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Clinical Research Article

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Subclinical Hypothyroidism Represents Visceral Adipose Indices, Especially in Women With Cardiovascular Risk

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Abbreviations: ABSI, a body shape index; AR_{10y}, absolute risk of cardiovascular event in 10 years; BMI, body mass index; BRI, body roundness index; CV, cardiovascular; CVAI, Chinese visceral adiposity index; CVD, cardiovascular disease; DM, diabetes mellitus; EAT, epicardial adipose tissue; EU, euthyroid; FRS, Framingham risk score; FT4, free thyroxine; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MDCT, multidetector computed tomography; Mets, metabolic syndrome; OR, odds ratio; PCF, pericardial fat; SBP, systolic blood pressure; SCH, subclinical hypothyroidism; TAT, thoracic periaortic fat; TG, triglycerides; TSH, thyrotropin; VAT, visceral adipose tissue; WC, waist circumference.

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Abstract

Context: From previous studies, decreased thermogenesis and metabolic rate in the patients with overt and subclinical hypothyroidism lead to an increase in visceral adipose tissue (VAT) incidence, and which was associated with cardiovascular diseases. In this paper, we want to explore the relationship between various forms of VAT [pericardial (PCF), and thoracic periaortic adipose tissue (TAT)] and obesity indices [body shape index (ABSI), and body roundness index (BRI), Chinese visceral adiposity index (CVAI)] with subclinical hypothyroidism by gender.

Objective: This study aims to evaluate region-specific cardiovascular (CV) fat tissue (pericardial fat [PCF] and thoracic periaortic fat [TAT) and noninvasive visceral adipose indices (a body shape index [ABSI], body roundness index [BRI]), and Chinese visceral adiposity index [CVAI]) in patients with subclinical hypothyroidism (SCH) as compared to a control population and relative to variations in CV risk.

Methods: A total of 125 Taiwanese patients recently diagnosed with SCH (age: 52.9 ± 10.16 years, 41.6% female) and 1519 healthy volunteers (age: 49.54 ± 9.77 years, 29.0% female) were evaluated for this study. All participants underwent PCF and TAT assessment using a multidetector computed tomography scanner, ABSI, BRI, and CVAI evaluation using a mathematical formula. CV risk was classified by Framingham risk score (FRS).

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Results: Multivariable logistic regression models showed that the independent association of TAT and BRI with SCH were stronger in women than men. The adjusted model associations (odds ratio [OR]; 95% CI) with SCH for TAT and BRI in women were 2.61 (95% CI, 1.03-6.97) and 2.04 (95% CI, 1.07-3.92). The incidences of TAT and BRI third tertile were also higher in women with SCH (SCH vs euthyroid, TAT third tertile, 9 [17.3%] vs 35 [7.9%], $P = .04$; BRI third tertile, 22 [42.3%] vs 111 [25.2%], $P = .01$). In addition to BRI and TAT, there were higher risks of CVAI in SCH with intermediate/high FRS, especially in women (OR; 95% CI, TAT: 4.01; 95% CI, 1.01-6.640; BRI: 6.91; 95% CI, 1.03-10.23; CVAI: 7.81 95% CI, 1.01-12.03).

Conclusion: Our findings show that patients with SCH have significantly greater TAT, BRI, and CVAI values than control groups, especially in women (with different FRS).

Key Words: subclinical hypothyroidism, pericardial fat, thoracic periaortic fat, a body shape index, body roundness index, Chinese visceral adiposity index

Subclinical hypothyroidism (SCH) is a disease characterized by the lack of obvious clinical symptoms and signs; laboratory tests are defined as elevated levels of thyrotropin (TSH) despite the concentration of the serum thyroid hormone falling within the expected, normal range [1]. The prevalence of SCH is about 4% to 20% in the Western population [2, 3], with a higher incidence in aging women [3]. In Taiwan, the prevalence of subclinical hypothyroidism reported in the past was about 1.6% [4], but in recent reports, the prevalence rate reached 4.5% [5].

Decreased thermogenesis and metabolic rate in the patients with overt and subclinical hypothyroidism lead to an increase in visceral adipose tissue (VAT) incidence [6]. There is a substantial body of evidence that confirms VAT's association with systemic inflammation, metabolic syndrome (Mets), diabetes mellitus (DM), and cardiovascular disease (CVD) [7, 8]. Various forms of VAT are implicated in disease pathology, including visceral abdominal, pericardial fat (PCF), and thoracic periaortic adipose tissue (TAT).

PCF and TAT are subtypes of perivascular fat that have been identified as novel risk markers for CVD [9, 10]. A previous study found significantly higher TAT values in SCH patients than control groups as well as a significant correlation with TSH levels, but no differences with respect to sex [11]. A relationship between PCF and SCH has not been established; the majority of research has reported that increased epicardial adipose tissue (EAT) may contribute to cardiovascular (CV) adverse effects associated with SCH [12, 13]. Despite this, a recent study by Santos et al concluded that EAT is not a strong marker of CVD for SCH patients [2]. In fact, PCF must be anatomically and biochemically distinguished from EAT [14].

The body roundness index (BRI), a body shape index (ABSI), and the Chinese visceral adiposity index (CVAI) depict fat distribution and are reliable biomarkers of body fat accumulation in a Chinese and Iranian study [15, 16]. BRI (based on waist circumference [WC] and height) was proposed by Thomas et al in 2013 [17] and was demonstrated to be a novel anthropometric index better at detecting cardiometabolic abnormalities among Chinese women than body mass index (BMI) and waist-to-height ratio [18]. ABSI (based on height, weight, and BMI) has also been shown to be superior to BMI in predicting premature mortality [19] and is the best anthropometric index available for predicting the incidence of CVD among men [20]. Another indicator of Chinese visceral fat is the CVAI (based on WC and BMI; triglycerides [TGs], and high-density lipoprotein cholesterol [HDL-C]), which measures visceral adiposity among the Chinese general population, with separate formulas for men and women [15]. Studies have positively supported CVAI's ability to predict Mets and CVD in this population [21, 22].

