

## Original Article

# Association between Serum TSH Concentration and Body Mass Index in Euthyroid Subjects: The Role of Smoking

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## Abstract

**Background:** Data regarding the influence of minor changes in thyroid function on body mass index (BMI) are scarce and conflicting. This study aims to evaluate the association between normal levels of serum TSH and BMI, taking into consideration the effect of smoking tobacco.

**Methods:** In this cross-sectional community-based survey, 1581 randomly selected subjects who had no histories of thyroid disorders were studied within the framework of the Tehran Lipid and Glucose Study. Serum TSH and TPOAb were measured from the fasting serum samples. Weight and height were measured and BMI was calculated.

**Results:** TSH concentrations within the reference range were positively associated with BMI ( $P < 0.002$ ). Each unit increase of 1  $\mu\text{U/ml}$  in TSH was associated with an increase in mean BMI of 0.31  $\text{kg/m}^2$  (95% CI: 0.1 – 0.5,  $P < 0.002$ ), an association which remained significant after adjustments for sex, physical activity, and smoking and in the subgroup with negative thyroid autoimmunity. The association between BMI and TSH remained significant only in nonsmokers ( $P < 0.004$ ).

**Conclusion:** The results suggest that a significant positive association exists between TSH and BMI in euthyroid nonsmokers.

**Keywords:** Body mass index, smoking, thyroid function, thyrotropine

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## Introduction

Obesity is associated with numerous co-morbidities such as diabetes, cardiovascular diseases (CVD), hypertension, all-cause mortality and cancers.<sup>1,2</sup> Over the past 20 years, obesity has become a global epidemic.<sup>3</sup> Increase in caloric intake, decline in physical activity and smoking cessation, in addition to socioeconomic and genetic factors have been considered as predictors for obesity.<sup>4,5</sup>

Thyroid hormones effect bodyweight through modification of the basal metabolic rate. It is well-recognized that overt hypothyroidism is associated with weight gain; weight loss is a common symptom in patients with overt hyperthyroidism.<sup>6</sup> Some studies have revealed that low thyroid hormone levels, even within normal ranges, are associated with overweight and obesity.<sup>7,8</sup> Other studies have found no association in this regard.<sup>9</sup> In a study from an iodine sufficient area in Norway (HUNT), out of 27097 subjects, low thyroid function was associated with high body mass index (BMI) in both current smokers and those who have never smoked.<sup>10</sup> In 1853 euthyroid subjects in Australia, small differences in free T4 were associated with differences in BMI in nonsmokers; however, no significant relationship was found between BMI and TSH in both smokers and nonsmokers.<sup>11</sup> In a study in Northern Norway conducted on 10419 subjects, a positive association between TSH and BMI was found only in nonsmokers.<sup>8</sup> In consideration of the

conflicting published data, this study was designed to evaluate the association between serum TSH concentrations within the normal reference range and BMI.

## Subjects and Methods

This 2006 cross-sectional survey was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS), a community-based epidemiological survey conducted since 1999 to identify the prevalence and incidence of risk factors of CVD among residents of Tehran, an area of iodine sufficiency.<sup>12</sup> Of 15005 participants, 1999 subjects (aged  $\geq 20$  years) were randomly selected for this study. Each individual completed a self-administered health questionnaire that included personal details, family history of goiter, hyperthyroidism or hypothyroidism, use of thyroid hormones, symptoms and signs consistent with hyper- or hypothyroidism, current medication usage, smoking habits, and physical activity status. People with previously known thyroid disorders, those on thyroid medications, and patients with missing information on height, weight, smoking status, and physical activity were excluded. Thus, a total of 1581 subjects (79%) were eligible for the analysis and entered the study. Weight (kg) and height (m) were measured with the subjects barefooted, in light clothes, using standardized instruments. BMI was calculated as dividing the body weight (kg) by height in  $\text{m}^2$ . Physical activity level was assessed using a modifiable activity questionnaire (MAQ) in two categories; the active category was based on MET\*-minutes per week that equaled or exceeded 600; the inactive category was based on MET of minutes per week less than 600.<sup>13</sup> This level of intensity was previously recommended by the Center for Disease Control and Prevention (CDC) for health benefits. High reliability and moderate validity were found for the Persian translated MAQ

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**Table 1.** Linear regression analysis for BMI as dependent variable in the euthyroid group and subgroup of negative TPOAb subjects.

