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Impaired sensitivity to thyroid hormones is associated with increased body fat mass/muscle mass ratio (F/M) in the euthyroid population

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Abstract

Objective To explore the relationship between body fat mass/muscle mass ratio (F/M) and thyroid hormone sensitivity in the euthyroid population.

Methods Body compositions of 845 check-up individuals were determined using bioelectrical impedance analysis (BIA). Biochemical indexes including blood glucose, blood lipids, liver and kidney functions and thyrotropic hormones (THs) were detected. Free triiodothyronine to free thyroxine ratio (FT3/FT4), Thyroid Feedback Quantile-based Index (TFQI), Thyrotropin Thyroxine Resistance Index (TT4RI) and TSH Index (TSHI) were calculated for analysis.

Results TT4RI and TSHI showed increased trends with statistical difference, while FT3/FT4 and TFQI showed no difference among F/M quartile groups. After adjusting for confounding factors, F/M exhibited no correlation with FT3/FT4, but positive correlations with TFQI, TT4RI and TSHI. Gender subgroup analysis showed that F/M exhibited positive relationship with TFQI in females; exhibited positive correlations with TFQI, TT4RI and TSHI before the inflection points, but no correlations thereafter in males. Age subgroup analysis showed that F/M exhibited positive correlations with TFQI, TT4RI and TSHI, but no correlation with FT3/FT4 in age < 65 years group; exhibited no relationship with thyroid hormone sensitivity in age ≥ 65 years group. BMI subgroup analysis showed that F/M exhibited no relationship with thyroid hormone sensitivity in BMI < 25 kg/m^2 group; exhibited positive correlations with TFQI, TT4RI and TSHI before the inflection points, but no correlations thereafter in BMI ≥ 25, < 30 kg/m^2 group; exhibited positive correlation with TFQI before the inflection point, but no correlation thereafter in BMI ≥ 30 kg/m^2 group; exhibited no correlations with TT4RI and TSHI before the inflection points, but negative correlations with them thereafter in BMI ≥ 30 kg/m^2 group.

Conclusion Impaired central, but not peripheral sensitivity to thyroid hormones was associated with increased body fat mass/muscle mass ratio (F/M), this association was obvious in males, individuals with age < 65 years and BMI ≥ 25 kg/m^2, with different inflection points. Maybe F/M independently affects thyroid hormone sensitivity, we need more clinical and basic studies in the future.

Keywords Body fat mass/muscle mass ratio, Free triiodothyronine to free thyroxine, Thyroid feedback quantile-based Index, Thyrotropin thyroxine resistance index, TSH index

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Introduction

The World Health Organization (WHO) defines overweight and obesity as an excessive accumulation of fat that has adverse influences on health, quality of life and even life expectancy [1]. Obesity, particularly abdominal obesity, has been regarded as an independent risk factor for metabolic disorders such as diabetes mellitus, hypertension, hyperlipidemia [2, 3], as well as cardiovascular and cerebrovascular diseases [4, 5]. Obesity is also intimately associated with the levels of thyroid hormones, the incidence of hypothyroidism was notably elevated among obese individuals [6], particularly among females [7]. Yet, the specific mechanism remains unclear.

Thyroid hormones regulate appetite and body heat production, as well as glucose and lipid metabolisms [6]. In physiological conditions, TSH and FT4 are negatively correlated due to the negative feedback regulation of the hypothalamic-pituitary-thyroid axis [8]. However, in many cases we observed high levels of TSH co-existing with FT4 [9]. In order to explain this, The Thyroid Feedback Quantile-based Index (TFQI) was proposed as an index of central thyroid hormone sensitivity by Laclaustra et al. They proposed a hypothesis that thyroid hormone resistance occurs in the body under certain circumstances, and thyroid hormone sensitivity decreases [9]. Central thyroid hormone sensitivity indexes also include thyrotropin thyroxine resistance index (TT4RI) and TSH index (TSHI), which are also associated with many metabolic diseases [10, 11]. The FT3/FT4 ratio can be used to evaluate the rate of T4-to-T3 conversion, reflecting the peripheral tissue sensitivities of thyroid hormones, and the relationships with metabolic diseases including hyperglycemia, hyperlipemia and fatty liver have also been studied [12–14].

Previous studies have suggested that increased TSH and T3 levels in obese individuals may be a physiological mechanism for increasing energy expenditure to improve weight gain. In obese people with normal thyroid function, there were no correlations between resting energy expenditure and serum TSH and FT3 concentrations, despite increased resting energy expenditure [15]. Moreover, a decline in FT4 could also be observed, which might be associated with increased TSH [16]. Studies have also showed that FT4 was negatively correlated with BMI in obese patients, while TSH was positively correlated with BMI [17]. Conclusions regarding the relationships between thyroid hormones and obesity were also inconsistent, and the specific mechanisms were still under exploration.

It has recently been reported that impaired central sensitivity to thyroid hormones were significantly associated with the reductions of visceral fat area (VFA) and subcutaneous fat area (SFA) [18]. Given that body fat areas are affected by individual differences in height, and also thyroid hormones are critical regulators of muscle metabolism in both healthy and unhealthy conditions [19], in our study, we used body fat mass/muscle mass ratio (F/M) to evaluate the relationships between body compositions and thyroid hormone sensitivity. We examined the relationships between F/M and thyroid hormone sensitivity indices (TFQI, TT4RI, TSHI and FT3/FT4) in the physical examination population to investigate the impact of F/M on central and peripheral thyroid hormone sensitivity. Considering the differences in the impacts of agender, age and BMI on thyroid hormone, the corresponding subgroup analyses were conducted.

Materials and methods

In the Physical examination Center of Hefei First People's Hospital from January 2024 to June 2024, 29,909 individuals underwent health examinations. Among them, there were 1192 individuals completed the determinations of body compositions using bioelectrical impedance analysis. After excluding people who did not meet the criteria, we eventually included 845 eligible people (Fig. 1). Sample size calculation was performed using Power Analysis and Sample Size software 15, and the sample size we have calculated was 689.

Inclusion criteria: 1. Age 18–90 years old; 2. BMI > 18.5 kg/m^2.

Exclusion criteria: 1. Incomplete data; 2. History of hyperthyroidism and hypothyroidism; 3. Patients with abnormal thyroid function; 4. Severe liver and kidney insufficiency.

Body composition including height, weight, body fat mass (kg) and muscle mass(kg) were determined by fasting state in the morning by bioelectrical impedance analysis (BIA, DONGHUAYUAN MEDICAL, Beijing city). Subjects taked off excess clothing and jewelry, shoes and socks, stood on the metal base, held the handles with both hands, with arms naturally straight and slightly stretched to the sides of the body, legs do not touch each other. BMI was calculated as weight(kg)/height^2(m^2). Medical histories including hypertension, diabetes, hyperuricemia and hyperlipidemia were recorded. Thyroid hormones were determined by blood serum samples (chemiluminescence method. Abbott 12000SR), including thyrotropic hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4). The biochemical indexes of fasting blood-glucose (GLU), albumin (ALB), alanine transaminase (ALT), aspartic transaminase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), serum creatinine (SCr), uric acid (SUA), triglyceride (TG), total cholesterol

