The relation between changes in thyroid function and anthropometric indices during long-term follow-up of euthyroid subjects: the Tehran Thyroid Study (TTS)

Behrang Motamed¹, Anita Eftekharzadeh¹, Farhad Hosseini¹, Maryam Tohidi², Mitra Hashemini² and Fereidoun Azizi³

¹Obesity Research Center, ²Prevention of Metabolic Disorders, and ³Endocrine Research Center, Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence should be addressed to F Hosseini
Email
fhosseini@endocrine.ac.ir

Abstract

Objective: Uncertainties exist regarding the causal relationship between thyroid function tests (TFT) within the euthyroid range and anthropometric measures. This longitudinal cohort is aimed to examine the relationship between the two conditions.

Subjects and methods: Euthyroid participants of Tehran Thyroid Study (TTS) attending phase I (1999–2001) were included in this study and were followed up to phase IV (2008–2011). TSH and free T₄ (fT₄) levels as well as weight (Wt), waist circumference (WC), hip circumference (HC) and waist-to-hip ratio (WHR) were measured at both phases.

Results: 971 women and 784 men were included in the analysis. During 9.7 years of follow-up, increases in TSH levels, Wt and WHR as well as a decrease in fT₄ level were observed. Multivariable regression analysis showed a significant relationship between TSH changes and alterations in WC in women ($\beta=0.69$, $P=0.021$) and men ($\beta=0.61$, $P=0.038$). Moreover, a significant negative association of ΔfT_4 with changes in weight was documented ($\beta=-0.49$, $P=0.001$ in women and $\beta=-0.56$, $P<0.001$ in men). Additionally, we found a negative relationship between ΔfT_4 and ΔHC in men ($\beta=-0.36$, $P=0.001$).

Conclusion: In both genders, there was a positive relationship between changes in TSH and waist circumference and conversely a negative association of changes of fT₄ levels with weight over time.

European Journal of
Endocrinology
(2016) **175**, 247–253

Introduction

Thyroid hormones are known to affect the resting energy expenditure (REE) (1). While overt thyroid dysfunctions are known to be associated with some degrees of weight change, whether small changes in thyroid function – within the normal laboratory range – would lead to alterations in anthropometric indices or not is still a matter of debate (2).

Some cross-sectional studies have shown an association between high body mass index (BMI) and low

levels of free T₄ or high levels of TSH within the euthyroid range (3, 4, 5). Others have documented the relationship only in certain subgroups, including smokers (6, 7). There are also reports indicating an association between slight alterations in thyroid function and subcutaneous fat accumulation (8) or insulin resistance (9). However, these results are not agreed upon by all investigators, especially in elderly subgroups (10). Moreover, the presence of thyroid autoimmunity seems to affect this

Clinical Study	B Motamed and others	Thyroid function and anthropometric indices	175:4	248
----------------	----------------------	---	-------	-----

relationship (11). To overcome the potential flaw of cross-sectional studies, few cohorts have examined the effect of variation in thyroid function on measures of body mass. These longitudinal studies showed that an increase in TSH concentration within the reference range was positively associated with increases in weight (12), waist circumference (WC), waist-to-hip ratio (WHR) (13) and BMI (13, 14). Moreover, the Dan Thyroid longitudinal study recently concluded that, while there was an association between weight alteration and TSH change, TSH level was not a determinant of future weight change (15).

Considering the above-mentioned uncertainties regarding the causal relationship between thyroid function and anthropometric indices and the paucity of longitudinal studies addressing the issue, we conducted the present cohort to assess the association between TSH and free T_4 changes within the reference range and alterations in weight and other anthropometric measures in participants of the Tehran Thyroid Study (TTS).

Subjects and methods

Subjects

Participants of the Tehran Thyroid Study (TTS) were recruited for this study. Initiated in 1999, the TTS is an ongoing cohort being conducted within the context of the Tehran Lipid and Glucose Study (TLGS), a large population-based study for identification and prevention of noncommunicable diseases; profiles of both are fully described elsewhere (16, 17).

