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ORIGINAL RESEARCH

Gender-Specific Impact of Metabolic Obesity Phenotypes on the Risk of Hashimoto's Thyroiditis: A Retrospective Data Analysis Using a Health Check-Up Database

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Background: Hashimoto's thyroiditis (HT) is recognized as the most common autoimmune thyroid disease, often accompanied by the diffuse enlargement of thyroid with abundant blood flow and elevated level of thyroid autoantibodies. As obesity had a positive association with the risk of HT. Thus, this retrospective study was established to further explore the gender relationship between metabolic obesity phenotypes and the risk of Hashimoto's thyroiditis (HT).

Materials and Methods: Data for 3697 subjects aged ≥18 years were randomly collected from a Health check-up database from April to December 2019. Obesity was defined by general obesity (GO; body mass index [BMI] ≥28 kg/m^2) and abdominal obesity (AO; waist circumstance, male ≥90 cm, female ≥85 cm). Metabolic unhealthy was defined as having at least one metabolic syndrome component and a homeostasis model assessment of insulin resistance ≥2.5. Obesity phenotypes were divided into three groups: GO, AO, compound obesity (GO+AO). After adjustment for potential confounding factors, multivariate logistic regression was used to assess the association between metabolic obesity phenotypes and risk of HT by sex and explore the correlation between different obesity patterns and HT risk by metabolic health status.

Results: The incidence of HT was 23.5% and significantly higher among females than males with different metabolic phenotypes (26.2% vs 20.5%, $p<0.05$), except metabolically healthy AO. Compared with non-obese subjects, different metabolic obesity phenotypes were independent risk factors among males ($p<0.05$). Among females, unhealthy metabolic status with GO (adjusted odds ratio [OR]=2.62) or AO (adjusted OR=2.87) and metabolically healthy non-GO (adjusted OR=2.05) were risk factors of HT ($p<0.05$). Increasing BMI categories and waist circumstance quartiles were positively correlated with HT risk (p for trend <0.05). Subgroup analyses indicated that GO+AO (adjusted OR=2.52) or only AO (adjusted OR=2.41) were risk factors for HT for those with unhealthy metabolic status. Moreover, GO+AO (adjusted OR=2.37) was an independent risk factor for HT under healthy metabolic status.

Conclusion: GO+AO was associated with an increased risk of HT, identifying higher BMI/WC as a significant risk factor for HT. Males with unhealthy metabolic state or obesity and metabolically unhealthy females with obesity are high-risk group for HT. Additionally, only AO and GO+AO conferred increased risk of HT for individuals with metabolic abnormalities.

Keywords: Hashimoto's thyroiditis, metabolic obesity phenotypes, general obesity, abdominal obesity, retrospective data

Introduction

Epidemiological studies have shown that obesity remains a serious public health concern worldwide. Various comorbidities are associated with obesity, including metabolic disorders such as insulin resistance, type 2 diabetes, and immune disease.[1,2] It is worth noting that an increasing trend in thyroid autoimmunity is correlated with a high prevalence of obesity.[3] With the high prevalence of obesity, more attention should also be paid to the occurrence of thyroid

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autoimmune diseases. To our knowledge, Hashimoto's thyroiditis (HT), the most common autoimmune thyroid disease, ultimately leads to the destruction of thyroid tissue.[4] HT is characterized by lymphocytic infiltration and the presence of autoantibodies against thyroid peroxidase (TPO-Ab) and/or thyroglobulin (Tg-Ab).[5] A recent systematic review and meta-analysis demonstrated that obesity is an independent risk factor of HT, and it is supposed that a bilateral interaction exists between adiposity and thyroid autoimmune disease,[6] as evidence indicates that excessive adipose tissues can induce immune system dysfunction and activate the inflammatory process in the thyroid among genetically predisposed individuals.[7] A dramatic effect of obesity on the risk of thyroid autoimmune disease has been recognized in previous studies.

The risk of developing HT may differ between genders and obesity phenotypes. Considerable evidence has demonstrated that females are more susceptible to thyroid autoimmune diseases than males.[5,8] In addition, based on fat distribution in the body, general obesity (GO) defined by body mass index (BMI) reflects the overall status of adipose distribution, and abdominal obesity (AO) defined by waist circumference (WC) represents the visceral adipose tissue. Evidence indicates that macrophage infiltration occurs in visceral fat, and AO is associated with chronic inflammation and affects the autoimmune process.[9,10] Thus, obesity phenotypes comprise single GO, AO, and combined (compound obesity [GO+AO]). However, few studies have explored the effect of different obesity phenotypes on the risk of developing HT among males and females with different metabolic health states. Therefore, a retrospective study was performed to evaluate the association between different metabolic obesity phenotypes with the risk of developing HT among genders using a health check-up database.