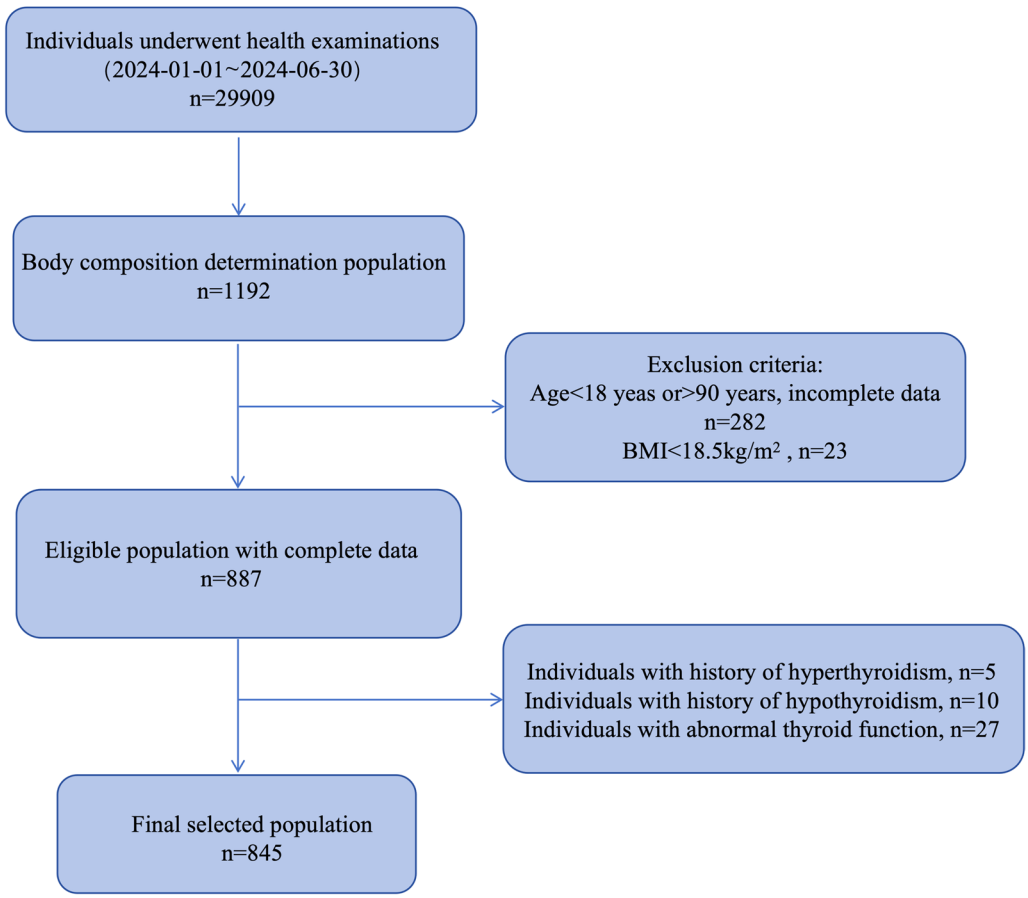

Fig. 1 Studied objects screening flow chart

(TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were all measured by well-trained technicians utilizing standardized laboratory methods (Roche automatic biochemical analyzer. combas 8000).

Index of Peripheral thyroid hormone sensitivity was calculated as FT3/FT4;

Three different indices of central thyroid hormone sensitivity were calculated [20, 21]:

$$\mathrm{TFQI} = (\mathrm{cdf})\ \mathrm{FT4} - (1 - (\mathrm{cdf})\ \mathrm{TSH});$$

$$\mathrm{TT4RI} = \mathrm{FT4\ (pmol/L)} \times \mathrm{TSH\ (mIU/L)};$$

$$\mathrm{TSHI} = \mathrm{Ln\ TSH\ (mIU/L)} + 0.1345 \times \mathrm{FT4\ (pmol/L)}.$$

Definition of hypertension [22]: ① History of hypertension, ② Systolic blood pressure ≥ 140 mmHg, ③ Diastolic blood pressure ≥ 90 mmHg, meet any of the diagnostic criteria.

Definitions of diabetes [23]: ① a history of diabetes, ② Fasting blood glucose ≥ 7.0 mmol/l, ③ Hemoglobin A1C ≥ 6.5%, meet any of the diagnostic criteria.

Definitions of hyperuricemia [24]: ① a history of hyperuricemia, ② Blood uric acid ≥ 420umol/l, meet any of the diagnostic criteria.

Definitions of hyperlipidemia [25]: ① a history of hyperlipidemia, ② TC ≥ 5.2 mmol/l, TG ≥ 1.7 mmol/l, LDL-C ≥ 3.4 mmol/l, HDL-C < 1.0 mmol/l, meet any of the diagnostic criteria.

Statistical analysis

We utilized GraphPad Prism 10.0.3 and Empower(R) (www.empowerstats.com, X&Y Solutions, Inc.) (Boston, MA) and R (http://www.r-project.org) for data analysis. The normality of the data was assessed using the Shapiro–Wilk test and Q-Q plot. Variables with a normal distribution were presented as mean ± standard deviation (SD), while skewed variables were expressed

Table 1 Baseline characteristics of total participants among F/M quartile groups

F/M quartile	F/MQ1	F/MQ2	F/MQ3	F/MQ4	*P*-value
N	211	211	211	212	
Age (years)	47.64 ± 13.13	45.64 ± 11.98	46.54 ± 10.94	49.51 ± 11.57	0.006
Muscle	49.47 ± 7.54	46.08 ± 8.62	43.65 ± 8.92	39.55 ± 7.72	< 0.001
Fat	12.62 ± 3.63	18.04 ± 3.48	20.91 ± 4.34	25.22 ± 6.05	< 0.001
BMI (kg/m2)	22.95 ± 2.26	24.28 ± 2.84	25.27 ± 3.14	26.85 ± 3.36	< 0.001
HbA1c (%)	5.69 ± 0.65	5.78 ± 0.89	5.80 ± 0.84	5.84 ± 1.01	0.351
GLU (mmol/l)	5.35 ± 1.05	5.54 ± 1.63	5.53 ± 1.42	5.51 ± 1.58	0.501
TG (mmol/l)	1.67 ± 1.79	1.89 ± 1.92	2.02 ± 1.86	1.73 ± 1.11	0.139
HDL-C (mmol/l)	1.39 ± 0.40	1.29 ± 0.36	1.27 ± 0.30	1.36 ± 0.33	< 0.001
LDL-C (mmol/l)	3.01 ± 0.94	3.03 ± 0.79	3.03 ± 0.74	3.14 ± 0.78	0.401
SUA (umol/l)	342.33 ± 81.39	339.67 ± 99.09	332.39 ± 95.90	308.96 ± 91.43	< 0.001
TSH (uIU/ml)	1.62 ± 0.83	1.77 ± 0.82	1.86 ± 0.84	2.04 ± 0.97	< 0.001
FT3 (pmol/l)	4.53 ± 0.51	4.46 ± 0.52	4.45 ± 0.52	4.30 ± 0.48	< 0.001
FT4 (pmol/l)	13.20 ± 1.61	13.17 ± 1.45	13.05 ± 1.41	12.68 ± 1.35	< 0.001
FT3/FT4	0.35 ± 0.05	0.34 ± 0.05	0.34 ± 0.04	0.34 ± 0.04	0.658
TFQI	− 0.05 ± 0.39	0.00 ± 0.39	0.01 ± 0.36	− 0.01 ± 0.33	0.312
TT4RI	21.24 ± 11.12	23.16 ± 10.51	24.11 ± 11.02	25.51 ± 11.44	< 0.001
TSHI	2.14 ± 0.51	2.24 ± 0.49	2.27 ± 0.49	2.31 ± 0.46	0.002
Gender					< 0.001
Female	28 (13.27%)	75 (35.55%)	107 (50.71%)	176 (83.02%)	
Male	183 (86.73%)	136 (64.45%)	104 (49.29%)	36 (16.98%)	
Hypertension					0.034
No	169 (80.09%)	148 (70.14%)	161 (76.30%)	147 (69.34%)	
Yes	42 (19.91%)	63 (29.86%)	50 (23.70%)	65 (30.66%)	
Hyperuricemia					0.236
No	178 (84.36%)	169 (80.09%)	174 (82.46%)	185 (87.26%)	
Yes	33 (15.64%)	42 (19.91%)	37 (17.54%)	27 (12.74%)	
Dyslipidemia					0.068
No	99 (46.92%)	83 (39.34%)	75 (35.55%)	77 (36.32%)	
Yes	112 (53.08%)	128 (60.66%)	136 (64.45%)	135 (63.68%)	
Diabetes					0.272
No	201 (95.26%)	200 (94.79%)	193 (91.47%)	202 (95.28%)	
Yes	10 (4.74%)	11 (5.21%)	18 (8.53%)	10 (4.72%)	