There are inconclusive opinions regarding SCH's ability to accurately determine CVD risk. Increasing evidence suggests that an association exists between atherosclerotic CVD and SCH [23, 24]; one meta-analysis study reported that SCH patients have an increased risk of CVD [23], and a similar population-based study noted SCH is an independent predictor for CVD [25]. Despite this, a 20-year cohort investigation did not establish a significant association between SCH and CVD [26].

Sex-linked variations have been demonstrated in visceral fat deposition patterns and regional fat tissue distribution [27]. The mechanisms that underlie the progression of SCH to visceral adiposity may differ based on sex, although additional research is required. While SCH has been established as a predisposing factor for increased CV risk, there is less literature available about the effect of visceral adipose indices (BRI, ABSI, CVAI, PCF, TAT) in SCH patients by sex.

We hypothesize that body fat distribution in SCH or euthyroid (EU) groups could be identified using noninvasive,

clinically measurable surrogates (BRI, ABSI, and CVAI) or region-specific CV fat tissue quantification via multidetector computed tomography (MDCT; PCF and TAT). We aim to assess the correlation between obesity indices and SCH risk by sex in different FRS risk group.

Materials and Methods

Study Population

From 2005 to 2009, a total of 2904 individuals participated in a CV health survey program at a tertiary medical center in Taipei, Taiwan. Patients provided serum used to measure thyroid hormones and other clinical data, such as the results of MDCT imaging. To avoid prospective confounding effects on thyroid functions, we excluded individuals who had 1) malignant disease, 2) an abnormal liver function test (glutamic oxaloacetic transaminase/glutamic pyruvic transaminase levels that were 2-fold more than the upper normal limits, 3) an abnormal renal function test (serum creatinine > 1.5 mg/dL), 4) a history of thyroid disease, or 5) were taking thyroxine or an antithyroid drug (Fig. 1).

After exclusion, a total of 1519 EU and 125 SCH participants (age: 49.5 ± 9.8 years; 29.0% females; age: 52.9 ± 10.2 years; 41.6% females) remained for analysis. The study protocol was granted MacKay Memorial Hospital Institutional Review Board Approval of Clinical Trial (No. 18MMHIS137), and all participants gave written informed consent.

A detailed physical examination and a thorough review of the baseline characteristics and medical history were performed using structured questionnaires. A history of hypertension (HTN) was defined as systolic blood pressure (SBP) higher than 140 mm Hg, diastolic blood pressure higher than 90 mm Hg, or a previous diagnosis of HTN with current medications. A history of DM was defined as a fasting glucose level greater than 126 mg/dL, or glycated hemoglobin A_{1c} more than 6.5%, or the current use of any diabetic medication for treating previously diagnosed DM.

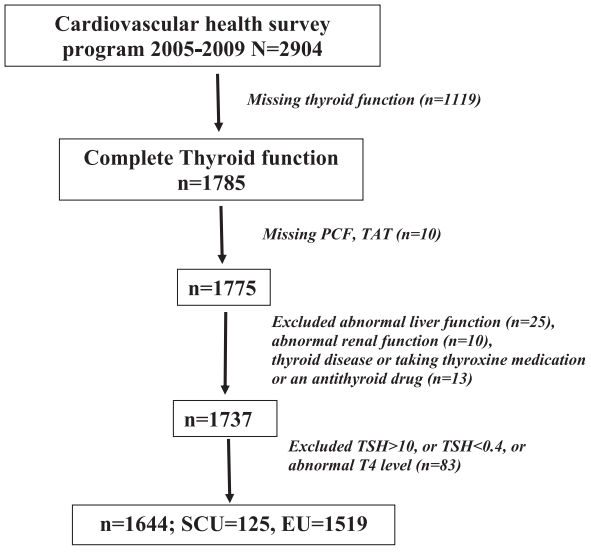

Figure 1. Selection of the study population.

Baseline Anthropometric Measurements

All baseline characteristics and anthropometric measurements, including age, body height, body weight (BW), BMI, and WC, were collected. Height was measured by using a standard stadiometer. Weight was measured in light clothes by using a set of standard calibrated electronic scales. The WC and hip circumference were measured using a constant-tension tape. WC was measured at the midpoint between the lowest rib and the upper point of the iliac crest and at the end of normal expiration. Standardized sphygmomanometer cuff-defined resting blood pressure values were measured while resting. Anthropometric measurements such as height, weight, WC, hip circumference, and blood pressure were examined and recorded by trained nurses who were blinded to the patient's information in a laboratory center.

Laboratory Data Acquisition and Analysis

To measure TSH and free thyroxine (FT4), serum was collected after 12 hours of fasting and prior to MDCT. FT4 and TSH (DiaSorin) were quantified by immunoradiometric assay using a commercially available kit. Because all participants had been ruled out for acute or severe health problems, the potential confusion of nonthyroidal diseases would be ignored. Participants were asked to discontinue medications and stop consuming food approximately 24 hours prior to blood collection to greatly reduce thyroid function interference.

A Hitachi 7170 Automatic Analyzer (Hitachi Corp) was used to measure the levels of fasting glucose, glycated hemoglobin A_{1c} (hexokinase method), total cholesterol, LDL-C and HDL-C (homogenous enzymatic colorimetric assay), and TGs.

Classification Based on Thyroid Function and Framingham Risk Score

The reference ranges for FT4 and TSH were 1.0 to 1.71 ng/dL, and 0.4 to 4.0 mIU/mL, respectively. In the SCH group, serum levels ranged from 4.1 to 10.0 mU/L, and those in the EU group were between 0.5 and 3.9 mU/L. The serum FT4 level in the SCH and EU group was in normal range [4, 5].

