and body weight in small, selected samples of obese individuals^{20,21} or those with thyroid disease.²² Some,^{20,21} but not all,²² have reported an association between thyroid function and body weight. Although variation in thyroid function within the reference range has been related to weight change in population-based samples, prior studies were limited by the use of self-reported weight gain²³ and the lack of an adequate control for baseline weight²⁴ (a known risk factor for weight gain²⁵) in multivariable analyses. Thus, it is not known whether variation in thyroid function within the reference range is associated with body weight, or whether subtle changes in thyroid function are associated with changes in weight over time. In this study, we determined the relations be-

tween thyroid function, as assessed by measurement of serum thyrotropin (TSH) concentrations, and body weight and weight change in a large community-based cohort. We hypothesized, based on knowledge of the fundamental role of thyroid hormone in regulating metabolism, that higher levels of serum TSH within the reference range may be associated with lesser degrees of thyroid hormone activity, and consequently with greater cross-sectional body weight. Furthermore, we postulated that incremental changes in serum TSH concentrations over time may be associated with longitudinal weight gain.

METHODS

STUDY SAMPLE

Participants for this study were drawn from the Framingham Heart Study. Beginning in 1948, 5209 men and women aged 28 to 62 years were enrolled.¹⁹ Offspring of the original cohort and their spouses (n=5124) were enrolled in the Offspring Study cohort starting in 1971. The selection criteria and design of the Offspring Study have been described previously.^{26,27} The study sample for the present study consisted of 3583 Offspring Study cohort participants who attended the third (*baseline*; 1983-1987) and fourth (*follow-up*; 1987-1991) examinations. Of these, 2407 were available for the final analyses after the following exclusions: use of thyroid hormone therapy at baseline (n=121) and at follow-up (n=40); missing covariates (n=92); missing serum TSH values (n=736); serum TSH concentration of less than 0.5 mIU/L (n=52) or higher than 5.0 mIU/L at baseline (n=108); or serum TSH concentrations of less than 0.5 mIU/L (n=20) or higher than 10.0 mIU/L at follow-up (n=7). Eligibility thresholds based on serum TSH values were slightly more liberal at the follow-up examination to ensure inclusion of participants who had moderate changes in serum TSH concentrations over time. The participants with available serum TSH values were similar to those with missing values with respect to body weight and body mass index. More women than men had missing TSH values (24.5% vs 19.7%; $P < .001$). Men with missing serum TSH values were slightly older than men with serum TSH values (51.0 vs 48.0 years; $P < .001$); there were no differences among women.

SERUM TSH ASSAY

Concentrations of TSH were measured on fasting morning samples using a chemoluminescence assay (London Diagnostics, Eden Prairie, Minnesota) with a lower limit of detection of 0.01 mIU/L. The interassay coefficients of variation were 5% (at 1 mIU/L) and 11% (at 0.04 mIU/L) as previously described.²⁸ Serum-free thyroxine levels were not measured.

RISK FACTOR ASSESSMENT

At each examination, weight was measured to the nearest pound with the participant wearing only a gown without shoes or slippers and standing in the middle of the scale (Detecto scale; Worcester Scale Co Inc, Webb City, Massachusetts) with the weight equally distributed on both feet. The scale is calibrated with a 22.5-kg weight monthly and professionally calibrated annually. Smoking status was defined by tobacco use in the year preceding the examination. For longitudinal analyses, the following 3-level smoking variable was defined: never, current, or quit in the interim. Women were considered to be postmenopausal if their menstrual periods had stopped for at least 1 year; a separate 3-level variable was constructed for baseline, interim, or no menopause for longitudinal analyses.