Mean ± SD for continuous variables and P-value was calculated by One-Way ANOVA analysis or Mann–Whitney U tests. % for categorical variables and P-value was calculated by chi-square test

Abbreviations: BMI, body mass index; TSH, thyrotropic hormone; FT3, free triiodothyronine; FT4, free thyroxine; GLU, fasting blood-glucose; SUA, uric acid; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TFQI, Thyroid Feedback Quantile-based Index; TSHI, TSH index; TT4RI, thyrotropin thyroxine resistance index

as median (25th percentile, 75th percentile). We conduct sample size calculation using Power Analysis and Sample Size software 15. Differences in continuous variables in the F/M quartile groups were compared using One-Way ANOVA, and we used Bonferroni correction multiple hypothesis testing. Smoothing function and threshold effect analysis were employed to determine the relationships of F/M with TFQI, TT4RI, TSHI and FT3/FT4. Log-likelihood ratio tests were conducted on both single-line linear regression model and two-stage linear regression model. The same analysis was performed for gender, age and BMI subgroups. Statistical significance was considered if $P < 0.05$.

Results

Analyses of thyroid hormones Sensitivity indexes in groups of F/M ratio quartile using One-Way ANOVA

We divided the studied population into four groups according to F/M quartile: F/MQ1: F/M ranged 0.0563 to 0.3397, F/MQ2: F/M ranged 0.3397 to 0.4320, F/

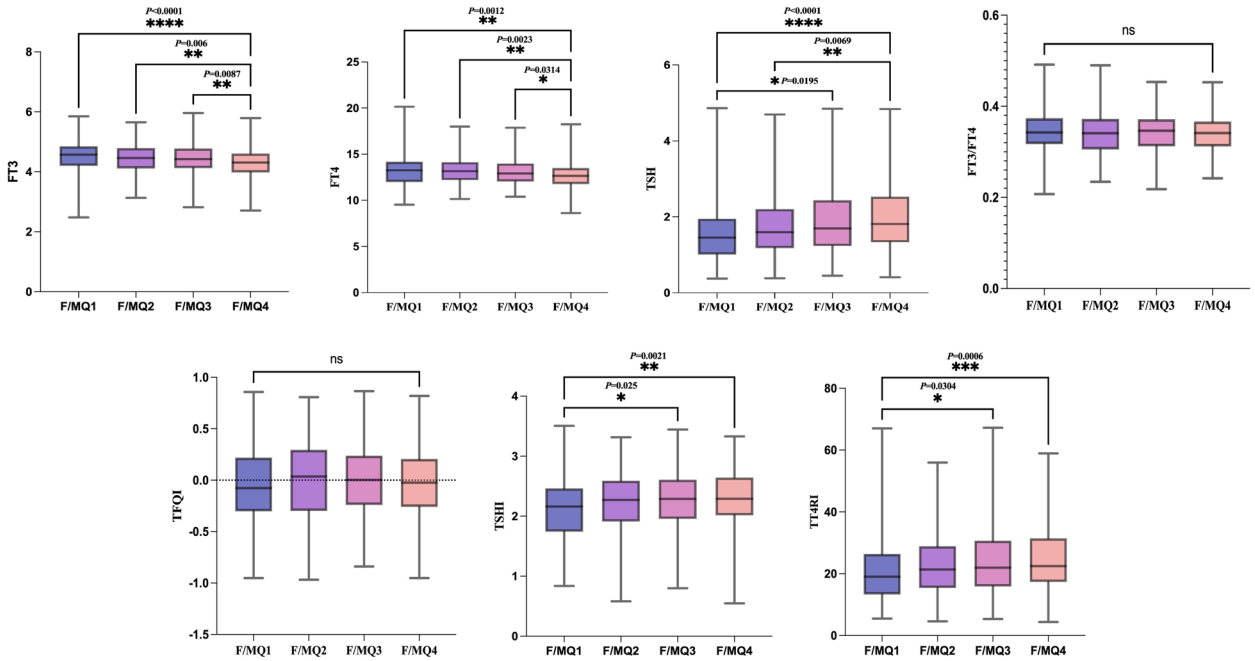

Fig. 2 The comparisons of indexes of thyroid hormones among four groups divided by F/M ratio using inter-quartile range

Table 2 The associations of F/M with thyroid hormone sensitivity

	FT3/FT4	TFQI	TT4RI	TSHI
Exposure: F/M	Outcome: β (95% CI) *P* – value			
Model I				
One-line effect	−0.03 (−0.06, 0.00) 0.0504	0.52 (0.26, 0.79) < 0.0001	9.07 (1.11, 17.04) 0.0258	0.59 (0.24, 0.94) 0.0010
Model II				
Inflection point (k)	0.56	0.69	0.69	0.69
< K segment effect 1	−0.05 (−0.08, −0.01) 0.0236	0.60 (0.30, 0.89) < 0.0001	10.42 (1.39, 19.46) 0.024	0.67 (0.27, 1.07) 0.001
> K segment effect 2	−0.01 (−0.06, 0.05) 0.8567	0.19 (−0.51, 0.88) 0.5990	2.88 (−18.25, 24.01) 0.7893	0.01 (−0.92, 0.94) 0.9850
Effect difference	0.04 (−0.03, 0.11) 0.2482	−0.41 (−1.19, 0.37) 0.3041	−7.54 (−31.38, 16.29) 0.5354	−0.66 (−1.71, 0.39) 0.2155
The predicted value of the equation at the inflection point	0.34 (0.34, 0.35)	0.02 (−0.04, 0.07)	26.46 (24.83, 28.09)	2.36 (2.29, 2.43)
Log-likelihood ratio test	0.245	0.301	0.533	0.212

Outcome: β (95% CI) *P*-value, adjusted for age, gender, BMI, GLU, HbA1c, LDL-C, TC, HDL-C and SUA

β: regression coefficient, CI Confidence interval

MQ3: F/M ranged 0.4320 to 0.537, F/MQ4: F/M ranged 0.537 to 1.19. With increased trends of F/M ratio, TT4RI (P<0.001) and TSHI (P=0.002) exhibited increased trends with significant statistical difference (P<0.001), while FT3/FT4 (P=0.658) and TFQI (P=0.312) showed no statistical difference among F/M quartile groups. There were significant differences of age, BMI and gender among F/M quartile groups, so three subgroup analyses were performed below, by adjusting for multiple confounding factors (Table 1, Figure 2).

