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The association between thyroid function and insulin resistance as measured by the metabolic score for insulin resistance (METS-IR): insights from NHANES 2007–2012

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Abstract

Background Altered thyroid function has been linked to insulin resistance (IR), but its relationship with the Metabolic Score for Insulin Resistance (METS-IR), a novel non-insulin-based index of IR, remains unclear. This study aimed to investigate the association between thyroid function status and METS-IR in a U.S. population.

Methods This cross-sectional study utilized data from 6,507 adults (aged ≥ 20 years) participating in the National Health and Nutrition Examination Survey from 2007 to 2012. Thyroid function status was categorized into five groups based on thyroid-stimulating hormone and free thyroxine levels. METS-IR was calculated from measures of fasting glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and body mass index (BMI). Multivariate regression analyzed the relationship between thyroid status and METS-IR after adjusting for potential confounders.

Results Higher thyroid-stimulating hormone levels were positively associated with METS-IR (β = 0.003, 95% CI 0.001–0.004, $p = 0.021$). Subclinical hypothyroidism in males and subclinical hyperthyroidism in females showed significant correlations with higher METS-IR. Thyroid peroxidase antibodies (TPO Ab) positivity strengthened the association between overt hypothyroidism and METS-IR.

Conclusions This study demonstrates significant associations between thyroid function status, particularly subclinical thyroid dysfunction, and insulin resistance as measured by METS-IR in a U.S. population. Thyroid status may serve as an early marker of insulin resistance risk.

Keywords Thyroid function, Insulin resistance, METS-IR

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Introduction

Thyroid disorders affect approximately 200 million people worldwide, with over 12% of the U.S. population expected to develop a thyroid condition during their lifetime [1, 2]. Traditionally, based on hormonal levels, individuals have been categorized into three main groups: hypothyroidism, euthyroidism, and hyperthyroidism [3]. However, for a more nuanced understanding of thyroid function and its effects, some research considers a broader spectrum of thyroid states [4, 5]. Euthyroidism represents normal thyroid hormone production and levels. Subclinical hypothyroidism is characterized by mildly insufficient thyroid stimulating hormone production and normal thyroid hormones levels, while overt hypothyroidism indicates a severe deficiency of thyroid hormones. Conversely, subclinical hyperthyroidism is marked by a mild overproduction of thyroid stimulating hormone, and overt hyperthyroidism represents a pronounced excess of thyroid hormones. The prevalence of these conditions varies, with categories of hypothyroidism affecting approximately 4.6% of the U.S. population and hyperthyroidism affecting about 1.3% of Americans [6, 7]. These thyroid dysfunctions can have far-reaching effects on various metabolic processes, including glucose metabolism and insulin sensitivity [8].

Insulin resistance (IR) is defined as reduced sensitivity of muscles, liver, and adipose tissue to insulin, resulting in an impaired biological response and leading to compensatory hyperinsulinemia over time [9–11]. IR is associated with several chronic conditions, including obesity, type 2 diabetes, metabolic syndrome, cardiovascular disease, and non-alcoholic fatty liver disease [12, 13]. While the hyperinsulinemic-euglycemic clamp test remains the gold standard for measuring IR, its clinical application is limited due to ethical and economic considerations. Consequently, the metabolic score for insulin resistance (METS-IR) was developed as a novel, non-insulin-based index derived from routinely measured markers such as fasting plasma glucose, triglycerides, high-density lipoprotein cholesterol, and body mass index [14, 15]. METS-IR has demonstrated high accuracy comparable to the clamp test and strong associations with cardiometabolic conditions, highlighting its potential as a practical tool for detecting and preventing IR-related diseases [16].

Previous studies have linked both hypo- and hyperthyroidism to IR, as measured by various IR indices [17, 18]. Thyroid hormones are known to counteract insulin's direct effects and stimulate processes like hepatic glucose production and breakdown. However, thyroid hormones also upregulate the expression of key genes involved in glucose uptake and metabolism within tissues, working in concert with insulin. This includes the glucose transporter GLUT4 and the enzyme phosphoglycerate kinase, which enhance glucose disposal and utilization in peripheral tissues [19–22]. Prior research has reported associations between thyroid function and IR using the homeostatic model assessment of insulin resistance (HOMA-IR), a commonly employed IR index [4]. However, the relationship between thyroid hormones and METS-IR remains unclear.

Therefore, this study aims to investigate the relationship between thyroid function, categorized into five distinct states, and IR, as assessed by METS-IR, in a representative U.S. population using available national health data.

Methods

Study design and participants

This investigation utilized data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2007 and 2012. NHANES is a comprehensive, cross-sectional survey program designed to assess the health and nutritional status of adults and children in the United States (US). The survey employs a complex, multistage probability sampling design to select participants representative of the non-institutionalized civilian U.S. population.

The study protocol adhered to the guidelines set forth by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided informed consent prior to data collection. Detailed information about the NHANES methodology and data collection procedures is available on the Centers for Disease Control and Prevention (CDC) website (https://www.cdc.gov/nchs/nhanes/).