The 10-year Framingham risk score (FRS), a point system based on age, sex, SBP, TC, HDL-C, and smoking, was calculated according to the National Cholesterol Education Program guidelines [27]. The absolute risk of a CV event in 10 years (AR_{10y}) was divided into 3 FRS categories: low risk (< 10%), intermediate risk (10%-20%), and high risk (> 20%) [10, 27].

Biochemical Measurements

The CVAI score was calculated using the specific formula for the Chinese population [28]:

Men: CVAI = −267.93 + 0.68 × age + 0.03 × BMI + 4.00 × WC + 22.00 × log10 (TG) − 16.32 × HDL

Women: CVAI = −187.32 + 1.71 × age + 4.23 × BMI + 1.12 × WC + 39.76 × log10 (TG) − 11.66 × HDL

ABSI was calculated as $WC/(BMI^{2/3} \times height^{1/2})$ and expressed in $m^{11/6}kg^{-2/3}$ [19].

BRI = 364.2 − 365.5 × (1 − [WC/2π]2/[0.5 × height2)½ [29]

BMI was calculated as weight/height squared (kg/m^2).

Multidetector Computed Tomography Scanning Protocol

Scanning was performed using a 16-slice MDCT scanner (Sensation 16; Siemens Medical Solutions) with 16- × 0.75-mm collimation, rotation time of 420 ms, and tube voltage of 120 kV. During one breath-hold, images were acquired from above the level of tracheal bifurcation to that below the base of the heart by using prospective electrocardiogram-triggering with the center of the acquisition at 70% of the R-R interval. Using the raw data, the images were reconstructed with standard kernel in 3-mm thick axial nonoverlapping slices and a 25-cm field of view [10].

Measurements of Pericardial Fat and Thoracic Periaortic Fat

The VATs of PCF and TAT were quantized at a dedicated workstation using an MDCT (Aquarius 3D Workstation). The semiautomatic segmentation technique was implemented for quantification of fat volumes. We traced the region of interest manually and defined the fat tissue as pixels within a window of −195 to −45 HU and a window center of −120 HU. PCF was defined as the volume-based burden of total adipose tissue located within the pericardial sac (Fig. 2A). The TAT tissue was defined as the total adipose tissue volume surrounding the thoracic aorta (as periaortic fat), which extends 67.5 mm from the level of bifurcation of the pulmonary arteries (Fig. 2B) with cranial-caudal coverage of the thoracic aorta [10].

Reproducibility for Multidetector Computed Tomography-Derived Visceral Adiposity

The reproducibility of PCF and TAT was evaluated by performing repeated measurements of 40 randomized cases with the initial results and clinical data blinded between readers and has been published before [10]. The intraobserver and interobserver coefficients of variation for PCF were 4.27%, 4.87% and 6.58%, 6.81% for TAT, respectively.

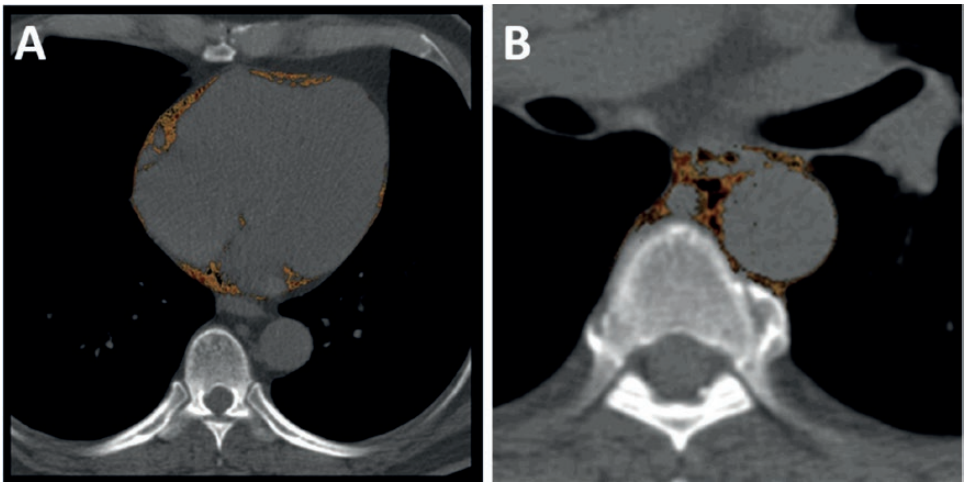

Figure 2. Multidetector computed tomography demonstrated pericardial and thoracic periaortic fat tissue measures. A, Pericardial adipose tissue: the fat between the heart and the pericardium. B, Thoracic periaortic adipose tissue: the fat surrounding the thoracic aorta (shown in axial view) [10]. Orange regions indicate visceral fat tissue.

Statistical Analysis

Continuous variables are expressed as the mean ± SD or median values (interquartile range), whereas categorical variables are presented as absolute values and percentages. The independent *t* test was used to test for differences in normally distributed continuous variables and the Mann-Whitney *U* test was used for comparisons involving abnormally distributed variables. Categorical variables were compared with the chi-square test or Fisher exact test as appropriate. Pearson correlation analysis was used to evaluate the correlations between 5 anthropometric indices and metabolic parameters, age, and thyroid function. Multivariable logistic regression models were performed to estimate the odds ratios (ORs) and 95% CI of SCH associated with these 5 indices in 4 models for men and women (model 1: unadjusted; model 2: adjusted for age; model 3: adjusted for factors in model 2 plus smoking; [a]model 3 means: adjusted for factors in model 2 plus smoking and BMI; model 4: adjusted for factors in model 3 plus SBP, FPG, HDL-C, LDL-C, and FRS); and 3 models in different CV risks groups (model 1: unadjusted; model 2: adjusted for age and smoking; * means model 2: adjusted for age, smoking, and BMI; model 3: adjusted for factors in model 2 plus SBP, FBG, LDL-C, and HDL-C), respectively. A *P* value less than .05 was considered statistically significant, and all analyses were performed using the SPSS 15.0 statistical package (SPSS Inc).

