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The non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) is associated with thyroid hormones and thyroid hormone sensitivity indices: a cross-sectional study

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Abstract

Background Lipids and thyroid hormones (TH) are closely interrelated. However, previous studies have not mentioned the linkage encompassing the non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio (NHHR) alongside TH level, as well as sensitivity indices.

Methods This cross-sectional study leverages expansive datasets from the National Health and Nutrition Examination Survey (NHANES) spanning 2007 to 2012. Weighted multivariate linear regression, smoothed curve fitting and sensitivity analyses were used to investigate the associations of the NHHR with the thyroid. Subgroup analyses and interaction tests were conducted to determine the robustness of the findings across diverse segments of the population, ensuring the consistency and generalizability of the observed associations.

Results The NHHR was significantly positively correlated with free triiodothyronine (FT3) levels, thyroid-stimulating hormone (TSH) levels, the FT3 to FT4 ratio (FT3/FT4), and the quantile-based thyroid feedback index for FT3 ($TFQI_{FT3}$) and negatively correlated with free thyroxin (FT4) levels [0.17(0.07–0.27), $P=0.001$; 0.60 (0.03–1.17), $P=0.040$; 0.06 (0.04–0.08), $P<0.0001$; 0.23 (0.16–0.30), $P<0.0001$; and -0.65 (-1.05–-0.24), $P=0.002$]. Smoothed curve fitting revealed nonlinear correlations of the NHHR with thyroid function and thyroid hormone sensitivity indices. In subgroup analyses, interaction tests, and smoothed curve fitting analyses, different populations presented largely consistent statistical differences.

Conclusion Among American adults, the NHHR was significantly positively correlated with FT3 levels, TSH levels, the FT3/FT4 and the $TFQI_{FT3}$. Conversely, a negative association was noted between the NHHR and FT4 levels.

Keywords NHHR, Thyroid function, Thyroid hormone sensitivity indices, NHANES, Cross-sectional study

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Introduction

TH are among the crucial regulators of metabolism, playing an exceedingly important role in maintaining human homeostasis. TH primarily include thyroxine (T4) and triiodothyronine (T3), whose free forms, FT4 and FT3, respectively, are the key players that regulate the biological effects of TH. Within peripheral tissues, T3 is generated mainly through the enzymatic transformation of T4 by deiodinase iodothyronine (DIO), which is a pivotal mechanism in metabolism regulation. Consequently, the FT3/FT4 reflects the bioavailability of TH, with lower values indicating reduced TH effects at the same synthesis rate [1].

The homeostasis of TH is modulated by the hypothalamus–pituitary–thyroid (HPT) axis, which uses negative feedback mechanisms to maintain balance. Andreas Jostel et al. introduced the thyroid stimulating hormone index (TSHI) as a means to assess the responsiveness or sensitivity of the pituitary gland to TH. Specifically, higher TSHI values may indicate lower central thyroid hormone sensitivity, indicative of weakened TH-mediated negative feedback on the pituitary gland, which in turn leads to relatively higher TSH levels [2]. Furthermore, the total thyroxine resistance index (TT4RI) and total triiodothyronine resistance index (TT3RI) are tools that are used to assess the extent of thyroid hormone resistance in the body, reflecting the sensitivity of pituitary thyrotropin cells to TH [3]. Nevertheless, Laclaustra et al. reported that thyroid feedback quartile indices ($TFQI_{FT3}$ and $TFQI_{FT4}$) are more sensitive than TT4RI and TSHI and are considered indicators for evaluating the sensitivity of central tissues to TH [4].

There is a close relationship between TH and lipids. TH can affect the degradation, excretion, and transport of cholesterol, regulating the balance of cholesterol in the body [5–8]. Furthermore, hypercholesterolemia, a condition characterized by elevated cholesterol levels, has been shown to impact thyroid function, potentially leading to hypothyroidism [9–12]. However, there is currently no consensus on the relationship between various components of cholesterol and TH [13–16].

The NHHR, a novel and comprehensive metric of atherogenic lipids [17], offers more precise information about lipid metabolism, and it is determined by calculating the ratio of non-high-density lipoprotein (non-HDL) cholesterol, which is obtained by subtracting high density lipoprotein (HDL) from total cholesterol (TC), to HDL. Research has shown that, compared with traditional lipid markers, the NHHR has greater predictive power for various metabolic diseases, including cardiovascular diseases [18], non-alcoholic fatty liver disease (NAFLD) [19], type 2 diabetes mellitus (T2DM), and metabolic syndrome [20, 21].

However, previous research has not been mentioned the linkage encompassing NHHR alongside TH, as well as sensitivity indices. This study focused on the American adult population from 2007 to 2012 in the NHANES database, and the differences between the populations with different characteristics were investigated separately by subgroup analysis.

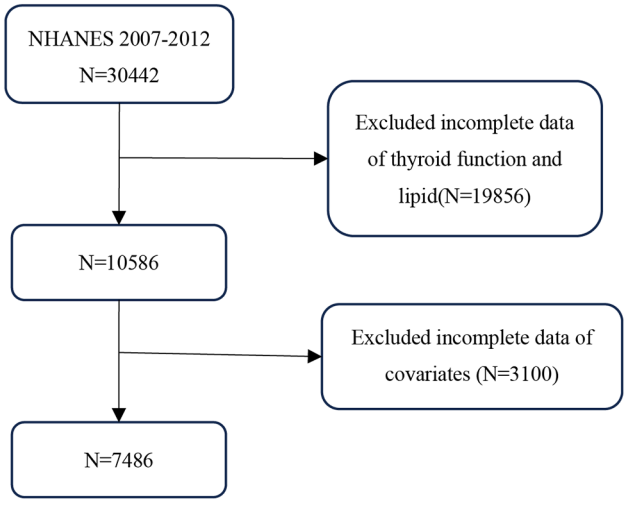

Fig. 1 Flowchart of the sample selection from NHANES 2007–2012

Materials and methods

Study population

The data that were gathered from NHANES, a comprehensive program that utilizes sophisticated stratified multistage sampling techniques to evaluate the health and nutritional profiles of American individuals. Three cycles from 2007 to 2012 were selected for the study because they were the only cycles that included both full thyroid function and lipid data. The initial study population consisted of 30,442 adults, excluding 1,9856 individuals with missing FT3, FT4, TSH, and NHHR data and 3,100 individuals with missing covariates such as smoking, alcohol consumption, and education; the final population included 7,486 individuals (Fig. 1).

NHHR

The NHHR, an acronym for the non-HDL-C to HDL-C ratio, was derived from the participants' lipid profiles, with non-HDL-C calculated by subtracting HDL-C from TC.

Thyroid function and thyroid hormone sensitivity indices

To assess thyroid function comprehensively, FT3, FT4, and TSH were chosen as key indicators. The reference ranges were set to 2.5–3.9 ng/dL for FT3, 7.74–20.64 pmol/L for FT4, and 0.34–5.60 mIU/L for TSH. The sensitivity of peripheral tissues to TH is described with the FT3/FT4. Central sensitivity was described with the relatively more sensitive $TFQI_{FT3}$ and $TFQI_{FT4}$, which were

measured using the cumulative distribution function (cdf), and they were calculated to represent the quartile-based index of thyroid feedback with the following formulas: $TFQI_{FT3}$ = cdf FT3-(1-cdfTSH) and $TFQI_{FT4}$ = cdfFT4-(1-cdfTSH), where TFQI values ranging from −1 to 1, increasing values represent a gradual decrease in sensitivity [4].