To ensure independence of observations, each participant was included only once by removing duplicates using their unique sequence number (SEQN) across NHANES cycles (2007–2012). From an initial pool of 60,126 participants in the 2007–2012 NHANES cycles, we applied specific inclusion and exclusion criteria to define our study population. The inclusion criteria comprised participants drawn from the 2007–2012 cycles of the NHANES who were aged 20 years or older and had available data recorded for thyroid-stimulating hormone (TSH), free thyroxine (T4), fasting blood glucose (FBG), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and body mass index (BMI). These variables are necessary for categorizing thyroid function status and calculating the METS-IR which is the main outcome of interest. Participants were excluded if they were pregnant women, missing or had incomplete data for any of the variables needed to compute the METS-IR score, missing thyroid function test results (TSH and free T4), had inconsistent or discordant thyroid function testing precluding clear classification into one of the predefined thyroid status groups. First, we excluded participants with missing data for TSH, T4, FBG, TG, HDL-C, or BMI,

which reduced the sample to 7,107 individuals. We then excluded pregnant women, further reducing the sample to 7,003 participants. Finally, to focus on the adult population, we excluded participants under the age of 20 years. This last criterion resulted in our final study cohort of 6,507 participants (Fig. 1).

To address potential bias from participant exclusion, we conducted a non-response analysis comparing key characteristics between included ($n=6,507$) and excluded ($n=53,619$) participants. Exclusions were primarily due to missing data on main parameters (TSH, free T4, FBG, TG, HDL-C, or BMI) required for thyroid function classification and METS-IR calculation. We compared age, sex, race/ethnicity, BMI, and presence of diabetes and hypertension between the two groups using t-tests for continuous variables and chi-square tests for categorical variables. Results showed that excluded participants were slightly younger (mean age 56.3 vs. 58.5 years, $p<0.001$), more likely to be male (51.2% vs. 47.7%, $p<0.001$), and had a lower prevalence of diagnosed diabetes (10.2% vs. 12.7%, $p<0.001$) compared to included participants. No significant differences were observed in BMI or hypertension prevalence. While these differences were statistically significant due to the large sample size,

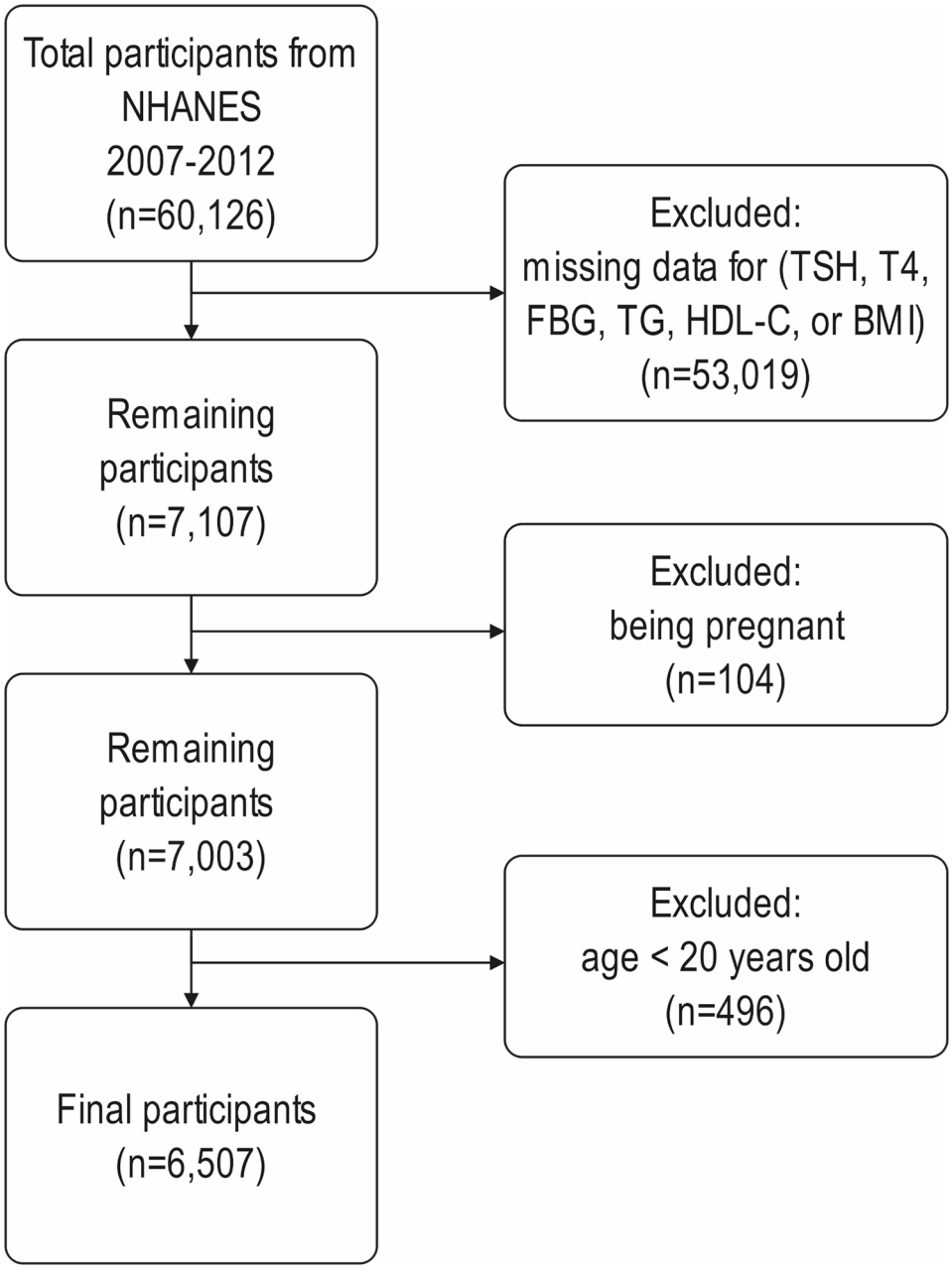

Fig. 1 Flowchart of participant selection

the absolute differences were small and unlikely to substantially impact our main findings.