STATISTICAL ANALYSIS

We decided a priori to perform all analyses separately in men and women because of the well-known differences in thyroid disease prevalence in women compared with men.²⁹ Our TSH assay varied over time; therefore, statistical calibration to the Third National Health and Nutrition Examination Survey (NHANES III) data²⁹ was carried out using log-normal transformations within sex-specific age groups. Briefly, we divided women and men in our sample into 5-year age groups (30-34, 35-39, 40-44, etc) and standardized their log-transformed values within each group. Then we imposed NHANES III-based means, medians, and standard deviations corresponding to the log-transformed values. This was achieved by first multiplying the log-transformed standardized values by the standard deviation of the log-transformed log-normal variable calculated as

$$\sqrt{\log[(\sigma/\mu - \lambda)^2 + 1]},$$

where μ and σ denote the NHANES III-based log-normal means and standard deviations and λ is the shift variable calculated using the NHANES III-based median, minimum, and maximum:

$$\frac{(\text{Minimum} \times \text{Maximum} - \text{Median Squared})}{(\text{Minimum} + \text{Maximum} - 2 \times \text{Median})}$$

and adding the corresponding mean calculated as

$$\log[(\mu - \lambda)^2 / \sqrt{\sigma^2 + (\mu - \lambda)^2}].$$

The resulting number was then exponentiated and a shift parameter λ was added to obtain the final value. This method preserved not only the age-group and sex-specific means and standard deviations but also the medians.

We analyzed TSH concentrations as a continuous variable and as quartiles. When used as a continuous variable, TSH concentration was natural logarithmically transformed because of its skewed distribution; results are presented as weight change per 1-unit increase in log TSH concentration. To formally test for differences between women and men, we pooled the sexes and fit a sex interaction term in the multivariable models on sex-standardized weight. For quartile-based analyses, we examined sex-specific quartiles of serum TSH concentrations in relation to weight and weight change. Continuous and quartile-based analyses of TSH concentrations consisted of the following 3 models:

1. Cross-sectional association of serum TSH concentrations and body weight at the baseline examination using multivariable linear regression models, adjusting for age, smoking, and menopausal status.
2. Relations of baseline serum TSH concentrations to the longitudinal change in body weight at follow-up, adjusting for age, 3-level smoking status, 3-level menopause status, and baseline weight using multivariable linear regression.
3. Sex-specific association between change in serum TSH concentration and change in body weight at follow-up, adjusting for age, 3-level smoking status, 3-level menopause status, and baseline weight using multivariable linear regression.

Secondary analyses were performed to determine whether participants in the highest decile of weight change were more likely to have elevated serum TSH values at follow-up compared with the rest of the sample. For these analyses, we relaxed our eligibility criteria to permit inclusion of participants regardless of their serum TSH value to increase the clinical relevance; however, participants reporting use of thyroid hormone therapy were not included because we were unable to assess recent medication changes. Two sex-specific analyses were performed, adjusting only for age: determination of the log-transformed mean serum TSH

concentration at follow-up in participants in the upper decile of weight change at follow-up compared with the remainder of the sample; and determination of the odds ratio of having a serum TSH concentration higher than 5.0 mIU/L among participants in the upper decile of weight change at follow-up compared with the participants in the lower 9 deciles.

For all analyses, a 2-tailed $P < .05$ was considered significant. We used SAS, version 9.1 statistical software to perform all computations.³⁰

RESULTS

Overall, data for 1117 women and 1290 men were available for analysis. The average interval between the baseline and follow-up examinations was 3.5 years. The women weighed an average of 66.6 kg at the baseline examination and 68.0 kg at follow-up (**Table**). The men weighed an average of 84.1 kg at baseline and 85.1 kg at follow-up. The prevalence of obesity at baseline was 14.3%. The mean baseline serum TSH concentration was 1.91 mIU/L in women and 1.70 mIU/L in men.

CROSS-SECTIONAL RELATIONS OF BASELINE SERUM TSH CONCENTRATIONS AND BODY WEIGHT

In analyses modeling TSH concentration as a continuous variable, an increase of 1 U of log TSH concentration was associated with a 4.2-kg greater weight in women ($P < .001$) and 1.9-kg greater weight in men ($P = .01$); the sex interaction term was of borderline statistical significance ($P = .07$). In quartile-based analyses, there was a similar strong and graded positive relation between increasing quartiles of serum TSH concentrations and higher body weight at baseline. Women with the lowest quartile of TSH concentration had a mean weight of 64.5 (95% confidence interval [CI], 62.9-66.1) kg, whereas women in the highest quartile of TSH concentration had a mean weight of 70.2 (95% CI, 68.5-71.8) kg (**Figure 1**; $P < .001$ for trend). Men in the lowest quartile of TSH concentration had a mean weight of 82.8 (95% CI, 81.4-84.2) kg, whereas those in the highest quartile had a mean weight of 85.6 (95% CI, 84.2-86.9) kg ($P = .007$ for trend).