Independent variables	Euthyroid subjects			Negative TPOAb euthyroid subjects		
	$\beta^*$	95% CI	<i>P</i>	$\beta$	95% CI	<i>P</i> <sup>†</sup>
TSH	0.31	0.116–0.505	<0.002	0.4	0.17–0.62	<0.001
Age	0.18	0.001–0.036	<0.04	0.18	-0.001–0.37	<0.05

\* Unstandardized regression coefficient; † *P* <0.05: statistically significant.

in Tehran's adult population. For adjusting measurements smokers were classified as current, non- and ex-smokers.

#### Laboratory measurements

For each participant, a fasting serum sample stored frozen at -70°C, until necessary for measurements of serum TSH and TPOAb. In those with abnormal serum TSH levels, serum total T<sub>4</sub> (TT4) and T3 uptake were measured and free T4 index (FTI) was calculated. Normal serum TSH concentrations in this population ranged from 0.3 – 5.8 µU/mL based on the 2.5 and 97.5 TSH percentiles in the previous study.<sup>14</sup> Serum TSH concentrations were measured by IRMA (Isotope Kit, Budapest, Majarestan) and TT4 was measured by RIA (Isotope Kit, Budapest, Majarestan). The inter- and intra-assay coefficients of variations for all measured parameters were 3.1% and 3.8%, respectively. T3 uptake was measured by Elisa (Elisa Kit, Pishtaz Tebe Co., Tehran, Iran). Free thyroxin index (FTI) was calculated by multiplying T4 by T3 uptake. The FT4I normal range was 1.13 – 4.6. Inter- and intra-assay coefficients of variations were 4.1 and 5.5, respectively. TPOAb was measured by Elisa (Orgentec Co., Germany) and levels ≥ 40 IU/mL were considered positive.

#### Definitions

Hyper- and hypothyroidism were defined based on the normal values of serum TSH (derived from the results of the reference population in the present survey) and FT4I. Subclinical hypothyroidism was defined as: FT4I = 1.13 – 4.6 with TSH > 5.8 µU/mL; clinical hypothyroidism was considered to be TSH > 5.8µU/mL and FT4I < 1.13. Subclinical hyperthyroidism was defined as TSH < 0.3 µU/mL and FT4I = 1.13 – 4.6; clinical hyperthyroidism was defined as TSH < 0.3 µU/mL with FT4I > 4.6.<sup>14</sup>

Subjects with serum TSH values within the reference range (0.3 – 5.8 µU/mL) were considered to be euthyroid. In our study we did not separately analyze subclinical and overt types due to the small sample size within each group. Therefore, the subclinical and overt types were combined under one category of thyroid dysfunction.

#### Statistics

The linear regression model was applied to assess the association between TSH as an independent variable and BMI as a dependent variable. In this model, age, sex, physical activity and smoking were added as covariables. BMI was considered to have normal distribution with visual inspection of the histograms. Analysis was performed for subjects with TSH within the normal reference range and a subgroup of negative TPOAb subjects within this population. The study population was divided into 3 groups of euthyroid, hypo- and hyperthyroid. Euthyroid subjects with serum TSH values within the normal reference range were divided by tertile (0.3 – 1.3, 1.3 – 2.2, 2.2 – 5.8). Analysis of covariance (ANCOVA) was applied to compare the mean values of BMI among 5 groups of thyroid functions. Considering the lowest tertile range as the reference group, logistic regression analysis was used to compare

the odds ratio for obesity for each category of thyroid function. All measurements were adjusted for age, sex, and smoking status (current, ex- and nonsmokers) and physical activity. Stratified analysis was performed for smokers and nonsmokers. *P* < 0.05 was statistically significant.