Thyroid function status and measurement of insulin resistance score

The METS-IR, calculated as:

$$\text{METS-IR} = \frac{\ln\left((2 \times \text{FBG}) + \text{TG}\right) \times \text{BMI}}{\ln(\text{HDL} - \text{C})}$$

Where FBG is Fasting Blood Glucose (mg/dL), TG is Triglycerides (mg/dL), BMI is Body Mass Index (kg/m^2), and HDL-C is High-Density Lipoprotein Cholesterol (mg/dL) [23].

Blood samples were collected after an 8-hour overnight fast. FBG and TG were measured using enzymatic assays and automated biochemical analyzers. Serum TG was quantified using Roche Modular P and Roche Cobas 6000 chemistry analyzers. BMI was calculated as weight (kg) divided by height squared (m^2).

This composite score incorporates glucose metabolism, lipid profile, and body composition to provide a comprehensive assessment of insulin resistance risk.

Thyroid function status is determined through analysis of serum TSH and T4 levels. Based on these key thyroid function indicators and in accordance with established clinical guidelines, participants were classified into five distinct categories: overt hypothyroidism, subclinical hypothyroidism, euthyroid, subclinical hyperthyroidism, and overt hyperthyroidism. Euthyroid served as the reference group, representing normal thyroid function. Participants exhibiting discordant or inconsistent thyroid function test results were excluded from the study. Normal reference ranges for TSH and FT4 were 0.4–4.5 mIU/ml and 0.78–1.86 ng/dL [24, 25].

Covariates

We collected information on various demographic and lifestyle characteristics that have been shown to be associated with thyroid function. These included age, sex, race/ethnicity, education level, marital status, health insurance status, body mass index (BMI), physical activity levels, and smoking status. In addition to demographic information, we collected data on participants' past medical history, including self-reported physician diagnoses of conditions such as diabetes and heart disease. Race, educational level, and marital status were divided into categories matching the standard NHANES response options. We categorized participants' smoking status into 3 groups based on their responses to questions on smoking history: Never smokers (smoked less than 100 cigarettes in their lifetime), Past smokers (smoked at least 100 cigarettes lifetime but do not currently smoke), and Current smokers (smoked over 100 cigarettes lifetime and still smoke either daily or some days [26]. Family income was divided into three categories based on the ratio of family income to poverty, including < 1.30, 1.30 ≥ & < 3.49, and ≥ 3.50 [27]. Hyperlipidemia was defined as total cholesterol of 200 mg/dL or more, TG of 150 mg/dL or higher, low-density lipoprotein of 130 mg/dL or above, or current use of cholesterol-lowering medications [28]. The presence of diabetes mellitus was determined based on self-reported diagnosis, use of anti-diabetic medications, or insulin use [29].

Laboratory measurements included standard clinical chemistry panels as well as thyroid stimulating hormone, free thyroxine, free triiodothyronine, thyroglobulin antibody, and thyroid peroxidase antibodies (TPO Ab)levels. These provided biomarkers of thyroid function to evaluate in association with the above demographic, lifestyle, and past medical history covariates.

Statistical analysis

All statistical analyses were performed using the R statistical software package (http://www.R-project.org, The R Foundation) and EmpowerStats (4.1), using MEC-weighted [30].

Descriptive statistics were generated for all variables of interest. Continuous variables were expressed as weighted means with standard deviations, providing a measure of the data's dispersion. Categorical variables were presented as weighted percentages. Between-group comparisons were conducted using weighted analysis of variance (ANOVA) for continuous variables and Rao-Scott chi-square tests for categorical variables.

To investigate the relationship between thyroid function status and the METS-IR, we employed multiple linear regression analyses. The models were adjusted for potential confounders including age, sex, race/ethnicity, and the presence of hypertension, hyperlipidemia, and diabetes mellitus. Also, in model 3, we adjusted the analyses only for age, sex, and race/ethnicity.

To further investigate the potential influence of autoimmune thyroid disease on the relationship between thyroid status and insulin resistance, participants were categorized as positive or negative for TPO Ab, a well-established marker of thyroid autoimmunity. Previous studies have demonstrated that TPO Ab positivity can modulate the metabolic effects of thyroid dysfunction through mechanisms related to low-grade inflammation [25]. Subgroup analyses stratified by TPO Ab status were conducted to test if TPO positivity strengthen the association between thyroid dysfunction and insulin resistance. The normal range for TPO Ab is < 16IU/mL [31].