BASELINE SERUM TSH CONCENTRATION AND WEIGHT CHANGE AT FOLLOW-UP

There was no relation between log TSH concentration (modeled as a continuous variable) and weight change during follow-up in women ($P = .25$) or men ($P = .90$), and no sex interaction was observed ($P = .33$ for the interaction term). In the quartile-based analysis, baseline serum TSH concentration was not related to weight change during the 3.5 years of follow-up in either sex (**Figure 2**).

CHANGE IN SERUM TSH CONCENTRATION AND WEIGHT CHANGE AT FOLLOW-UP

At follow-up, the changes in serum TSH concentrations (Δ TSH) ranged from -2.45 to 7.49 mIU/L in women and -3.02 to 6.79 mIU/L in men. In women, weight increased by 2.3 kg for every 1-unit increment in log TSH concentrations in women ($P < .001$) and by 1.1 kg in men

Table. Characteristics of Study Sample at Baseline and Follow-up^a

Characteristic	Women (n = 1117)	Men (n = 1290)
Baseline		
Age, y	48 (10)	48 (10)
Weight, kg	66.6 (13.6)	84.1 (12.5)
BMI	25.3 (5.1)	27.2 (3.6)
Serum TSH concentration, mIU/L ^b	1.91 (0.88)	1.70 (0.79)
Current smoking, %	30	28
Postmenopausal, %	50	
Follow-up		
Weight, kg	68.0 (14.5)	85.1 (13.0)
Weight change, kg	1.5 (5.6)	1.0 (5.0)
BMI	26.0 (5.4)	27.7 (3.8)
Serum TSH concentration, mIU/L	1.96 (1.04)	1.83 (0.96)
Serum TSH change, mIU/L ^c	0.06 (0.86)	0.13 (0.81)
Current smoking, %	25	24
Postmenopausal, %	59	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); TSH, thyrotropin.

^aUnless otherwise indicated, data are expressed as mean (SD).

^bThe 25th, 50th, and 75th percentiles of serum TSH concentrations among women were 1.21, 1.76, and 2.44 mIU/L, respectively; among men, 1.13, 1.53, and 2.09 mIU/L, respectively.

^cThe 25th, 50th, and 75th percentiles of change in serum TSH concentrations among women were -0.34, 0.02, and 0.42 mIU/L, respectively; among men, -0.29, 0.09, and 0.46 mIU/L, respectively.

($P = .002$); the sex interaction term was of borderline significance ($P = .049$). When the analyses were limited to those with a TSH concentration of less than 5 mIU/L at follow-up, resulting in the exclusion of an additional 15 men and 16 women, results were minimally attenuated: weight increased by 1.9 kg per every 1-unit increase in log TSH concentration ($P < .001$) in women and by 1.0 kg per every 1-unit increase in log TSH concentration ($P = .007$) in men. In the quartile-based analysis, there was a strong, graded positive relation between Δ TSH concentration and weight change (**Figure 3**); the mean weight change increased from 0.5 kg in the lowest quartile of Δ TSH concentration to 2.3 kg in the highest quartile ($P < .001$ for trend) in women, and from 0.4 kg in the lowest quartile of Δ TSH concentration to 1.3 kg in the highest quartile ($P = .007$ for trend) in men. When serum TSH concentration at follow-up was limited to a serum TSH concentration of less than 5.0 mIU/L, the results were not materially changed (data not shown).

UPPER DECILE OF WEIGHT CHANGE OVER TIME AND SERUM TSH CONCENTRATION AT FOLLOW-UP

In a secondary analysis of participants at follow-up, including those with abnormal serum TSH values who were not taking thyroid hormone therapy ($n = 2632$), we compared the participants in the upper decile of weight change (from baseline to follow-up) with the rest of the group. In women, those in the upper decile of weight change ($n = 130$) gained a mean of 12.0 (range, 7.7-48.2) kg; the mean serum TSH concentration in this group at follow-up was 2.86 mIU/L, compared with 2.41 mIU/L in the rest of the sample. After adjustment for age, the dif-