Smoothing function and threshold effect analysis of the correlation between F/M and thyroid hormone sensitivity

After adjusting for confounding factors including age, agender, BMI, GLU, HbA1c, LDL-C, TC, HDL-C and SUA, we found that F/M exhibited no correlation with FT3/FT4 (β (95%CI): −0.03 (−0.06, 0.00), P=0.0504), but positive correlations with TFQI (β (95%CI): 0.52 (0.26, 0.79), P < 0.0001), TT4RI (β (95%CI): 9.07 (1.11,

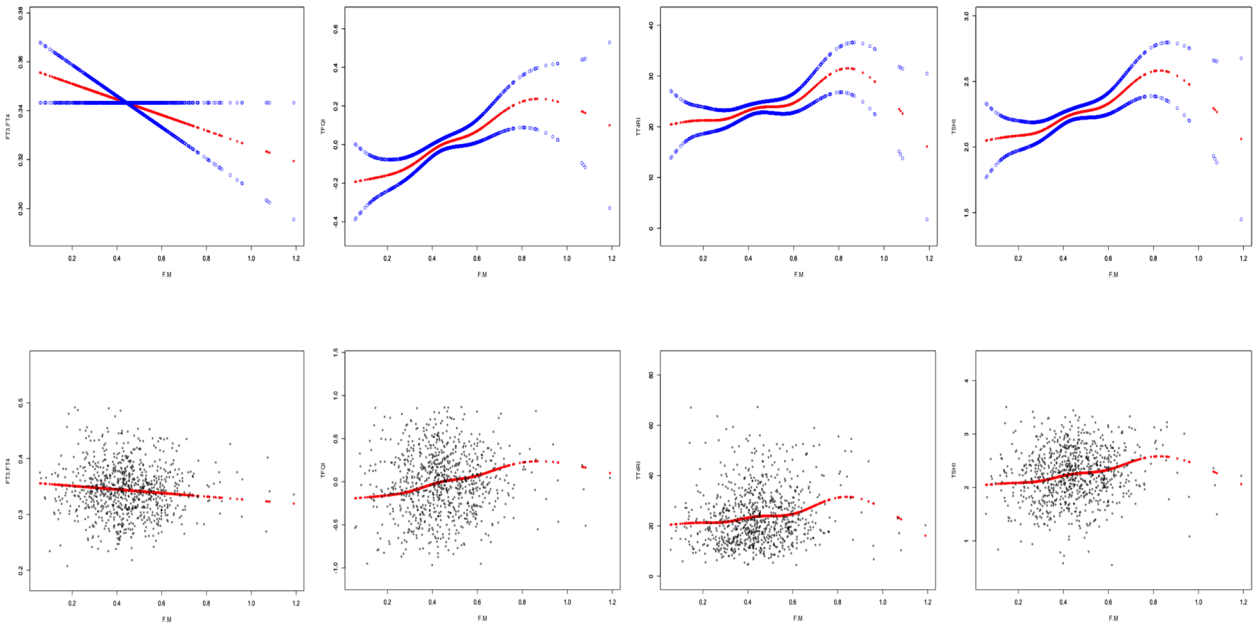

Fig. 3 Smooth curve fitting diagrams of the relationships between F/M and thyroid hormone sensitivity indexes

17.04), $P=0.0258$) and TSHI (β (95%CI): 0.59 (0.24, 0.94), $P=0.0010$) (Table 2, Fig. 3).

Smoothing function and threshold effect analysis of the correlation between F/M and thyroid hormone sensitivity in BMI subgroup

In BMI < 25 kg/m^2 group, F/M exhibited no relationships with FT3/FT4 (β (95%CI): 0.01 (−0.03, 0.05), $P=0.5131$), TFQI (β (95%CI): 0.23 (−0.10, 0.57), $P=0.1667$), TT4RI (β (95%CI):3.96 (−5.67, 13.59), $P=0.4203$) and TSHI (β (95%CI):0.31 (−0.12, 0.74), $P=0.1539$). In BMI ≥ 25, < 30 kg/m^2 group, F/M exhibited positive correlations with TFQI (β(95%CI): 1.64 (0.78, 2.49), $P=0.0002$, inflection point: F/M = 0.41), TT4RI (β (95%CI): 42.62 (11.79, 73.44), $P=0.0071$, inflection point: F/M = 0.39) and TSHI (β (95%CI): 2.06 (0.88, 3.23), $P=0.0007$, inflection point: F/M = 0.41) before the inflection points, but no correlations thereafter. In BMI ≥ 30 kg/m^2 group, F/M exhibited negative correlation with FT3/FT4 before the inflection point at F/M = 0.42 (β (95%CI): −2.99 (−5.59, −0.38), $P=0.0296$), but no correlation thereafter; exhibited positive correlation with TFQI before the inflection point at F/M = 0.42 (β (95%CI): 24.35 (2.32, 46.37), $P=0.0357$), but no correlation thereafter; exhibited no correlations with TT4RI and TSHI before the inflection points, but negative correlations with TT4RI (β (95%CI): −101.16 (−173.14, −29.19), $P=0.0085$, inflection point: F/M = 0.86) and TSHI (β (95%CI): −3.54 (−6.47, -0.60), $P=0.0227$, inflection point: F/M = 0.83) thereafter(Table 3, Fig. 4).

Smoothing function and threshold effect analysis of the correlation between F/M and thyroid hormone sensitivity in age subgroup

In age < 65 years group, F/M exhibited positive correlations with TFQI (β (95%CI): 0.54 (0.28, 0.81), $P<0.0001$), TT4RI (β (95%CI): 8.27 (0.20, 16.33), $P=0.0448$) and TSHI (β (95%CI): 0.55 (0.18, 0.91), $P=0.0031$), but no correlation with FT3/FT4 (β (95%CI): −0.03 (−0.07, 0.00), $P=0.0523$); In age ≥ 65 years group, F/M exhibited no relationships with thyroid hormone sensitivity (Table 4, Fig. 5).

Smoothing function and threshold effect analysis of the correlation between F/M and thyroid hormone sensitivity in gender subgroup

In female group, F/M showed positive relationship with TFQI (β (95%CI): 0.51 (0.12, 0.89), $P=0.0101$), but no relationships with FT3/FT4 (β (95%CI): −0.03 (−0.07, 0.02), $P=0.2375$), TT4RI (β (95%CI): 8.85 (−3.15, 20.85), $P=0.1491$) and TSHI (β (95%CI): 0.51 (−0.01, 1.03), $P=0.0532$); In male group, F/M exhibited positive correlations with TFQI (β (95%CI): 0.85 (0.41, 1.29), $P=0.0002$, inflection point: F/M = 0.57), TT4RI (β (95%CI): 14.87 (1.92, 27.83), $P=0.0249$, inflection point: F/M = 0.58) and TSHI (β (95%CI): 0.92 (0.34, 1.50), $P=0.0019$, inflection point: F/M = 0.58) before the