Covariates

Adjustments were made for covariates associated with the NHHR and thyroid function, including sociodemographic factors [age, sex, race, education level, marital status, and poverty index (PIR)], health behaviours (smoking status and alcohol intake), and health-related conditions [body mass index (BMI), thyroid anti-peroxidase antibodies (TPOAb), thyroid-stimulating hormone receptor antibodies (TRAb), urine iodine, hypertension, and diabetes]. Subgroup analyses categorized individuals by age (<45, 45–59, and >60 years) and BMI (<25, 25-29.9, and >30 kg/m^2).

Statistical analysis

The statistical approach used in this study conformed to the guidelines of the Centers for Disease Control and Prevention (CDC), meticulously incorporating the precise NHANES sampling weights into the analyses. For continuous variables, data are presented as weighted means accompanied by standard errors (SEs). Categorical variables are presented using weighted proportions. To explore the complex relationships between the NHHR, thyroid function, and sensitivity markers, weighted t tests, chi-square tests, and multivariate linear regression models were employed, with adjustments for an array of covariates across three models. Trend tests, subgroup analyses, and interaction analyses were conducted. Finally, smoothed curve fitting for thyroid function parameters and thyroid hormone sensitivity parameters in the total subject population was performed to analyse the nonlinear relationships between these parameters. In addition, people who had or could not be identified as having thyroid disease, who consumed foods or medications that affected thyroid function, and who were missing total triglyceride (TG) and LDL data were excluded. TG and LDL were subsequently included as covariates, and sensitivity analyses were performed on the remaining $n=3220$ subjects. All statistical computations were executed utilizing the R statistical software version 3.4.3 in conjunction with Empower software (www.empowerstats.com), with the statistical significance set to $P<0.05$.

Results

Participant characteristics

The study included 7,486 participants, with 49.73% males and 50.27% females. The average age was 46.8±16.7 years. On the basis of their NHHR levels, the participants were stratified into quartiles, revealing significant differences across demographic and clinical characteristics, such as sex, race, education, marital status, PIR, smoking and alcohol consumption habits, as well as various biochemical indices, including TC, HDL-C, BMI, TPOAb, TGAb, FT3, FT4, TSH, FT3/FT4, and $TFQI_{FT3}$. Moreover, higher NHHR values were positively associated male sex, Mexican American ethnicity, non-Hispanic white ethnicity, lower levels of educated, current smoking habits, hypertension, and BMI, TC, FT3, TSH, FT3/FT4, and $TFQI_{FT3}$ values, while the opposite was true for female sex, Hispanic ethnicity, higher levels of education, lack of hypertension, HDL-C, and FT4 levels. Clinical characteristics and biochemical indices of the subjects are displayed in Table 1.

Correlations of the NHHR with thyroid function parameters

Within the fully adjusted framework, the translated NHHR demonstrated a statistically significant positive correlation with FT3 [0.17 (0.07–0.27), $P=0.001$] and TSH [0.60 (0.03–1.17), $P=0.040$], whereas a negative correlation with FT4 [-0.65 (-1.05–-0.24), $P=0.002$] was observed. Upon further examination of the NHHR quartiles within the fully adjusted model, individuals in the uppermost quartile presented negative associations with FT3 [0.09 (0.04–0.15), $P=0.001$] and TSH [0.42 (0.11–0.73), $P=0.008$] and positive association with FT4 [-0.36 (-0.58–-0.14), $P=0.002$]. The trend test showed that all the variables were significantly associated (Table 2). Smoothed curve fitting and threshold effect tests revealed nonlinear relationships between FT3, FT4, and the NHHR, pinpointing significant inflection points (Table 3; Fig. 2).

Correlations of the NHHR with thyroid hormone sensitivity indices

In Model 3, the translated NHHR was significantly positively correlated with FT3/FT4 [0.06 (0.04–0.08), $P<0.0001$] and $TFQI_{FT3}$ [0.23 (0.16–0.30), $P<0.0001$], whereas the correlation with $TFQI_{FT4}$ [-0.06 (-0.14–0.02), $P=0.145$] was negative but not significantly different. When grouped into quartiles, the NHHR remained significantly positively correlated with FT3/FT4 and $TFQI_{FT3}$. Individuals in the uppermost NHHR quartile compared with the lowest showed a 0.03-fold increase in FT3/FT4 and a 0.12-fold increase in $TFQI_{FT3}$, with all trend tests revealing significant differences (Table 4). Smoothed curve fitting and threshold effect tests revealed nonlinear correlations for both FT3/FT4 and $TFQI_{FT3}$, and the FT3/FT4 log-likelihood ratio test revealed that the inflection points were both significant (Table 3; Fig. 2).

