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Higher Sensitivity to Thyroid Hormones may be Linked to Maintaining the Healthy Metabolic Condition in Population with Obesity: New Insight from NHANES

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Short Title: Metabolic Healthy Obesity and Sensitivity to Thyroid Hormones

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Abstract

Introduction: Obesity contributes to the pathogenesis of diverse metabolic diseases, yet the mechanism underlying metabolically healthy obesity (MHO) remains elusive. Thyroid hormones and sensitivity to them have a major impact on metabolism. Our study aimed to investigate the association between MHO and thyroid hormone sensitivity.

Methods: Thyroid hormone indices, including the thyroid-stimulating hormone (TSH) index (TSHI), the thyrotroph thyroxine sensitivity index (TTSI), the thyroid feedback quantile-based index (TFQI), and the parametric thyroid feedback quantile-based Index (PTFQI), were calculated based on a non-institutionalized U.S. sample in the National Health and Nutrition Examination Survey (NHANES, 2007–2012). Participants were divided into four groups (metabolically healthy non-obesity (MHNO), metabolically unhealthy non-obesity (MUNO), MHO, and metabolically unhealthy obesity (MUO)) according to their body mass index and metabolic profiles. Linear regression, logistic regression, and restricted cubic splines were employed to analyze the association between thyroid hormone indices and metabolic phenotypes.

Results: A total of 4,857 participants (49.6% men; mean age, 42.6 years) were included, with 1,539 having obesity and 235 identified as MHO. Participants with MHO exhibited lower levels of TSH, TSHI, TTSI, TFQI, and PTFQI compared with the MHNO group (all $P < 0.05$), while the differences among MHNO, MUNO, and MUO groups were not statistically significant (all $P > 0.05$). Among participants with obesity, TSH, TSHI, TTSI, TFQI, and PTFQI were positively associated with metabolic abnormality (all $P < 0.05$).

Discussion/Conclusion: Participants with MHO exhibited higher thyroid hormone sensitivity among various obesity phenotypes, even when compared with those with MHNO. A positive association was observed between metabolic abnormality and thyroid hormone sensitivity, while the trend of TSH was observed to be consistent with sensitivity to thyroid hormone indices in discriminating metabolic abnormality. Hence, TSH has the potential to serve as a convenient index for detecting sensitivity to thyroid hormones and further metabolic conditions.

Introduction

The prevalence of obesity and the average BMI of the global population have grown rapidly in the last few decades. Obesity is a chronic relapsing progressive disease associated with a variety of complications, including type 2 diabetes, cardiovascular diseases, cancer, and premature death[1]. However, some individuals with obesity do not exhibit overt cardio-metabolic abnormalities and have been reported to have favorable prognoses[2]. This subgroup is described as having metabolically healthy obesity (MHO). Compared with unhealthy individuals with obesity, individuals with MHO have a superior metabolic profile characterized by a lower degree of systemic inflammation, a high level of insulin sensitivity, lower amounts of ectopic fat, and greater cardio-respiratory fitness[2]. However, the mechanism behind MHO remains elusive.

Thyroid hormones play a crucial role in the human endocrine system that influences energy expenditure by regulating cellular respiration and thermogenesis, thereby affecting the resting metabolic rate and promoting lower body weight[3]. Previous research has suggested a positive association between thyroid hormones and the prevalence and incidence of diabetes, seemingly contradicting the metabolic-enhancing effects of thyroid hormones[4]. Moreover, hypothyroidism has been identified as a risk factor for abnormal glucose metabolism[5]. Some scholars have discovered that greater skeletal muscle mass in obesity enhances thyroid activity and in turn improves the metabolic condition[6]. Genetically, obesity and thyroid diseases are influenced by common genes, such as dysregulated BUB1, further evidencing that both disorders are tightly interrelated conditions. The recent study by Laclaustra et al. proposed that sensitivity to thyroid hormones may conciliate the conflicting results between thyroid hormones and diabetes[7]. Subsequently, they confirmed the relationship between sensitivity to thyroid hormones and obesity, metabolic syndrome (MetS), diabetes, and diabetes-related mortality by using two newly developed sensitivity to thyroid hormone indices, namely the Thyroid Feedback Quantile-based Index (TFQI) and the Parametric Thyroid Feedback Quantile-based Index (PTFQI)[7]. Previous research has also suggested that thyroid-stimulating hormone (TSH) values alone cannot objectively reflect thyroid function, since its secretion is subject to negative feedback inhibition of peripheral fT4 concentrations; the researchers proposed a TSH index (TSHI) to estimate thyrotropic pituitary function[8]. Based on these findings, we speculated that sensitivity to thyroid hormones might be the underlying pathological mechanism that determines whether an individual has MHO or metabolic unhealthy obesity (MUO).

We conducted a cross-sectional study based on data of the non-institutionalized population in the U.S. to investigate whether the thyroid hormones and their derived indices were associated with different metabolic phenotypes and weight.

