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Original Article

Thyroid function is associated with body mass index and fasting plasma glucose in Thai euthyroid population

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ABSTRACT

Aims: Several population-based studies found the associations between body mass index and thyroid function within the normal range. Furthermore, these thyroid functions are related with insulin resistance and plasma glucose levels. This study aimed to investigate the associations between thyroid functions and metabolic parameters in Thai euthyroid population.

Methods: Participants from the Thai National Thai Health Examination Survey were randomly measured for TSH, FT4, anti-thyroperoxidase, and anti-thyroglobulin. Euthyroidism was defined by TSH 0.27–4.20 mIU/L and FT4 0.93–1.71 ng/dL.

Results: A total of 2242 euthyroid participants were included. Fifty-one percent were female. Mean age, fasting plasma glucose, and body mass index were 55 ± 21 years, 93 ± 29 mg/dL, and 23.4 ± 4.6 kg/m^2, respectively. Multivariate regression analysis after age and sex adjustment showed a negative association of serum FT4 with body mass index ($\beta = -0.070$, $p = 0.001$) and the relationship was still significant after subjects with positive anti-thyroperoxidase were excluded ($\beta = -0.068$, $p = 0.003$). In contrast, serum TSH was positively associated with body mass index ($\beta = 0.052$, $p = 0.012$). Moreover, serum FT4 was positively associated with fasting plasma glucose levels ($\beta = 0.097$, $p < 0.001$).

Conclusions: Small variations of serum TSH and FT4 within the reference range may contribute to the differences in metabolic indexes such as body mass index and fasting plasma glucose.

1. Introduction

Thyroid hormones regulate body metabolisms such as thermogenesis, cholesterol, and carbohydrate metabolism [1]. Overt thyroid dysfunction has a strong impact on body weight [2]. Hyperthyroidism leads to weight loss, while hypothyroidism induces weight gain. However, the association between thyroid function within the reference range and metabolic parameters, such as body weight and plasma glucose concentrations, is still a subject of debate.

Thyroid disease and obesity are common diseases with a substantial overlap. Several large cross-sectional population-based cohort studies have shown that body weight was associated with levels of serum thyroid hormone and thyroid stimulating hormone (TSH), even within the normal reference range [3–6]. The studies of euthyroid people had shown that high levels of serum TSH were associated with high body mass index (BMI) [3–11]. High levels of serum free thyroxine (FT4) were associated with lower BMI [3,11–13]. In addition, the differences in the detail of the results were influenced by smoking status [4,5], sex difference [9,14], and the presence of anti-thyroperoxidase (TPO) [14,15]. Among of the positive trials, there are a number of results that had shown a lack of association between thyroid function and BMI [15,16].

Diabetes mellitus is the common metabolic derangement associated with obesity. Of the euthyroid subjects, T4 levels were negatively associated with fasting plasma glucose (FPG) in the former study [17]. Oppositely, triiodothyronine (T3), and ratio of T3-to-T4 levels showed a positive relation with FPG levels [17–19]. The relationships between thyroid function and insulin resistance were demonstrated in many studies, FT4 had a negative association while TSH had a positive association with homeostatic model

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assessment-insulin resistance (HOMA-IR) [20–23]. However, the inconsistent results were reported [24–26].

The associations between thyroid autoantibody and metabolic parameters were rarely studied in the euthyroid population. Data from large population-based study suggested that obesity associated with several autoimmune diseases [27], but a causal link between obesity and thyroid autoimmunity has not been clearly established. Marzullo et al. reported a two-fold greater in the prevalence of anti-TPO in obese subjects compared with controls [28]. In addition, no relationship between TSH and BMI was found in the subjects with negative thyroid autoimmunity [15,16]. The ethnicity and regions are known to affect the thyroid function and autoimmunity status, but the data in Thai population is limited. The aim of this study was to investigate the relationship between thyroid functions, thyroid autoimmunity, and metabolic parameters in Thai euthyroid population.

2. Material and methods

2.1. Study population

The National Health Examination Surveys have been conducted every 5 years since 1991. The fourth Thai National Health Survey was a nationally representative cross-sectional health examination survey of the non-institutionalized Thai population aged ≥15 years conducted in 2009 using a multistage stratified sampling. The sampling process has been described in detail elsewhere [29]. Briefly, the sampling units in each of the four stages of selection included (i) five provinces in each of the four main regions of the country (North, Northeast, Central, and South) as well as Bangkok; (ii) three to five districts in each selected province; (iii) 13 to 14 electoral units or villages from each of the urban and rural areas; and (iv) eight to ten males and females from each electoral unit or village (Fig. 1). The final sample size was targeted at 21,960 individuals, and the final sample included 20,450 individuals with a response rate of 93.1%.