Materials and Methods

Study Design and Subjects

Data were collected for subjects who underwent annual health check-ups at Huadong Sanatorium from April to December 2019. Inclusion criteria were as follows: subjects who completed the questionnaire regarding lifestyle and medical history; underwent thyroid ultrasound, and blood parameters included hematologic index of thyroid function (FT3, FT4 and TSH) and antithyroid antibody status (Tg-Ab, TPO-Ab). We excluded subjects who were less than 18 years old and those without information closely related to our research. A total of 3697 subjects were finally included in our study. The mean (standard deviation) age of subjects was 45.74 years (11.42). The percentage of males and females was 47.2% (n=1745) and 52.8% (n=1952), respectively.

Demographic characteristics included age, gender, smoking status, and alcohol consumption, and smoking was defined as at least three cigarettes per day for 12 sequential months, whereas alcohol consumption was defined as more than 3 drinks per week for 12 consecutive months. In addition, personal medical information included a diagnosis of chronic diseases, such as diabetes, hypertension, or cardiac-cerebral vascular disease.

Anthropometric Measurements

Body weight, height, WC, and hip circumference (HC) were measured by well-trained nurses; body height was measured in centimeters (cm) using a stadiometer. WC was measured to the nearest 0.1 cm around the horizontal level at the high point of the iliac crest. BMI was calculated as the body weight in kilograms divided by the square of the body height in meters (kg/m^2).

Clinical Measurements

In the morning, blood specimens (8~10mL) were obtained from the antecubital vein of subjects after at least an overnight 8-h fast. The serum was placed at room temperature for 30 min and centrifuged at 3000 rpm for 10 min in a low-temperature high-speed centrifuge. The following biochemical parameters including serum levels of glucose, triglycerides (TGs), total cholesterol (TC), low-density-lipoprotein cholesterol, high-density-lipoprotein cholesterol (HDL-C) were measured by a Beckman Coulter AU5400 Automatic Biochemistry Analyzer (Beckman Coulter, USA). White blood cells, neutrophils, and lymphocytes were measured by Sysmex XE-5000 automatic blood analyzer (Sysmex, Japan). Additionally, laboratory indicators related to thyroid function including free

triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) were also tested by Beckman Coulter UniCel DxI 800 Chemiluminescence immunoassay analyzer (Beckman Coulter, USA). Thyroid autoimmune antibodies (TPO-Ab, Tg-Ab), were measured using Abbott I4000 Chemiluminescence immunoassay analyzer (Abbott, USA). All blood specimen were tested within 24 h at the Medical Laboratory Center of Huadong Sanatorium.

Definition of Metabolic Obesity Phenotypes

Metabolically unhealthy subjects were defined as those having at least one of the following metabolic abnormalities:[11–13] (1) fasting blood glucose ≥100 mg/dL or currently receiving glucose-lowering therapy; (2) blood pressure ≥130/85 mmHg or currently receiving anti-hypertension treatment; (3) elevated TG level (≥1.7 mmol/L) or current lipid-lowering treatment; (4) low HDL-C level (<1.0 mmol/L in men or <1.3 mmol/L in women); or (5) insulin resistance, defined as a HOMA-IR score ≥2.5. Conversely, metabolically healthy subjects were defined as having none of the metabolic abnormalities mentioned above, as previously applied.[11,14]

The definition of obesity was in accordance with the Chinese standard of BMI and WC:[15,16] as underweight (BMI <18.5 kg/m^2), normal-weight (BMI 18.5–23.9 kg/m^2), overweight (BMI 24.0–27.9 kg/m^2). GO was defined as BMI ≥28.0 kg/m^2, whereas AO was defined as WC ≥90 cm for men and ≥85 cm for women.

According to metabolic health status and obesity patterns, metabolic obesity phenotypes were divided into eight categories as follows:[17] (1) MHNGO, metabolically healthy non-GO; (2) MHGO, metabolically healthy GO; (3) MUNGO, metabolically unhealthy non-GO; (4) MUGO, metabolically unhealthy GO; (5) MHNAO, metabolically healthy non-AO; (6) MHAO, metabolically healthy AO; (7) MUNAO, metabolically unhealthy non-AO; and (8) MUAO, metabolically unhealthy AO.

In addition, obesity was classified into three phenotypes, as follows: GO without AO (Go[+]AO[−]), AO without GO (GO[−]AO[+]), compound obesity (GO[+]AO[+]).