Results

Baseline Characteristics According to Thyroid Functional Status

Of 1644 participants, 125 (7.6%) were SCH patients and 1519 (92.4%) were EU individuals. Sex is strongly correlated with obesity and CV risk factor, and we therefore compared the characteristics all participants according to sex (Table 1).

The SCH group comprised a greater quantity of women and older individuals than the EU group (women, SCH vs EU, 52 [41.6%] vs 441 [29.0%], $P < .001$; age, SCH vs EU, 52.9 ± 10.16 vs 49.54 ± 9.77, $P < .001$). The participants' history of smoking and diabetes was comparable, but HTN was higher in men with SCH. Minimal differences in clinical and biochemical traits were noted between the SCH and the EU groups. Significant variations in 10-year FRS were observed between men in the 2 respective groups (SCH vs EU: 15.29 ± 12.00 vs 12.30 ± 11.62, $P = .03$); and the incidence of intermediate and high AR_{10y} was higher in male participants with SCH ($P = .01$).

Significant age discrepancies were not observed between the female participants in both groups (SCH vs EU, 53.83 ± 10.00 vs 51.44 ± 9.85, $P = .10$). We found that the anthropomorphic clinical indices (BMI, BRI, and CVAI) and the VAT (TAT) were higher in the women with SCH ($P < .05$).

Odds Ratios of Region-Specific Cardiovascular Fat Tissue and Noninvasive Visceral Adipose Indices With Risk of Subclinical Hypothyroidism

Multivariable logistic regression models showed that the ORs for SCH increased with TAT and BRI score for women in 4 models (Table 2). The independent association of TAT and BRI with SCH were stronger in female participants than their male counterparts. The adjusted model associations (OR, 95% CI) with SCH for TAT and BRI in women were 2.61 (95% CI, 1.03-6.97) and 2.04 (95% CI, 1.07-3.92) (model 4).

These association predictors were essentially unaffected by adjusting for age and lifestyle factors (models 2 and 3). After considering the impact of blood pressure, FPG, HDL-C, LDL-C, and FRS on association estimators, the OR increased by 30% in TAT and by about 10% in BRI in women (model 4).

A Comparison of the Incidence of Region-Specific Cardiovascular Fat Tissue and Noninvasive Visceral Adipose Indices According to Thyroid Functional Status

Table 3 compares the participants' region-specific CV fat tissue and noninvasive visceral adipose indices. The TAT, BRI, and CVAI were higher in the women with SCH group (SCH vs EU: 5.48 ± 3.43 vs 4.24 ± 2.30; 3.69 ± 1.22 vs 3.37 ± 1.22; 83.29 ± 36.5 vs 69.29 ± 39.30, $P < .05$). The incidences of TAT and BRI third tertile were also higher in women with SCH (SCH vs EU, TAT third tertile, 9 [17.3%] vs 35 [7.9%], $P = .04$; BRI third tertile, 22 [42.3%] vs 111 [25.2%], $P = .01$). The incidence of ABSI third tertile was higher in men with SCH (SCH vs EU, 35 [47.9%] vs 383 [35.5%], $P = .01$). In the female participants, the incidence of region-specific CF fat tissue and noninvasive visceral adipose indices was marginally greater in individuals with SCH as opposed to the EU individuals.

Baseline Characteristics According to Thyroid Functional Status and Absolute Risk of Cardiovascular Event in 10 Years by Framingham Risk Score

According to FRS score, the participants with low risk and intermediate/high risk were 995 and 649 individuals, with

Table 1. Baseline characteristics according to thyroid functional status by sex

	Men (N = 1151)			Women (N = 493)		
	SCH	EU		SCH	EU	
Variables	(n = 73)	(n = 1078)	*P*	(n = 52)	(n = 441)	*P*
Age, y	52.23 ± 10.29	48.76 ± 9.64	.003	53.83 ± 10.00	51.44 ± 9.85	.10
TSH, μIU/mL	5.82 ± 1.75	1.90 ± 0.78	< .001	6.12 ± 2.63	1.96 ± 0.81	< .001
FT4, ng/dL	1.26 ± 0.13	1.33 ± 0.15	< .001	1.20 ± 0.13	1.28 ± 0.15	.001
Smoking, n (%)	16 (21.9%)	219 (20.3%)	.74	0 (0.0%)	10 (2.3%)	.61
Diabetes, n (%)	5 (6.8%)	80 (7.4%)	.86	3(5.8%	29 (6.6%)	.99
HTN, n (%)	23 (31.5%)	226 (21.0%)	.03	11 (21.2%)	66 (15.0%)	.25
BMI	25.08 ± 3.18	25.29 ± 3.51	.62	24.43 ± 3.75	23.21 ± 3.43	.02
WC, cm	86.40 ± 13.52	87.45 ± 9.15	.36	80.26 ± 9.07	77.83 ± 9.37	.08
Obesity, n (%)	17 (23.3%)	285 (26.4%)	.55	10 (19.2%)	60 (13.6%)	.27
SBP, mm Hg	122.89 ± 15.81	123.52 ± 16.43	.75	122.58 ± 21.66	119.14 ± 18.29	.21
DBP, mm Hg	78.11 ± 11.11	78.24 ± 10.15	.91	72.98 ± 10.62	73.23 ± 10.37	.87
FPG, mg/dL	104.26 ± 28.63	103.97 ± 26.55	.93	98.75 ± 16.87	98.27 ± 20.39	.87
PPG, mg/dL	132.73 ± 63.56	124.63 ± 54.61	.24	124.35 ± 39.99	124.24 ± 42.37	.99
HbA_{1c}, %	6.03 ± 1.00	5.89 ± 0.95	.23	5.72 ± 0.57	5.80 ± 0.75	.45
TC, mg/dL	207.10 ± 35.25	202.60 ± 38.21	.33	208.92 ± 36.84	203.67 ± 37.97	.34
HDL-C, mg/dL	47.30 ± 11.36	48.37 ± 11.86	.45	59.87 ± 11.44	61.39 ± 15.00	.39
LDL-C, mg/dL	135.51 ± 29.32	133.22 ± 32.08	.55	131 ± 32.93	127.03 ± 34.61	.45
TGs, mg/dL	172.58 ± 128.88	156.44 ± 154.04	.38	126 ± 97.53	111.71 ± 64.06	.17
FRS (%)	15.29 ± 12.00	12.30 ± 11.62	.03	7.36 ± 8.94	5.69 ± 5.86	.19
Low AR10y, n (%)	26 (35.6%)	567 (52.6%)	.01	42 (80.8%)	360 (81.6%)	.31
Intermediate AR10y, n (%)	22 (30.1%)	277 (25.7%)		5 (9.6%)	59 (13.4%)	
High AR10y, n (%)	25 (34.2%)	234 (21.7%)		5 (9.6%)	22 (5.0%)	
PCF	83.04 ± 34.51	80.35 ± 31.47	.48	69.56 ± 36.37	65.35 ± 28.79	.33
TAT	8.67 ± 4.30	8.10 ± 3.90	.24	5.48 ± 3.43	4.24 ± 2.30	.01
ABSI	0.08 ± 0.01	0.08 ± 0.004	.60	0.08 ± 0.01	0.08 ± 0.01	.89
BRI	3.63 ± 1.12	3.72 ± 1.09	.51	3.69 ± 1.22	3.37 ± 1.22	.04
CVAI	98.58 ± 58.95	99.13 ± 42.10	.92	83.29 ± 36.50	69.29 ± 39.30	.01