In brief, individuals aged ≥ 20 years, residents of district No. 13 of Tehran, were selected using multistage cluster random sampling. Baseline measurement including weight, height, waist and hip circumference, and body mass index (BMI) were recorded and fasting blood samples were obtained. All participants were invited for follow-up studies at 3 years intervals.

Participants in phase I (1999–2001) and IV (2008–2011) of the TTS were included in our study if they had (i) available required data in both phases I and IV, including weight; waist and hip circumference; TSH, fT_4 and TPO Ab levels; and (ii) TSH and fT_4 levels within the national reference ranges in both phases I and IV.

Our exclusion criteria consisted of (i) history of overt or subclinical thyroid diseases (hyperthyroidism, hypothyroidism, thyroid nodules and goiter); (ii) current use or history of thyroid treatments (thyroid hormones/antithyroid medications, corticosteroids, Iodine ablation and surgery); and (iii) pregnancy.

Reference levels for normal TSH and free T_4 levels were drawn from a study of Tehranian population (18) aimed to determine reference intervals for TSH and fT_4 based on the criteria of the National Academy of Clinical Biochemistry (NACB). According to this study, the national reference range for TSH level was set as 0.32–5.96 U/L, and normal range for fT_4 level was defined as 11.84–19.95 pmol/L.

Written informed consent was obtained from all participants. Following approval by the Research Ethics Committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences, the study was conducted in accordance with the principles of the Declaration of Helsinki.

Measurements

The participants were interviewed by trained staff to obtain demographic data, medical history, detailed personal and family history regarding possible thyroid disease such as goiter, hyperthyroidism or hypothyroidism and current medication as well as history of iodine ablation, smoking habits and taking any medication that could interfere with thyroid function test results. According to smoking status, participants were categorized as (i) never-smokers or (ii) current smokers or quitters. Physical activity was assessed by the Lipid Research Clinics (LRC) questionnaire (19). Additionally, female subjects were classified into two groups regarding their menstrual status: (i) nonmenstruating for at least the past 1 year or (ii) currently menstruating women.

For all participants, a brief physical examination including anthropometric measurements was performed by trained physicians at baseline and every 3 years thereafter. Anthropometric measurements were taken with shoes removed and having the participant wearing light clothes. Using digital scales, weight was recorded in kilograms, and was documented to the nearest 100 g. Height was measured with participants in a standing position, using a tape meter, with the shoulders in normal alignment. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of the umbilicus using an unstretched tape meter, without any pressure to the body surface, and was recorded to the nearest 0.1 cm. Hip circumference was measured at the widest girth of the hip and was rounded to the nearest 0.1 cm. All measurements were taken by the same person.

Fasting blood samples were drawn between 07:00 and 09:00 h after an overnight fast into Vacutainer tubes at each assessment. Blood centrifugation was performed

within 30 min of drawing. Free thyroxine (ft_4) and TSH levels were determined on -70°C stored serum samples by the electrochemiluminescence immunoassay (ECLIA) method in both phases I and IV, using Roche Diagnostics kits and Roche/Hitachi Cobas e411 analyzer (GmbH, Mannheim, Germany). Lyophilized quality control material (Lyphochek Immunoassay Plus Control, Bio-Rad Laboratories) was used to monitor the accuracy of assay; the intra- and interassay CVs were 1.3 and 3.7% for ft_4 and 1.5 and 4.5% for TSH determinations respectively. Thyroid peroxidase antibody (TPO Ab) was assayed by immunoenzymometric assay (IEMA) using related kit (Monobind, Costa Mesa, CA, USA) and the Sunrise ELISA reader (Tecan Co, Salzburg, Austria); intra- and interassay CVs were 3.9 and 4.7% respectively.