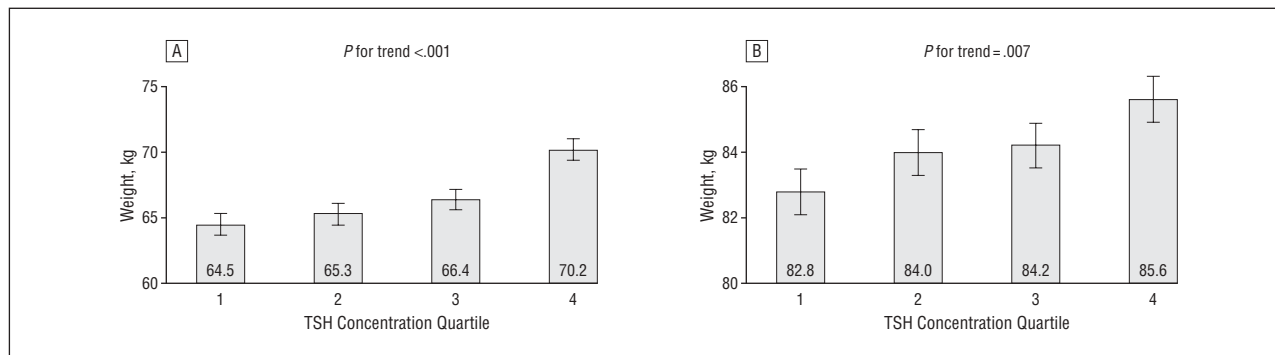


Figure 1. Mean (SE) multivariable-adjusted body weight according to the quartile of serum thyrotropin (TSH) concentration at baseline among women (A) and men (B), adjusted for age, smoking status, and menopausal status (in women). Error bars represent standard error. The quartiles of TSH concentrations for men and women are given in the footnote to the Table.

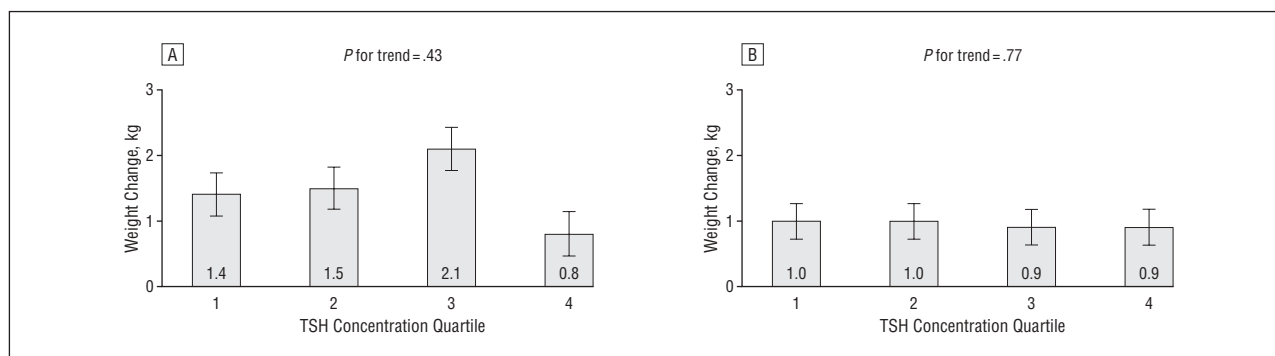


Figure 2. Mean (SE) multivariable-adjusted mean change in body weight according to the quartile of baseline serum thyrotropin (TSH) concentration among women (A) and men (B), adjusted for age, smoking status, menopausal status (in women), and baseline weight. Error bars represent standard error. The quartiles of TSH concentrations for men and women are given in the footnote to the Table.