Clinical characteristics are expressed as mean ± SD for continuous variables and n (%) for categorical variables. *P* values were derived from independent 2-sample *t* test for continuous variables, and categorical variables were expressed as percentages and compared with the χ^2 test or Fisher exact test.

Abbreviations: ABSI, a body shape index; AR10y, absolute risk of cardiovascular event in 10 years by FRS; BMI, body mass index; BRI, body roundness index; CVAI, Chinese visceral adiposity index; DBP, diastolic blood pressure; EU, euthyroid; FPG, fasting plasma glucose; FT4, free thyroxine; HTN, hypertension; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FRS, Framingham risk score; Obesity, BMI ≥ 27; PCF, pericardial fat; PPG, postprandial plasma glucose; SBP, systolic blood pressure; SCH, subclinical hypothyroidism; TAT, thoracic periaortic adipose tissue; TC, total cholesterol; TGs, triglycerides; TSH, thyrotropin; WC, waist circumference.

68 of 927 of SCH individuals and 57 of 592 of those in the EU group (Table 4). We found that the TAT, BRI, and CVAI were higher in the women with SCH group and intermediate/high CV risk ($P < .05$), and other indices (eg, WC) were higher in the women with SCH group (borderline statistically difference, $P = .05$). TAT was higher in the women with SCH group and those with low CV risk ($P = .01$)

Odds Ratios of Region-Specific Cardiovascular Fat Tissue and Noninvasive Visceral Adipose Indices With Risk of Subclinical Hypothyroidism in Different Absolute Risks of Cardiovascular Event in 10 Years by Framingham Risk Score

Multivariable logistic regression models indicated that the ORs for SCH increased with TAT, BRI, and CVAI score for women in 3 models (Table 5). The independent association was stronger in women than in men. In the intermediate/high CV risk group, the adjusted model associations (OR, 95% CI) with SCH for TAT, BRI, and CVAI in women were 4.01 (95% CI, 1.01-6.64), 7.04 (95% CI, 1.02-11.29), and 7.81 (95% CI, 1.01-12.03) (model 3).

Even after adjusting for age and lifestyle factors, the association estimators remained essentially unchanged (model 2). When factoring in blood pressure, FPG, HDL-C, LDL-C, and FRS, the OR increased by 80% in TAT, by about 13% in BRI, and by about 50% in the CVAI for women group (model 3).

Discussion

The prevalence rate of SCH in our study is 7.6% and higher in women (10.5% vs 6.3%, $P < .01$), which is compatible

Table 2. Odds ratio of regional-specific cardiovascular fat tissue and noninvasive visceral adipose indices with risk of subclinical hypothyroidism

Variables	PCF[a]			TAT[a]			ABSI			BRI			CVAI		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Men															
Model 1	0.97	(0.59-1.57)	.89	1.42	(0.88-2.88)	.15	1.67	(1.04-2.69)	.03	1.10	(0.67-1.79)	.71	1.10	(0.68-1.78)	.70
Model 2	0.81	(0.49-1.35)	.42	1.11	(0.66-1.85)	.70	1.39	(0.80-2.29)	.20	0.96	(0.58-1.58)	.87	0.94	(0.57-1.53)	.79
Model 3	0.81	(0.49-1.34)	.41	1.09	(0.66-1.83)	.73	1.38	(0.84-2.28)	.20	0.96	(0.58-1.57)	.86	0.93	(0.57-1.52)	.77
Model 4	0.78	(0.47-1.32)	.36	1.12	(0.65-1.92)	.69	1.37	(0.83-2.28)	.22	1.00	(0.58-1.71)	.99	0.95	(0.54-1.67)	.86
Women															
Model 1	1.24	(0.62-2.46)	.54	2.43	(1.09-5.39)	.03	0.82	(0.42-1.62)	.57	2.18	(1.21-3.94)	.01	1.49	(0.74-2.97)	.26
Model 2s	0.99	(0.47-2.09)	.97	2.19	(0.98-5.31)	.05	0.71	(0.35-1.42)	.33	1.96	(1.04-3.68)	.04	1.17	(0.52-2.61)	.70
Model 3	0.98	(0.46-2.06)	.95	2.32	(1.02-5.65)	.04	0.71	(0.35-1.43)	.34	1.98	(1.05-3.72)	.03	1.21	(0.54-2.72)	.64
Model 4	1.07	(0.50-2.31)	.86	2.61	(1.03-6.97)	.04	0.70	(0.34-1.41)	.32	2.04	(1.07-3.92)	.03	1.56	(0.61-3.98)	.36

Model 1: Unadjusted.
Model 2: Adjusted for age.
Model 3: Adjusted for factors in model 2 plus smoking.
Model 4: Adjusted for factors in model 3 plus SBP, FPG, HDL-C, LDL-C, and FRS.
Abbreviations: ABSI, a body shape index; BMI, body mass index; BRI, body roundness index; CVAI, Chinese visceral adiposity index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FRS, Framingham risk score; OR, odds ratio; PCF, pericardial fat; SBP, systolic blood pressure; TAT, thoracic periaortic adipose tissue.
[a]Model 3: Adjusted for factors in model 2 plus smoking and BMI.