The study project was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health and Faculty of Medicine Ramathibodi Hospital, Mahidol University. All participants provided written informed consent. All methods were performed in accordance with relevant guidelines and regulations.

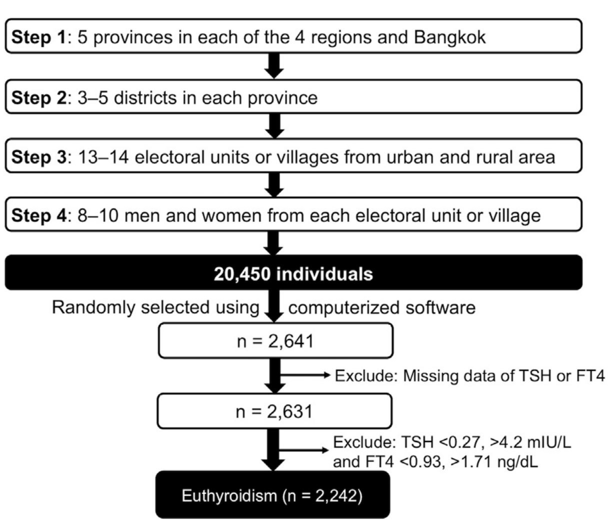

Fig. 1. Recruitment of reference population.

2.2. Data collection

Demographic data, medical history, and lists of current medications were obtained during a face-to-face interview using standard questionnaires. Certified field research assistants performed a physical examination. Pregnant women, subjects with a reported history of thyroid disorder, and those with moderate-to-severe ill health were excluded from the study. Also excluded were any subject who had been taking medication that affects thyroxine-binding globulin (TBG) (i.e. estrogen), or medications that could affect thyroid function (i.e. amiodarone, carbamazepine, lithium, phenytoin, and excess iodine ingestion). Height, weight, and waist circumference were measured by a standardized procedure. Three serial measurements of blood pressure were made by using standardized automatic blood pressure monitor (model A100; Microlife, Taipei, Taiwan). The systolic and diastolic blood pressures were averaged on the second and third measurement.

Venous blood samples were obtained from participants in the morning after fasting 12 h overnight. Plasma glucose was measured at the provincial laboratory using a hexokinase enzyme method with standardized technique. Serum samples were frozen and transferred to the central laboratory center at the Ramathibodi Hospital, for further analysis. A subsample of serum for measurement of thyroid function and thyroid autoantibody levels was randomly selected from each age group, sex, and region. In each stratum, 25 individuals were randomly selected using computer software. A total of 2700 serum samples were selected, from which 2641 were ultimately available for use in serum analysis.

2.3. Serum analysis

TSH, FT4, anti-TPO, and anti-thyroglobulin (anti-Tg) were measured by electrochemiluminescence immunoassay on a Cobas e411 analyzer (Roche Diagnostics, Mannheim, Germany). The assays had intra-assay precisions of 1.31%, 3.6%, 9.2%, and 6.1%, respectively. The corresponding normal ranges of serum TSH, FT4, anti-TPO, and anti-Tg are 0.27–4.2 mIU/L, 0.93–1.71 ng/dL, 0–34 IU/mL, and 0–115 IU/mL, respectively. Euthyroid state was defined by TSH 0.27–4.20 mIU/L and FT4 0.93–1.71 ng/dL. Plasma glucose was measured as described before.

2.4. Statistical analysis

The STATA software version 13 (StataCorp LLC, College Station, Texas, USA) was used for analyses. Data are shown as mean ± standard deviation (SD) for normally distributed values and median (interquartile range) for non-normally distributed values or percentage as appropriate. Pearson or Spearman coefficients were used to determine correlations between two variables. Association between thyroid function, BMI, and FPG were calculated by univariate followed by multivariate Cox regression after adjustments for age and sex. Bonferroni multiple-comparison test was used to evaluate TSH group and BMI group for normally distributed values and quantile regression was used for non-normally distributed values. *P*-values < 0.05 were considered significant.