Table 1 The baseline characteristics of individuals by quartiles of the NHHR

Variable	Total	Q1	Q2	Q3	Q4	*P*-value
Age (years)	46.8 ± 16.7	46.6 ± 18.5	47.5 ± 16.8	47.0 ± 16.0	46.0 ± 14.6	0.3033
Sex (%)						< 0.0001
Male	49.73	34.08	44.00	58.26	66.31	
Female	50.27	65.92	56.00	41.74	33.69	
Race (%)						< 0.0001
Mexican American	8.02	5.53	7.28	9.74	10.02	
Non-Hispanic White	5.23	3.93	5.06	5.46	6.82	
Non-Hispanic black	70.19	70.65	70.24	69.88	69.92	
Other Hispanic	10.91	14.53	11.57	9.23	7.53	
Other Race	5.65	5.36	5.86	5.69	5.71	
Education (%)						< 0.0001
Less than 9th grade	5.83	4.64	5.43	5.93	7.75	
9–11th grade	12.59	9.71	11.33	13.55	16.64	
High School	22.99	20.79	22.34	23.89	25.49	
College graduate or above	58.59	64.85	60.90	56.63	50.11	
Marry (%)						0.0286
Married/ living with partner	64.62	60.71	68.06	64.87	65.22	
Separated/ divorced/widowed	17.85	19.08	16.71	17.03	18.68	
Never married	17.53	20.21	15.23	18.10	16.11	
PIR (%)						0.0002
<1.3	18.73	15.89	19.18	17.49	23.42	
1.3–3.49	33.97	34.50	30.90	37.78	32.24	
≥ 3.5	47.30	49.62	49.92	44.73	44.34	
Smoking (%)						< 0.0001
Current smoker	20.64	16.77	17.55	22.25	27.38	
Former smoker	24.60	24.90	24.29	27.07	21.48	
Never smoker	54.76	58.33	58.16	50.67	51.15	
Alcohol user (%)						0.0032
Current	67.51	69.87	66.26	65.89	68.01	
Former	9.71	7.43	8.47	12.18	11.08	
Never	22.77	22.70	25.27	21.92	20.91	
Hypertension (%)						0.0973
Yes	30.78	27.68	31.48	31.93	32.52	
No	69.22	72.32	68.52	68.07	67.48	
Diabetes (%)						0.8580
Yes	8.74	8.54	8.46	8.64	9.54	
No	91.25	91.46	91.54	91.36	90.46	
BMI (kg/m^2)	28.43 ± 6.26	25.60 ± 5.48	28.18 ± 6.03	29.51 ± 6.02	31.04 ± 6.27	< 0.0001
TC (mg/dl)	196.02 ± 41.14	175.05 ± 35.67	188.39 ± 36.29	200.68 ± 33.72	226.69 ± 42.26	< 0.0001
HDL-C (mg/dl)	53.73 ± 15.80	69.29 ± 15.90	55.49 ± 11.00	47.49 ± 8.31	39.23 ± 7.23	< 0.0001
TPOAb (IU/ml)	25.02 ± 102.16	25.98 ± 101.12	34.98 ± 134.66	19.19 ± 78.89	18.99 ± 80.40	0.0035
TGAb (IU/ml)	10.50 ± 82.35	9.19 ± 80.77	5.37 ± 50.08	11.89 ± 85.35	16.70 ± 107.73	0.0499
Urine iodine (μg/L)	251.70 ± 1140.35	277.71 ± 1230.86	227.73 ± 743.41	239.22 ± 1474.67	262.82 ± 908.77	0.7942
FT3 (pg/ml)	3.24 ± 0.55	3.15 ± 0.60	3.23 ± 0.72	3.27 ± 0.38	3.33 ± 0.40	< 0.0001
FT4 (pmol/L)	10.34 ± 2.10	10.48 ± 2.56	10.37 ± 2.01	10.36 ± 1.83	10.11 ± 1.84	0.0045
TSH (mIU/L)	2.13 ± 3.17	1.98 ± 2.10	2.09 ± 2.14	2.00 ± 1.20	2.52 ± 5.90	0.0023
FT3/FT4	0.50 ± 0.11	0.48 ± 0.10	0.49 ± 0.13	0.50 ± 0.10	0.52 ± 0.11	< 0.0001

Table 1 (continued)

Variable	Total	Q1	Q2	Q3	Q4	*P*-value
$TFQI_{FT3}$	0.09 ± 0.38	-0.01 ± 0.38	0.07 ± 0.38	0.13 ± 0.35	0.19 ± 0.37	< 0.0001
$TFQI_{FT4}$	-0.00 ± 0.40	-0.00 ± 0.39	0.01 ± 0.40	0.00 ± 0.40	-0.01 ± 0.41	0.7175

Mean ± SD for continuous variables: *P*-value was calculated by weighted linear regression model. (%) for categorical variables: *P*-value was calculated by weighted chi-square test

NHHR, non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio; PIR, income-poverty ratio; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TPOAb, antithyroid peroxidase autoantibody; TGAb, anti-thyroglobulin antibodies; BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; FT3/FT4, FT3/FT4 ratio; $TFQI_{FT3}$, $TFQI_{FT4}$, thyroid feedback quantile-based index

*$P < 0.05$

Table 2 Association between NHHR with thyroid function

	Model 1		Model 2		Model 3	
	β(95%CI)	*P*	β(95%CI)	*P*	β(95%CI)	*P*
FT3	0.33 (0.23, 0.43)	< 0.0001	0.19 (0.10, 0.29)	< 0.0001	0.17 (0.07, 0.27)	0.001
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.08 (0.03, 0.13)	0.003	0.07 (0.02, 0.12)	0.005	0.06 (0.01, 0.11)	0.016
Quartile 3	0.12 (0.06, 0.17)	< 0.0001	0.07 (0.02, 0.12)	0.003	0.06 (0.01, 0.11)	0.018
Quartile 4	0.18 (0.12, 0.23)	< 0.0001	0.10 (0.05, 0.15)	< 0.0001	0.09 (0.04, 0.15)	0.001
P for trend		< 0.0001		0.000		0.003
FT4	-0.62 (-0.99, -0.26)	0.001	-0.78 (-1.16, -0.40)	< 0.0001	-0.65 (-1.05, -0.24)	0.002
Quartile 1	Ref		Ref		Ref	
Quartile 2	-0.11 (-0.31, 0.09)	0.280	-0.16 (-0.36, 0.04)	0.127	-0.12 (-0.33, 0.08)	0.234
Quartile 3	-0.10 (-0.30, 0.10)	0.333	-0.15 (-0.35, 0.05)	0.140	-0.08 (-0.29, 0.12)	0.423
Quartile 4	-0.36 (-0.57, -0.16)	0.000	-0.43 (-0.64, -0.22)	< 0.0001	-0.36 (-0.58, -0.14)	0.002
P for trend		0.001		< 0.0001		0.002
TSH	0.70 (0.14, 1.25)	0.014	0.94 (0.36, 1.52)	0.002	0.60 (0.03, 1.17)	0.040
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.04 (-0.27, 0.34)	0.808	0.07 (-0.23, 0.38)	0.640	0.12 (-0.17, 0.40)	0.421
Quartile 3	0.02 (-0.28, 0.32)	0.908	0.11 (-0.19, 0.42)	0.473	0.02 (-0.27, 0.31)	0.873
Quartile 4	0.45 (0.15, 0.76)	0.004	0.59 (0.28, 0.91)	0.000	0.42 (0.11, 0.73)	0.008
P for trend		0.003		0.000		0.010

Model 1: Non-adjusted

Model 2: Adjusted for age, sex, race, education level, PIR, marry, smoke, alcohol

Model 3: Adjusted for age, sex, race, education level, PIR, marry, smoke, alcohol, BMI, TGAb, TPOAb, urine iodine, diabetes, and hypertension

CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone

Subgroup analysis

Subgroup analysis on the basis of age, sex, and BMI revealed that the relationships between the NHHR and thyroid function and sensitivity indices were generally consistent across different demographics compared with the total subject population. The interaction test between the populations revealed a significant difference only in the relationship between the NHHR and FT4 (Fig. 3).

Sensitivity analysis

Sensitivity analyses are performed on the remaining subjects after applying a more stringent correction for the nadir criterion. These findings highlighted that the translated NHHR had a statistically significant positive relationship with FT3, TSH, FT3/FT4, and $TFQI_{FT3}$ but a negative correlation with FT4. In tests of the NHHR four-level subgroups, largely consistent conclusions were reached. The results of the trend tests were also almost always significantly different (Table 5).