Assessment of HT and Thyroid Function

The diagnosis of HT was based on ultrasound characteristics of the thyroid and an elevated level of Tg-Ab or TPO-Ab. Specifically, the ultrasound Examination indicated diffuse enlargement of the thyroid with abundant blood supply combined with TPO-Ab >5.61 IU/mL or Tg-Ab >4.11 IU/mL. Thyroid function parameters included TSH (reference: 0.56–5.91 μIU/mL), FT3 (reference: 3.28–6.47 pmol/L), FT4 (reference: 7.64–16.03 pmol/L), Tg-Ab (reference: 0–4.11 IU/mL), and TPO-Ab (reference: 0–5.61 IU/mL).

Statistical Analysis

All statistical analyses were performed using SPSS 25.0 software package (SPSS Institute, Chicago, IL). Continuous variables are expressed as mean ± standard deviation or median (interquartile range) based on evaluation of the normal distribution by Shapiro–Wilk test, whereas categorical variables are presented as the frequency with percentages. Comparisons of basic characteristics specified by gender were conducted using the *t*-test or Mann–Whitney *U*-test for continuous variables, whereas the chi-square test was used for categorical variables. To evaluate the correlations between metabolic obesity phenotypes and the risk of HT, multiple logistic regression was used after adjustment for potential confounding factors, including age, smoking, alcohol consumption, hypertension, TGs, HDL-C, FT4, and TSH. Non-obese subjects with healthy metabolism were treated as a reference group. In addition, a comparison of different metabolic status combined with obesity defined by BMI or WC with the risk of HT was conducted in males and females separately. Meanwhile, WC was categorized into the following quartiles: Q1 (<73 cm), Q2 (73–79.9 cm), Q3 (80–87.9 cm), and Q4 (≥88 cm). We performed a test for linear trends by entering the median value of each quartile interval of WC as a continuous variable in the adjusted models, and linear trend analysis for BMI was conducted based on the different ranges of values described above. A two-tailed *p*-value <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Population

The study included 3697 subjects (age: 45.74±11.42 years, range: 18~95 years), of which 1745 were males and 1952 females. The prevalence of HT was 20.5% in males and 26.2% in females (χ^2=16.72, p<0.001). In addition, the prevalence of HT was significantly higher in females than males in different metabolic obesity phenotypes, except for MHAO (Figures 1 and 2). Baseline characteristics of the subjects are shown according to the presence of HT separately in males and females (Table 1). Males diagnosed with HT tended to have higher WC, HC, WHR (waist to hip ratio), BMI, incidence of hypertension, TGs, TSH

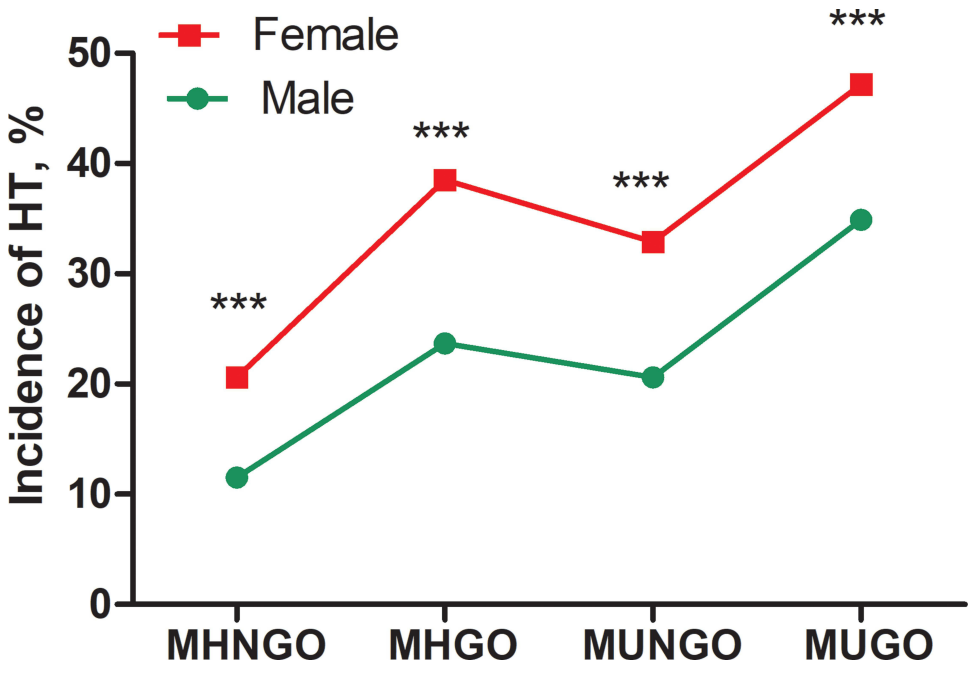

Figure 1 Comparison of HT incidence between males and females with different metabolic status and obesity defined by BMI. ***:p<0.001.