3. Results

After excluded missing data, the complete data was 2631 participants. Euthyroid participants defined as normal TSH and FT4 were included. Final sample was 2242 participants (Fig. 1). Approximately 50% of participants were male, mean age was 54.9 ± 21.2 years old, mean BMI was 23.4 ± 4.6 kg/m^2, and 31.9% of participants were obesity according to the Asia-Pacific criteria. 8.16% of participants had hypertension. Mean TSH was 1.8 ± 0.8

mIU/L and FT4 was 1.3 ± 0.2 ng/dL. A 14.7% of participants had positive anti-TPO and 11.1% of participants had positive anti-Tg. Mean FPG levels were 93 ± 28.5 mg/dL and 6.3% of participants had a diagnosis of diabetes mellitus by criteria of FPG ≥126 mg/dL (Table 1). Distribution of age, BMI, FT4, and TSH were in normal distribution (Fig. 2).

Univariate analysis of thyroid function and BMI revealed that age, male gender, FT4, TSH, and anti-TPO were significantly correlated with BMI. Multivariate analysis of thyroid function and BMI (Table 2) found that serum TSH was positively associated with BMI ($\beta = 0.052$, $p = 0.012$). Serum FT4 was negatively associated with BMI ($\beta = -0.070$, $p = 0.001$). Moreover, the relationship was still significant after subjects with positive anti-TPO were excluded (TSH, $\beta = 0.045$, $p = 0.047$ and FT4, $\beta = -0.068$, $p = 0.003$). No association was found between thyroid autoantibodies and BMI (Table 2).

Univariate analysis of thyroid function and FPG revealed that, age, BMI, and FT4were significantly correlated with FPG. Multivariate analysis of thyroid function and FPG (Table 3) showed that serum FT4 was positively associated with FPG levels ($\beta = 0.097$, $p < 0.001$). In addition, the association was still seen in non-diabetes group ($\beta = 0.115$, $p < 0.001$), while no association between TSH and thyroid autoantibodies was shown (Table 3).

BMI was categorized into 3 groups according to Asia-Pacific criteria; underweight (BMI < 18 kg/m^2), normal weight (BMI between 18 and 23.5 kg/m^2), and overweight/obesity groups (BMI > 23.5 kg/m^2). Mean TSH tends to be higher in the overweight/obesity group without statistically significance. Mean FT4 was significantly lower in the overweight/obesity group than other groups (underweight vs overweight, $p = 0.048$; normal weight vs overweight/obesity, $p = 0.018$). Both anti-TPO and anti-Tg tend to be higher in the underweight group than the others, but only anti-TPO had statistically significance (underweight vs normal weight, $p < 0.01$; underweight vs overweight, $p < 0.01$) (Fig. 3).

Table 1
Baseline characteristics of the participants.

	N = 2242
Male, no. (%)	1115 (49.7%)
Age (years)	54.9 ± 21.2
Height (cm)	157.8 ± 8.6
Weight (kg)	58.3 ± 13.0
BMI (kg/m^2)	23.4 ± 4.6
Obesity (BMI > 25 kg/m^2): no. (%)	714 (31.9%)
BMI (kg/m^2) in obese subjects	28.6 ± 3.4
SBP (mmHg)	127.2 ± 21.5
SBP > 140 mmHg, no. (%)	530 (23.6%)
SBP in subjects with SBP > 140 mmHg	157.4 ± 16.3
DBP (mmHg)	74.9 ± 11.5
DBP > 90 mmHg, no. (%)	224 (10.0%)
DBP in subjects with DBP > 90 mmHg	96.6 ± 7.4
SBP > 140 and DBP > 90 mmHg, no. (%)	183 (8.2%)
TSH (mIU/L)	1.80 ± 0.8
FT4 (ng/dL)	1.3 ± 0.2
Anti-TPO (IU/mL)	12.8 (9.1, 21.7)
Anti-TPO > 34 IU/mL, no. (%)	329 (14.7%)
Median (IQR) anti-TPO who had levels > 34 IU/mL	85.12 (48.1, 238.8)
Anti-Tg (IU/mL)	15.8 (11.9, 23.0)
Anti-Tg > 115 IU/mL, no. (%)	248 (11.1%)
Median (IQR) anti-Tg who had levels > 115 IU/mL	375.5 (192.3, 822.5)
FPG (mg/dL)	93.0 ± 28.5
FPG ≥ 126 mg/dL, no. (%)	141 (6.3%)
Mean FPG who had levels ≥ 126 mg/dL	172.7 ± 61.3

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; FT4, free thyroxine; IQR, interquartile range; SBP, systolic blood pressure; Tg, thyroglobulin; TPO, thyroperoxidase; TSH, thyroid stimulating hormone.