Discussion

TH occupy a pivotal position in modulating the intricate processes of metabolism, development, and growth within mammalian systems. T3 and T4 directly influence cholesterol synthesis and metabolism. The release of TH is intricately orchestrated by the HPT axis and simultaneously exerts negative feedback regulatory effects on thyrotropin-releasing hormone (TRH) and TSH [22]. Furthermore, TSH has been shown to regulate hepatic lipid and cholesterol homeostasis [6]. To assess pituitary thyrotropin function accurately and reverse physiological TSH suppression, indices such as TSHI, $TFQI_{FT3}$, and $TFQI_{FT4}$ have been introduced to assess the sensitivity of central tissues to TH [2, 4]. Dyslipidaemia can lead to various common diseases, including atherosclerosis, T2DM and NAFLD [23–25]. Notably, overt hypothyroidism has emerged as a standalone risk factor for NAFLD, distinct from other metabolic contributors, as affirmed by multiple studies [26, 27]. Abnormal thyroid function is

Table 3 The nonlinear relationship between NHHR with thyroid function and thyroid hormones sensitivity indices

	Adjust β(95%CI), *P*-value
FT3	
Fitting by the standard linear model	0.01 (0.01, 0.02) 0.0009
Inflection point	2.33
NHHR<2.33	0.06 (0.03, 0.10) 0.0009
NHHR>2.33	0.01 (-0.00, 0.02) 0.1618
P for Log-likelihood ratio	0.008
FT4	
Fitting by the standard linear model	-0.11 (-0.15, -0.08) < 0.0001
Inflection point	5.76
NHHR<5.76	-0.17 (-0.21, -0.12) < 0.0001
NHHR>5.76	0.05 (-0.04, 0.15) 0.2569
P for Log-likelihood ratio	< 0.001
TSH	
Fitting by the standard linear model	0.06 (0.01, 0.10) 0.0154
Inflection point	4.83
NHHR<4.83	0.10 (0.03, 0.16) 0.0037
NHHR>4.83	-0.02 (-0.11, 0.08) 0.7084
P for Log-likelihood ratio	0.087
FT3/FT4	
Fitting by the standard linear model	0.01 (0.00, 0.01) < 0.0001
Inflection point	5.76
NHHR<5.76	0.01 (0.01, 0.01) < 0.0001
NHHR>5.76	-0.00 (-0.01, 0.00) 0.636
P for Log-likelihood ratio	0.003
$TFQI_{FT3}$	
Fitting by the standard linear model	0.02 (0.02, 0.03) < 0.0001
Inflection point	2.95
NHHR<2.95	0.06 (0.04, 0.08) < 0.0001
NHHR>2.95	0.01 (0.00, 0.02) 0.0019
P for Log-likelihood ratio	< 0.001
$TFQI_{FT4}$	
Fitting by the standard linear model	-0.02 (-0.02, -0.01) < 0.0001
Inflection point	5.76
NHHR<5.76	-0.02 (-0.03, -0.01) < 0.0001
NHHR>5.76	-0.00 (-0.02, 0.02) 0.8754
P for Log-likelihood ratio	0.067

CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; FT3/FT4, FT3/FT4 ratio; $TFQI_{FT3}$, $TFQI_{FT4}$, thyroid feedback quantile-based index

correlated with heightened vulnerability to cardiovascular diseases, cholesterol gallstones, and a broad spectrum of metabolic disorders [28–30]. Therefore, early detection of thyroid function or dyslipidaemia is very important in prophylactic and therapeutic strategies to mitigate the onset and progression of these conditions.

The NHHR, a newly proposed comprehensive lipid parameter, has significant advantages over traditional lipid indices in the prediction of a variety of metabolic diseases. The NHHR was significantly positively correlated with FT3, TSH, FT3/FT4 and $TFQI_{FT3}$. Conversely, a negative association was noted between the NHHR and FT4.

One possible mechanism is that cholesterol is ubiquitous in the membrane structure of mammalian cells and occupies a pivotal position in maintaining membrane fluidity, permeability, and microstructure [31]. Excessive cholesterol can reduce membrane fluidity, disrupt membrane microdomains, and subsequently affect the function of membrane proteins, ultimately leading to cellular dysfunction and death [11]. Additionally, cholesterol is extensively involved in the formation of intracellular membrane structures, such as the endoplasmic reticulum membrane and the mitochondrial membrane [31]. Excessive cholesterol can cause dysfunction in these membrane structures, including structural disorders of transport proteins on the mitochondrial surface, triggering mitochondrial stress, etc [31]. Therefore, the accumulation of excessive cholesterol is associated with various systemic diseases.

Recent investigations have shown that cholesterol has adverse effects on thyroid function. Animal models have demonstrated that mice fed with a HDL diet exhibited markedly heightened levels of TSH and T4, coupled with a notable decrease in T3 concentrations, compared to those fed with a normal diet [32]. Histological findings further revealed that the area of thyrotropin-producing cells and their proportion in total pituitary cells may increase, accompanied by a commensurate upregulation of TSHβ subunit expression, a key modulator of hormonal distinctiveness and functionality [33]. Furthermore, clinical evaluations have consistently confirmed a robust positive association between TC and TSH levels, as documented in multiple studies [10, 33, 34]. Collectively, these observations suggest that aberrant cholesterol accumulation may adversely disrupt the complex interplay within the pituitary–thyroid axis.

The regulation of cholesterol levels by TH may also contribute to the relationship between the NHHR and TH. TH affects cholesterol uptake and synthesis by manipulating the expression patterns of the sterol regulatory element-binding protein-2 (SREBP-2) gene, a pivotal regulator that regulates the transcription of the LDL-receptor (LDL-R) gene, thereby affecting both cholesterol uptake and synthesis [35, 36]. The thyroid hormone receptor (TR) can compete with liver X-activated receptor (LXR) for binding, leading to T3-induced inhibition of ATP-binding cassette transporter A1 (ABCA-1), which is a crucial player in HDL biogenesis [37]. TSH can regulate cholesterol homeostasis by inhibiting hepatic bile acid synthesis to reduce cholesterol excretion [6, 38].

Additionally, studies have delved into the interconnections between thyroid hormone sensitivity indices and other diseases. Roef GL et al. argued that an elevated FT3/FT4 is indicative of adverse metabolic profiles and increased cardiovascular risk factors [39]. Yang S and their team posit a positive correlation between TFQI and