Table 3. A comparison of the incidence of region-specific cardiovascular fat tissue and noninvasive visceral adipose indices according to thyroid functional status

	Men			Women		
Variables	SCH	EU	*P*	SCH	EU	*P*
PCF	83.04 ± 34.51	80.35 ± 31.47	.48	69.56 ± 36.37	65.35 ± 28.79	.33
PCF (3rd tertile, n/%)	28 (38.4%)	422 (39.1%)	.89	12 (23.1%)	86 (19.5%)	.54
TAT	8.67 ± 4.30	8.10 ± 3.90	.24	5.48 ± 3.43	4.24 ± 2.30	.01
TAT (3rd tertile, n/%)	38 (52.1%)	467 (43.3%)	.15	9 (17.3%)	35 (7.9%)	.04
ABSI	0.08 ± 0.01	0.08 ± 0.004	.60	0.08 ± 0.01	0.08 ± 0.01	.89
ABSI (3rd tertile, n/%)	35 (47.9%)	383 (35.5%)	.03	12 (23.1%)	118 (26.8%)	.57
BRI	3.63 ± 1.12	3.72 ± 1.09	.51	3.69 ± 1.22	3.37 ± 1.22	.04
BRI (3rd tertile, n/%)	28 (38.4%)	390 (36.2%)	.71	22 (42.3%)	111 (25.2%)	.01
CVAI	98.58 ± 58.95	99.13 ± 42.10	.92	83.29 ± 36.50	69.29 ± 39.30	.01
CVAI (3rd tertile, n/%)	31 (42.5%)	433 (40.2%)	.70	12 (23.1%)	74 (16.8%)	.04

Abbreviations: ABSI, a body shape index; BRI, body roundness index; CVAI, Chinese visceral adiposity index; EU, euthyroid; PCF, pericardial fat; SCH, subclinical hypothyroidism; TAT, thoracic periaortic adipose tissue.

with the rate in the Western population (4%-20%) [2, 3] and more common in females and aged individuals [2], but a higher prevalence rate than that in Taiwan (1.6%-4.5%) [4, 5]. The main differences are the age and sex of the people involved in this study.

The manifestation of hypothyroidism with CVD in VAT is well established, but the effect of SCH is unclear [30]. In the literature, different adipose compartments have different endocrine functions. It has been clearly proved that VAT will also accompany different metabolic risks and morbidities [31, 32]. For example, VAT is a more pathogenic fat that is more likely to cause metabolism and CVD risks than subcutaneous adipose tissue [31, 32].

In our study, we found a higher risk of TAT and BRI in an SCH group of Taiwanese women, and an increased impact of CVAI in an SCH with intermediate/high CV risk group. A strong correlation was found between BRI and CVAI in all groups. Region-specific cardiovascular fat tissue (PCF and TAT) is one kind of visceral fat reservoir that is proposed to have a negative effect on blood vessels in a localized manner [33, 34]. TAT can envelope the aorta, contributing to CV pathogenesis and potentially

Table 4. Baseline characteristics according to thyroid functional status and absolute risk of cardiovascular event in 10 years by Framingham risk score