Materials and Methods

Study design and participants

The study was an observational cross-sectional study. Participants were recruited from the series of National Health and Nutrition Examination Survey (NHANES), which is an ongoing, cross-sectional, probability sampling, multistage survey run by the National Center for Health Statistics. Data were drawn from the continuous biennial cycles for the period 2007–2012[9]. This study protocol of NHANES was reviewed and approved by the National Center for Health Statistics Research Ethics Review Board. The approval numbers for the protocol were (Protocol #2011-17) and (Protocol #2005-06). Signed informed consent was obtained from all participants. Due to the need for fasting blood samples, participants were enrolled who were examined in the morning session. Of the 10,135 participants who accepted the morning examination session with ages between 12 and 80 years initially reviewed for this study, 4,990 participants without a test for thyroid function and 288 participants with missing values for relevant variables were excluded. Finally, 4,857 participants were included in subsequent analyses. Specific inclusion and exclusion criteria are outlined in Figure 1.

Thyroid function and sensitivity to thyroid hormone indices

Participants underwent a fasting blood draw in the morning session after a 9-hour fast[10]. TSH was measured with the Access HYPERsensitive human thyroid-stimulating hormone (hTSH) assay, a 3rd generation, two-site immunoenzymatic (“sandwich”) assay. Free T3 was measured with the Access

Free T3 assay, a competitive binding immunoenzymatic assay. Free T4 was measured with the Access Free T4 assay, a two-step enzyme immunoassay. The reference ranges of TSH, fT3, and fT4 were 0.24–5.4 μIU/mL, 2.5–3.9 pg/mL, and 0.6-1.6 ng/dL, respectively. The fT3/ fT4 ratio was calculated as fT3 (pmol/L) divided by fT4 (pmol/L). TSHI was calculated using the following formula:
$TSHI = \log TSH_{(mUI/L)} + 0.1345 \times fT4_{(pmol/L)}$.
The Thyrotroph Thyroxine Sensitivity Index (TTSI) was calculated as
$TTSI = fT4_{(pmol/L)} \times TSH_{(mUI/L)}$.[10]
To calculate the Thyroid Feedback Quantile-based Index (TFQI), fT4 and TSH were first converted to quantiles between 0 and 1 by applying the empirical cumulative distribution function (*cdf*) of the population to hormone concentration. Then, TFQI was calculated as
$TFQI = cdf\ fT4 - (1 - cdf\ TSH)$.[7]
The Parametric Thyroid Feedback Quantile-based Index (PTFQI) was an approximation of TFQI with the same range and interpretation, which can be obtained using the standard normal cumulative distribution:
$PTFQI = \Phi\left(\frac{fT4-\mu_{fT4}}{\sigma_{fT4}}\right) - \left(1 - \Phi\left(\frac{\ln TSH-\mu_{\ln TSH}}{\sigma_{\ln TSH}}\right)\right)$.[7]

Metabolic phenotypes and obesity

Currently, there is no unified definition of MHO. For this study, we defined metabolically healthy subjects as those who met all of the proposed criteria in the BioSHaRE-EU Healthy Obese Project[11], including systolic blood pressure (SBP) ≤ 130 mmHg, diastolic blood pressure (DBP) ≤ 85 mmHg, no anti-hypertensive drug treatment, fasting plasma glucose (FPG) ≤ 6.1 mmol/L, no blood glucose-lowering medication or diagnosis of type 2 diabetes, fasting triglycerides ≤ 1.7 mmol/L, no drug treatment for elevated triglycerides, HDL cholesterol > 1.03 mmol/L for men and > 1.3 mmol/L for women, no drug treatment for reduced HDL cholesterol, and no diagnosis of cardiovascular diseases[2]. Obesity was defined as BMI of 30 kg/m2 or greater[12]. All participants were divided into four groups according to their metabolic phenotypes and obesity classification, namely metabolically healthy non-obesity (MHNO), metabolically unhealthy non-obesity (MUNO), metabolically healthy obesity (MHO), and metabolically unhealthy obesity (MUO).

Other variables

Demographic characteristics (age, gender, and race/ethnicity), previous medical history, and drug use were queried during the home interview using standard questionnaires. Anthropometry (height and weight) and body measure examinations (SBP and DBP) were conducted in the mobile examination center by trained health technicians and recorders. BMI was defined as the individual's weight divided by the square of their height. Laboratory data (FPG, HDL cholesterol, LDL cholesterol, total cholesterol, and triglycerides) were obtained following the laboratory procedures manual[10]. FPG ≥ 7 mmol/L, glycated hemoglobin ≥ 6.5%, self-reported history of diabetes, or being treated with glucose-lowering medication were defined as diabetes[13]. Participants with self-reported history of heart attack, coronary heart disease, angina/angina pectoris, congestive heart failure, and stroke were defined as having cardiovascular disease.

Statistical analysis

All analyses were performed with the statistical programming language R (version 4.1.2) and incorporated appropriate sample weights and design variables to account for the complex survey design according to NHANES analytic guidelines. A two-sided P value < 0.05 defined statistical significance.