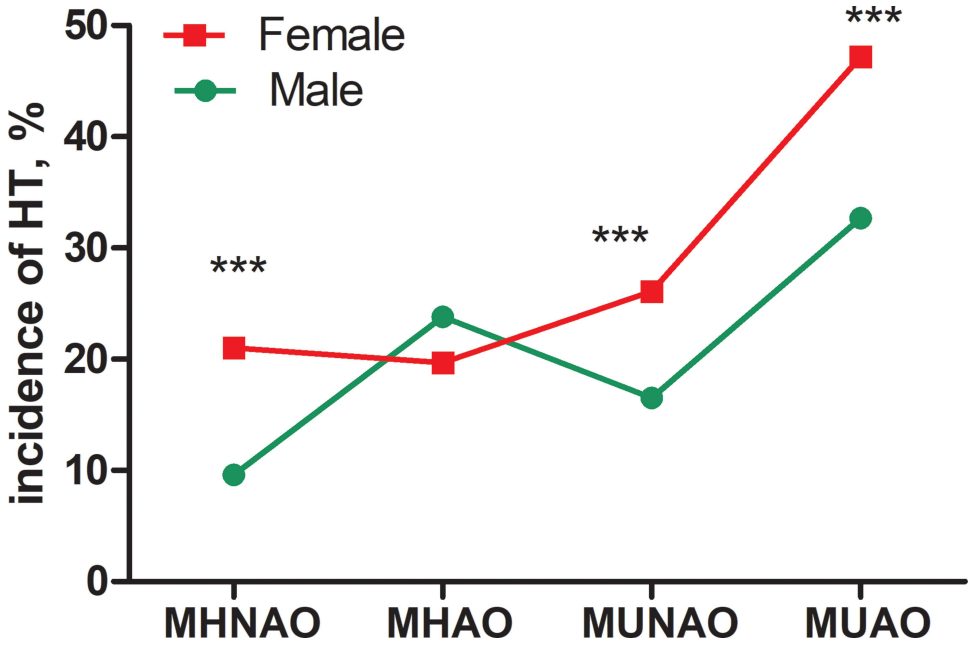

Figure 2 Comparison of HT incidence between males and females with different metabolic status and obesity defined by WC. ***:p<0.001.