TSH was categorized into quartiles. Individuals who had TSH levels in the highest quartile had significantly higher BMI than those in the lowest quartile of TSH (BMI in lowest and highest TSH quartile were 22.9 ± 4.3 kg/m^2 and 23.8 ± 4.8 kg/m^2, respectively ($p = 0.009$) (Fig. 4).

4. Discussion

This cross-sectional study demonstrated a significant positive relationship between serum TSH level within normal range and the BMI in a large Thai population. Among euthyroid subjects, serum FT4 was negatively associated with the BMI as well. Furthermore, we revealed a positive association between FT4 and FPG levels. No association was found between FPG, thyroid autoantibodies, and BMI.

Andersen et al. suggested that an alteration in the thyroid function outside of the individual reference range but within the laboratory reference range, would not be normal for that person [30]. Our results supported that small differences in FT4 and TSH levels, even within the normal laboratory range of thyroid function may contribute to body weight regulation. Similar to the findings of many previous studies, there was a positive correlation between serum TSH and BMI in euthyroid subjects [7]. Obese individuals seem to have higher TSH [31–33]. There is bidirectional interaction between the thyroid hormone and adipose tissue. Thyroid hormones play a critical role in thermogenesis and regulate the energy expenditure that affecting body weight. Conversely, hormones and cytokines from the adipose tissue also interact with hypothalamic-pituitary-thyroid axis by regulating adipogenesis, fat metabolism, and thermogenesis [34]. Leptin is an adipocyte-derived hormones or adipokines that communicates information about body fat store to the central nervous system. Leptin promotes thyrotropin relasing hormone gene expression via direct action on the paraventricular nucleus and indirect action on the arcuate nucleus of the hypothalamus, eventually stimulating TSH release [35]. Leptin also increase T4 to T3 conversion by deiodinase in a tissue-specific manner [36]. TSH can also induce leptin release via TSH receptors on the surface of adipocytes [37].

Although the data regarding TSH and BMI are in the uniform direction, the correlations between thyroid hormones and BMI are less consistent. These results indicated that TSH was strongly associated with BMI, while thyroid hormones may have weak association. The discrepant results can be attributed from several factors such as shorter half-life of thyroid hormone than TSH, laboratory assay, and inclusion criteria of patients. Most studies showed a negative association between FT4 and BMI [3,12,13], while FT3 levels were reported as increased in obese individuals [19,33,38,39]. The paradoxical opposing relationship of FT3 (positive) and FT4 (negative) with BMI is of particular interest, because active form of thyroid hormone, T3, increases energy expenditure, and hence would be anticipated to be negatively correlated with fat mass. An explanation could be that increased fat mass results in increased conversion of T4 to T3 and subsequently prevent fat accumulation. However, the mechanism for increasing FT3 remains unclear. Unfortunately, FT3 data did not provide in the present study.

Previous studies showed that low FT4 was inversely associated with insulin resistance index in a euthyroid population [21,40–42]. Higher levels of FT3 in subjects with impaired fasting glucose [18], while serum TSH and thyroid antibody positivity were not associated with FPG levels or insulin resistance indexes [21]. These finding are similar to our study that FT4 rather than TSH levels, are associated with insulin resistance. A better understanding of the complex nature of the thyroid-pituitary hypothalamic regulation of thyroid hormones is required to explain the results. Despite obesity