Baseline characteristics were reported as means or percentages with standard errors. Standard errors were estimated using Taylor series linearization. The associations between thyroid hormone indices and metabolic phenotypes and obesity groups were investigated by linear regression. The results were visualized using forest plots. Furthermore, we analyzed the association between thyroid hormone indices and metabolic phenotype. The odds ratios (ORs) for the risk of metabolically unhealth were computed using logistic regression. Thyroid hormone indices were z-standardized before the linear regression and logistic regression analyses. To model the non-linear effects between thyroid hormone indices and metabolic phenotypes in participants with obesity, restricted

cubic splines with three knots (10th, 50th, and 90th of exposure) were used, with the median value of each anthropometric measure serving as the reference.

Results

Clinical characteristics

The data of 4,857 non-institutionalized U.S. citizens over 12 years of age were analyzed. Participants' mean age was 42.6 years, and 49.6% were male. In total, 1,539 participants had a BMI ≥ 30 kg/m^2, and 235 of them were identified as having MHO. Baseline characteristics are displayed in Table 1. Overall, metabolically healthy participants tended to be younger and had higher levels of fT3 and fT3/fT4 ratio, as well as lower levels of fT4, TSH, TSHI, TTSI, TFQI, and PTFQI.

Association between thyroid hormones indices and different metabolic phenotypes

Figure 2 and Table S1 show the association of metabolic phenotypes and obesity group with thyroid hormone indices in the whole population. Using the MHNO group as a reference, participants with MUNO and MUO had higher levels of fT3 (β = 0.136, P < 0.001; and β = 0.157, P < 0.001, respectively). Conversely, compared with the MHNO group, participants with MUNO, MHO, or MUO tended to have lower levels of fT4, although there was no statistically significant difference (P > 0.05). The result for the fT3/fT4 ratio was consistent with fT3. Participants with MUNO, MHO, or MUO had higher levels of fT3/fT4 ratio than the MHNO group (β = 0.131, P = 0.001; β = 0.126, P = 0.015; and β = 0.173, P < 0.001, respectively). On the other hand, TSH and the four composite indices (TSHI, TTSI, TFQI, and PTFQI) showed similar results. Compared with the MHNO group, participants in the MHO group had lower levels of TSH, TSHI, TTSI, TFQI, and PTFQI, while the differences among MHNO, MUNO, and MUO groups were not significant.

The risk of metabolic abnormality with thyroid hormones indices

We further investigated whether these thyroid hormone indices were linked with higher risks of metabolic abnormality in participants with obesity (Fig. 3 and Table S2). In the univariate analysis, fT3 and fT3/fT4 were negatively associated with metabolic abnormality in participants with obesity (OR = 0.79, 95% confidence interval [CI], 0.65–0.96, P = 0.021; and OR = 0.77, 95% CI, 0.55–1.07, P = 0.120, respectively). These associations were inverted after adjusting for age and sex, however, although they did not achieve statistical significance (OR = 1.21, 95% CI, 0.97–1.51, P = 0.087; and OR = 1.31, 95% CI, 0.87–1.98, P = 0.189, respectively, in the multivariate analysis). In both the univariate and the multivariate analysis, fT4 was not associated with metabolic abnormality (all P > 0.05). TSH, TSHI, TTSI, TFQI, and PTFQI yielded similar results. These five indices were positively associated with metabolic abnormality, regardless of adjustment for confounders. The results from the multivariate logistic regression showed that each standard deviation increase in TSH, TSHI, TTSI, TFQI, and PTFQI, as the continuous variable, was associated with, respectively, a 1.88-fold (95% CI: 1.21–3.51, P = 0.006), 1.35-fold (95% CI: 1.12–1.63, P = 0.003), 1.54-fold (95% CI: 1.17–2.02, P = 0.003), 1.28-fold (95% CI: 1.06–1.54, P = 0.010), and 1.31-fold (95% CI: 1.08–1.59, P = 0.006) increased risk of metabolic abnormality in participants with obesity, while there was no such association between metabolic abnormality and the indices of sensitivity to thyroid hormones in participants without obesity (Fig. S1). In the restricted cubic splines analysis (Fig. 4), the risk of metabolic abnormality displayed a non-monotonic variation with fT3, fT4, and fT3/fT4. In contrast, TSH, TSHI, TTSI, TFQI, and PTFQI demonstrated a monotonically increasing cubic regression line with metabolic abnormality.

Discussion/Conclusion

To our knowledge, this is the first study to compare thyroid hormone sensitivity among individuals with different obesity phenotypes. Based on a cross-sectional study of the U.S. population, the results demonstrated that participants with MHO had higher thyroid hormone sensitivity among various metabolic phenotypes, even when compared with those with MHNO. Sensitivity to thyroid hormone indices was positively associated with metabolic abnormality in participants with obesity. Notably, the trend observed in TSH was consistent with sensitivity to thyroid hormone indices in discriminating metabolic abnormality. Thus, TSH may be suitable as a convenient indicator for clinical application.