Variables	Low risk										Intermediate/high risk									
	Men					Women					Men					Women				
	SCH (n = 26)		EU (n = 567)		*P*	SCH (n = 42)		EU (n = 360)		*P*	SCH (n = 47)		EU (n = 511)		*P*	SCH (n = 10)		EU (n = 81)		*P*
Age, y	45.5	12.0	43.0	9.0	.31	52.0	9.8	49.8	12.0	.14	57.0	14.0	54.0	10.0	.18	65.5	12.3	61.0	11.5	.47
TSH, μIU/mL	**5.5**	**2.4**	**1.7**	**1.1**	**< .001**	**5.3**	**1.8**	**1.8**	**1.1**	**< .001**	**5.4**	**1.6**	**1.9**	**1.1**	**< .001**	**6.0**	**2.9**	**2.1**	**1.5**	**< .001**
FT4, ng/dL	**1.2**	**0.3**	**1.3**	**0.2**	**.01**	**1.2**	**0.2**	**1.3**	**0.2**	**.001**	**1.3**	**0.1**	**1.3**	**0.2**	**.001**	**1.2**	**0.3**	**1.3**	**0.2**	**.04**
Smoking, %	2	7.7	53	9.3	.56	0	0.0	7	1.9	.46	14	29.8	166	32.5	.70	0	0.0	3	3.7	.99
Diabetes, %	0	0.0	5	0.9	.80	0	0.0	9	2.5	.37	5	10.6	75	14.7	.45	3	30.0	20	24.7	.71
HTN, %	1	3.8	29	5.1	.62	4	9.5	21	5.8	.26	22	46.8	197	38.6	.27	7	70.0	45	55.6	.51
BMI	23.9	4.0	24.2	3.9	.61	23.3	3.9	22.2	4.2	.06	25.4	3.9	25.6	4.3	.44	26.5	4.8	24.5	4.7	.10
WC, cm	84.5	7.8	85.0	11.0	.69	78.0	10.6	75.0	10.5	.14	88.0	8.0	90.0	11.0	.42	**87.5**	**12.0**	**83.0**	**12.8**	**.05**
Obesity, %	5	19.2	107	18.9	.56	6	14.3	37	10.3	.28	12	25.5	178	34.8	.20	4	40.0	23.00	28.4	.48
SBP, mm Hg	110.0	11.8	116.0	18.0	.42	116.0	20.0	110.0	18.0	.30	128.0	22.0	130.0	20.0	.24	143.0	27.0	138.0	21.0	.15
DBP, mm Hg	70.0	10.5	74.0	10.0	.32	70.0	16.3	70.0	15.0	.63	80.0	20.0	80.0	13.0	.68	87.0	13.5	80.0	13.5	.39
FBG, mg/dL	93.0	11.5	96.0	10.0	.36	92.0	10.5	93.0	9.0	.89	100.0	21.0	102.0	22.0	.43	107.0	39.0	106.0	22.0	.97
PC glucose, mg/dL	99.0	22.3	101.0	30.5	.34	107.0	32.0	110.0	34.0	.98	123.5	72.0	119.0	63.0	.50	145.0	124.8	140.5	76.5	.80
HbA_{1c}, %	5.6	0.6	5.6	0.3	.77	5.6	0.4	5.6	0.5	.63	6.0	0.8	5.9	0.8	.55	5.9	1.0	6.1	0.8	.40
TC, mg/dL	191.0	32.8	194.0	45.0	.78	201.5	46.3	197.0	49.0	.14	214.0	52.0	209.0	49.0	.32	211.5	109.3	218.0	47.0	.63
HDL-C, mg/dL	48.5	14.0	50.0	16.0	.49	60.0	15.8	61.0	18.8	.73	48.0	16.0	44.0	12.0	.38	51.5	13.3	53.0	19.0	.94
LDL-C, mg/dL	129.0	34.8	127.0	41.0	.69	124.0	36.3	120.0	42.0	.10	140.0	54.0	139.0	45.0	.85	118.5	75.3	144.0	52.0	.23
TGs, mg/dL	109.0	67.8	113.0	79.0	.82	96.0	68.0	88.0	53.0	.14	163.0	105.0	146.0	109.0	.47	181.0	108.5	140.0	84.5	.59
FRS, %	5.32	4.54	5.03	3.78	.67	4.0	2.6	3.2	3.2	.08	16.66	18.42	16.27	12.20	.65	18.3	20.5	13.8	6.1	.23
PCF	65.4	24.5	68.3	34.3	.43	54.9	25.4	57.0	28.1	.99	83.01	31.05	83.23	41.92	.77	105.4	74.8	81.3	42.0	.16
TAT	5.3	6.0	6.2	3.2	.37	**3.7**	**2.5**	**3.3**	**1.8**	**.01**	8.67	4.94	9.23	5.17	.98	**9.2**	**8.9**	**6.4**	**4.3**	**.04**
ABSI	0.1	0.0	0.1	0.0	.78	0.1	0.0	0.1	0.0	.74	0.1	0.004	0.1	0.005	.45	0.1	0.0	0.1	0.0	.87
BRI	3.2	1.1	3.2	1.1	.38	3.2	1.4	2.9	1.3	.10	3.82	1.07	3.98	1.27	.37	**4.8**	**1.5**	**4.1**	**1.8**	**.03**
CVAI	82.9	40.6	82.0	50.9	.73	71.8	45.7	59.3	44.1	.02	110.4	45.8	114.3	48.2	.47	**132.9**	**37.4**	**112.3**	**40.5**	**.04**

Clinical characteristics are expressed as median (interquartile range) for continuous variables and n (%) for categorical variables. *P* values were derived from Mann-Whitney for continuous variables, and categorical variables were expressed as percentages and compared with the χ^2 test or Fisher exact test. Bold part mean statistical significant difference.

Abbreviations: ABSI, a body shape index; AR10y, absolute risk of cardiovascular event in 10 years by FRS; BMI, body mass index; BRI, body roundness index; CVAI, Chinese visceral adiposity index; DBP, diastolic blood pressure; EU, euthyroid; FPG, fasting plasma glucose; FT4, free thyroxine; HTN, hypertension; HbA_{1c}, glycated hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FRS, Framingham risk score; Obesity, BMI ≥ 27; PCF, pericardial fat; PPG, postprandial plasma glucose; SBP, systolic blood pressure; SCH, subclinical hypothyroidism; TAT, thoracic periaortic adipose tissue; TC, total cholesterol; TGs, triglycerides; TSH, thyrotropin; WC, waist circumference.

Table 5. Odds ratio of region-specific cardiovascular fat tissue and noninvasive visceral adipose indices with risk of subclinical hypothyroidism according to absolute risk of cardiovascular event in 10 years by Framingham risk score