For variables with skewed distributions, such as TSH and METS-IR, logarithmic transformations were applied to approximate normality. Regression coefficients (β)

were reported along with their 95% confidence intervals to quantify the associations.

All statistical tests were two-sided, with a significance level set at $p<0.05$. To address multiple comparisons, we implemented appropriate correction methods, such as the Bonferroni correction or false discovery rate control, where necessary. Sensitivity analyses were conducted to assess the robustness of our findings and to evaluate the impact of potential outliers or influential observations. To assess the robustness of our findings, we conducted several sensitivity analyses. We re-ran our regression models after excluding participants with extreme METS-IR or TSH values (>3 SD from the mean) to evaluate the impact of potential outliers. We also performed stratified analyses by age groups, sex, and TPO Ab status to examine potential subgroup differences. Additionally, we investigated both continuous and categorical representations of thyroid function and explored potential non-linear relationships using restricted cubic splines.

Result

Baseline characteristics

The study comprised 6,507 participants with a mean age of 58.52±16.30 years. The majority were female (52.33%) and non-Hispanic white (54.66%). Baseline characteristics were compared according to thyroid function status (Table 1). The final cohort of 6,507 participants was classified into thyroid function categories as follows: 5,805 (89.2%) participants were euthyroid, 467 (7.18%) had subclinical hypothyroidism, 156 (2.4%) had subclinical

Table 1 The demographic information and baseline characteristics of all groups

Variables	Total	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroid	Subclinical hyperthyroidism	Overt hyperthyroidism	*p*-value
Number (%)	6507 (100)	21 (0.32)	467 (7.18)	5805 (89.21)	156 (2.40)	58 (0.89)	
Age, mean (SD)	58.52 (16.30)	65.76 (15.36)	64.83 (14.97)	57.75 (16.29)	62.92 (14.93)	70.59 (13.01)	< 0.001
Gender, N (%)							
Male	3102 (47.67)	12 (57.14)	185 (39.61)	2834 (48.82)	62 (39.74)	9 (15.52)	< 0.001
Female	3405 (52.33)	9 (42.86)	282 (60.39)	2971 (51.18)	94 (60.26)	49 (84.48)	
1.30–3.49	2333 (35.85)	10 (47.62)	251 (53.75)	1975 (34.00)	73 (46.80)	24 (41.38)	
≥ 3.50	2274 (34.95)	9 (42.86)	113 (24.20)	2089 (35.99)	35 (22.44)	28 (48.28)	
Smoking, N (%)							
Never smoker	3687 (56.66)	0 (0)	257 (55.03)	3308 (56.98)	92 (58.98)	30 (51.72)	< 0.001
Past smoker	1293 (19.87)	0 (0)	98 (20.98)	1161 (20.00)	23 (14.74)	11 (18.96)	
Current smoker	1527 (23.47)	21 (100)	112 (23.99)	1336 (23.02)	41 (26.28)	17 (29.31)	
BMI (kg/m^2), mean (SD)	29.59 (6.71)	31.55 (9.23)	30.49 (7.85)	29.59 (6.65)	28.00 (4.85)	26.48 (4.48)	< 0.001
SBP (mmHg), mean (SD)	129.44 (20.97)	118.57 (23.77)	132.43 (21.76)	129.14 (20.63)	132.07 (26.20)	132.00 (28.06)	< 0.001
DBP (mmHg), mean (SD)	68.38 (14.75)	69.33 (10.15)	67.49 (12.03)	68.70 (14.71)	63.07 (17.53)	57.46 (23.01)	< 0.001
Glucose, plasma (mg/dL), mean (SD)	120.87 (50.82)	118.28 (27.37)	127.47 (55.87)	120.22 (49.69)	130.45 (78.23)	108.36 (12.09)	0.002
Direct HDL-Cholesterol (mg/dL), mean (SD)	53.02 (15.76)	48.19 (10.75)	52.37 (16.32)	53.11 (15.84)	53.20 (12.54)	50.94 (12.95)	< 0.001
Triglyceride (mg/dL), mean (SD)	150.92 (134.98)	177.61 (61.91)	160.29 (91.87)	151.19 (139.72)	124.23 (75.60)	110.87 (41.71)	0.011
METS-IR, mean (SD)	45.14 (12.56)	48.69 (11.25)	47.35 (14.77)	45.09 (12.43)	42.13 (9.95)	39.69 (8.80)	< 0.001
HTN, N (%)							
Yes	3535 (94.34)	20 (100)	251 (92.62)	3124 (94.29)	100 (97.09)	40 (100)	0.003
No	212 (5.66)	0 (0)	20 (7.38)	189 (5.71)	3 (2.91)	0 (0)	
HLP, N (%)							
Yes	2551 (82.05)	0 (0)	130 (75.15)	2324 (82.85)	78 (79.59)	19 (61.29)	< 0.001
No	558 (17.95)	2 (100)	43 (24.85)	481 (17.15)	20 (20.41)	12 (38.71)	
DM, N (%)							
Yes	1784 (27.42)	18 (85.71)	172 (36.83)	1508 (25.99)	64 (41.02)	22 (37.93)	< 0.001
No	4572 (70.30)	3 (14.29)	292 (62.53)	4150 (71.53)	92 (58.98)	35 (60.34)	
Borderline	148 (2.28)	0 (0)	3 (0.64)	144 (2.48)	0 (0)	1 (1.73)	