Table 1 Baseline Characteristics of All Subjects According to HT by Gender

Characteristic	Overall (n=3697)	Males (n=1745)		*p* value	Females (n=1952)		*p* value
		HT (n=358)	Non-HT (n=1387)		HT (n=512)	Non-HT (n=1440)	
Age (years)	45.74±11.42	48.93±10.85	48.06±11.22	0.190	45.03±11.43	42.95±11.06	<0.001
Smoking (n, %)	1004 (27.2%)	169 (47.2%)	639 (46.1%)	0.441	56 (10.9%)	140 (9.7%)	0.721
Drinking (n, %)	646 (17.5%)	134 (37.4%)	484 (34.9%)	0.386	11 (2.1%)	17 (1.2%)	0.130
WC (cm)	80.54±10.15	90.24±7.86	86.90±7.58	<0.001	76.13±8.64	73.57±7.03	<0.001
HC (cm)	93.55±5.81	97.36±5.78	97.39±5.30	<0.001	92.37±5.99	91.23±5.07	<0.001
WHR	0.86±0.08	0.92±0.05	0.91±0.05	<0.001	0.82±0.07	0.81±0.06	<0.001
BMI (kg/m^2)	23.93±3.35	26.43±3.08	25.15±2.90	<0.001	23.27±3.57	22.37±2.87	<0.001
SBP (mmHg)	119.14±16.24	129.38±15.54	124.83±13.61	<0.001	115.52±16.20	112.41±15.44	<0.001
DBP (mmHg)	72.56±10.50	77.99±11.19	75.69±9.78	<0.001	70.43±9.76	68.96±9.71	0.003
Hypertension (n, %)	364 (9.8%)	77 (21.5%)	171 (12.3%)	<0.001	41 (8.0%)	75 (5.2%)	0.029
FBG (mmol/L)	5.23±1.02	5.54±1.46	5.46±1.20	0.286	5.04±0.62	5.01±0.70	0.391
DM (n, %)	169 (4.6%)	29 (8.1%)	100 (7.2%)	0.571	12 (2.3%)	28 (1.9%)	0.588
TC (mmol/L)	4.79 [4.23, 5.40]	4.89 [4.28, 5.46]	4.85 [4.25, 5.43]	0.695	4.68 [4.11, 5.32]	4.75 [4.22, 5.37]	0.108
TG (mmol/L)	1.12 [0.76, 1.74]	1.76 [1.19, 2.44]	1.48 [1.02, 2.15]	<0.001	0.96 [0.66, 1.47]	0.85 [0.62, 1.18]	<0.001
LDL-C (mmol/L)	2.84 [2.42, 3.30]	2.99 [2.52, 3.39]	2.95 [2.53, 3.36]	0.760	2.75 [2.36, 3.20]	2.75 [2.36, 3.21]	0.964
HDL-C (mmol/L)	1.37 [1.16, 1.60]	1.19 [1.05, 1.37]	1.22 [1.07, 1.40]	0.054	1.45 [1.23, 1.68]	1.53 [1.34, 1.76]	<0.001
WBC ($\times 10^9$/L)	5.87±1.39	6.27±1.38	6.23±1.43	0.666	5.54±1.30	5.55±1.28	0.921
NE ($\times 10^9$/L)	3.24±1.02	3.40±0.98	3.43±1.04	0.626	3.08±1.01	3.08±0.97	0.878
FT3 (pmol/L)	4.80 [4.45, 5.17]	5.01 [4.69, 5.35]	4.99 [4.65, 5.35]	0.518	4.63 [4.32, 4.96]	4.62 [4.31, 4.99]	0.977
FT4 (pmol/L)	11.06 [10.12, 12.11]	10.91 [9.85, 11.90]	11.33 [10.36, 12.32]	<0.001	10.89 [9.92, 11.86]	10.97 [10.03, 11.98]	0.105
TSH (mU/L)	1.99 [1.41, 2.81]	2.19 [1.60, 3.02]	1.83[1.32, 2.56]	<0.001	2.33 [1.64, 3.38]	1.99 [1.39, 2.77]	<0.001

Notes: Normally distributed continuous variables are presented as the mean ± standard deviation. Non-normally distributed continuous variables are presented as the mean [interquartile range]. Categorical variables are presented as the number (percentage).

Abbreviations: HT, Hashimoto's thyroiditis; WC, waist circumference; HC, hip circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; DM, diabetes mellitus; WBC, white blood cells; NE, neutrophils; TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, thyroxine.

and lower FT4. Females diagnosed with HT were more likely to be older and to have high WC, HC, WHR, BMI, incidence of hypertension, TGs, HDL-C, and TSH.

Association Between Metabolic Obesity Phenotypes and the Risk of HT Separately in Males and Females

Table 2 shows the associations between eight metabolic obesity phenotypes and the risk of HT. After the adjustment for age, smoking, alcohol consumption, hypertension, TGs, HDL-C, FT4, and TSH (Model 2), multivariate logistic regression analysis showed that metabolic unhealthy status or GO/AO could increase the risk of developing HT among males. Furthermore, unhealthy metabolism state increased the risk of developing HT among males with GO (adjusted odds ratio [OR]=3.78) or AO (adjusted OR=4.55). Additionally, females with healthy metabolism state were not susceptible to developing HT. In contrast, unhealthy metabolism state increased the risk of developing HT among females with GO; moreover, metabolically unhealthy females with GO or AO still had the highest risk of developing HT.

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Table 2 Association Between Metabolic Obesity Phenotypes and the Risk of HT Separately in Males and Females