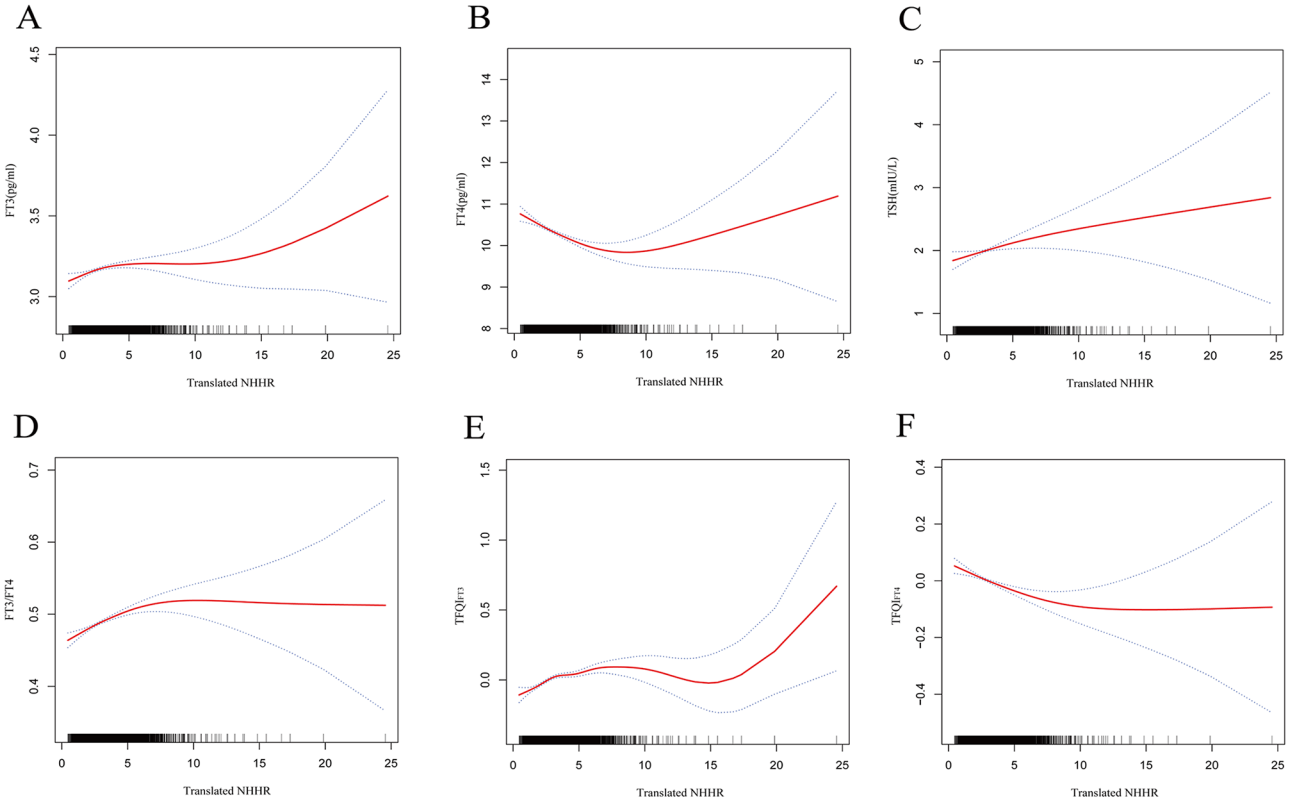

Fig. 2 Smoothed curve fitting model for the association of NHHR with thyroid hormone and sensitivity **A**-**F** respectively represent smoothed curve fitting models for the association of NHHR with FT3, FT4, TSH, FT3/FT4, TFQI$_{FT3}$, TFQI$_{FT4}$

Table 4 Association between NHHR with thyroid hormones sensitivity indices

	Model 1		Model 2		Model 3	
	β(95%CI)	***P***	**β(95%CI)**	***P***	**β(95%CI)**	***P***
FT3/FT4	0.08 (0.06, 0.10)	< 0.0001	0.07 (0.05, 0.09)	< 0.0001	0.06 (0.04, 0.08)	< 0.0001
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.01 (0.00, 0.02)	0.011	0.01 (0.00, 0.02)	0.006	0.01 (0.00, 0.02)	0.026
Quartile 3	0.02 (0.01, 0.03)	0.000	0.02 (0.01, 0.03)	0.002	0.01 (0.00, 0.02)	0.048
Quartile 4	0.04 (0.03, 0.05)	< 0.0001	0.04 (0.03, 0.05)	< 0.0001	0.03 (0.02, 0.04)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
TFQI$_{FT3}$	0.36 (0.29, 0.42)	< 0.0001	0.28 (0.21, 0.34)	< 0.0001	0.23 (0.16, 0.30)	< 0.0001
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.07 (0.03, 0.10)	0.000	0.06 (0.03, 0.10)	0.000	0.05 (0.01, 0.08)	0.006
Quartile 3	0.13 (0.09, 0.16)	< 0.0001	0.10 (0.07, 0.14)	< 0.0001	0.08 (0.05, 0.12)	< 0.0001
Quartile 4	0.19 (0.15, 0.23)	< 0.0001	0.15 (0.11, 0.18)	< 0.0001	0.12 (0.08, 0.16)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
TFQI$_{FT4}$	-0.04 (-0.11, 0.03)	0.255	-0.07 (-0.14, 0.01)	0.071	-0.06 (-0.14, 0.02)	0.145
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.02 (-0.02, 0.06)	0.347	0.01 (-0.03, 0.05)	0.555	0.02 (-0.02, 0.06)	0.357
Quartile 3	0.01 (-0.03, 0.04)	0.774	-0.00 (-0.04, 0.04)	0.876	0.00 (-0.04, 0.04)	0.869
Quartile 4	-0.01 (-0.05, 0.02)	0.472	-0.03 (-0.07, 0.01)	0.186	-0.02 (-0.06, 0.02)	0.365
P for trend		0.304		0.109		0.212

Model 1: Non-adjusted

Model 2: Adjusted for age, sex, race, education level, PIR, marry, smoke, alcohol

Model 3: Adjusted for age, sex, race, education level, PIR, marry, smoke, alcohol, BMI, TGAb, TPOAb, urine iodine, diabetes, and hypertension

CI, confidence interval; FT3/FT4, FT3/FT4 ratio; TFQI$_{FT3}$, TFQI$_{FT4}$, thyroid feedback quantile-based index