The circulating levels of thyroid hormones are stabilized by a negative feedback mechanism exerted on the hypothalamus–pituitary–thyroid (HPT) axis under physiological conditions[14]. Deiodinase

iodothyronine catalyzes the thyroxine, the main secretory form of thyroid hormones, to form the bioactive T3, which subsequently plays physiological roles via combination with thyroid hormone receptor (THR)[15]. Hence, THR also affected the levels of circulating thyroid hormones. The syndrome of resistance to thyroid hormone is an autosomal-recessive condition characterized by the coexistence of high levels of TSH and thyroid hormones. Yet, compared with the congenital, a more common acquired resistance to thyroid hormones exists resulting from homeostatic compensatory response has been proposed and is increasingly being supported[16]. Prolonged fasting reduces TSH and upregulates the pituitary sensitivity to thyroid hormones[17, 18]. Conversely, both thyroid hormones and TSH levels trended higher in individuals with morbid obesity[19].

The development of metabolic dysfunction is likely to alter the HPT axis's set-point and peripheral thyroid hormone sensitivity. Even within the euthyroid range, the alterations of thyroid hormones exert effects on the development of metabolic disorders. Low-normal thyroid function, defined as lower fT4 or higher TSH within the euthyroid range, is closely related to insulin resistance[20], dyslipidemia[21], obesity[22] and MetS[23]. Mounting evidence suggests that impaired sensitivity to thyroid hormone is tightly linked to diabetes and MetS[7]. Previous studies have revealed that the expression of receptors of thyroid hormones, such as THR, is reduced when metabolic disorders occur and significantly increased when metabolic function improves[24, 25]. Furthermore, application of THRβ selective agonists was unable to promote energy consumption significantly in mice with diet-induced obesity. The studies mentioned above imply that impaired sensitivity to thyroid hormones may be present in metabolic derangements[26]. Additionally, impaired HPT sensitivity has been considered clinically relevant in metabolic diseases[17, 27]. In a bidirectional way, thyroid hormones are affected by adiposity. Leptin, a hormone secreted from adipocytes in direct proportion to adipose mass, has been shown to act on multiple levels of the HPT axis, such as upregulating the production of TRH[28, 29]. Higher levels of TSH secretion are stimulated by the increasing TRH release[30, 28], which in turn promotes thyroid function. Collectively, the proposed interaction between thyroid function and MetS is complex[31], and impaired sensitivity to thyroid hormones seems to play an important role.

In light of the complex interplay among the hormones on the HPT axis, an individual parameter may be less likely to provide an accurate reflection of thyroid status. By assessing the intricate connections among TSH, fT3, and fT4 through thyroid hormone sensitivity indicators, novel insights into thyroid status could be obtained. Initially, TSHI and TTSI were proposed as indices for assessing central sensitivity to thyroid hormones, which reflects the thyroid status of the pituitary gland[8]. In recent years, TFQI and its parametric version, PTFQI, have been found to be more robust in evaluating thyroid hormone sensitivity. The creators of the new indices discovered a positive association between TFQI or PTFQI and metabolic diseases, such as obesity, MetS, and diabetes, in the total population and even the euthyroid population[7]. Similarly, a euthyroid study conducted in China demonstrated a positive association between reduced sensitivity to thyroid hormones and A-FABP[27]. Consistent with these previous studies, the present study observed lower sensitivity to thyroid hormones in metabolically unhealthy individuals.

Appleton et al. proposed that the MHO phenotype represented a transient state of health before progressing toward significant metabolic abnormalities and disease. In their study, MHO conferred nonsignificant risks of developing diabetes and cardiovascular disease during long-term follow-up compared with subjects with MHUO, while the increased diabetes risk was attributable to those who progressed from MHO to MUO. Most previous studies have indicated that more peripheral fat distribution, less secretory adipose tissue, or reduced adipokine responsiveness might be the characteristic signatures of MHO[32, 33]. Yet the underlying mechanisms of the favorable metabolic profile of subjects with MHO remain unknown. The present study determined for the first time that individuals with MHO displayed higher thyroid hormone sensitivity, even compared with participants with MHNO. It is therefore reasonable to speculate that subjects with MHO might have an innate advantage of higher sensitivity to thyroid hormones even with obesity, enabling them to retain their metabolic indicators within a normal range and gain less central fat. However, we cannot rule out the possibility of a compensatory increase in thyroid hormone secretion before transitioning to an

unhealthy state, by analogy with the compensatory increased rate of insulin secretion in the early stages of diabetes[34]. These hypotheses require now to be tested by longitudinal studies.
A broadly consistent trend was observed for all central sensitivity to thyroid hormone indices, fully reflective of the characteristic of the population with MHO as having higher sensitivity to thyroid hormones. Nie et al. reported that fT3/fT4 could partly reflect the peripheral sensitivity to thyroid hormones[27]. No similar finding emerged from the present study, however, possibly due to the quantification complexity of peripheral resistance. It was gratifying to note that the trend of TSH, currently the most commonly used measure for thyroid function and surveillance, was in close agreement with the central sensitivity indices. It is well established that TSH is closely linked with metabolism. An association was commonly observed between relatively higher levels of TSH and the diagnosis of Mets and could even be detected in euthyroid individuals with normal TSH[35]. In fact, positive association between TSH levels and some indices of glucose/lipid metabolism, such as glycemia, glycosylated hemoglobin, fasting plasmatic insulin, HOMA-IR index, and serum triglyceride, has been supported by some cross-sectional studies and longitudinal cohort studies[36]. The present study indicated that serum TSH of individuals with MHO was at a relatively low level, which was unaffected by the increased weight. Once again, this finding provided supporting evidence that the healthy metabolic characteristic of this special population was related to thyroid hormone metabolism, which could be sensitively reflected by TSH levels. While we cannot confirm whether a causal link exits between TSH and TH sensitivity, this study indicated that TSH might be a clinically simple, convenient, and cost-effective biomarker reflecting the sensitivity to thyroid hormones. More longitudinal research is necessary to verify this finding and explore the cut-off points of serum TSH among different population.
This study also has certain limitations. First, due to the cross-sectional design of the study, causal connections cannot be inferred from the results. Second, thyroid function tests were performed on only a third of the participants aged 12 years or older in three cycles of the NHANES survey (2007–2012), resulting in a limited sample size compared with other NHANES studies. Third, this study was unable to adjust for all potential thyroid function associated confounding factors, such as diet[37], body composition[38] and anti-thyroid therapies. Fourth, the past medical history was self-reported and may be subject to recall bias. Fifth, this study was based on the U.S. non-institutionalized population, so these findings may not be generalizable to other regions.