Table 3 The associations of F/M with thyroid hormone sensitivity in BMI subgroup

	FT3/FT4	TFQI	TT4RI	TSHI
BMI < 25 kg/m2				
Model I				
One-line effect	0.01 (− 0.03, 0.05) 0.5131	0.23 (− 0.10, 0.57) 0.1667	3.96 (− 5.67, 13.59) 0.4203	0.31 (− 0.12, 0.74) 0.1539
Model II				
Inflection point (k)	0.17	0.17	0.54	0.6
< K segment effect 1	0.24 (− 0.18, 0.65) 0.2624	− 1.79 (− 5.20, 1.63) 0.3062	7.67 (− 4.07, 19.40) 0.2009	0.45 (− 0.03, 0.93) 0.0691
> K segment effect 2	0.00 (− 0.04, 0.05) 0.8484	0.32 (− 0.04, 0.68) 0.0846	− 11.65 (− 41.51, 18.21) 0.4448	− 0.76 (− 2.53, 1.02) 0.4039
Effect difference	− 0.23 (− 0.66, 0.20) 0.2881	2.10 (− 1.44, 5.64) 0.2450	− 19.32 (− 54.29, 15.65) 0.2794	− 1.20 (− 3.14, 0.73) 0.2236
The predicted value of the equation at the inflection point	0.35 (0.34, 0.35)	− 0.04 (− 0.11, 0.04)	24.80 (23.07, 26.53)	2.31 (2.22, 2.40)
Log-likelihood ratio test	0.283	0.24	0.274	0.218
BMI ≥ 25, < 30 kg/m2				
Model I				
One-line effect	− 0.02 (− 0.06, 0.03) 0.4242	0.40 (0.04, 0.76) 0.0295	11.11 (− 0.23, 22.46) 0.0558	0.49 (− 0.00, 0.98) 0.0523
Model II				
Inflection point (k)	0.56	0.41	0.39	0.41
< K segment effect 1	− 0.06 (− 0.12, 0.01) 0.0765	1.64 (0.78, 2.49) 0.0002	42.62 (11.79, 73.44) 0.0071	2.06 (0.88, 3.23) 0.0007
> K segment effect 2	0.05 (− 0.04, 0.13) 0.3053	− 0.11 (− 0.59, 0.37) 0.6453	0.86 (− 13.79, 15.51) 0.9084	− 0.16 (− 0.82, 0.50) 0.6352
Effect difference	0.10 (− 0.01, 0.22) 0.0872	− 1.75 (− 2.84, − 0.65) 0.0020	− 41.76 (− 79.78, − 3.73) 0.0322	− 2.22 (− 3.73, − 0.70) 0.0043
The predicted value of the equation at the inflection point	0.34 (0.33, 0.35)	0.06 (0.01, 0.12)	23.70 (21.80, 25.60)	2.30 (2.22, 2.38)
Log-likelihood ratio test	0.082	0.002	0.029	0.004
BMI ≥ 30 kg/m2				
Model I				
One-line effect	− 0.09 (− 0.22, 0.03) 0.1437	0.15 (− 0.90, 1.20) 0.7792	− 18.81 (− 50.28, 12.67) 0.2477	− 0.47 (− 1.88, 0.93) 0.5112
Model II				
Inflection point (k)	0.42	0.42	0.86	0.83
< K segment effect 1	− 2.99 (− 5.59, − 0.38) 0.0296	24.35 (2.32, 46.37) 0.0357	7.98 (− 28.68, 44.65) 0.6716	0.82 (− 0.92, 2.56) 0.3590
> K segment effect 2	− 0.06 (− 0.18, 0.07) 0.3778	− 0.17 (− 1.21, 0.88) 0.7583	− 101.16 (− 173.14, − 29.19) 0.0085	− 3.54 (− 6.47, − 0.60) 0.0227
Effect difference	2.93 (0.30, 5.56) 0.0347	− 24.51 (− 46.80, − 2.22) 0.0366	− 109.15 (− 195.96, − 22.34) 0.0177	− 4.36 (− 8.07, − 0.64) 0.0264
The predicted value of the equation at the inflection point	0.37 (0.35, 0.39)	− 0.10 (− 0.27, 0.07)	38.72 (31.26, 46.17)	2.81 (2.48, 3.13)
Log-likelihood ratio test	0.019	0.02	0.008	0.013

Outcome: β (95% CI) *P*-value, adjusted for age, gender, GLU, HbA1c, LDL-C, TC, HDL-C and SUA

β: regression coefficient, CI Confidence interval

inflection points, but no correlations thereafter (Table 5, Fig. 6).

Discussion

The global prevalence of overweight and obesity was steadily increasing recent years [1, 26], especially during the COVID-19 pandemic, with increased related mortalities [27]. It is the same situation in China, the latest national prevalence estimates were 6.8% for overweight and 3.6% for obesity in children younger than 6 years, 11.1% for overweight and 7.9% for obesity in children and adolescents, and 34.3% for overweight and 16.4% for obesity in adults [28]. Not only was obesity prevalent among young individuals,