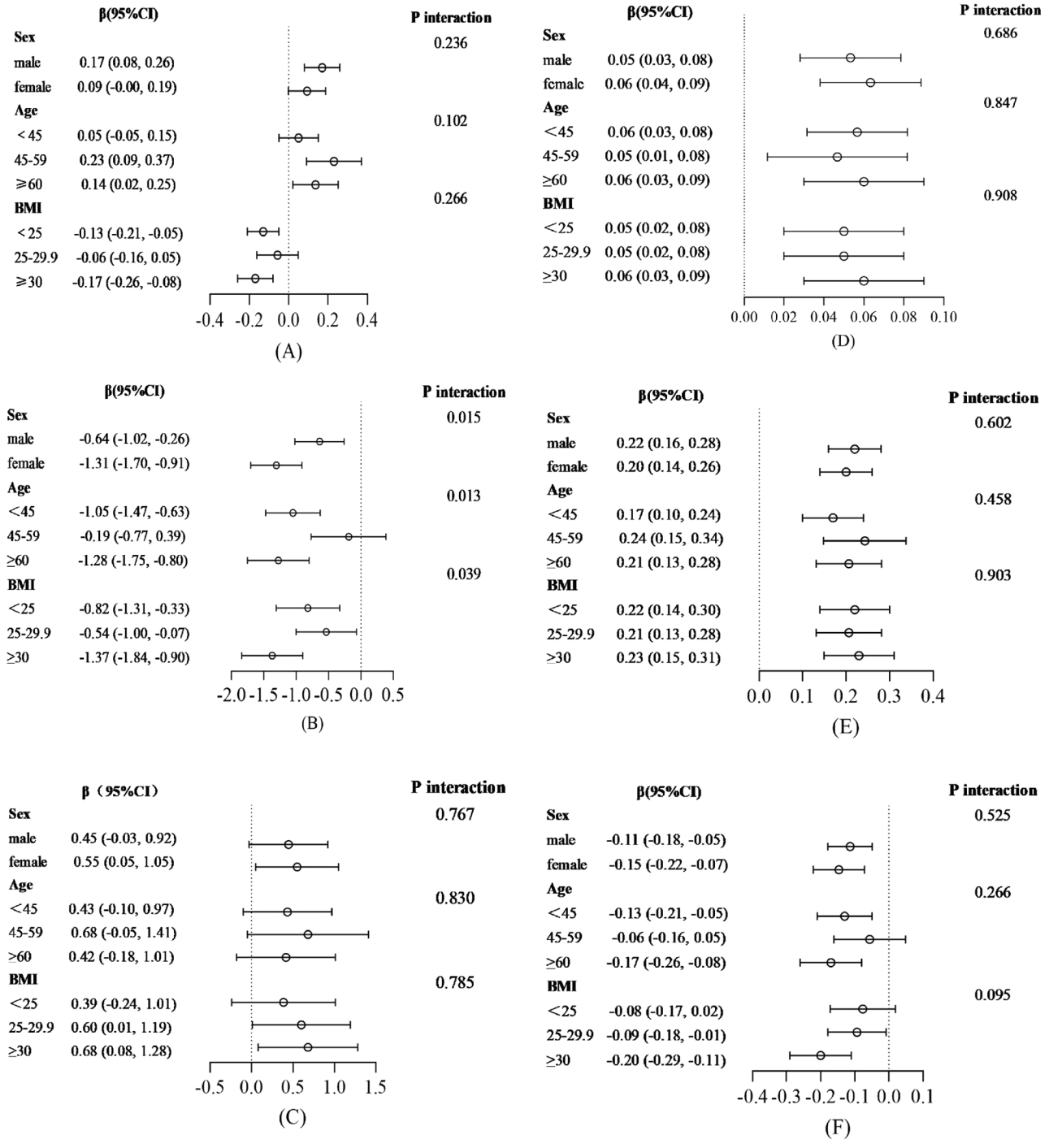

Fig. 3 Subgroup analysis for the association of NHHR with thyroid hormone and sensitivity. (**A**)-(**F**) respectively represent subgroup analyses for the association of NHHR with FT3, FT4, TSH, FT3/FT4, $TFQI_{FT3}$, $TFQI_{FT4}$

blood pressure parameters, as well as indicators of arterial rigidity [40]. Studies have demonstrated that FT3/FT4 and TFQI are inversely related to disease mortality and adverse outcomes [41, 42]. The NHHR is also a significant predictor of cardiovascular disease. These findings may contribute to a more accurate assessment of patients' cardiovascular risk.

Based on research results, there exists a close correlation between the NHHR and TH, as well as sensitivity indices, with consistent outcomes observed across subgroup analyses. This reflects the interplay between

Table 5 Sensitivity analysis association between NHHR with thyroid function and sensitivity indices

	Model 1		Model 2		Model 3	
	β(95%CI)	*P*	β(95%CI)	*P*	β(95%CI)	*P*
FT3	0.32 (0.23, 0.41)	< 0.0001	0.25 (0.16, 0.34)	< 0.0001	0.21 (0.12, 0.30)	< 0.0001
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.09 (0.03, 0.14)	0.001	0.10 (0.05, 0.15)	< 0.0001	0.09 (0.04, 0.14)	0.000
Quartile 3	0.12 (0.07, 0.17)	< 0.0001	0.11 (0.06, 0.16)	< 0.0001	0.09 (0.04, 0.14)	0.000
Quartile 4	0.19 (0.13, 0.24)	< 0.0001	0.14 (0.10, 0.19)	< 0.0001	0.12 (0.07, 0.18)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
FT4	-0.57 (-0.91, -0.23)	0.001	-0.54 (-0.89, -0.18)	0.003	-0.56 (-0.93, -0.18)	0.003
Quartile 1	Ref		Ref		Ref	
Quartile 2	-0.27 (-0.46, -0.08)	0.006	-0.25 (-0.44, -0.05)	0.012	-0.24 (-0.44, -0.05)	0.015
Quartile 3	-0.30 (-0.49, -0.11)	0.002	-0.30 (-0.49, -0.10)	0.003	-0.30 (-0.50, -0.10)	0.004
Quartile 4	-0.34 (-0.53, -0.15)	0.001	-0.31 (-0.50, -0.11)	0.002	-0.32 (-0.53, -0.11)	0.003
P for trend		0.002		0.007		0.008
TSH	0.51 (0.28, 0.75)	< 0.0001	0.51 (0.28, 0.75)	< 0.0001	0.27 (0.02, 0.51)	0.032
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.23 (0.10, 0.37)	0.001	0.22 (0.09, 0.35)	0.001	0.13 (-0.00, 0.25)	0.053
Quartile 3	0.13 (-0.00, 0.26)	0.056	0.12 (-0.01, 0.26)	0.064	0.00 (-0.13, 0.13)	0.966
Quartile 4	0.30 (0.17, 0.43)	< 0.0001	0.31 (0.18, 0.45)	< 0.0001	0.17 (0.03, 0.31)	0.016
P for trend		0.000		0.000		0.062
FT3/FT4	0.05 (0.04, 0.06)	< 0.0001	0.04 (0.03, 0.05)	< 0.0001	0.04 (0.02, 0.05)	< 0.0001
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.01 (0.01, 0.02)	< 0.0001	0.01 (0.01, 0.02)	< 0.0001	0.01 (0.01, 0.02)	0.000
Quartile 3	0.02 (0.01, 0.03)	< 0.0001	0.02 (0.01, 0.03)	< 0.0001	0.02 (0.01, 0.02)	< 0.0001
Quartile 4	0.03 (0.02, 0.04)	< 0.0001	0.02 (0.02, 0.03)	< 0.0001	0.02 (0.01, 0.03)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
$TFQI_{FT3}$	0.37 (0.30, 0.44)	< 0.0001	0.33 (0.27, 0.40)	< 0.0001	0.25 (0.18, 0.32)	< 0.0001
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.10 (0.06, 0.13)	< 0.0001	0.10 (0.07, 0.14)	< 0.0001	0.07 (0.04, 0.11)	0.000
Quartile 3	0.13 (0.09, 0.17)	< 0.0001	0.12 (0.08, 0.16)	< 0.0001	0.08 (0.05, 0.12)	< 0.0001
Quartile 4	0.21 (0.17, 0.24)	< 0.0001	0.18 (0.15, 0.22)	< 0.0001	0.13 (0.09, 0.17)	< 0.0001
P for trend		< 0.0001		< 0.0001		< 0.0001
$TFQI_{FT4}$	0.03 (-0.04, 0.10)	0.369	0.05 (-0.02, 0.12)	0.165	-0.01 (-0.08, 0.07)	0.881
Quartile 1	Ref		Ref		Ref	
Quartile 2	0.01 (-0.03, 0.05)	0.575	0.01 (-0.03, 0.05)	0.523	-0.01 (-0.04, 0.03)	0.771
Quartile 3	0.00 (-0.04, 0.04)	0.908	0.00 (-0.04, 0.04)	0.877	-0.02 (-0.06, 0.02)	0.303
Quartile 4	0.01 (-0.03, 0.05)	0.601	0.02 (-0.02, 0.06)	0. 226	-0.01 (-0.05, 0.03)	0.697
P for trend		0.718		0.281		0.663