Comparisons were conducted using weighted analysis of variance (ANOVA) for continuous variables and Rao-Scott chi-square tests for categorical variables. Statistical significance is defined as $p<0.05$. *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high-density lipoprotein cholesterol, *METS-IR* metabolic score for insulin resistance, *HTN* hypertension, *HLP* hyperlipidemia, *DM* diabetes mellitus

hyperthyroidism, 58 (0.9%) had overt hyperthyroidism, and 21 (0.3%) had overt hypothyroidism. Approximately 89% of participants exhibited euthyroidism and had the lowest mean age. Regarding thyroid status, subclinical hypothyroidism was the most prevalent ($N=467$, 7.18%). With the exception of overt hypothyroidism, all other thyroid dysfunction groups had significantly higher proportions of female participants. Insulin levels were significantly higher in those with subclinical thyroid dysfunction. METS-IR scores were significantly elevated among participants with hypothyroid dysfunction.

Thyroid function and METS-IR

TSH levels were found to be positively correlated with METS-IR, after adjusting for potential confounding factors including age, gender, race, BMI, hypertension, hyperlipidemia, and diabetes mellitus (beta coefficient 0.003, 95% CI 0.001–0.004, $p=0.021$) (Table 2). While the association was negative and not statistically significant among female participants, male participants exhibited a statistically prominent positive association between TSH and METS-IR after adjusting for the same covariates (beta coefficient 0.008, 95% CI 0.001–0.014, $p<0.001$). Free thyroxine (freeT4) levels demonstrated a negative correlation with METS-IR that did not reach statistical significance after adjustment (beta coefficient −0.001, 95% CI -0.010-0.002, $p=0.201$) (Fig. 2).

Furthermore, categorical regression analysis adjusting for the aforementioned covariates revealed that only subclinical hypothyroidism among male participants (beta coefficient 0.021, 95% CI 0.002–0.040, $p=0.004$) and subclinical hyperthyroidism among female participants (beta coefficient 0.028, 95% CI 0.004–0.063, $p=0.035$) were significantly associated with METS-IR (Table 3).

In response to the observed associations between subclinical hypo/hyperthyroidism and METS-IR, and the lack of similar associations with overt hypo/hyperthyroidism, we conducted a non-parametric re-analysis using the Kruskal-Wallis H test, which yielded a significant result (H=33.26, $p>0.001$), indicating differences in METS-IR across the different TSH categories. To further explore these differences, Dunn's post-hoc test was performed, revealing statistically significant differences between Euthyroid and Subclinical Hypothyroidism ($p=0.026$), Euthyroid and Subclinical Hyperthyroidism ($p=0.033$), and between Overt Hyperthyroidism and Subclinical Hypothyroidism ($p>0.001$). However, the differences between Overt Hypothyroidism and other categories were not statistically significant ($p>0.001$), which could be attributed to the smaller sample sizes in the overt categories.

Table 2 Association between thyroid status and METS-IR

Model	Variable	Total ($n=6507$)			Male ($n=3102$)			Female ($n=3405$)		
		Beta	95% CI	*P* value	Beta	95% CI	*P* value	Beta	95% CI	*P* value
1	TSH	0.024	0.015 0.036	< 0.001	0.029	0.025 0.033	< 0.001	0.018	0.013 0.024	< 0.001
2	TSH	0.003	0.001 0.004	0.021	0.008	0.001 0.014	< 0.001	-0.002	-0.007 0.001	0.310
3	TSH	0.009	0.007 0.010	0.006	0.015	0.011 0.018	< 0.001	0.001	0.000 0.002	0.072
1	Free T4	-0.043	-0.052 -0.033	< 0.001	-0.071	-0.095 -0.054	< 0.001	-0.031	-0.077 0.002	0.064
2	Free T4	-0.001	-0.010 0.002	0.201	-0.014	-0.018 0.001	0.184	-0.001	-0.009 0.007	0.933
3	Free T4	-0.012	-0.019 -0.006	0.089	-0.029	-0.036 -0.017	0.103	-0.009	-0.013 -0.007	0.217

Model 1 was unadjusted. Model 2 was adjusted for age, sex, race/ethnicity, and the presence of hypertension, hyperlipidemia, and diabetes mellitus. **Model 3 was adjusted for** age, sex, and race/ethnicity. *P*-values < 0.05 were considered as statistically significant. *CI* confidence interval