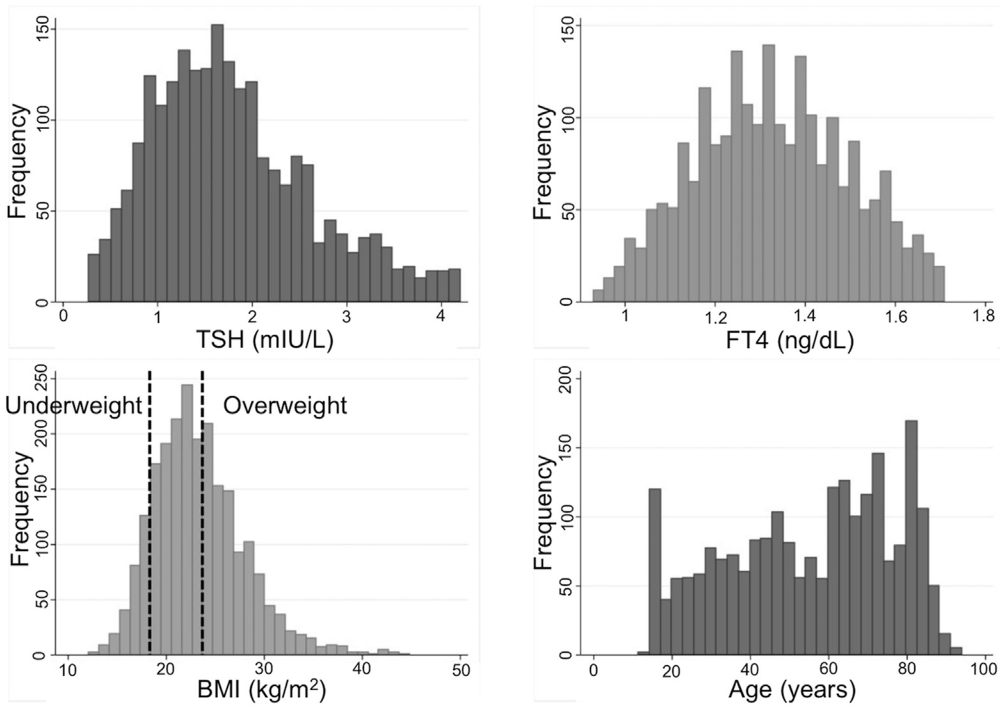

Fig. 2. The distribution of TSH, FT4, BMI, and age in euthyroid participants.

Table 2
Multivariate analysis of thyroid function and body mass index.

	Overall (N = 2242)				Anti-TPO < 34 IU/mL (N = 1913)			
	β	Coefficient	p-value	95% CI	β	Coefficient	p-value	95% CI
TSH	0.052	0.285	0.012	25.34, 28.75	0.045	0.249	0.047	0.003, 0.497
FT4	−0.070	−1.903	0.001	−3.031, −0.776	−0.068	−1.849	0.003	−3.069, −0.629
Anti-TPO					−0.049	−0.036	0.031	−0.069, −0.003
Age	−0.100	−0.217	<0.001	−0.031, −0.013	−0.069	−0.014	0.003	−0.024, −0.005
Male	−0.103	−0.949	<0.001	−1.328, −0.571	−0.117	−1.073	<0.001	−1.483, −0.663

Abbreviations: CI, confidence interval; FT4, free thyroxine; TPO, thyroperoxidase; TSH, thyroid stimulating hormone.

Table 3
Multivariate analysis of thyroid function and fasting plasma glucose.

	Overall (N = 1909)				FPG < 126 mg/dL (N = 1800)			
	β	Coefficient	p-value	95% CI	β	Coefficient	p-value	95% CI
FT4	0.097	16.356	<0.001	9.574, 23.139	0.115	8.681	<0.001	5.573, 11.789
Age	0.230	0.308	<0.001	0.254, 0.362	0.275	0.163	<0.001	0.139, 0.187
Male					0.050	1.279	0.016	0.237, 2.323
BMI	0.181	1.125	<0.001	0.875, 1.375	0.207	0.581	<0.001	0.466, 0.696

Abbreviations: BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; FT4, free thyroxine; TPO, thyroperoxidase.

may influence *per se* the thyroid function, these contrast findings is not easily explained. Although the association between low FT4 and HOMA-IR found in one of the study in non-obese subjects [43], other study has failed to show such an association in non-obese population [44].

The presence of anti-TPO was more common in the obese group [28,45]. Leptin may increase susceptibility to thyroid autoimmunity, and lead to induce subtle thyroid dysfunction [46]. However, the present study revealed that TSH and FT4 levels were still associated with BMI despite excluded subjected with positive anti-TPO. The similar findings were not observed in the study by Diez et al. [15]. These evidences support that obesity by itself may be responsible for the small alterations in thyroid function. Morbid obese patients with negative thyroid antibodies had a significant lower FT4 and higher TSH compared with normal weight euthyroid subjects [47]. Previous studies showed leptin was associated with thyroid autoimmunity independent of obesity [28,48]. In consistent with the other studies [47,49], anti-TPO levels were significantly higher in underweight group than normal weight or overweight/obesity in our study. To date, a clearly established clinical association between obesity and autoimmune thyroid disease is not established. Moreover, traditional markers of thyroid immunity,