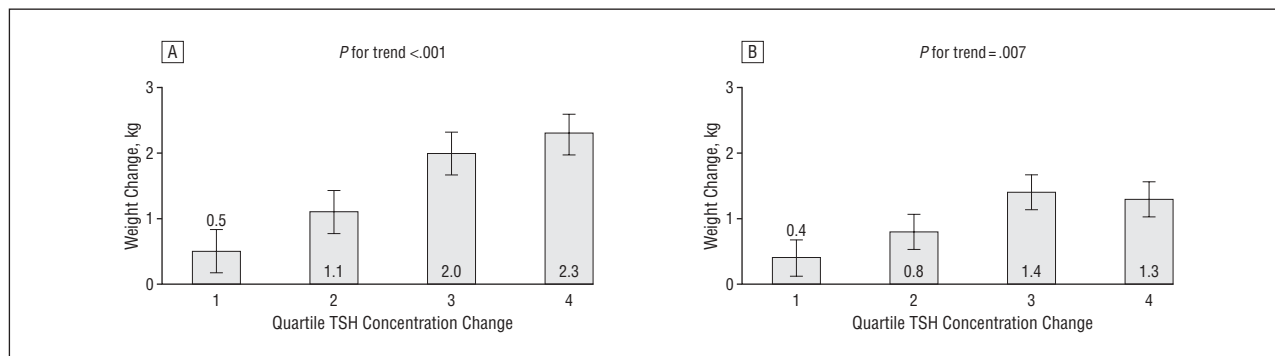


Figure 3. Mean (SE) multivariable-adjusted mean change in body weight according to quartile of change in serum thyrotropin (TSH) concentration among women (A) and men (B), adjusted for age, smoking status, menopausal status (in women), and baseline weight. Error bars represent standard error. The quartiles of TSH concentrations for men and women are given in the footnote to the Table.

ference in log serum TSH concentration was higher among women who gained more weight ($P = .02$). More women in the highest decile of weight change had elevated TSH concentrations at follow-up (serum TSH concentration, >5.0 mIU/L) compared with the rest of the sample (9.2% vs 5.7%), although this difference was of borderline statistical significance ($P = .06$). In men, the mean serum TSH concentration among those in the highest decile of weight change was 1.87 mIU/L (mean weight change, 9.6 [range, 6.8-21.8] kg) compared with 2.04 mIU/L in the rest of the sample ($P = .64$). In men, 2.2% of those in the highest decile of weight change had a serum TSH concentra-

tion higher than 5.0 mIU/L at follow-up compared with 2.7% of the remainder of the sample ($P = .80$).

COMMENT

PRINCIPAL FINDINGS

In our community-based sample of participants with thyroid function within the reference range, we observed that the baseline serum TSH concentration was strongly and linearly associated with cross-sectional weight in women and men. During 3.5 years of follow-up, baseline serum

TSH concentrations were not associated with change in weight. However, change in serum TSH concentrations over time (within the reference range) was strongly and linearly associated with weight gain. Models analyzing TSH concentration as a continuous variable yielded results consistent with quartile-based models.

COMPARISON WITH PREVIOUS STUDIES

Data on the association of thyroid function within the range of normal variation and body weight are limited. Patients with overt hypothyroidism lose weight when treated,¹⁸ and patients with hyperthyroidism gain weight when treated.^{17,31} Among patients with subclinical hypothyroidism, thyroid hormone therapy has not resulted in significant weight loss.^{18,19} However, these studies have been limited by small sample sizes and short follow-up.

There have been few studies of thyroid function and body weight among individuals with normal thyroid function. A Danish study²⁷ found the following positive cross-sectional association between body mass index and serum TSH concentration: between the lowest and highest quintiles of TSH values, body weight differed by 5.5 kg. A direct comparison of these findings and our results is not possible because these investigators performed sex-pooled analyses and included serum TSH values above and below the accepted reference range. Nonetheless, the results are consistent, lending support to the notion that thyroid function may be an important determinant of body weight. Among 6164 participants from the Tromso Study, women but not men were found to have an association between change in TSH values and body mass index.²⁴ During 7 years of follow-up, changes in TSH concentration were associated with changes in body weight in sex-pooled analyses; sex-specific analyses were not significant. However, baseline weight was not accounted for in these analyses, a notable limitation given the strong cross-sectional association between weight and TSH concentration. Our data add the important findings that change in serum TSH concentrations over time may be associated with change in body weight, and we extend these findings to women and men after adjustment for several potential important confounders.