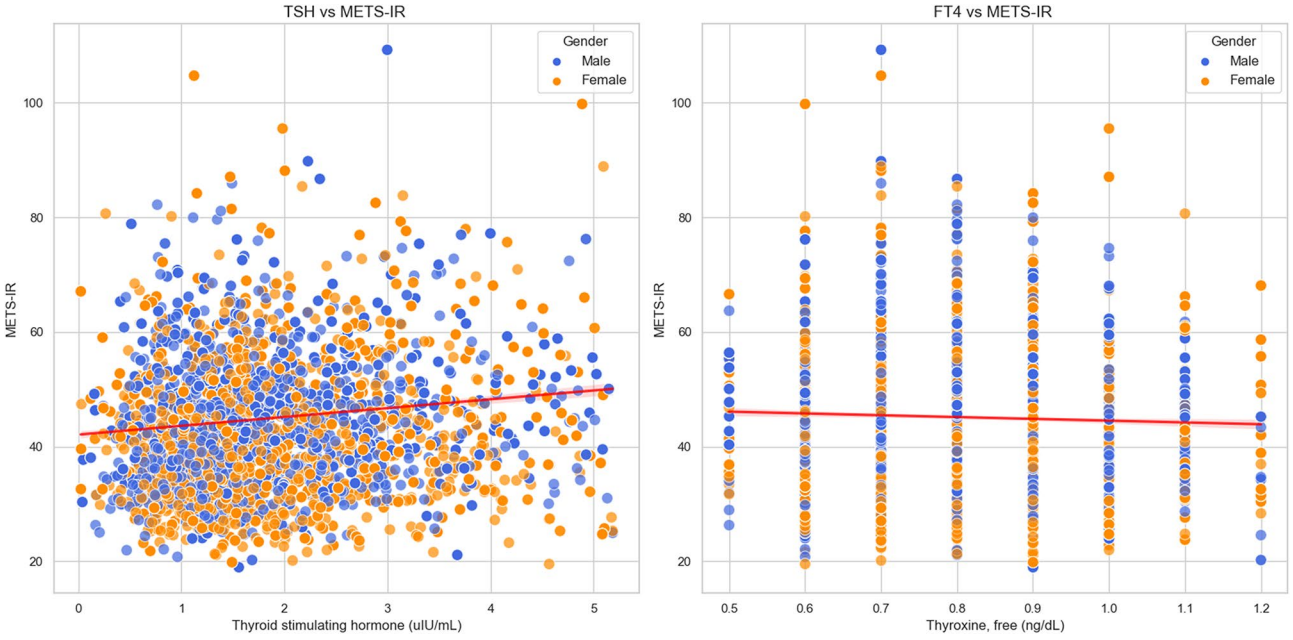

Fig. 2 Association between METS-IR and TSH and free T4 levels with regression lines and 95% confidence intervals

Subgroup analysis based on TPO status

For TPO positive individuals, overt hypothyroidism was significantly associated with higher insulin resistance levels compared to the euthyroid baseline (Beta coefficient 0.213, 95% CI 0.027-0.400, $p=0.025$). Additionally, while not statistically significant, overt hyperthyroidism showed a trend towards lower insulin resistance in this group (Beta coefficient −0.262, 95% CI -0.541-0.015, $p=0.064$).

Conversely, in the TPO negative subgroup, both overt and subclinical hyperthyroidism were significantly associated with reduced insulin resistance (p-values of 0.006 and 0.019, respectively). Subclinical hypothyroidism in TPO negative individuals also showed a positive correlation with higher insulin resistance, which was statistically significant (Beta coefficient 0.046, 95% CI 0.018–0.075, $p=0.002$) (Table S1).

Thyroid function and METS-IR in euthyroid group

The subgroup analysis among euthyroid participants revealed a significant association between TSH and METS-IR, after adjusting for confounding factors. This association was present in the total as well as when analyzing males and females separately ($p<0.001$ for total and males, $p=0.007$ for females). However, free T4 did not exhibit a statistically significant correlation with METS-IR in the euthyroid subgroup (Table S2).

Discussion

This population-based, cross-sectional study provides new findings on the relationship between METS-IR and thyroid function, either as a continuous or a categorical variable. To guide interpretation, we present three regression models - an unadjusted association, a fully adjusted estimate addressing all potential confounders, and an intermediate adjustment controlling for key demographic factors, offering a balanced effect size between the approaches. We found that higher TSH levels was positively associated with METS-IR, adjusting for confounders. Notably, gender differences emerged in subclinical disorders: males showed increased risk with subclinical hypothyroidism, while females showed increased risk with subclinical hyperthyroidism. Additionally, TPO positivity strengthened the association in overt hypothyroidism, suggesting a potential role of autoimmunity in this relationship. Also, our study found a significant association with TSH rather than free T4 in the euthyroid group.

To our knowledge, this is the first study to assess the association between thyroid status and METS-IR. We controlled for confounding covariates to ensure that our results were reliable and applicable to a broad range of individuals, followed by collecting data from a representative sample of the US population. The relationship we observed between thyroid function and METS-IR suggests that even small changes in thyroid status might impact insulin sensitivity. This finding could have important clinical implications, potentially suggesting more attention to thyroid function in patients at risk for metabolic disorders.