Status of Metabolically Healthy and Obesity Phenotypes	Total (n=3697)	HT cases (n, %)	Unadjusted Model		Model 1		Model 2	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Males (n=1745)								
GO defined by BMI								
MHNGO	488	56 (11.5%)	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
MHGO	38	9 (23.7%)	2.39 (1.08–5.32)	0.032	2.40 (1.08–5.34)	0.031	2.50 (1.11–5.60)	0.027
MUNGO	930	192 (20.6%)	2.01 (1.46–2.77)	<0.001	1.98 (1.43–2.74)	<0.001	1.86 (1.31–2.66)	0.001
MUGO	289	101 (34.9%)	4.14 (2.87–5.99)	<0.001	4.13 (2.85–5.99)	<0.001	3.78 (2.50–5.72)	<0.001
AO defined by WC								
MHNAO	425	41 (9.6%)	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
MHAO	101	24 (23.8%)	2.92 (1.67–5.11)	<0.001	2.96 (1.69–5.19)	<0.001	3.14 (1.78–5.54)	<0.001
MUNAO	650	107 (16.5%)	1.85 (1.26–2.71)	0.002	1.87 (1.27–2.76)	0.001	1.85 (1.22–2.78)	0.004
MUAO	569	186 (32.7%)	4.55 (3.15–6.56)	<0.001	4.68 (3.22–6.82)	<0.001	4.55 (3.00–6.90)	<0.001
Females (n=1952)								
GO defined by BMI								
MHNGO	1173	242 (20.6%)	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
MHGO	13	5 (38.5%)	2.40 (0.78–7.42)	0.127	2.49 (0.81–7.69)	0.113	2.05 (0.66–6.38)	0.215
MUNGO	677	223 (32.9%)	1.89 (1.53–2.34)	<0.001	1.79 (1.43–2.24)	<0.001	1.55 (1.17–2.05)	0.002
MUGO	89	42 (47.2%)	3.44 (2.22–5.34)	<0.001	3.34 (2.15–5.21)	<0.001	2.62 (1.59–4.32)	<0.001
AO defined by WC								
MHNAO	1064	223 (21.0%)	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
MHAO	122	24 (19.7%)	0.92 (0.58–1.48)	0.740	0.89 (0.55–1.43)	0.624	0.83 (0.51–1.34)	0.438
MUNAO	459	120 (26.1%)	1.34 (1.03–1.72)	0.027	1.31 (1.01–1.70)	0.044	1.15 (0.84–1.57)	0.380
MUAO	307	145 (47.2%)	3.38 (2.58–4.41)	<0.001	3.24 (2.43–4.30)	<0.001	2.87 (2.01–4.09)	<0.001

Notes: Model 1: adjusted for age, smoking, and alcohol consumption. Model 2: adjusted for age, smoking, alcohol consumption, hypertension, TG, HDL-C, FT4, TSH.

Abbreviations: HT, Hashimoto's thyroiditis; MHNGO, metabolically healthy non-general obesity; MHGO, metabolically healthy general obesity; MUNGO, metabolically unhealthy non-general obesity; MUGO, metabolically unhealthy general obesity; MHNAO, metabolically healthy non-abdominal obesity; MHAO, metabolically healthy abdominal obesity; MUNAO, metabolically unhealthy non-abdominal obesity, MUAO, metabolically unhealthy abdominal obesity.

Association Between BMI Categories/WC Quartiles and the Risk of HT

Table 3 shows the associations between BMI categories/WC quartiles and the risk of HT, after adjustment for age, smoking, alcohol consumption, hypertension, TGs, HDL-C, FT4, and TSH (Model 2); the multivariable-adjusted ORs (95% CIs) for HT comparing underweight, overweight, and GO with normal weight as the reference were 1.28 [0.80, 2.06], 1.21 [0.96, 1.53], and 1.75 [1.19, 2.58], respectively (p for trend <0.05). Meanwhile, the multivariable-adjusted ORs (95% CIs) for HT comparing WC quartiles 2, 3, and 4 to the lowest quartiles were 0.82 [0.63, 1.07], 1.13 [0.80, 1.60], and 1.77 [1.10, 2.83], respectively (p for trend <0.05).

Association Between Obesity Phenotypes and the Risk of HT Separately in Metabolically Healthy and Unhealthy Subjects

We compared different obesity phenotypes with non-obesity in terms of the risk of HT in different metabolic states (Figure 3). After adjusting for potential confounders, multivariable regression analysis indicated that individuals with only abdominal obesity (adjusted OR=2.41, 95% CI: 1.90–3.07, p<0.001) or GO+AO (adjusted OR=2.52, 95% CI: 1.93–3.29, p<0.001) had a significant risk of developing HT in the metabolically unhealthy state. Among individuals in the metabolically healthy state, only GO+AO increased the risk of developing HT (adjusted OR=2.37, 95% CI: 1.17–4.78, p=0.016).