Conclusions

This representative study based on the U.S. population found that individuals with MHO demonstrated higher sensitivity to thyroid hormones among various metabolic phenotypes, even compared with the population with MHUO. This finding offered insights into the possible explanation for the better metabolic condition among the population with MHO. Additional studies are warranted to further confirm our finding and elucidate the underlying mechanisms. Although various new indices have emerged in endlessly, we feel that the usefulness and potential of the available indicator should also be fully explored. In the present study, the most frequently used thyroid functional and surveillance index, TSH, demonstrated a similar tendency for reflecting the metabolic condition to the composite indices of sensitivity to thyroid hormones. Hence, it is reasonable to speculate that TSH has the potential to serve as a convenient index for detecting sensitivity to thyroid hormones and further metabolic conditions among the population with obesity.

Statements

Statement of Ethics

This study protocol of NHANES was reviewed and approved by the National Center for Health Statistics Research Ethics Review Board. The approval numbers for the protocols were (Protocol #2011-17) and (Protocol #2005-06). Signed informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ying-shan Liu: visualization, investigation and writing-original draft. Xiao-cong Liu: data analysis, validation and writing-original draft preparation. Jian Kuang: methodology, writing-reviewing and supervision. Hai-xia Guan: conceptualization, writing-reviewing and supervision. Jian Kuang and Hai-xia Guan are co-corresponding authors.

Data Availability Statement

The data that support the findings of this study are openly available in NHANES, https://www.cdc.gov/nchs/nhanes/index.htm. Further enquiries can be directed to the corresponding author.

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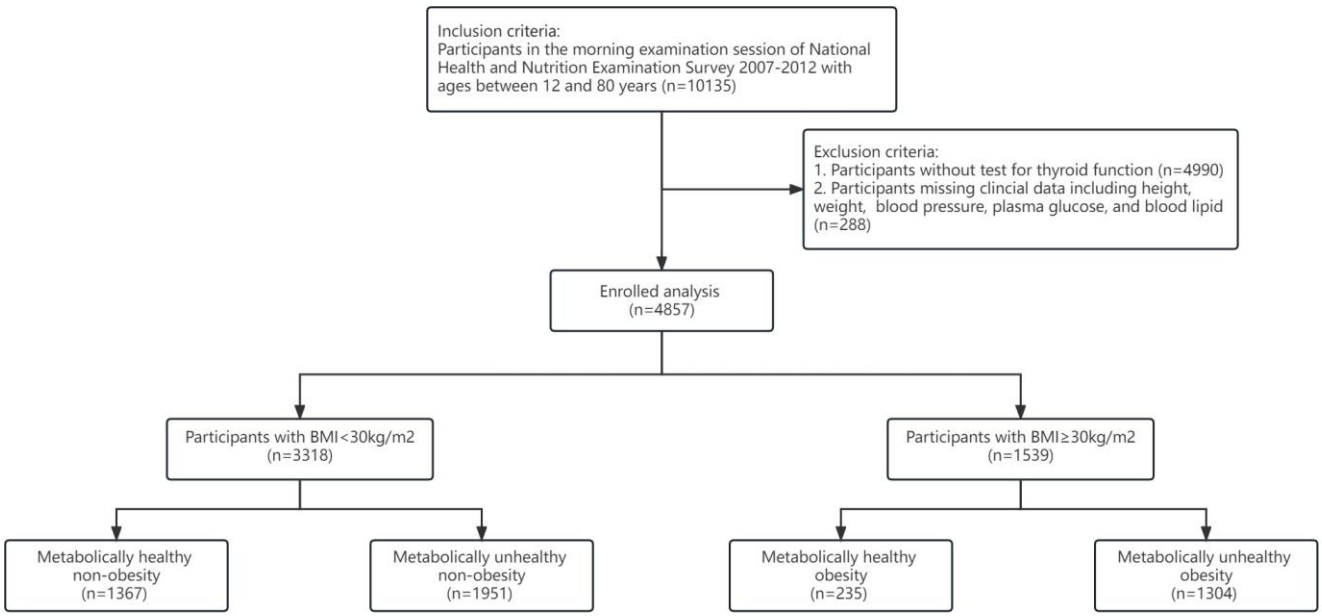
Figure Legends