Model 1: Non-adjusted;

Model 2: Adjusted for age, sex, race, education level, PIR, marry, smoke, alcohol;

Model 3: Adjusted for age, sex, race, education level, PIR, marry, smoke, alcohol, BMI, TGAb, TPOAb, TG, LDL-C, urine iodine, diabetes, and hypertension

CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.FT3/FT4, FT3/FT4 ratio; $TFQI_{FT3}$, $TFQI_{FT4}$, thyroid feedback quantile-based index

lipid metabolism and thyroid function, as well as the interdependence among different physiological systems. Understanding these relationships can aid in a more comprehensive evaluation of patients' overall health status and potential risks while also providing new insights into diagnosis and treatment strategies. In clinical work, personalized treatment programs should be developed with the specific conditions of patients to mitigate the likelihood of cardiovascular disease and other complications. Moreover, further in-depth research on the intricate mechanisms that underpin the link between the NHHR and thyroid disease is needed to provide more scientific and effective guidance for clinical care.

Strengths and constraints

One of the pivotal strengths of this research stems from its solid data foundation, namely, a large-scale, nationally representative dataset comprising American adults. The NHHR was analysed as both a continuous variable and a categorical variable, adjusting for covariates to ensure

robust results. Subgroup analyses provided deeper insights into the complex relationship between the NHHR and thyroid function across different population groups. However, there are still several limitations of this study. Although the analyses were adjusted for various potential covariates, the potential effects of other confounding variables affecting lipid and thyroid levels could not be completely eliminated. Additionally, the design, which selected cross-sectional data, poses inherent constraints in elucidating the potential causal relationships and underlying mechanisms between the NHHR and thyroid function, precluding the direct establishment of a causal link between the two.

Conclusion

Among American adults, the NHHR was significantly positively correlated with FT3, TSH, FT3/FT4 and $TFQI_{FT3}$. Conversely, a negative association was noted between the NHHR and FT4. The potential mechanisms of action still require further investigation.

Abbreviations

TH	Thyroid hormones
NHHR	Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio
NHANES	National Health and Nutrition Examination Survey
FT3	Free triiodothyronine
TSH	Thyroid-stimulating hormone
FT3/FT4	FT3/FT4 ratio
$TFQI_{FT3}$	Quantile-based thyroid feedback index for FT3
FT4	Free thyroxin
T4	Thyroxine
T3	Triiodothyronine
DIO	Deiodinase iodothyronine
HPT	Hypothalamus-pituitary-thyroid
TSHI	Thyroid stimulating hormone index
TT4RI	Total thyroxine resistance index
TT3RI	Total triiodothyronine resistance index
$TFQI_{FT3}$ and $TFQI_{FT4}$	Thyroid feedback quartile indices
non-HDL	Non-high-density lipoprotein cholesterol
HDL	High density lipoprotein
TC	Total cholesterol
NAFLD	Non-alcoholic fatty liver disease
T2DM	Type 2 diabetes mellitus
Cdf	Cumulative distribution function
PIR	Poverty index
BMI	Body mass index
TPOAb	Thyroid anti-peroxidase antibodies
TRAb	Thyroid-stimulating hormone receptor antibodies
CDC	Centers for Disease Control and Prevention
SE	Standard errors
TG	Total triglyceride
CI	Confidence interval
TRH	Thyrotropin-releasing hormone
SREBP-2	Sterol regulatory element-binding protein-2
LDL-R	LDL-receptor
TR	Thyroid hormone receptor
LXR	Liver X-activated receptor
ABCA-1	ATP-binding cassette transporter A1

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Author contributions

Y-CL performed the computations and manuscript writing; Y-WC and X-L were involved in the acquisition of data; X-HW, XM and M-LT were involved in the interpretation of the data; L-Z and H-QZ were involved in conceptualization and funding acquisition. All authors contributed to the article and approved the submitted version.

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Data availability

The datasets generated and analysed during the current study are available in the NHANES database (https://www.cdc.gov/nchs/nhanes).

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by The National Center for Health Statistics Institutional Review Board. All participants provided their written informed consent to participate in this study.

Competing interests

The authors declare no competing interests.

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References

1. Nie X, Ma X, Xu Y, Shen Y, Wang Y, Bao Y. Increased serum adipocyte fatty acid-binding protein levels are Associated with decreased sensitivity to thyroid hormones in the Euthyroid Population. Thyroid. 2020;30:1718–23.
2. Jostel A, Ryder WD, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH Index. Clin Endocrinol (Oxf). 2009;71:529–34.
3. Yagi H, Pohlenz J, Hayashi Y, Sakurai A, Refetoff S. Resistance to thyroid hormone caused by two mutant thyroid hormone receptors beta, R243Q and R243W, with marked impairment of function that cannot be explained by altered in vitro 3,5,3'-triiodothyroinine binding affinity. J Clin Endocrinol Metab. 1997;82:1608–14.
4. Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM, Mateo-Gallego R, Casasnovas JA, Guallar-Castillon P, Cenarro A, Civeira F. Impaired sensitivity to thyroid hormones is Associated with Diabetes and metabolic syndrome. Diabetes Care. 2019;42:303–10.
5. Brenta G, Berg G, Arias P, Zago V, Schnitman M, Muzzio ML, Sinay I, Schreier L. Lipoprotein alterations, hepatic lipase activity, and insulin sensitivity in subclinical hypothyroidism: response to L-T(4) treatment. Thyroid. 2007;17:453–60.
6. Sinha RA, Singh BK, Yen PM. Direct effects of thyroid hormones on hepatic lipid metabolism. Nat Rev Endocrinol. 2018;14:259–69.
7. Duntas LH. Thyroid disease and lipids. Thyroid. 2002;12:287–93.
8. Tan KC, Shiu SW, Kung AW. Plasma cholesteryl ester transfer protein activity in hyper- and hypothyroidism. J Clin Endocrinol Metab. 1998;83:140–3.
9. Song Y, Liu J, Zhao K, Gao L, Zhao J. Cholesterol-induced toxicity: an integrated view of the role of cholesterol in multiple diseases. Cell Metab. 2021;33:1911–25.
10. Li X, Zhen D, Zhao M, Liu L, Guan Q, Zhang H, Ge S, Tang X, Gao L. Natural history of mild subclinical hypothyroidism in a middle-aged and elderly Chinese population: a prospective study. Endocr J. 2017;64:437–47.
11. Musso G, Gambino R, Cassader M. Cholesterol metabolism and the pathogenesis of non-alcoholic steatohepatitis. Prog Lipid Res. 2013;52:175–91.
12. Perego C, Da Dalt L, Pirillo A, Galli A, Catapano AL, Norata GD. Cholesterol metabolism, pancreatic β-cell function and diabetes. Biochim Biophys Acta Mol Basis Dis. 2019;1865:2149–56.
13. Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V. Thyroid dysfunction and serum lipids: a community-based study. Clin Endocrinol (Oxf). 2005;63:670–5.