## Results

The study population (1581 subjects) was comprised of 701 (44.3%) males and 880 (55.7%) females with a mean age of 52 ± 13 years. Of these, 1250 (79.1%) were nonsmokers, while 186 (11.8%) were current smokers, and 140 (8.9%) were ex-smokers. There were 1455 (92%) euthyroid subjects, 85 (5.4%) hypothyroid, and 41 (2.6%) hyperthyroid. Current smokers comprised 24.1% of men and 1.9% of women.

There was a significant positive association between TSH and BMI in euthyroid subjects, both overall and in nonsmokers. In model 1 (age adjusted) each unit increase of 1 µU/mL TSH was associated with an increase in mean BMI of 0.31 kg/m<sup>2</sup> (95% CI: 0.1 – 0.5, *P* < 0.002, R<sup>2</sup> = 0.02); this association remained significant after further adjustments for age and sex in model 2, and marginally significant in the multivariate model (adjusted for age, sex, physical activity, and smoking; *P* = 0.01; Table 1). In the strata for negative TPOAb euthyroid subjects, each unit increase of 1 µU/mL TSH was associated with an increase in mean BMI of 0.4 kg/m<sup>2</sup> (95% CI: 0.2 – 0.6, *P* < 0.001, R<sup>2</sup> = 0.03). In the same subgroup, after further adjustments for sex, smoking and physical activity, the association remained significant (*P* = 0.03).

Stratified analysis for smokers and nonsmokers showed a significant association between BMI and TSH only in nonsmokers (*P* < 0.004) after an adjustment for age, whereas in smokers no association was found between TSH and BMI (*P* > 0.1). In nonsmokers, each unit increase of 1 µU/ml TSH was associated with an increase in mean BMI of 0.36 kg/m<sup>2</sup> (95% CI: 0.1 – 0.6, *P* = 0.003). After further adjustments for age, sex and physical activity, the association remained marginally significant in nonsmokers (*P* = 0.07).

There was upward trend in mean BMI in 3 categories of thyroid function (tertile of TSH within the normal range; *P* = 0.02; Table 2), which remained significant only in nonsmokers.

Linear regression analysis showed no association between serum TSH values and waist circumferences, except in women, in whom each increase in TSH was associated with a 0.8 mm increase in waist circumference (*P* < 0.04).

## Discussion

The main finding of this study was the correlation between a lower serum TSH concentration and higher BMI in all euthyroid subjects. This correlation was significant only in nonsmokers, which indicated that smoking possibly modified the relationship between TSH and BMI. Although this observational study has not estab-

**Table 2.** Mean BMI in 5 categories of thyroid function in the study population (smokers and nonsmokers).

TSH ( $\mu\text{U/mL}$ )	Hyperthyroid* ( $<0.3$ )	Lower tertile ( $0.3\text{--}1.3$ )	Middle tertile ( $1.3\text{--}2.2$ )	Upper tertile ( $2.2\text{--}5.8$ )	Hypothyroid* ( $>5.8$ )	P
<b>All</b>						
n	41	468	467	515	85	<0.001
BMI ( $\text{kg/m}^2$ )	28.0	28.2	28.8	29.0	30.0	
<b>Smokers</b>						
n	5	73	47	54	7	<0.1
BMI ( $\text{kg/m}^2$ )	25.5	27.2	26.9	27.6	28.4	
<b>Nonsmokers</b>						
n	36	395	420	461	78	<0.004
BMI ( $\text{kg/m}^2$ )	28.4	28.4	29.0	29.1	30.1	

\*Hyper- and hypothyroid in this study included both clinical and subclinical types of thyroid dysfunction.

lished any casual relationship between TSH and BMI, there are some plausible explanations and study results that have supported this hypothesis. Data on the association between normal range thyroid function and BMI are controversial, thus it is not clear whether this relationship is modified by smoking.