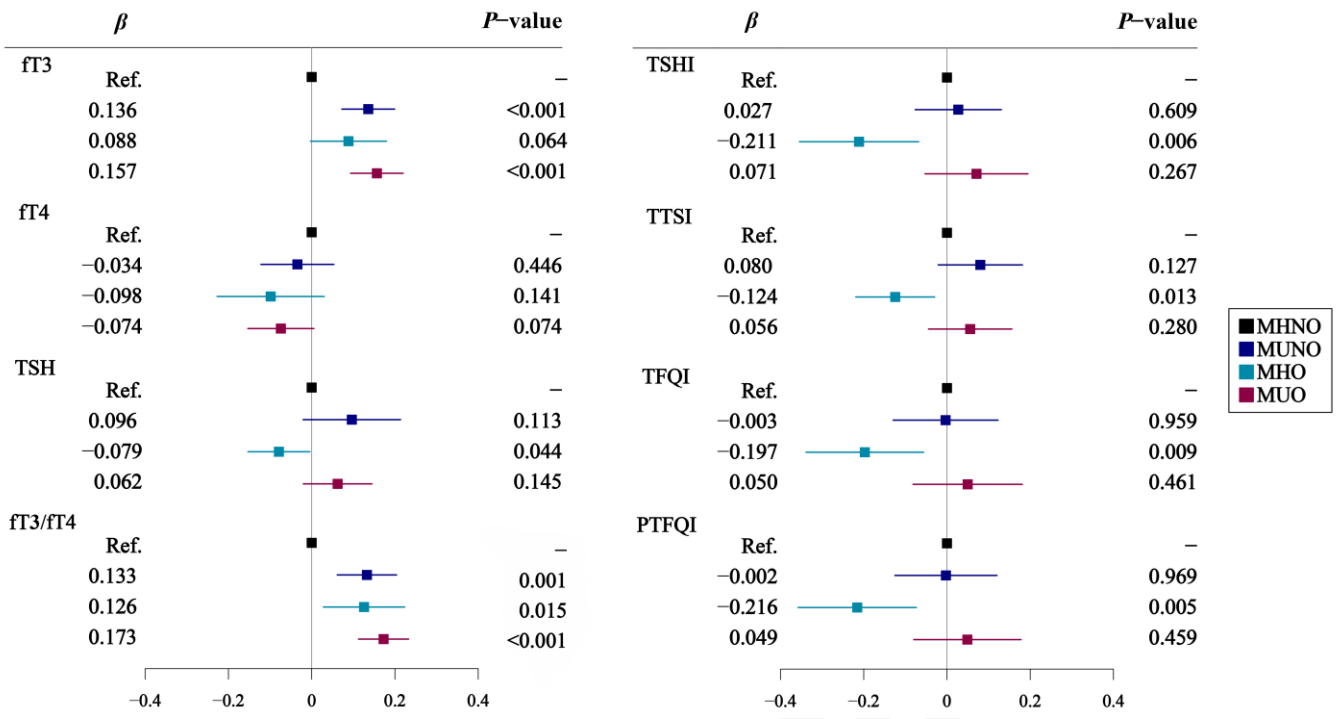
Fig. 1. The study flow chart.