Our study's use of METS-IR to assess insulin resistance in relation to thyroid function offers new insights into this complex relationship. IR, a state where cells fail to respond properly to insulin, leading to compensatory hyperinsulinemia, has been linked to various metabolic

Table 3 Association between categorical thyroid status and METS-IR

Model	Variable	Total ($n=6507$)				Male ($n=3102$)				Female ($n=3405$)			
		Beta	95% CI		P value	Beta	95% CI		P value	Beta	95% CI		P value
1					< 0.001				< 0.001				< 0.001
	Overt hypothyroidism	0.089	-0.027	0.205	0.132	-0.074	-0.214	0.065	0.296	0.296	0.108	0.486	0.002
	Subclinical hypothyroidism	0.039	0.013	0.065	0.003	0.012	-0.024	0.049	0.503	0.064	0.030	0.100	< 0.001
	Euthyroid	0 (ref)				0 (ref)				0 (ref)			
	Subclinical hyperthyroidism	-0.057	-0.100	-0.014	0.009	-0.154	-0.216	-0.092	< 0.001	0.015	-0.044	0.074	0.619
	Overt hyperthyroidism	-0.113	-0.183	0.043	0.002	0.046	-0.114	0.208	0.570	-0.120	-0.202	-0.039	0.004
2					< 0.001				< 0.001				< 0.001
	Overt hypothyroidism	0.009	-0.025	0.024	0.674	0.033	-0.008	0.109	0.078	-0.055	-0.134	0.021	0.247
	Subclinical hypothyroidism	0.012	-0.002	0.032	0.069	0.021	0.002	0.040	0.004	0.001	-0.014	0.017	0.803
	Euthyroid	0 (ref)				0 (ref)				0 (ref)			
	Subclinical hyperthyroidism	0.004	-0.014	0.027	0.566	-0.029	-0.059	0.000	0.052	0.028	0.004	0.063	0.035
	Overt hyperthyroidism	0.027	-0.011	0.048	0.201	0.009	-0.041	0.078	0.702	0.017	-0.009	0.046	0.112
3					< 0.001				< 0.001				< 0.001
	Overt hypothyroidism	0.031	0.021	0.044	0.523	-0.049	-0.058	-0.034	0.264	0.174	0.106	0.203	0.426
	Subclinical hypothyroidism	0.019	0.008	0.037	0.057	0.014	0.005	0.022	0.033	0.027	0.018	0.039	0.449
	Euthyroid	0 (ref)				0 (ref)				0 (ref)			
	Subclinical hyperthyroidism	-0.034	-0.056	-0.012	0.088	-0.107	-0.129	-0.086	0.069	0.019	0.015	0.026	0.049
	Overt hyperthyroidism	-0.059	-0.081	-0.036	0.104	0.032	0.008	0.067	0.891	0.001	-0.003	0.004	0.097

Model 1 was unadjusted. Model 2 was adjusted for age, sex, race/ethnicity, and the presence of hypertension, hyperlipidemia, and diabetes mellitus. **Model 3 was adjusted for** age, sex, and race/ethnicity. *P*-values < 0.05 were considered as statistically significant. *CI* confidence interval

disorders including type 2 diabetes, cardiovascular disease, and fatty liver disease [32–35]. Several surrogate markers have been developed and improved to simply measure IR instead of the euglycemic–hyperinsulinemic clamp technique, the gold standard, due to its invasive and expensive nature [36, 37].

Previous studies reported increased HOMA-IR in both hypothyroidism and hyperthyroidism and decreased insulin sensitivity index (ISI), Balfiore, and Matsuda indices for hyperthyroidism compared to euthyroid controls [38–41]. More recently, non-insulin-based indices like TyG and METS-IR have gained attention for their ease of calculation and cost-effectiveness in epidemiological studies. TyG, calculated from TG and FPG, and METS-IR, calculated from HDL-C, TG, FPG, and BMI, are the non-insulin-based indices, quantifying peripheral insulin sensitivity [15, 32, 42]. TyG index is proven to have a positive correlation with overt hypothyroidism and a negative correlation with overt hyperthyroidism in a previous study based on the Korean population [4]. However, recent comparisons between METS-IR and markers like TyG have demonstrated better performance of METS-IR in the diagnosis of impaired insulin sensitivity [15, 43]. Our study is the first to evaluate METS-IR in the context of thyroid function, potentially explaining why our results reveal associations not previously detected.

Altered thyroid function, whether hypo- or hyperthyroidism, has been shown to increase insulin resistance, not only in overt thyroid dysfunction but also in subclinical disorders or even alterations of hormone levels in the reference range, as we also proved [44]. The complex interplay between thyroid hormones and glucose metabolism involves multiple tissues and molecular pathways, explaining the bidirectional relationship we observed between thyroid status and insulin sensitivity. At the hepatic level, thyroid hormones directly stimulate gluconeogenesis and glycogenolysis through transcriptional regulation of key enzymes, including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase [45, 46]. They also upregulate the GLUT2 glucose transporter and induce lipogenesis, actions that can antagonize insulin signaling [47]. In peripheral tissues such as muscle and fat, thyroid hormones enhance insulin-stimulated glucose uptake by upregulating GLUT4 expression and glycolytic enzymes [48]. Additionally, they target mitochondrial proteins like uncoupling protein 3 (UCP3) and PGC-1α, influencing oxidative metabolism and energy expenditure [49]. The mechanisms underlying insulin resistance differ between hyper- and hypothyroidism. In hyperthyroidism, the primary mechanism appears to be glucose overproduction that overwhelms the body's clearance capacity, even in the presence of normal or elevated insulin levels [50]. This aligns with our observation of increased insulin resistance in subclinical hyperthyroidism, particularly in female participants. Conversely, hypothyroidism contributes to insulin resistance through multiple mechanisms, including increased adiposity and visceral fat accumulation due to weight gain, structural and functional changes in muscle tissues, and decreased glucose transporter expression, reducing cellular glucose uptake [51, 52]. These findings help explain the association we found between higher TSH levels and increased METS-IR scores.