POTENTIAL MECHANISMS

There are multiple potential explanations for our findings. There is a well-known association between energy expenditure, thermogenesis, and thyroid function.³² Lower serum triiodothyronine concentrations (associated with higher serum TSH concentrations) were associated with decreased resting metabolic rate in postobese individuals.³³ In a study of hypothyroid patients receiving long-term treatment with thyroid hormone in whom the dose was varied so as to result in serum TSH concentrations of 0.1 to 10.0 mIU/L, there was a strong inverse association between increases in serum TSH concentration and decreases in resting energy expenditure (by as much as 15%).³⁴ The authors estimated that this difference could result in an expenditure of approximately 75 to 150 kcal/d, which could result in significant weight gain over time; unfortunately concomitant changes in weight were not reported. Given that low resting energy expenditure is associated with subsequent weight gain,¹⁶

this observation provides a plausible mechanism for the association of change in serum TSH concentration and weight gain over time.

It is intriguing that baseline serum TSH concentrations were strongly associated with baseline body weight, but not with change in body weight over time. Only when the serum TSH concentration increased over time did we find an association with increasing body weight. This finding suggests the possibility of an intrinsic body weight set point that may maintain individuals at a given body weight. Only when there is a slight perturbation in metabolism, as detected by an increase in serum TSH concentration, is an association observed with weight gain.

Our results were stronger in women, although we observed relations similar in directionality in men but with smaller effect sizes. We believe that these sex-related differences in the associations between serum TSH concentration and body weight are probably not related to statistical power; we estimated that we had 92% power to detect in men an effect size similar to that observed in women. Other explanations for our sex-specific findings may be related to the differential effects of thyroid function on body weight and metabolism in women vs men. Fat oxidation is higher in men compared with women³⁵; whether this is mediated in part through thyroid function is unknown. The preponderance of thyroid disease in women²⁹ suggests a differential effect of thyroid pathophysiologic mechanisms in men compared with women.

STRENGTHS AND LIMITATIONS

The strengths of our study include a well-characterized, large community-based sample. We excluded participants with serum TSH values outside the range considered physiologic. We had well-characterized covariate data, enabling us to perform multivariable-adjusted analyses. Study limitations include the observational design, so we cannot infer causality. Indeed, one might question whether weight gain may cause increases in serum TSH concentrations. However, in a study of subjects admitted to a metabolic ward, those who lost 10% of their body weight had a decline in serum TSH concentrations from 3.1 to 2.4 mIU/L, whereas those who gained 10% of their body weight had no change in serum TSH concentration.³⁶ Thus, it is unlikely that the increases in serum TSH concentration in our study are due to weight gain alone. An additional limitation of our study is that we did not measure free thyroxine levels. Nonetheless, serum TSH concentrations are generally considered to be the most sensitive marker of thyroid function. In our community-based sample, it is unlikely that other rare causes of hypothyroidism are driving the associations observed. Our sample was nearly entirely white, and our results may not be generalizable to other ethnic groups. Finally, we were unable to account for other covariates known to be associated with body weight and weight change, including diet and physical activity.

CLINICAL IMPLICATIONS

The identification of change in thyroid function as a risk factor for weight gain might help guide research into the identification, prevention, and treatment of individuals at

risk for the development of excess adiposity.³⁷ Confirmation of our findings in other samples is warranted, and in particular more longitudinal studies are warranted. We attempted to answer the clinical question of whether derangements in thyroid function are present in community-dwelling individuals who gain excess amounts of body weight. In doing so, we found that mean serum TSH concentrations were higher among women in the upper decile of weight change, and that these women were at nonsignificantly increased odds of having serum TSH concentrations higher than 5.0 mIU/L. Therefore, abnormalities in thyroid function may play a small role in significant weight gain among women in an unselected sample.

In conclusion, thyroid function (as assessed by serum TSH concentrations) within the reference range is associated with body weight in both sexes. Our findings raise the possibility that modest increases in serum TSH concentrations within the reference (physiologic) range may be associated with weight gain.

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Author Contributions: Dr Fox had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Fox, Pencina, D'Agostino, Murabito, Seely, and Vasan. Acquisition of data: D'Agostino. Analysis and interpretation of data: Fox, Pencina, D'Agostino, Murabito, Seely, Pearce, and Vasan. Drafting of the manuscript: Fox and Vasan. Critical revision of the manuscript for important intellectual content: Pencina, D'Agostino, Murabito, Seely, Pearce, and Vasan. Statistical analysis: Fox, Pencina, and D'Agostino. Administrative, technical, and material support: Vasan.

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