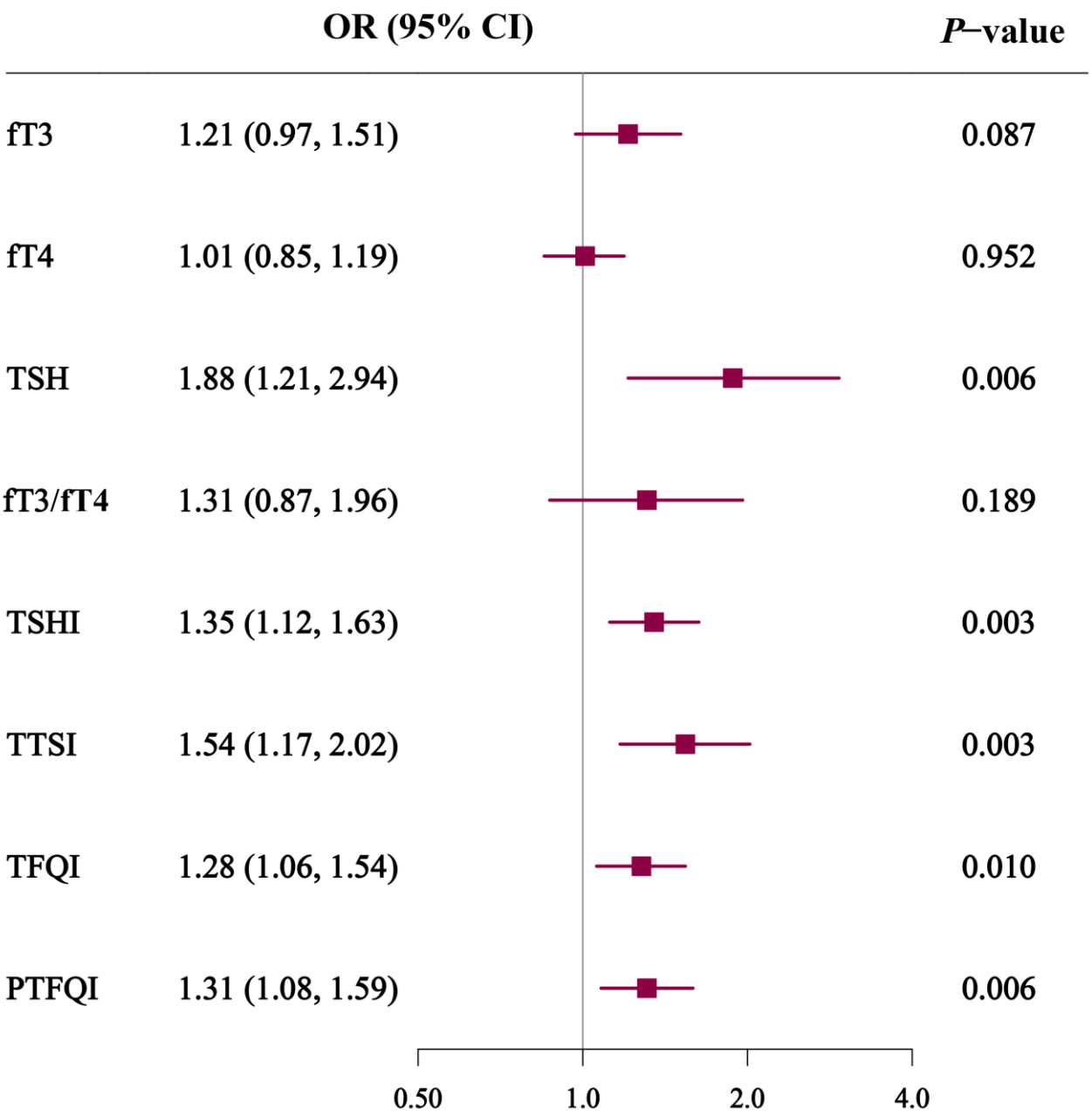
Fig. 2. Association of thyroid hormones indices with different metabolic phenotypes and weight in the whole population after z-score normalization (n=4857). β (box) and 95% CI (horizontal line) were shown in the forest plot. βs were estimated using linear regression adjusted for age and gender.

Fig. 3. The risk of metabolic abnormality with thyroid hormones indices (per SD increment) in participants with obesity (n=1539). OR (box) and 95% CI (horizontal line) were shown in the forest plot. ORs were estimated using Logistic regression adjusted for age, gender and BMI.

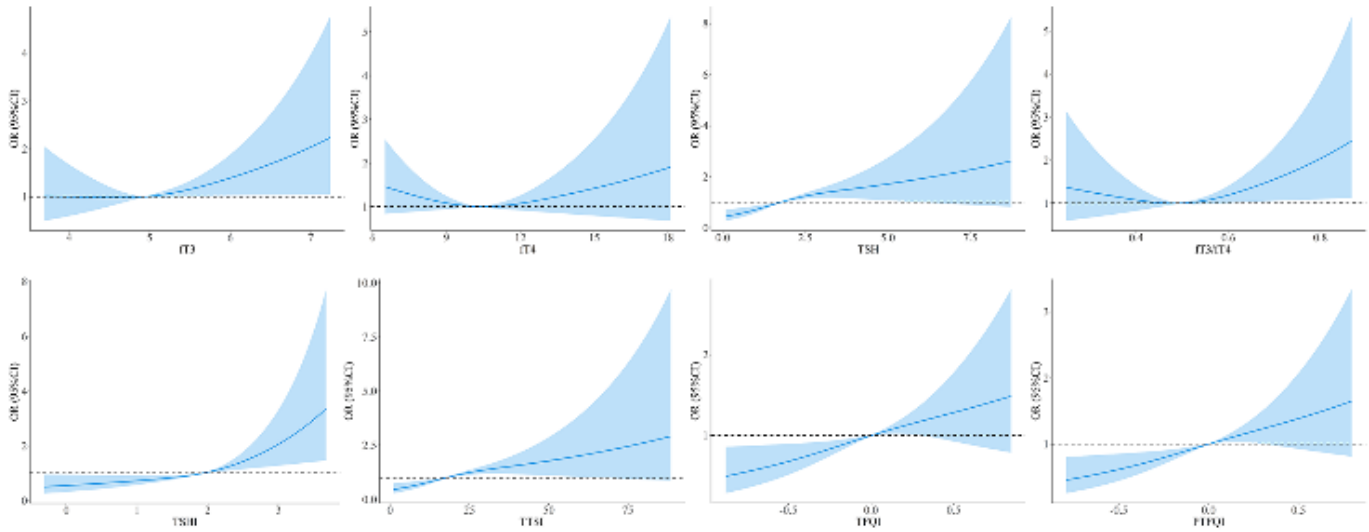
Fig. 4. Spline analyses of metabolic abnormality with thyroid hormones indices in participants with obesity (n=1539). Solid lines indicate odds ratio (OR) and dashed lines indicate 95% CIs from restricted cubic spline regression. Restricted cubic splines were constructed with three knots at the 10th, 50th, and 90th percentiles. The results were adjusted for age, gender, and BMI.