Discussion

This retrospective study enrolled 3697 subjects, examining complete medical records from a health check-up database. We evaluated the association between different metabolic obesity phenotypes with the risk of HT specified by gender at baseline. The incidence of HT in females was higher than males of different metabolic obesity types, except for MHAO. In males, after further adjustment for confounding factors, obesity was a significant independent risk factor for HT among individuals in either healthy or unhealthy metabolic states. Moreover, obesity combined with unhealthy metabolic status had an additive effect on the risk of HT, whereas in females, only GO and AO were not independent risk factors of HT. Nevertheless, obesity coexisting with an unhealthy metabolic state contributed comprehensively to risk of HT in females. In addition, increased WC quartiles and increasing BMI were positively associated with an elevated risk of HT (p for

Table 3 Test for Linear Trend for Association Between BMI Categories and Quartiles of WC with HT Risk

Obesity Phenotype	Total (n=3697)	HT cases (n, %)	Unadjusted Model		Model 1		Model 2	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
GO defined by BMI								
<18.5	125	27 (21.6%)	1.12 [0.72, 1.74]	0.618	1.32 [0.83, 2.11]	0.238	1.28 [0.80, 2.06]	0.304
18.5–23.9	1822	360 (19.8%)	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
24–27.9	1256	308 (24.5%)	1.32 [1.11, 1.57]	0.002	1.23 [0.97, 1.55]	0.088	1.21 [0.96, 1.53]	0.113
≥28	445	161 (36.2%)	2.30 [1.84, 2.88]	<0.001	1.81 [1.24, 2.66]	0.002	1.75 [1.19, 2.58]	0.005
p for trend			<0.001		0.017		0.026	
AO defined by WC								
Q1(<73cm)	911	203 (22.3%)	1.00 (reference)	–	1.00 (reference)	–	1.00 (reference)	–
Q2(73–79.9cm)	861	172 (20.0%)	0.87 [0.69, 1.09]	0.235	0.81 [0.63, 1.06]	0.119	0.82 [0.63, 1.07]	0.141
Q3(80–87.9cm)	988	217 (22.0%)	0.98 [0.79, 1.22]	0.867	1.10 [0.79, 1.54]	0.578	1.13 [0.80, 1.60]	0.492
Q4(≥88cm)	937	278 (29.7%)	1.47 [1.19, 1.82]	<0.001	1.73 [1.09, 2.75]	0.021	1.77 [1.10, 2.83]	0.018
p for trend			<0.001		0.012		0.010	

Notes: Model 1: adjusted for age, smoking, and alcohol consumption. Model 2: adjusted for age, smoking, alcohol consumption, hypertension, TGs, HDL-C, FT4, TSH.

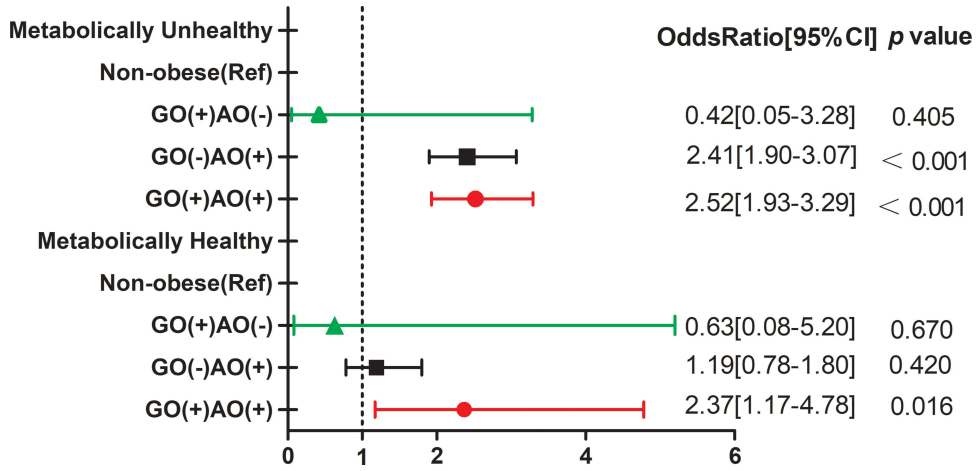

Figure 3 Association between different obesity types with HT risk in metabolically healthy and unhealthy states.

trend <0.05), and AO and GO+AO were independent risk factors for HT in metabolically unhealthy individuals. However, only GO+AO was an independent risk factor for HT in metabolically healthy individuals. According to the results described above, our finding indicate that different metabolic obesity phenotypes may affect the risk level of HT by gender differently.