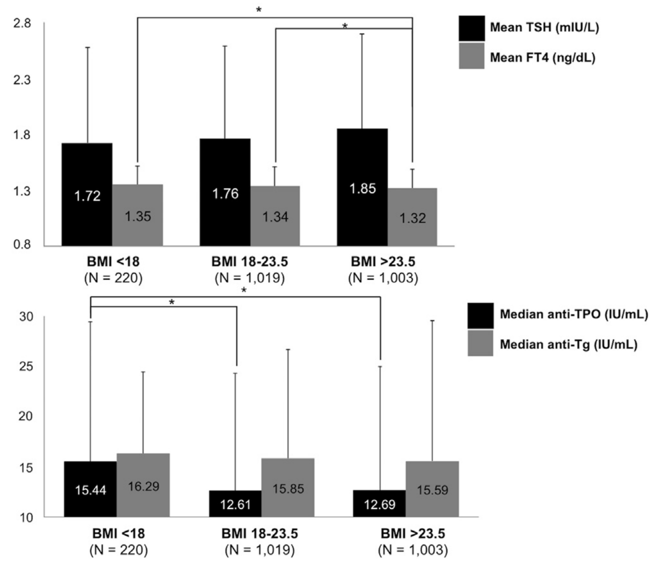

Fig. 3. TSH, FT_4, and thyroid antibody according to BMI groups; *p-value < 0.05.

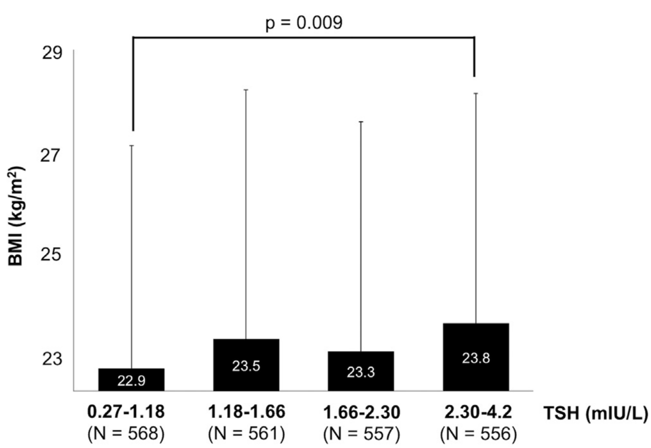

Fig. 4. Mean BMI according to the quartile of serum TSH concentration.

such as anti-TPO may be not sensitive to detect thyroid autoimmunity [50]. In addition, ultrasonography of the thyroid did not perform in this study.

Strength of this study was the large number of the participants and collected data from different regions of country that can represent general Thai population. To our knowledge, this is the first study that evaluated the associations between thyroid function, obesity, and plasma glucose levels in a euthyroid population in Southeast Asian region. Limitations of this study were no data on factors that may affect BMI such as caloric intake, physical activity, and smoking. No data are available on body composition, serum leptin levels, and insulin resistance indexes. The nature of cross-sectional study does not allow concluding the true relationship between metabolic parameters and thyroid function. Moreover, TSH measurement is widely known to have a large within-individual variation, and the fact that the determination of TSH relied on a single measurement. Further longitudinal studies or prospective studies are required for in-depth understanding of the mechanisms that TSH level might influence body weight.

For clinical implications of the present study, the reference range of thyroid function may not apply for specific groups such as patients with obesity and diabetes mellitus. A change in body weight may affect thyroid function. Narrowing normal range of thyroid function may need to be optimized to control body weight. TSH and FT4 concentrations may be predictive of regain in weight that may occur during weight loss interventions.

5. Conclusions

In euthyroid subjects, small variations in serum TSH and FT4 may contribute to the differences in metabolic indexes such as BMI and FPG levels. These findings suggest that differences in thyroid function within the population reference range could influence the prevalence of obesity and diabetes mellitus.

Author contributions

A.L., B.O., and C.S. designed the study, collected and analysed data, interpreted results and prepared the manuscript. W.A. interpreted results and revised the manuscript. L.C. collected data and assayed thyroid function and antibodies. All Authors reviewed the final draft submitted.

Competing Interests

All authors declare that they have no competing interests.

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2018.11.004.

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