Statistical analysis

TSH levels and ft_4 concentrations were analyzed as continuous variables. Categorical variables are shown as percent/numbers and continuous variables are presented as mean $\pm$ s.d. or median (IQR 25–75). The t -test, Mann-Whitney or χ^2 tests were employed to compare means, medians or categorical data respectively. Univariate analysis and multivariable regression models were run to examine the relationship between changes in TSH and ft_4 and alterations in weight, waist circumference and waist-to-hip ratio. Multivariable analyses were adjusted for age, smoking status (in men; ref, nonsmoker), physical activity (ref, light and moderate activity), menstrual status and baseline measurements (including weight, WC, HC and

WHR). Statistical analyses were conducted by SPSS 16.0 statistical software package (SPSS). A threshold of $P < 0.05$ was set as significance level.

Results

From among 6217 participants attended the TTS phases I and IV, blood samples from 4161 individuals were available, from whom and based on inclusion and exclusion criteria, 1755 individuals (55.3% female) entered the study. Median length of follow-up was 9.7 years (IQR 9.1–10.3 years). The mean age of the participants was 43.5 ± 13.8 years at the baseline and 53.3 ± 13.7 years at follow-up. Among the individuals recruited, 9.5% of women and 5.2% of men had positive antiperoxidase antibodies at phase I. The corresponding numbers for smokers were 4 and 38.4% respectively. Median baseline serum TSH level was 1.58 U/L (1.05–2.31) and 1.33 U/L (0.89–1.86) for women and men, correspondingly. At baseline, 303 women had reached menopause by definition (Table 1).

There were significant differences between women and men in age, weight, WC, HC, WHR, TSH level and ft_4 level in both phases. Weight, HC, WHR and ft_4 were also significantly different between the two genders (Table 1).

At follow-up, we observed an increase in TSH levels (0.52 ± 0.91 U/L in women; 0.51 ± 0.73 U/L in men) as well as weight (2.96 ± 7.02 kg in women; 3.98 ± 7.29 kg in men), WC (8.15 ± 9.14 cm in women; 8.58 ± 7.18 cm in men) and WHR (0.10 ± 0.07 in women; 0.06 ± 0.05 in men). Also, a slight decrease in free T_4 level was recorded

Table 1 Characteristics of participants attending both phases I (1999–2001) and IV (2008–2011) of Tehran Thyroid Study. All data are presented as mean $\pm$ s.d. unless otherwise specified. Smoking and menstrual statuses are presented as n (%). TSH levels are presented by median (IQR: 25–75).

	Phase I		Phase IV	
	Women ($n=971$)	Men ($n=784$)	Women ($n=971$)	Men ($n=784$)
Age* (years)	42.2 ± 13.3	45.1 ± 14.3	52.0 ± 13.2	54.8 ± 14.1
Smoking (%)				
Never smoked	928 (95.6)	479 (61.1)	924 (95.2)	458 (58.4)
Quit/current smoker	39 (4.0)	301 (38.4)	44 (4.5)	324 (41.3)
Menstrual status (%)				
Menstruating	653 (67.3)	–	437 (45.0)	–
Nonmenstruating	303 (31.2)	–	475 (48.9)	–
Weight* (kg)	68.1 ± 11.8	75.7 ± 12.7	71.1 ± 12.4	79.7 ± 13.7
Waist circumference* (cm)	88.5 ± 12.2	89.9 ± 11.2	96.6 ± 11.9	98.5 ± 10.4
Hip circumference* (cm)	104.5 ± 9.5	97.1 ± 7.0	102.6 ± 9.1	100.2 ± 7.2
Waist-to-hip ratio*	0.85 ± 0.08	0.92 ± 0.07	0.94 ± 0.08	0.98 ± 0.06
TSH level* (U/L)	1.58 (1.05–2.31)	1.33 (0.89–1.86)	2.1 (1.49–2.98)	1.8 (1.29–2.53)
ft_4 level* (pmol/L)	15.06 ± 1.67	15.83 ± 1.67	14.80 ± 1.67	15.32 ± 1.67
Anti-TPO Ab positive (%)	92 (9.5)	41 (5.2)	101 (10.4)	50 (6.4)

* P value for differences between genders in each phase was <0.01 .