14. O'Brien T, Katz K, Hodge D, Nguyen TT, Kottke BA, Hay ID. The effect of the treatment of hypothyroidism and hyperthyroidism on plasma lipids and apolipoproteins AI, AII and E. Clin Endocrinol (Oxf). 1997;46:17–20.
15. Muls E, Blaton V, Rosseneu M, Lesaffre E, Lamberigts G, De Moor P. Serum lipids and apolipoproteins A-I, A-II, and B in hyperthyroidism before and after treatment. J Clin Endocrinol Metab. 1982;55:459–64.
16. Roos A, Bakker SJ, Links TP, Gans RO, Wolffenbuttel BH. Thyroid function is associated with components of the metabolic syndrome in euthyroid subjects. J Clin Endocrinol Metab. 2007;92:491–6.
17. Sheng G, Liu D, Kuang M, Zhong Y, Zhang S, Zou Y. Utility of Non-high-density Lipoprotein Cholesterol to high-density lipoprotein cholesterol ratio in evaluating Incident Diabetes Risk. Diabetes Metab Syndr Obes. 2022;15:1677–86.
18. Zhu L, Lu Z, Zhu L, Ouyang X, Yang Y, He W, Feng Y, Yi F, Song Y. Lipoprotein ratios are better than conventional lipid parameters in predicting coronary heart disease in Chinese Han people. Kardiol Pol. 2015;73:931–8.
19. Kwok RM, Torres DM, Harrison SA. Vitamin D and nonalcoholic fatty liver disease (NAFLD): is it more than just an association? Hepatology. 2013;58:1166–74.
20. Kim SW, Jee JH, Kim HJ, Jin SM, Suh S, Bae JC, Kim SW, Chung JH, Min YK, Lee MS, et al. Non-HDL-cholesterol/HDL-cholesterol is a better predictor of metabolic syndrome and insulin resistance than apolipoprotein B/apolipoprotein A1. Int J Cardiol. 2013;168:2678–83.
21. Lin D, Qi Y, Huang C, Wu M, Wang C, Li F, Yang C, Yan L, Ren M, Sun K. Associations of lipid parameters with insulin resistance and diabetes: a population-based study. Clin Nutr. 2018;37:1423–9.
22. Ortiga-Carvalho TM, Chiamolera MI, Pazos-Moura CC, Wondisford FE. Hypothalamus-pituitary-thyroid Axis. Compr Physiol. 2016;6:1387–428.
23. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: an update. Metabolism. 2016;65:1109–23.
24. Berberich AJ, Hegele RA. A Modern Approach to Dyslipidemia. Endocr Rev. 2022;43:611–53.
25. Wu L, Parhofer KG. Diabetic dyslipidemia. Metabolism. 2014;63:1469–79.
26. Chung GE, Kim D, Kim W, Yim JY, Park MJ, Kim YJ, Yoon JH, Lee HS. Non-alcoholic fatty liver disease across the spectrum of hypothyroidism. J Hepatol. 2012;57:150–6.
27. Bano A, Chaker L, Plompen EP, Hofman A, Dehghan A, Franco OH, Janssen HL, Darwish Murad S, Peeters RP. Thyroid function and the risk of nonalcoholic fatty liver disease: the Rotterdam Study. J Clin Endocrinol Metab. 2016;101:3204–11.
28. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. Nat Rev Cardiol. 2017;14:39–55.
29. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes Mellitus: two closely Associated disorders. Endocr Rev. 2019;40:789–824.
30. Kube I, Zwanziger D. Thyroid dysfunction and cholesterol gallstone disease. Exp Clin Endocrinol Diabetes. 2020;128:455–61.
31. Cortes VA, Busso D, Maiz A, Arteaga A, Nervi F, Rigotti A. Physiological and pathological implications of cholesterol. Front Biosci (Landmark Ed). 2014;19:416–28.
32. Ayuob NN, El-Hawwary AA, Huwait EA, Mubarak WAE, Balgoon MJ. Red grape juice protects the rat thyroid gland against hypercholesterolemic changes. Ultrastructural and biochemical evidences. Rom J Morphol Embryol. 2019;60:921–9.
33. Yang J, Zhang X, Liu Z, Yuan Z, Song Y, Shao S, Zhou X, Yan H, Guan Q, Gao L, et al. High-cholesterol Diet disrupts the levels of hormones derived from anterior pituitary basophilic cells. J Neuroendocrinol. 2016;28:12369.
34. Wang Y, Li Q, Yuan Z, Ma S, Shao S, Wu Y, Wang Z, Li Q, Gao L, Zhao M, Zhao J. Statin use and benefits of thyroid function: a retrospective cohort study. Front Endocrinol (Lausanne). 2021;12:578909.
35. Lopez D, Abisambra Socarrás JF, Bedi M, Ness GC. Activation of the hepatic LDL receptor promoter by thyroid hormone. Biochim Biophys Acta. 2007;1771:1216–25.
36. Shin DJ, Osborne TF. Thyroid hormone regulation and cholesterol metabolism are connected through sterol Regulatory element-binding Protein-2 (SREBP-2). J Biol Chem. 2003;278:34114–8.
37. Huuskonen J, Vishnu M, Pullinger CR, Fielding PE, Fielding CJ. Regulation of ATP-binding cassette transporter A1 transcription by thyroid hormone receptor. Biochemistry. 2004;43:1626–32.
38. Song Y, Xu C, Shao S, Liu J, Xing W, Xu J, Qin C, Li C, Hu B, Yi S, et al. Thyroid-stimulating hormone regulates hepatic bile acid homeostasis via SREBP-2/HNF-4α/CYP7A1 axis. J Hepatol. 2015;62:1171–9.
39. Roef GL, Rietzschel ER, Van Daele CM, Taes YE, De Buyzere ML, Gillebert TC, Kaufman JM. Triiodothyronine and free thyroxine levels are differentially associated with metabolic profile and adiposity-related cardiovascular risk markers in euthyroid middle-aged subjects. Thyroid. 2014;24:223–31.
40. Yang S, Wang Z, Li J, Fu J, Guan H, Wang W. Thyroid feedback quantile-based index is Associated with blood pressure and other hemodynamic measures: a cross-sectional study. Endocr Pract. 2022;28:1055–61.
41. Yuan D, Zhang C, Jia S, Liu Y, Jiang L, Xu L, Zhang Y, Xu J, Xu B, Hui R, et al. Predictive value of free triiodothyronine (FT3) to free thyroxine (FT4) ratio in long-term outcomes of euthyroid patients with three-vessel coronary artery disease. Nutr Metab Cardiovasc Dis. 2021;31:579–86.
42. Yu T, Tian C, Song J, He D, Wu J, Wen Z, Sun Z, Sun Z. Value of the fT3/fT4 ratio and its combination with the GRACE risk score in predicting the prognosis in euthyroid patients with acute myocardial infarction undergoing percutaneous coronary intervention: a prospective cohort study. BMC Cardiovasc Disord. 2018;18:181.

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