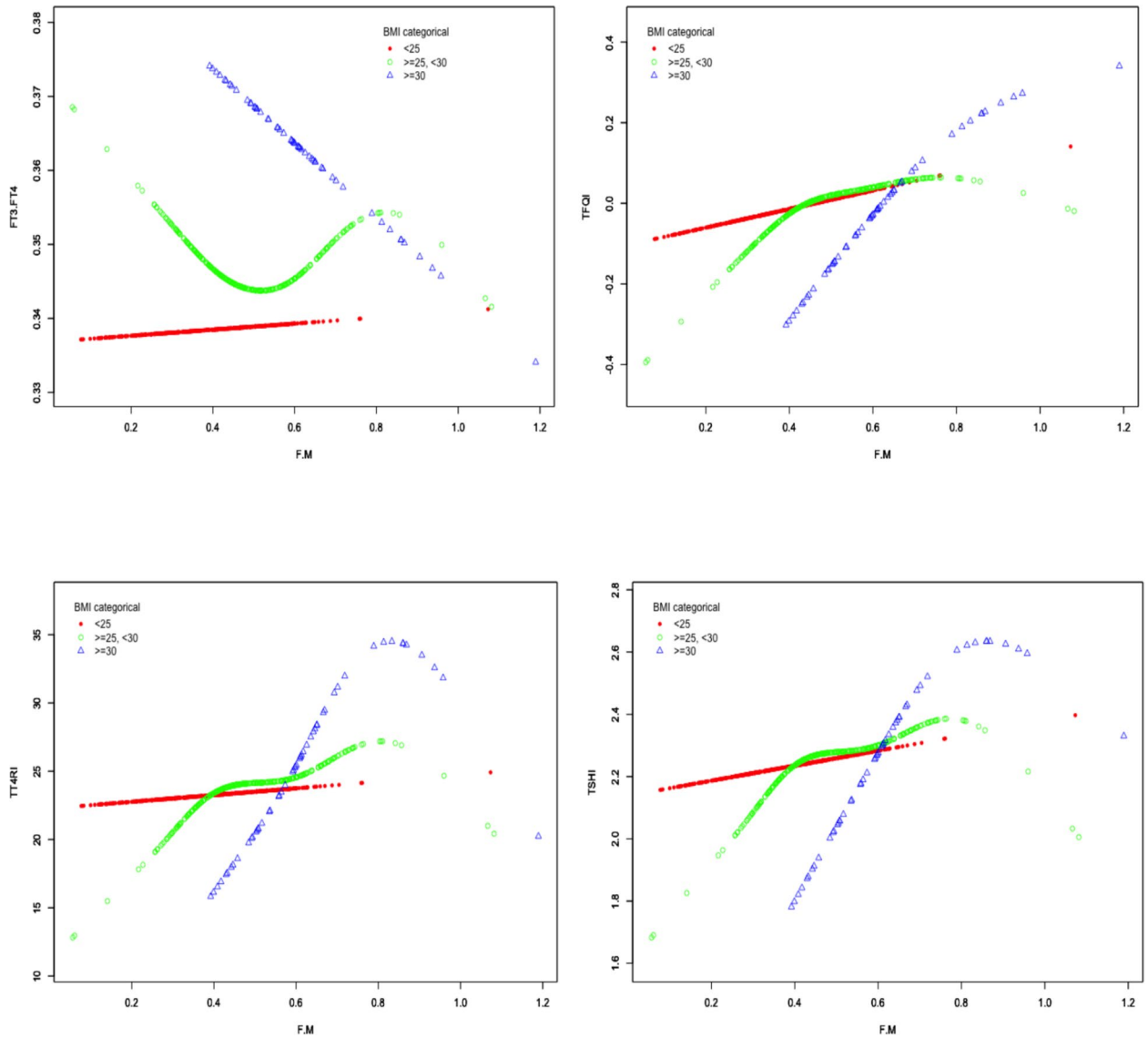

Fig. 4 Smooth curve fitting diagrams of the relationships between F/M and thyroid hormone sensitivity indexes in BMI subgroup

but also among middle-aged and elderly populations, particularly postmenopausal women. This trend may be attributed to the age-related decline in basal metabolic rate and the significant decrease in estrogen levels following menopause [29].

Inadequate oxidation of adipocytes, hypoxia, and oxidative stress resulting from excessive fat accumulation contribute to cellular inflammation and fibrosis, all of which have implications on cardiovascular health and increased mortality [30]. Obese patients with diabetes are at significantly increased risks of developing diabetic nephropathy, as well as cardiovascular and cerebrovascular diseases [31]. Obese individuals defined by body mass index (BMI), waist circumference (WC) or waist to height ratio (WtHR), who concurrent suffered from hypertension and diabetes, were closely associated with the increased risk of mortality related to these conditions [32]. Therefore, the impact of obesity on physical health should not be underestimated.

Previous studies have shown that thyroid hormones play important roles in obesity. In middle-aged individuals, there were positive correlations between FT3 and BMI, WC, triglycerides, blood pressure, blood sugar, and other metabolic indicators [33]. Elevated levels of thyroid hormones were closely associated with higher fat mass and lower muscle mass [34]. Whether in terms of fat percentage (according to the 1998 criteria of the World Health Organization, fat% ≥ 25% for men and ≥ 30% for

Table 4 The associations of F/M with thyroid hormone sensitivity in age subgroup

	FT3/FT4	TFQI	TT4RI	TSHI
Age < 65 years				
model I				
One-line effect	−0.03 (−0.07, 0.00) 0.0523	0.54 (0.28, 0.81) < 0.0001	8.27 (0.20, 16.33) 0.0448	0.55 (0.18, 0.91) 0.0031
model II				
inflection point (k)	0.21	0.68	0.26	0.26
< K segment effect 1	0.05 (−0.15, 0.26) 0.6194	0.63 (0.32, 0.93) < 0.0001	−9.48 (−39.99, 21.03) 0.5427	−0.13 (−1.49, 1.24) 0.8545
> K segment effect 2	−0.04 (−0.07, −0.00) 0.0351	0.19 (−0.53, 0.90) 0.6096	10.55 (1.65, 19.46) 0.0205	0.63 (0.23, 1.03) 0.0019
Effect difference	−0.09 (−0.30, 0.12) 0.4094	−0.44 (−1.25, 0.37) 0.2870	20.03 (−13.19, 53.25) 0.2376	0.76 (−0.73, 2.24) 0.3164
The predicted value of the equation at the inflection point	0.35 (0.34, 0.35)	0.02 (−0.04, 0.07)	21.06 (19.64, 22.47)	2.15 (2.09, 2.22)
Log-likelihood ratio test	0.406	0.284	0.234	0.313
Age ≥ 65 years				
model I				
One-line effect	0.01 (−0.12, 0.14) 0.8632	0.18 (−0.98, 1.34) 0.7593	26.81 (−12.41, 66.03) 0.1855	0.85 (−0.68, 2.39) 0.2819
model II				
inflection point (k)	0.22	0.41	0.69	0.76
< K segment effect 1	0.25 (−0.35, 0.86) 0.4113	0.72 (−0.93, 2.37) 0.3938	20.72 (−22.61, 64.06) 0.3526	1.15 (−0.52, 2.82) 0.1842
> K segment effect 2	−0.01 (−0.14, 0.13) 0.9240	−0.14 (−1.49, 1.22) 0.8429	49.82 (−28.82, 128.46) 0.2194	−0.99 (−5.33, 3.35) 0.6574
Effect difference	−0.26 (−0.89, 0.37) 0.4216	−0.86 (−2.72, 1.00) 0.3687	29.10 (−56.96, 115.16) 0.5102	−2.13 (−6.85, 2.58) 0.3785
The predicted value of the equation at the inflection point	0.32 (0.30, 0.34)	0.10 (−0.05, 0.25)	24.86 (18.20, 31.53)	2.37 (2.07, 2.66)
Log-likelihood ratio test	0.382	0.328	0.473	0.338

Outcome: β (95% CI) *P*-value, adjusted for gender, BMI, GLU, HbA1c, LDL-C, TC, HDL-C and SUA

β: regression coefficient, CI Confidence interval

women) or BMI standard obesity (BMI ≥ 25 kg/m2), FT3 and FT3/FT4 levels were positively correlated with obesity [35]. Additionally, low levels of FT4 in overweight and obese individuals were independently correlated with insulin resistance [36]. Meanwhile, numerous studies have also demonstrated the impacts of obesity on thyroid hormones. In postmenopausal women, the levels of FT4, TSH, and HOMA-IR were significantly increased in the obese group. After adjusting for age and BMI, there was a negative correlation between visceral fat and FT4 level, as well as positive correlations between visceral fat and FT3 and FT3/FT4 levels [37]. In individuals with normal thyroid function, there was a positive correlation between visceral fat area and FT3 [38]. Furthermore, the increased visceral fat content among obese patients served as an independent predictor for TSH level [39]. Obesity was associated with increased thyrotropin, and the changes in thyroid hormone levels were consequences of weight gain rather than the cause of obesity. It has been observed that increases in body weight by 0.6 kg for women and 0.7 kg for men corresponded to a rise in TSH levels by 1 mIU/L [40]. Hypothyroidism was only associated with moderate weight gain, typically attributed to the changes in body compositions. Thyroid hormone replacement therapy generally resulted in mild weight loss (less than 10%), indicating that severe obesity was not commonly a result of hypothyroidism [16]. This theory was further supported by the fact that following weight loss achieved by bariatric surgery [41] or a low-calorie diet [42], there were significant decreases in TSH, FT3, and T3 levels, with subsequent normalization of thyroid function. In conclusion, the relationships between obesity and thyroid hormones were not consistently established and remained in the stage of ongoing research and exploration.