Clinical Study	B Motamed and others	Thyroid function and anthropometric indices	175:4	250
----------------	----------------------	---	-------	-----

Table 2 Changes in TSH and fT_4 levels and anthropometric measures in participants across phase I (1999–2001) through phase IV (2008–2011) of Tehran Thyroid Study. All data are presented as mean $\pm$ s.d.

	Women (n=971)	Men (n=784)
Δ Weight* (kg)	2.96 $\pm$ 7.02	3.98 $\pm$ 7.29
Δ Waist circumference** (cm)	8.15 $\pm$ 9.14	8.58 $\pm$ 7.18
Δ Hip circumference* (cm)	–1.87 $\pm$ 6.14	3.12 $\pm$ 4.63
Δ Waist-to-hip ratio*	0.10 $\pm$ 0.07	0.06 $\pm$ 0.05
Δ TSH** (U/L)	0.52 $\pm$ 0.91	0.51 $\pm$ 0.73
Δ Free T_4 * (pmol/L)	–0.25 $\pm$ 1.51	–0.56 $\pm$ 1.41

*P value for differences between genders was <0.01; **P value for differences between genders were not significant.

in both genders (–0.25 $\pm$ 1.51 pmol/L in women; –0.56 $\pm$ 1.41 pmol/L in men) (Table 2). When comparing anti-TPO Ab positive and negative individuals, we found a statistically significant difference in changes in HC and WHR between the two groups ($P=0.026$ and 0.040 respectively) (data not shown).

Univariate linear regression analysis in women showed a weak positive relationship between TSH changes and alterations in WC ($\beta=0.81$, $P=0.011$) and WHR ($\beta=0.005$, $P=0.032$). Similar findings were observed in men ($\beta=0.89$, $P=0.011$ for WC and $\beta=0.005$, $P=0.028$ for WHR) (Table 3). Notably, the association with WHR was lost in anti-TPO positive individuals (data not shown).

Considering changes in fT_4 levels, univariate linear regression analysis revealed a significant negative association with changes in weight ($\beta=-0.78$, $P<0.001$ in women and $\beta=-0.95$, $P<0.001$ in men), WC ($\beta=-0.59$, $P=0.002$ in women and $\beta=-0.54$, $P=0.003$ in men) and HC ($\beta=-0.48$, $P<0.001$ in women and $\beta=0.53$, $P<0.001$ in men) (Table 3). However, when running the univariate

analysis in anti-TPO positive subjects, we observed no significant association between fT_4 changes and anthropometric indices (data not shown).

After adjusting for age, smoking status (in men), physical activity, menstrual status in women and baseline anthropometric measures, multivariable regression model consisting of weight, WC, HC and WHR was conducted to examine the association of Δ TSH and ΔfT_4 with anthropometric indices. Our analysis showed that there was a positive relationship between TSH changes and alterations in WC in women ($\beta=0.69$, $P=0.021$) (Table 4). Similarly, in men, we found a significant association between TSH changes and Δ WC ($\beta=0.61$, $P=0.038$) (Table 4). Moreover, our analysis revealed a significant negative association of ΔfT_4 with changes in weight ($\beta=-0.49$, $P=0.001$ in women and $\beta=-0.56$, $P<0.001$ in men). Additionally, there was a negative relationship between ΔfT_4 and Δ HC in men ($\beta=-0.36$, $P=0.001$) (Table 4). Notably, no significant relationship between ΔfT_4 and anthropometric measures was observed in anti-TPO Ab positive subjects in multivariable analysis (data not shown).

Discussion

In this longitudinal study, we observed TSH changes within laboratory ranges to be positively associated with slight increase in waist circumference in both genders. Moreover, alterations in fT_4 were also found to have significant negative relationship with changes in weight and hip circumference during 9.7 years of follow-up.

Not many longitudinal studies have focused on the association between thyroid function test within the

Table 3 Univariate analysis showing the relationship between changes in TSH and fT_4 levels and anthropometric changes in the participants across phase I (1999–2001) through phase IV (2008–2011) of Tehran Thyroid Study (TTS). $P<0.05$ was set as a significant level.