Our findings demonstrated an association between subclinical thyroid dysfunction and increased METS-IR, but no significant relationship for overt hypo- or hyperthyroidism. This discrepancy can potentially be explained by differences in thyroid hormone sensitivity, compensatory mechanisms, glucose homeostasis, inflammation profiles, and patient populations between subclinical and overt thyroid conditions [53–55]. In subclinical states, thyroid levels are mildly deviated and sensitivity remains, enabling hormone effects on insulin resistance; compensations may mask these impacts in overt disorders. Additionally, normoglycemia in subclinical disease permits clearer IR analysis versus confounded glucose metabolism in overt states, and subclinical conditions tend to correlate more strongly with IR in normoglycemic populations versus complex multifactorial metabolic interplay seen in overt thyroid disease cohorts [53].

TPO positivity can influence the metabolic effects of thyroid dysfunction according to several studies. A study conducted by Korevaar et al. showed TPO positivity was linked to higher risks of premature delivery, spontaneous premature delivery, and very premature delivery [56]. These relationships remained significant after accounting for TSH and FT4 levels, indicating TPO positivity confers independent metabolic effects. Furthermore, a cross-sectional Chinese population study revealed metabolic disorders were tied to elevated thyroid autoantibody levels in euthyroid subjects, with gender differences [57]. This implies a complex interplay between TPO positivity and metabolism, even in individuals with normal thyroid function. Our finding that TPO Ab positivity strengthened the association between overt hypothyroidism and higher METS-IR scores aligns with these previous studies demonstrating metabolic detriments in the presence of thyroid autoimmunity.

While our study provides valuable insights into the relationship between thyroid function and insulin resistance as measured by METS-IR, several limitations should be considered. The cross-sectional design precludes establishing causal relationships, necessitating future longitudinal studies to elucidate temporal dynamics. Although our sample was large and representative of the US population, generalizability to other ethnic groups or populations with different iodine status or thyroid disease prevalence may be limited. Finally, our reliance on

single measurements of thyroid hormones and METS-IR components may not fully capture their dynamic nature, and hormonal fluctuations could influence our results. Despite adjusting for known confounders, residual confounding by unmeasured factors such as dietary habits, physical activity levels, and genetic predisposition cannot be ruled out. Longitudinal studies using repeated measurements of thyroid function and METS-IR are necessary to confirm the association between thyroid status and METS-IR. Nonetheless, our study's strengths, including its large sample size, use of a novel and sensitive insulin resistance index, and comprehensive confounder adjustment, lend credibility to our findings and provide a solid foundation for future research into the complex interplay between thyroid function and metabolic health.

Conclusion

This large population-based study using NHANES data provides novel insights into the relationship between varying states of thyroid function and levels of insulin resistance as quantified by the METS-IR index. Specifically, we found that higher levels of TSH within the reference range, as well as certain subclinical thyroid disorders such as hypothyroidism in males and hyperthyroidism in females, were significantly associated with an increased risk of insulin resistance after adjusting for potential confounding factors. These findings indicate that even subtle alterations in thyroid function may impact metabolic health through effects on glucose homeostasis and peripheral insulin sensitivity. As METS-IR has demonstrated high accuracy in diagnosing insulin resistance and related cardiometabolic diseases, our results suggest that assessing thyroid function could serve as an early screening tool to aid in primary care settings. Considering the growing global burden of both thyroid disorders and insulin resistance-related conditions, continued efforts to elucidate their complex interplay remain vital for public health.

Supplementary Information

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Supplementary Material 1: Table S1. Association between categorical thyroid status and METS-IR according to TPO status. Table S2. Association between thyroid status and METS-IR in euthyroid group.

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None to declare.

Author contributions
Study concept and design: SAN; Acquisition of data: SAN and FS; Analysis and interpretation of data: SAN and HMV; Drafting of the manuscript: SAN and FS; Critical revision of the manuscript for important intellectual content: SAN and HMV; Study supervision: SAN and FS. All individuals listed as (co)-authors have met the authorship criteria, and nobody who qualifies for authorship is omitted from the list. The final manuscript was corrected and approved by all authors.

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Data availability
The data analyzed in this study are available in the National Health and Nutrition Examination Survey (NHANES) 2007-2012 dataset, which can be accessed from the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx). NHANES is a publicly available resource, and all investigators who adhere to the NHANES data use agreement are granted access. Instructions for requesting and accessing the NHANES data files can be found on the NHANES website. The data that support the findings of this study are openly available in NHANES.

Declarations

Ethics approval and consent to participate
This study utilized publicly available deidentified data from the National Health and Nutrition Examination Survey (NHANES) 2007–2012. As the data analysis was performed on anonymous secondary data, ethics approval and participant consent were not required. The data collection protocols and consent procedures for the NHANES 2007–2012 were approved by the National Center for Health Statistics Research Ethics Review Board (approval number: Protocol #2005-06). Written informed consent was obtained from all NHANES participants prior to enrollment. This study complies fully with the Declaration of Helsinki ethical principles for medical research involving human subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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