Based on the aforementioned findings, an increase in body fat mass/muscle mass (F/M) was found to be associated with a decrease in the sensitivity of central, but not peripheral thyroid hormone. Subgroup analysis based on age indicated that F/M had a more pronounced relationship with central thyroid hormone sensitivity in individuals aged < 65 years, but did not have a significant impact on individuals with age ≥ 65 years. In terms of gender subgroup, F/M exhibited weaken positive correlation with central thyroid hormone sensitivity index of TFQI, but not TT4RI and TSHI in

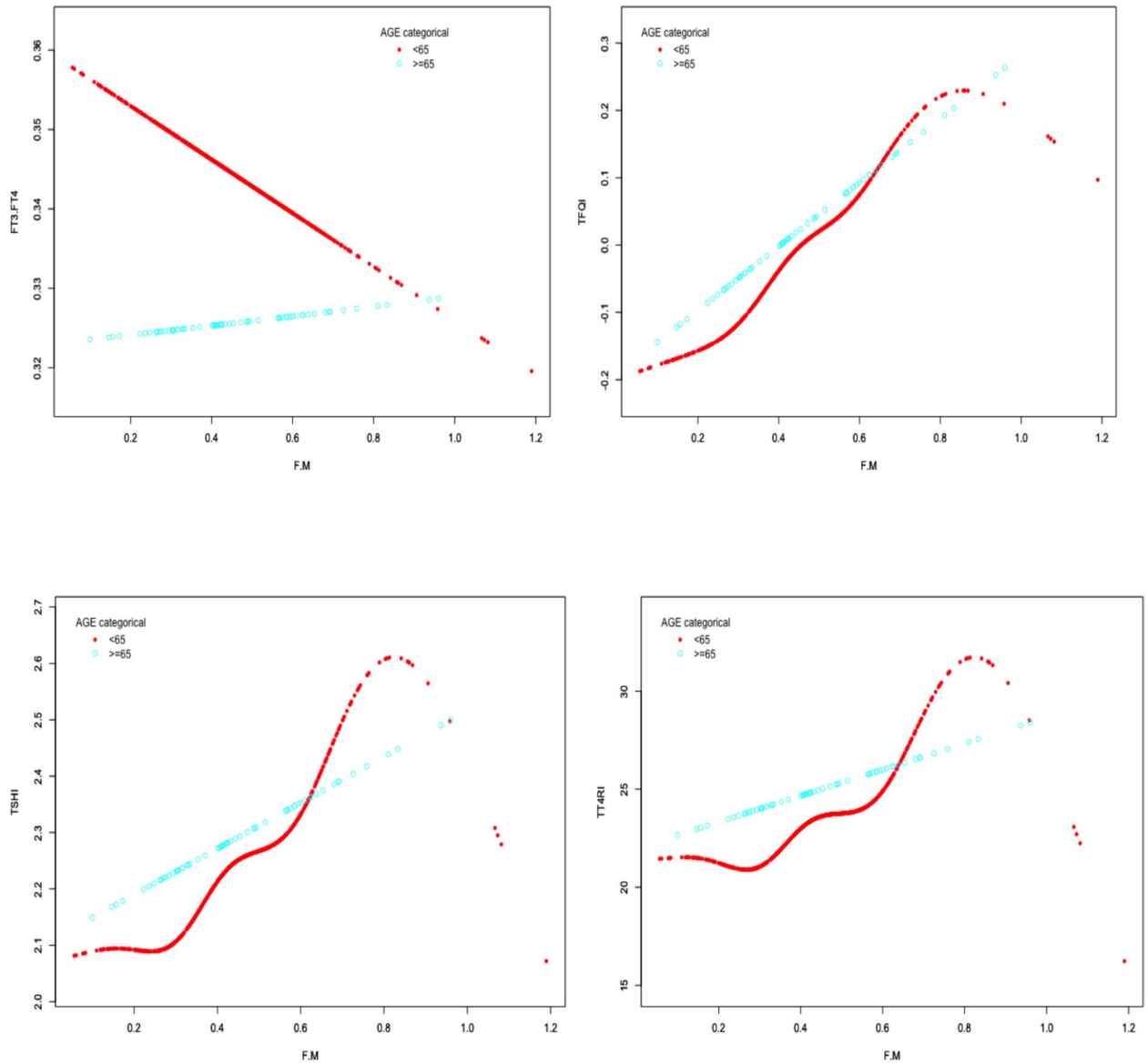

Fig. 5 Smooth curve fitting diagrams of the relationships between F/M and thyroid hormone sensitivity indexes in age subgroup

female group. In male group, F/M exhibited significant positive correlation with central thyroid hormone sensitivity before the inflection, but no correlation thereafter. Subgroup analysis based on BMI indicated that F/M had a positive relationship with central thyroid hormone sensitivity in individuals with BMI ≥ 25 kg/m^2, but this correlation disappears at a certain level of F/M. Individuals with BMI ≥ 30 kg/m^2 showed negative relationship between F/M and central thyroid hormone sensitivity when F/M reached a high level. The possible reason maybe when the proportion of body fat reaches a high level in male and obese people, thyroid function decreases and thyroid hormone resistance decreases significantly, this leads to the disappearance of their positive correlation, or even a negative correlation, but the exact mechanism is unclear (Additional file 1).

Similar to the impact of obesity on insulin resistance, obesity may also lead to a relative resistance to thyroid hormone levels, resulting in a weakened effect of thyroid hormones. This may be an important factor contributing to the decrease in basal metabolic rate (BMR) associated with higher levels of body fat in overweight individuals [43].

The possible mechanisms of thyroid hormone resistance in obesity may be explained as follows: Firstly, there is an interaction between thyroid hormone and

Table 5 The associations of F/M with thyroid hormone sensitivity in gender subgroup

	FT3/FT4	TFQI	TT4RI	TSHI
Female				
Model I				
One-line effect	−0.03 (−0.07, 0.02) 0.2375	0.51 (0.12, 0.89) 0.0101	8.85 (−3.15, 20.85) 0.1491	0.51 (−0.01, 1.03) 0.0532
Model II				
Inflection point (k)	0.4	0.32	0.76	0.76
< K segment effect 1	−0.09 (−0.21, 0.02) 0.1084	−0.54 (−2.24, 1.16) 0.5326	10.81 (−2.09, 23.71) 0.1015	0.62 (0.06, 1.17) 0.0311
> K segment effect 2	−0.01 (−0.06, 0.05) 0.7711	0.63 (0.20, 1.06) 0.0043	−5.04 (−40.65, 30.58) 0.7817	−0.21 (−1.75, 1.33) 0.7876
Effect difference	0.09 (−0.05, 0.22) 0.2131	1.17 (−0.67, 3.02) 0.2136	−15.85 (−54.09, 22.40) 0.4173	−0.83 (−2.48, 0.83) 0.3273
The predicted value of the equation at the inflection point	0.33 (0.32, 0.34)	−0.10 (−0.17, −0.04)	28.25 (25.73, 30.78)	2.42 (2.31, 2.53)
Log-likelihood ratio test	0.207	0.207	0.411	0.321
Male				
Model I				
One-line effect	−0.04 (−0.08, 0.01) 0.1269	0.49 (0.12, 0.85) 0.0088	7.29 (−3.50, 18.07) 0.1861	0.50 (0.02, 0.99) 0.0419
Model II				
Inflection Point (k)	0.2	0.57	0.58	0.58
< K segment effect 1	0.14 (−0.11, 0.40) 0.2596	0.85 (0.41, 1.29) 0.0002	14.87 (1.92, 27.83) 0.0249	0.92 (0.34, 1.50) 0.0019
> K segment effect 2	−0.05 (−0.10, −0.00) 0.0455	−0.85 (−1.83, 0.13) 0.0897	−22.30 (−52.49, 7.88) 0.1482	−1.14 (−2.48, 0.21) 0.0992
Effect difference	−0.20 (−0.47, 0.07) 0.1531	−1.70 (−2.86, −0.54) 0.0042	−37.18 (−72.61, −1.74) 0.0403	−2.06 (−3.64, −0.48) 0.0111
The predicted value of the equation at the inflection point	0.35 (0.34, 0.36)	0.08 (0.01, 0.15)	24.46 (22.33, 26.58)	2.31 (2.22, 2.41)
Log-likelihood ratio test	0.148	0.004	0.038	0.01