	Δ TSH (U/L)			Δ free T_4 (pmol/L)		
	r^2	β (CI 95%)	P	r^2	β (CI 95%)	P
Women						
Δ Wt (kg)	0.003	0.42 (–0.06, 0.91)	0.084	0.028	–0.78 (–1.07, –0.49)	<0.001
Δ WC (cm)	0.007	0.81 (0.18, 1.43)	0.011	0.009	–0.59 (–1.00, –0.21)	0.002
Δ HC (cm)	0.001	0.21 (–0.21, 0.63)	0.326	0.014	–0.48 (–0.73, –0.22)	<0.001
Δ WHR	0.005	0.01 (0.00, 0.01)	0.032	0.001	0.00 (–0.01, 0.00)	0.252
Men						
Δ Wt (kg)	0.004	0.61 (–0.08, 1.31)	0.085	0.033	–0.95 (–1.31, –0.59)	<0.001
Δ WC (cm)	0.008	0.89 (0.21, 1.57)	0.011	0.011	–0.54 (–0.90, –0.18)	0.003
Δ HC (cm)	0.004	0.39 (–0.05, 0.83)	0.082	0.026	–0.53 (–0.76, –0.31)	<0.001
Δ WHR	0.006	0.01 (0.00, 0.01)	0.028	0.000	0.00 (0.00, 0.00)	0.843

HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; Wt, weight.

Clinical Study	B Motamed and others	Thyroid function and anthropometric indices	175:4	251
----------------	----------------------	---	-------	-----

Table 4 Multivariable linear regression models showing the effect of thyroid function change on anthropometric indices in the participants across phase I (1999–2001) through phase IV (2008–2011) of Tehran Thyroid Study (TTS). $P < 0.05$ was set as a significant level.

	Δ TSH (U/L)			Δ free T_4 (pmol/L)		
	Adjusted r	β (CI 95%)	P	Adjusted r	β (CI 95%)	P
Women						
Δ Wt	0.137	0.38 (–0.070, 0.84)	0.098	0.145	–0.49 (–0.77, –0.20)	0.001
Δ WC	0.171	0.69 (0.11, 1.27)	0.021	0.167	–0.16 (–0.52, 0.20)	0.382
Δ HC	0.200	0.21 (–0.17, 0.59)	0.288	0.201	–0.17 (–0.41, 0.07)	0.155
Δ WHR	0.330	0.00 (0.00, 0.01)	0.071	0.328	0.00 (0.00, 0.00)	0.800
Men						
Δ Wt	0.312	0.43 (–0.15, 1.01)	0.151	0.322	–0.56 (–0.86, –0.26)	<0.001
Δ WC	0.310	0.61 (0.05, 1.18)	0.038	0.308	–0.23 (–0.53, 0.07)	0.139
Δ HC	0.221	0.25 (–0.14, 0.64)	0.212	0.231	–0.36 (–0.56, –0.15)	0.001
Δ WHR	0.355	0.00 (0.00, 0.01)	0.141	0.354	0.00 (0.00, 0.00)	0.321

The model is adjusted for age, menstruating status (in women), smoking status (in men), physical activity and baseline anthropometric measures. HC, hip circumference; WC, waist circumference; WHR, waist-to-hip ratio; Wt, weight.

reference range and weight alterations. However, they have documented conflicting results on the role of gender and smoking. Examining the effect of increased TSH on BMI in 6164 euthyroid individuals (54% female, mean age 59.7 ± 14.0) between years 1994 and 2001, the fifth Tromsø study showed a significant positive relationship between TSH changes and BMI alterations only in nonsmoker subjects (14). Also, Fox and coworkers revealed that in a 3.5-year follow-up of 2407 persons (46% female, mean age 48 ± 10), increases in TSH level were associated with statistically significant weight gain in both genders (12), although, they reported a smaller effect size in men. Accordingly, in a longitudinal study of 15 020 healthy individuals (66% female, median age 52 years (IQR 46–60)), the Hunt study showed that within normal laboratory range, there was a positive association between TSH raise and increase in weight, WC and BMI in both genders (13). On the other hand, another study by Gopinath and coworkers reported a strong positive relationship between TSH changes over a 5-year period and incident weight gain only in women (20). While insufficient study power in certain subgroups might provide some clarification about differences in observed effects sizes, the differences between our findings on anthropometric indices and above observations might best be explained by differences in number of studied individuals, length of follow-up and baseline characteristics (baseline weight, WC, etc.).