The risk of metabolically unhealthy obesity



The risk of metabolically unhealthy obesity

Table

Table 1. Baseline characteristics

Variables	Overall	MHNO	MUNO	MHO	MUO
Age, years	42.64 (0.42)	31.96 (0.62)	48.46 (0.61)	37.61 (0.94)	48.03 (0.52)
Gender-male, %	49.60 (0.74)	47.60 (1.88)	53.30 (1.86)	48.70 (4.64)	46.50 (1.41)
Race, %					
Mexican American	8.70 (0.95)	9.50 (1.12)	7.60 (0.82)	8.30 (2.00)	9.60 (1.54)
Other Hispanic	5.50 (0.92)	5.60 (0.95)	5.40 (1.02)	7.30 (1.55)	5.20 (1.00)
Non-Hispanic White	68.40 (2.22)	66.70 (2.27)	71.90 (2.25)	61.00 (4.22)	66.80 (3.37)
Non-Hispanic Black	11.20 (1.24)	10.90 (1.25)	8.40 (0.98)	18.40 (3.51)	14.40 (2.01)
Other	6.10 (0.68)	7.30 (1.15)	6.80 (1.06)	5.00 (1.64)	4.00 (0.80)
Diabetes, %	10.70 (0.52)	\	10.80 (0.79)	\	26.20 (1.71)
Cardiovascular disease, %	7.20 (0.60)	\	10.10 (0.95)	\	13.40 (1.44)
Hypoglycemic agents, %	4.40 (0.37)	\	4.20 (0.50)	\	11.00 (1.11)
Antihypertensive drugs, %	22.40 (0.86)	\	28.40 (1.46)	\	46.10 (1.62)
Lipid-lowering drugs, %	13.90 (0.77)	\	19.90 (1.44)	\	25.20 (1.78)
Examination Data					
Body mass index, kg/m2	27.78 (0.11)	23.33 (0.12)	25.30 (0.09)	33.94 (0.24)	35.82 (0.14)
Systolic blood pressure, mmHg	118.81 (0.40)	109.96 (0.41)	122.88 (0.58)	114.44 (0.87)	124.50 (0.70)
Diastolic blood pressure, mmHg	68.10 (0.39)	64.75 (0.55)	68.90 (0.50)	67.72 (0.70)	71.13 (0.55)
Laboratory Data					
Fasting plasma glucose, mmol/L	5.77 (0.03)	5.20 (0.01)	5.85 (0.03)	5.33 (0.03)	6.44 (0.08)
HDL-cholesterol, mg/dL	53.52 (0.40)	61.90 (0.69)	51.28 (0.45)	55.44 (0.94)	46.13 (0.40)
Total cholesterol, mg/dL	190.49 (0.94)	181.34 (1.52)	195.11 (1.53)	196.48 (2.64)	193.38 (1.97)
LDL-cholesterol, mg/dL	112.42 (0.68)	103.96 (1.13)	115.84 (1.25)	122.76 (2.37)	115.51 (1.52)
Triglyceride, mg/dL	125.46 (2.05)	77.35 (1.18)	145.04 (3.34)	91.28 (2.84)	162.79 (5.14)

Thyroid hormones indexes					
fT3, pmol/L	5.08 (0.02)	5.18 (0.04)	5.02 (0.03)	5.17 (0.06)	5.03 (0.02)
fT4, pmol/L	10.38 (0.07)	10.38 (0.09)	10.43 (0.09)	10.20 (0.14)	10.34 (0.08)
TSH, mIU/L	2.10 (0.08)	1.88 (0.04)	2.27 (0.17)	1.72 (0.09)	2.20 (0.08)
fT3/ fT4	0.500 (0.003)	0.510 (0.004)	0.500 (0.004)	0.520 (0.008)	0.500 (0.005)
TSHI	1.89 (0.02)	1.85 (0.02)	1.92 (0.03)	1.72 (0.05)	1.95 (0.03)
TTSI	20.96 (0.50)	19.15 (0.48)	22.32 (0.91)	17.29 (0.88)	21.95 (0.73)
TFQI	-0.004 (0.012)	-0.027 (0.018)	0.006 (0.016)	-0.091 (0.027)	0.026 (0.017)
PTFQI	-0.014 (0.010)	-0.034 (0.016)	-0.003 (0.014)	-0.095 (0.024)	0.014 (0.015)

Abbreviations: MHNO: metabolically healthy non-obesity; MUNO: metabolically unhealthy non-obesity; MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity; HDL: high-density lipoprotein; LDL: low-density lipoprotein; fT3: free Triiodothyronine; fT4: free Thyroxine**;** TSH: Thyroid stimulating hormone; TSHI: TSH index; TFQI: Thyroid Feedback Quantile-based Index; PTFQI: Parametric Thyroid Feedback Quantile-based Index.

Data are presented in mean or percent with standard error.