In agreement with our findings, Nyrnes et al. have investigated 6164 subjects in Northern Norway and found a significant positive correlation between serum TSH and BMI only in nonsmokers.<sup>8</sup> In contrast, in the HUNT study of 27097 individuals, the association of low thyroid function with high BMI was at least as strong in current smokers as it was in those who had never smoked.<sup>10</sup>

In a study by Knudsen et al. conducted on 4082 iodine deficient Danish subjects, a significant positive association was found between TSH categories and both BMI and obesity. They observed a negative association between BMI and free T4. In this study however, the results were not separately analyzed for smokers and nonsmokers.<sup>7</sup> In the Busselton Health Study of 2108 euthyroid subjects, small differences in free T4 were associated with differences in BMI in nonsmokers, but no relationship was found between TSH and BMI.<sup>11</sup> Our results differed from a study in UK by Manji et al. of 401 euthyroid subjects, which provided no evidence for any association between normal range thyroid status and BMI.<sup>9</sup> The discrepancies in the results of the above-mentioned studies may be due to differences in their study design, sample size, measurement technique, demographic, and iodine status.

The mechanism proposed to explain the correlation between thyroid function and body mass is the interaction effect between thyroid function and adipose tissue. The association between basal metabolic rate, thermogenesis, and thyroid function is well-known.<sup>15</sup> Association of low basal metabolic rate with subsequent weight change<sup>16</sup> provides a plausible explanation for the association of changes in serum thyroid hormones and weight gain over time; in support of this hypothesis, clinical trials have shown that treatment of hypo- and hyperthyroidism are associated with subsequent weight loss<sup>17</sup> and weight gain,<sup>18</sup> respectively. Our finding has also supported this hypothesis, in which only a slight perturbation in metabolism detected by an increase in serum TSH is associated with an increase in BMI. However in our study, this association was not strong enough to change the prevalence of obesity among different TSH categories. On the other hand, leptin and other adipokines secreted from adipose tissue may also influence thyroid function.<sup>19</sup> Clinical studies have reported that weight loss in obese subjects is associated with reduced thyroid function<sup>20,21</sup> and weight gain in those with anorexia nervosa may be followed by increased

thyroid function.<sup>22</sup>

In our study the relationship between BMI and TSH persisted when the analysis was confined to negative TPO antibody subjects, which was in contrast to a study in an outpatient clinic in Spain where the association between TSH and BMI observed in euthyroid subjects was not observed in the subgroup of subjects with negative thyroid autoimmunity.<sup>23</sup>

Smoking decreases body weight through increasing energy expenditure by its components such as nicotine and weight gain often occurs following smoking cessation.<sup>24</sup> Tobacco smoking has complex effects on thyroid function;<sup>25,26</sup> some studies report lower serum TSH concentrations in smokers than in nonsmokers.<sup>27,28</sup>

We have found a positive relation between TSH and BMI in only nonsmokers. Smokers exhibit a negative association in this regard which implies that smoking could mask or reverse this relationship.

The strengths of this study include a community-based design with a large sample size, careful adjustments for age, gender, smoking and physical activity status, in addition to exclusion of those with TSH values outside the reference interval and those with positive thyroid autoimmunity. Limitations of this study include the following: free thyroxine levels were not measured which could supply us with more information, and we were unable to include a few covariates such as diet energy intake, education and life style which could have affected BMI. Subjects with concomitant drug consumption and non-thyroidal illnesses which may have effects on both BMI and TSH were not excluded. Furthermore, it seems that measurement of lean body mass is more appropriate than total body mass, as some studies report that lean body mass is a better determinant of levothyroxine requirements than total body weight.<sup>29</sup>

In conclusion, our data support the idea that a small difference in thyroid function, even within the normal reference interval of TSH, may contribute to alterations in BMI among nonsmokers.

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