Notably, we observed a more pronounced increase in TSH levels than some other studies with similar length of follow-up. This larger increase might be due to the wider TSH level range in our euthyroid population. While we need to emphasize here that our larger TSH cutoff has been drawn from a study of Tehranian population mentioned

earlier (18), however, we believe that this greater increase did not influence our results, since our analyses were run on a per unit basis.

Addressing fT_4 changes, we found a significant negative association between ΔfT_4 and changes in weight in both genders. However, we observed the relationship between ΔfT_4 and HC alterations to be present only in men. The amount of predicted weight change per each unit of fT_4 change is rather small (–0.49 kg in women and –0.56 kg in men). Thereby, any clinical conclusion drawn from these results should take into consideration the actual amounts of weight gain or loss associated with fT_4 alterations within the normal references. Our study is the first study that has examined relationship between ΔfT_4 and alterations in anthropometric indices. Interestingly, our findings are in accordance with previous longitudinal and cross-sectional reports assessing the association between baseline fT_4 and weight changes. For instance, in a population-based study, Knudsen and coworkers found a negative association between BMI and categories of baseline serum fT_4 levels (2). Likewise, Shon and coworkers demonstrated that in euthyroid women, fT_4 was negatively correlated with BMI (21). Moreover, Dvoráková and coworkers observed that the inverse relationship between BMI and fT_4 was lost in men (22). On the other hand, another study on healthy individuals found that fT_4 was a predictor of abdominal subcutaneous fat, independent of age, sex and smoking (8). In accordance with above reports, recently, the longitudinal Dan Thyroid study showed that the relationship between ΔTSH and ΔfT_4 differed significantly between groups with different weight changes (15).

Our findings could be explained by the pathophysiological mechanism underlying the anthropometric

Clinical Study	B Motamed and others	Thyroid function and anthropometric indices	175:4	252
----------------	----------------------	---	-------	-----

changes observed in overt thyroid disorders. Resting energy expenditure (REE), which generally reflects obligatory thermogenesis in human, is known to be highly sensitive to thyroid hormone stimulation (23). In hypothyroidism, the obligatory thermogenesis is reduced and stimulation of brown fat tissue is increased (23). In turn, leptin, secreted by adipocytes, might increase thermogenesis by regulating thyrotropin-releasing hormone (TRH) neurons (24). Moreover, the moderate increase in free and total T_3 levels, frequently observed in obese individuals, leads to an increase in energy expenditure (25).

Notably, we found no significant relationship between ΔfT_4 and changes in anthropometric measures in anti-TPO antibody positive (Ab+) subjects in multivariable analysis. These results could not be compared directly with those of the previous studies, since a similar analysis has not been made by related investigations so far. Nevertheless, the rather small size of the anti-TPO Ab+ group might have affected the lack of association we observed.

Compared with the mean weight gain, we observed more increase in the mean WC among our population. Examining the rising trends of obesity and central obesity in the TLGS cohort, a related different pattern of rising between the two entities has been previously reported by our colleagues (26). Along with low physical activity and unhealthy diet, ecological characteristics of Tehran metropolis, which impose further unhealthy changes on life style and eating behavior of its inhabitants, might provide some explanation.

Our findings need to be interpreted in the context of limitations we encountered. We did not have data on fT_3 levels. Considering that little is known about the relation between changes in fT_3 levels and alterations in weight, assessing fT_3 levels would add to the interpretability and robustness of our results. Additionally, we did not have access to the nutritional information of our participants, and thereby no adjustment was made based on their nutritional status. Also, records on physical activity in phase one were collected based on qualitative Lipid Research Clinic (LRC) questionnaire, which has not been validated for Iranian population, and last but not least, due to their small group size, current smokers and ex-smokers were analyzed together.