Although the reason underlying the gender difference in the association between different metabolic obesity phenotypes and risk of HT is not clear, several possible factors may explain this difference based on previous research. First, males in Asia are characterized by the accumulation of visceral adipose tissue, also regarded as AO, and our study showed that prevalence of AO in males was significantly higher than in females (38.4% Vs 22.0%, $p<0.001$), which indicated that AO in males is more hazardous than in females. Visceral adipose tissue has been shown to be more biologically active than fat located in other regions.[18] Furthermore, excessive adipose depots located in the visceral region could contribute to chronic low-grade inflammation, as resident macrophages, endothelial cells, and T cells localize in visceral adipose tissue.[7,19,20] These immune-regulating cells are related to the exaggerated release of proinflammatory cytokines and control autoimmune reactions, ultimately inducing thyroid cell apoptosis.[21,22] Second, as estrogen and testosterone have a different biological effects in regulating thyroid function,[23,24] individuals with different metabolic obesity phenotypes can exhibit varied levels of sex hormones, which can affect the risk of developing HT. Finally, the proportion of females in a perimenopausal state, which is characterized by a drop in estrogen levels, could affect the correlation between obesity phenotype and HT risk.

Our study also demonstrated that AO is strongly associated with the risk of developing HT in individuals with metabolic disorders, and only GO was not associated with increased risk of HT, even in subjects with metabolic abnormalities, indicating that a large amount of adipose tissue in the visceral region has greater effect on the risk of developing HT. Although most studies have used BMI to represent GO, BMI does not accurately reflect the characteristics of fat distribution throughout the body. WC, a standardized parameter for assessing AO, is a measure of visceral adipose tissue; males with high WC had a significantly higher risk of HT, even without metabolic disorders. A previous cohort study also illustrated that TPO-Ab and Tg-Ab positivity was associated with a significant increasing trend with increased WC in males.[25] Nevertheless, a 9-year follow-up study reported no significant association between baseline AO phenotype and development of TPO-Ab positivity.[26] Our study also found that only AO was not associated with increased risk of developing HT among individuals without metabolic disorders, but those with AO accompanied by unhealthy metabolic status were more likely to develop HT. Notably, the coexistence of GO and AO increased the risk of developing HT in people with or without metabolically unhealthy status, indicating that the effect of GO+AO on HT risk is not markedly associated with metabolic factors.

Our results showed that metabolic disorders constitute an independent risk factor for HT in non-obese males but not females. However, previous research demonstrated conflicting results. A retrospective study exploring the association

between components of metabolic syndrome with the presence of thyroid antibodies found a negative association,[27] and other studies also showed no significant difference in the prevalence of metabolic syndrome between participants with and without autoimmune thyroiditis.[28,29] Conversely, a study by Tamer et al demonstrated that thyroid antibodies are positively related to blood lipid concentration (TGs and non–HDL-C) among premenopausal females diagnosed with HT.[30] Additionally, a recent study of 4775 participants showed a positive relationship between thyroid autoimmunity and metabolic syndrome in euthyroid subjects.[31] Meanwhile, a population-based study also demonstrated that metabolic disorders such as obesity or dyslipidemia are strongly associated with the prevalence of positive thyroid autoantibodies in euthyroid subjects in a gender-dependent manner.[32] The negative association described above may have resulted from the relatively small number of participants positive for thyroid antibodies. As a result, a prospective study should be established to investigate the association between metabolic parameters and HT, which could verify the effect of metabolic disorders on the risk of developing HT.

This study also had several limitations. First, this retrospective study could not determine a causal relationship between the different metabolic obesity phenotypes and the occurrence of HT; therefore, a cohort study is warranted to affirm the actual association. Second, this study was only a single-center investigation and could have been affected by potential selection bias; a multi-center study with a larger sample size is thus needed. Finally, adipokines were not evaluated in the different metabolic obesity types; measurement of various adipokines could provide deeper understanding of the mechanism underlying the association between obesity types and the risk of developing HT. In addition, recent studies illustrated that brain dysfunction existed in neurologically asymptomatic patients with HT,[33] and was characterized by reduced brain activity,[34] which indicated that cognitive functions needed to be monitored as a confounding factor in statistical analysis. Furthermore, family history of autoimmune thyroid disorders, as a genetic influencing factor for individuals on thyroid autoimmunity risk, also should be collected in further study.

Conclusion

In summary, this research is the first to demonstrate, based on a medical database, that individuals with higher BMI/WC have a higher risk of developing HT. In males, obesity and metabolic disorders were significant risk factors for HT. In females, the coexistence of obesity and unhealthy metabolic status was associated with greater risk of HT. Only AO and GO+AO were associated with increased risk of HT in individuals with metabolic abnormalities.

Ethics Approval and Informed Consent

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics and Research Committee of Huadong Sanatorium Health Examination Center (no. ECHS2021-08). Personal private information was deleted in advance, and statistical analyses were conducted with strict confidentiality and only used for scientific purposes. Thus, the requirement for informed consent from patients was waived.

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Disclosure

All authors declare they have no conflicts of interest in this work.

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