Outcome: Outcome: β (95% CI) *P*-value, adjusted for age, BMI, GLU, HbA1c, LDL-C, TC, HDL-C and SUA. β: regression coefficient, CI Confidence interval

leptin in the regulation of body composition. Research has indicated a positive correlation between visceral fat and leptin level, and the same positive correlation existed between leptin and TSH level [44]. Leptin, secreted by adipocytes, regulates the expression of thyrotropin-releasing hormone (TRH gene) in the paraventricular nucleus (PVN) and arcuate nucleus (ARC). TSH binds to leptin receptors in adipocytes, leading to the stimulation of leptin secretion. A complex positive feedback system exists between serum TSH and leptin. Additionally, leptin promotes the intracellular synthesis of T3 by regulating the activity of deiodinase in adipocytes [45, 46]. Secondly, the TSH receptor is expressed in both adipocytes and preadipocytes of animals and humans. Additionally, TSH has the ability to induce the transformation of preadipocytes into adipocytes [47, 48]. In obese patients, the expressions of TSH and TRalpha1 receptors in adipose tissue are reduced, leading to increased levels of TSH and FT3. Additionally, the local action of T3 is impaired due to changes in the expressions of thyroid receptors in adipocytes. However, hormone levels and central thyroid hormone resistance returned to normality after weight-loss surgery [41, 49]. Thirdly, the expressions of 5'-deiodonase (DIO2) in the subcutaneous adipose tissue of obese patients was decreased, leading to a reduction in local T4 to T3 conversion [50].

Limitations

Also, there were several limitations in our study. Firstly, for study design, our study was of a cross-sectional design and lacked longitudinal comparative data, thus the evidence of the relationship between body composition and thyroid hormone sensitivity was not sufficient. Secondly, for missing variables, we failed to include thyroid-related antibodies which may potentially affect thyroid hormones. Thirdly, for sample size, the small number of individuals with BMI ≥ 30 kg/m^2 reduced the credibility in studies of this population. In the future, we need to strengthen the study of obese population.

Conclusion

In conclusion, impaired central sensitivity to thyroid hormones is associated with increased body fat mass/muscle mass (F/M). We hypothesized that an increase in the F/M ratio would increase thyroid hormone resistance, but whether F/M independently affects thyroid hormone sensitivity needs to be verified by further clinical and

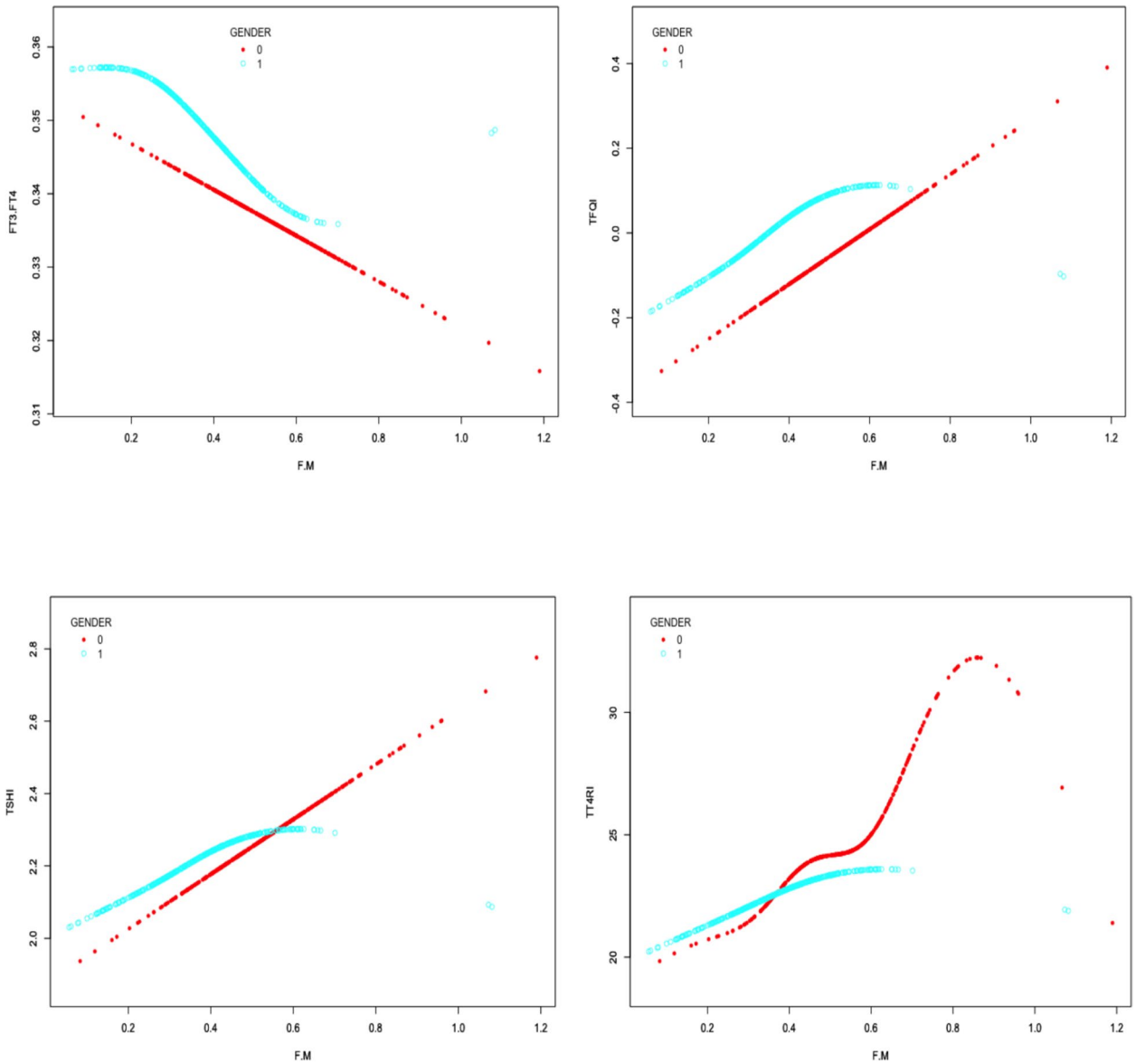

Fig. 6 Smooth curve fitting diagrams of the relationships between F/M and thyroid hormone sensitivity indexes in agender subgroup. 0 = female, 1 = male

basic studies in the future. We believe that the results could be helpful for obesity management in clinical work.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01693-w.

Additional file 1 (XLSX 478 KB)

Author contribution

Ying Li, Guojuan Wang and Qianqian Zhang wrote the main manuscript text, Li Chen, Yue Wang and Qibao Ye prepared figures and tables. All authors reviewed the manuscript.

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Data availability

The original data generated and analyzed in this study are included in the supplementary material and can be requested from corresponding author.

Declarations

Ethics approval and consent to participate

This study obtained consent from all participants and was approved by the Ethics Committee of Hefei City First People's Hospital in accordance with the Declaration of Helsinki. All participants had signed informed consents [No. 2024–167-01].

Conflict of interest
The authors declare no competing interests.

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