The strengths of the current survey include its longitudinal population-based design, substantial number of participants and relatively long follow-up duration. Moreover, nation-specified cutoffs for TSH and fT_4 have been used to define normal laboratory ranges. In addition, we have examined a comprehensive list of

actually measured anthropometric indices along with an inclusive range of possible confounding factors in our analysis.

In conclusion, we found a significant relationship between changes in TSH and waist circumference over time. Also alterations in fT_4 were negatively associated with changes in weight in both genders. However, role of thyroid autoimmunity as well as causal relationship between the two conditions need to be determined.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors wish to thank Ms Niloofar Shiva for her kind assistance in English editing of the manuscript.

References

- 1 Al-Adsani H, Hoffer LJ & Silva JE. Resting energy expenditure is sensitive to small dose changes in patients on chronic thyroid hormone replacement. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 1118–1125. (doi:10.1210/jcem.82.4.3873)
- 2 Knudsen N, Laurberg P, Rasmussen LB, Bulow I, Perrild H, Ovesen L & Jorgensen T. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 4019–4024. (doi:10.1210/jc.2004-2225)
- 3 Mehran L, Amouzegar A, Delshad H & Azizi F. Association between serum TSH concentration and body mass index in euthyroid subjects: the role of smoking. *Archives of Iranian Medicine* 2012 **15** 400–403.
- 4 Asvold BO, Bjoro T & Vatten LJ. Association of serum TSH with high body mass differs between smokers and never-smokers. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 5023–5027. (doi:10.1210/jc.2009-1180)
- 5 Lai Y, Wang J, Jiang F, Wang B, Chen Y, Li M, Liu H, Li C, Xue H, Li N *et al.* The relationship between serum thyrotropin and components of metabolic syndrome. *Endocrine Journal* 2011 **58** 23–30. (doi:10.1507/endocrj.K10E-272)
- 6 Sakurai M, Nakamura K, Miura K, Yoshita K, Takamura T, Nagasawa SY, Morikawa Y, Ishizaki M, Kido T, Naruse Y *et al.* Association between a serum thyroid-stimulating hormone concentration within the normal range and indices of obesity in Japanese men and women. *Internal Medicine* 2014 **53** 669–674. (doi:10.2169/internalmedicine.53.1387)
- 7 De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P & Giorgino R. Free triiodothyronine and thyroid stimulating hormone are directly associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. *Clinical Endocrinology* 2007 **67** 265–269. (doi:10.1111/cen.2007.67.issue-2)
- 8 Alevizaki M, Saltiki K, Voidonikola P, Mantzou E, Papamichael C & Stamatelopoulos K. Free thyroxine is an independent predictor