Variables	PCF[a]			TAT[a]			ABSI			BRI			CVAI		
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Low risk															
Men															
Model 1	0.56	(0.21-1.50)	.25	1.32	(0.56-3.10)	.53	1.31	(0.56-3.07)	.54	0.79	(0.29-2.14)	.65	0.96	(0.26-3.14)	.93
Model 2	0.52	(0.19-1.41)	.20	1.24	(0.52-2.95)	.62	1.24	(0.52-2.94)	.62	0.80	(0.30-2.18)	.67	0.96	(0.38-2.45)	.93
Model 3	0.48	(0.17-1.32)	.15	1.24	(0.51-3.05)	.63	1.18	(0.49-2.82)	.71	0.80	(0.28-2.27)	.67	0.96	(0.35-2.66)	.94
Women															
Model 1	0.84	(0.31–2.23)	.72	3.00	(0.78-11.55)	.11	0.69	(0.29-1.61)	.39	2.03	(1.00-4.13)	.049	0.91	(0.28-2.44)	.88
Model 2	0.64	(0.23–1.78)	.40	2.60	(0.67-10.15)	.17	0.61	(0.26-1.44)	.26	1.82	(0.89-3.73)	.10	0.71	(0.20-2.52)	.60
Model 3	0.64	(0.23–1.77)	.39	2.83	(0.71-11.34)	.14	0.60	(0.25-1.43)	.25	1.86	(0.87-3.96)	.11	0.87	(0.23-3.25)	.83
Men															
Model 1	0.98	(0.54-1.79)	.96	1.02	(0.55-1.90)	.95	1.54	(0.84-2.81)	.16	0.93	(0.51-1.69)	.82	0.81	(0.45-1.48)	.50
Model 2	0.94	(0.51-1.72)	.84	0.94	(0.50-1.78)	.85	1.42	(0.76-2.65)	.28	0.92	(0.50-1.67)	.78	0.81	(0.44-1.47)	.48
Model 3	1.00	(0.53-1.90)	.99	1.04	(0.53-2.05)	.91	1.47	(0.78-2.77)	.23	1.03	(0.54-1.97)	.92	0.90	(0.46-1.77)	.76
Women															
Model 1	2.92	(0.70-12.09)	.14	3.17	(1.02-5.22)	.03	1.19	(0.32-4.43)	.80	6.85	(1.08-10.61)	.02	6.85	(1.03-11.61)	.03
Model 2	2.69	(0.62-11.63)	.19	3.26	(1.07-5.54)	.03	1.16	(0.31-4.40)	.82	6.91	(1.03-10.23)	.03		(1.01-12.57)	.04
Model 3	4.05	(0.73-22.42)	.11	4.01	(1.01-6.64)	.04	1.39	(0.34-5.74)	.65	7.04	(1.02-11.29)	.03	7.81	(1.01-12.03)	.04

Model 1: Unadjusted.
Model 2: Adjusted for age and smoking.
Model 3: Adjusted for factors in model 2 plus SBP, FBG, LDL-C, and HDL-C.
Abbreviations: ABSI, a body shape index; BMI, body mass index; BRI, body roundness index; CVAI, Chinese visceral adiposity index; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; PCF, pericardial fat; SBP, systolic blood pressure; TAT, thoracic periaortic adipose tissue.
[a]Model 2: Adjusted for age, smoking, and BMI.

explaining the correlation between high TAT and SCH incidence [11]. In a previous study, the Framingham study found that even people with normal VAT had higher cardiometabolic risk if they had high TAT [9]. Our research findings also support the results that, in women with SCH, if the Framingham Research Index was intermediate to high, the TAT was higher than that of the control group (TAT: SCH/EU: 9.17 ± 8.91/6.43 ± 4.30, $P = .04$), and the risk of TAT was higher (OR = 4.01; 95% CI, 1.01-6.64). We did not find a relationship between PCF and SCH group in this study.

Continuing epidemiological evidence shows that simple and cheap anthropometric methods can be used to predict Mets, such as BRI [14], ABSI [19], and VAI [35], which have historically been used for clinical diagnosis [17, 19, 35]. BRI is a predictor of body fat and VAT volume and has been postulated to be an indicator of DM and CV health status [17, 36]. Some studies in China and Peru have found that BRI is a strong predictive index for the occurrence of Mets in men and women [37, 38]. Based on these findings, it has been suggested that BRI could be an effective yet simple clinical screening tool for cardiometabolic risks and Mets [17, 36].

VAI is a useful surrogate index for predicting cardiometabolic disorders in White populations [35], and the CVAI has a higher overall DM diagnostic ability than BMI, WC, and ABSI in Chinese adults [15]. Krakauer and Krakauer proposed the ABSI in 2012, and it was found to be a better index for measuring metabolic changes and disease risk in the United States than BMI and WC [19]. Some studies have found there is a positive correlation between ABSI and disease risk and mortality hazard [39, 40]. However, other studies have obtained opposite results [36, 41].

Our study found that elevated TAT, BRI, and CVAI scores correlate stronger with SCH women compared to men with SCH. Interestingly, these sex-related differences even pertain to intermediate/high CV risk (AR_{10y} by FRS). After multivariable logistic regression analysis, we found that higher risk of TAT and BRI in the SCH group; in addition to BRI and TAT, a higher risk of CVAI was noted in the SCH with intermediate/high FRS risk group, especially in women. The rationale underlying these observations is not clear, but it may be related to sex variations in the distribution of visceral fat deposition and regional adipose tissue [42]. The mechanisms that contribute to the

development of SCH from visceral adiposity may be different in men and women. In addition, age and sex are recognized risk factors for thyroid disease, and women in the third TAT, third BRI, and third CVAI tertile were older than men in the SCH group (data not shown), hence SCH risk is influenced by a number of biological factors, including age, sex, and unfavorable health traits. Based on our findings and the available literature, we propose that TAT, BRI, and CVAI serve as markers of SCH risk for women, even in the intermediate/high CV risk group. Visceral fat deposition should be prioritized by women to reduce the occurrence of negative health outcomes.

Key strengths of the study include the fact that, as far as we know, our study is the first to analyze the VAT by using noninvasive, clinically measurable surrogates (BRI, ABSI, and CVAI) or region-specific CV fat tissue quantified using MDCT (PCF and TAT) in identifying body fat distribution in SCH with different CV risk groups. Another advantage was that we analyzed for each sex. A lot of research has discussed fat distribution differences between the sexes. Therefore, our research found that SCH women even in low or intermediate/high CV risk groups had a higher VAT risk than men.

Our study has several limitations. First, the cross-sectional data analyses cannot make causal inferences regarding the relationships between TAT, BRI, and CVAI and SCH risks. Second, after stratification, the number of participants in each group was small, which would affect the effectiveness of statistics. In the future, a larger sample size and cohort study may be needed for causality analysis.

Conclusion

SCH participants who were at an intermediate-to-high risk of developing CAD (AR_{10y}) were significantly more likely to exhibit region-specific CV fat tissue (TAT) and noninvasive visceral adipose indices (CVAI and BRI) than EU individuals, especially in Taiwanese women. These findings suggest that mild thyroid failure also independently contributes to the development of abnormal fatty distribution.

Additional Information

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