- of subcutaneous fat in euthyroid individuals. *European Journal of Endocrinology* 2009 **161** 459–465. (doi:10.1530/EJE-09-0441)
- 9 Shin JA, Mo E, Kim ES, Moon SD & Han JH. Association between lower normal free thyroxine concentrations and obesity phenotype in healthy euthyroid subjects. *International Journal of Endocrinology* 2014 **2014** 104318. (doi:10.1155/2014/104318)
 - 10 Westerink J, van der Graaf Y, Faber DR & Visseren FL. The relation between thyroid-stimulating hormone and measures of adiposity in patients with manifest vascular disease. *European Journal of Clinical Investigation* 2011 **41** 159–166. (doi:10.1111/eci.2010.41.issue-2)
 - 11 Diez JJ & Iglesias P. Relationship between thyrotropin and body mass index in euthyroid subjects. *Experimental and Clinical Endocrinology and Diabetes* 2011 **119** 144–150. (doi:10.1055/s-0030-1265133)
 - 12 Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN & Vasan RS. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Archives of Internal Medicine* 2008 **168** 587–592. (doi:10.1001/archinte.168.6.587)
 - 13 Svarre A, Nilsen TI, Bjoro T, Asvold BO & Langhammer A. Serum TSH related to measures of body mass: longitudinal data from the HUNT Study, Norway. *Clinical Endocrinology* 2011 **74** 769–775. (doi:10.1111/cen.2011.74.issue-6)
 - 14 Nyrnes A, Jorde R & Sundsfjord J. Serum TSH is positively associated with BMI. *International Journal of Obesity* 2006 **30** 100–105. (doi:10.1038/sj.ijo.0803112)
 - 15 Bjergved L, Jorgensen T, Perrild H, Laurberg P, Krejbjerg A, Ovesen L, Rasmussen LB & Knudsen N. Thyroid function and body weight: a community-based longitudinal study. *PLoS ONE* 2014 **9** e93515. (doi:10.1371/journal.pone.0093515)
 - 16 Azizi F, Amouzegar A, Delshad H, Tohidi M, Mehran L & Mehrabi Y. Natural course of thyroid disease profile in a population in nutrition transition: Tehran Thyroid Study. *Archives of Iranian Medicine* 2013 **16** 418–423.
 - 17 Azizi F, Ghanbarian A, Momenan AA, Hadaegh F, Mirmiran P, Hedayati M, Mehrabi Y & Zahedi-Asl S. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials* 2009 **10** 5. (doi:10.1186/1745-6215-10-5)
 - 18 Amouzegar A, Delshad H, Mehran L, Tohidi M, Khafaji F & Azizi F. Reference limit of thyrotropin (TSH) and free thyroxine (FT4) in thyroperoxidase positive and negative subjects: a population based study. *Journal of Endocrinological Investigation* 2013 **36** 950–954.
 - 19 Ainsworth BE, Jacobs DR Jr & Leon AS. Validity and reliability of self-reported physical activity status: the Lipid Research Clinics questionnaire. *Medicine and Science in Sports and Exercise* 1993 **25** 92–98. (doi:10.1249/00005768-199301000-00013)
 - 20 Gopinath B, Liew G, Flood VM, Wang JJ, Kifley A, Stephen R, Leeder SR & Mitchell P. The association between weight gain and thyroid function in an older population. *Archives of Internal Medicine* 2008 **168** 2283–2284. (doi:10.1001/archinte.168.20.2283)
 - 21 Shon HS, Jung ED, Kim SH & Lee JH. Free T4 is negatively correlated with body mass index in euthyroid women. *Korean Journal of Internal Medicine* 2008 **23** 53–57. (doi:10.3904/kjim.2008.23.2.53)
 - 22 Dvorakova M, Hill M, Cerovska J, Pobisova Z, Bilek R, Hoskovcova P, Zamrazil V & Hainer V. Relationship between pituitary-thyroid axis hormones and anthropometric parameters in Czech adult population. *Physiological Research* 2008 **57** S127–S134.
 - 23 Silva JE. The thermogenic effect of thyroid hormone and its clinical implications. *Annals of Internal Medicine* 2003 **139** 205–213. (doi:10.7326/0003-4819-139-3-200308050-00018)
 - 24 Nilni EA, Vaslet C, Harris M, Hollenberg A, Bjorbak C & Flier JS. Leptin regulates prothyrotropin-releasing hormone biosynthesis. Evidence for direct and indirect pathways. *Journal of Biological Chemistry* 2000 **275** 36124–36133. (doi:10.1074/jbc.M003549200)
 - 25 Reinehr T. Obesity and thyroid function. *Molecular and Cellular Endocrinology* 2010 **316** 165–171. (doi:10.1016/j.mce.2009.06.005)
 - 26 Barzin M, Keihani S, Hosseiniapanah F, Serahati S, Ghareh S & Azizi F. Rising trends of obesity and abdominal obesity in 10 years of follow-up among Tehranian adults: Tehran Lipid and Glucose Study (TLGS). *Public Health Nutrition* 2015 **18** 2981–2989. (doi:10.1017/S1368980015000269)

Received 15 May 2016

Revised version received 26 June 2016

Accepted 7 July 2016