Independent and Opposite Associations of Trunk and Leg Fat Depots with Adipokines, Inflammatory Markers, and Metabolic Syndrome in Middle-Aged and Older Chinese Men and Women

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Objective: The objective was to investigate associations of regional fat depots with adipokines, inflammatory markers, and risk of metabolic syndrome (MetS) in a Chinese population.

Design and Methods: Trunk and leg fat mass were determined in a population-based sample of 1150 Chinese (479 men and 671 women) aged 50–70 yr by using whole-body dual-energy x-ray absorptiometry scan. Plasma adiponectin, plasminogen activator inhibitor-1 (PAI-1), retinol-binding protein 4 (RBP4), resistin, C-reactive protein, and IL-6 were measured. The updated National Cholesterol Education Program Adult Treatment Panel III criterion for Asian Americans was used to define MetS.

Results: Larger body-size adjusted trunk fat mass was significantly associated with lower adiponectin and higher PAI-1, RBP4, C-reactive protein, and IL-6 levels in both genders ($P < 0.05$). Larger body-size adjusted leg fat mass was significantly associated with higher adiponectin levels in both genders but lower RBP4 and PAI-1 concentrations in men ($P < 0.05$). Comparing with the lowest body-size adjusted leg fat mass tertile, the odds ratio (95% confidence interval) of MetS in the highest tertile was 0.33 (0.18–0.62; P for trend <0.001) for men and 0.43 (0.28–0.65; P for trend <0.001) for women. The association was attenuated with further controlling adipokines and inflammatory markers ($P = 0.09$ for men and $P = 0.004$ for women).

Conclusion: In contrast to trunk fat, large leg fat appears to have favorable effects on adipokines, inflammatory markers, and MetS risk among Chinese. The opposite associations between regional fat depots and MetS risk may partially mediated by adipokines and inflammatory status. **(*J Clin Endocrinol Metab* 95: 4389–4398, 2010)**

Obesity is an established risk factor for multiple metabolic abnormalities, including hyperglycemia, hypertension, dyslipidemia, type 2 diabetes, and cardiovascular disease (CVD). However, regional distribution of excess adipose tissue, particularly abdominal fat store, has been well documented to be associated even more strongly with cardiometabolic disease than the overall obesity per se (1). Some, but not all, previous studies have reported

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Abbreviations: BALF, Body-size adjusted leg fat mass; BATF, body-size adjusted trunk fat mass; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DXA, dual-energy x-ray absorptiometry; HbA_{1c}, hemoglobin A_{1c}; HDL, high density lipoprotein; LDL, low-density lipoprotein; LTR, leg fat/trunk fat ratio; MetS, metabolic syndrome; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; RBP4, retinol-binding protein 4.

favorable associations of leg or other peripheral fat depots with glucose metabolism (2–7), lipid profiles (2–4, 6–8), blood pressure (2–4, 7, 8), and other CVD risk factors (9, 10). Compared with other ethnicities, Asian people were known more likely to have abdominal obesity and also tend to suffer metabolic diseases under "normal weight" (11). Nonetheless, evidence is scarce regarding the effect of leg fat on the outcomes of metabolic diseases in Asians, especially in Chinese populations.

Adipose tissue, as an endocrine organ, not only secretes a number of adipokines, such as adiponectin, retinol-binding protein (RBP4), resistin, and plasminogen activator inhibitor 1 (PAI-1), but also promotes expression of inflammatory markers, such as IL-6, TNF-α, and C-reactive protein (CRP). All of these biomarkers are proposed to mediate the adverse effects of obesity on the pathogenesis of type 2 diabetes and CVD (12). However, most studies so far have focused on overall adiposity or abdominal obesity. Only a few studies have evaluated the association of the leg fat or peripheral fat with adiponectin (13–15) or PAI-1 (10) levels. Previously, we have reported significant associations of CRP, IL-6, adiponectin, RBP4, and resistin with risk of metabolic syndrome (MetS) and/or type 2 diabetes in middle-aged and older Chinese (16–20). Nevertheless, little is known about how and to what extent the association between regional body fat distribution and MetS risk could attribute to the multiple adipokines and inflammatory markers.

To elucidate these issues, the present study is aimed to investigate the associations of fat accumulation in trunk and leg measured by dual-energy x-ray absorptiometry (DXA) with MetS and various cytokines, including adiponectin, RBP4, resistin, PAI-1, CRP, and IL-6, in middle-aged and older Chinese men and women.

Materials and Methods

The study population was a subset of participants in the Nutrition and Health of Aging Population in China Project, a population based cross-sectional survey among 3289 residents aged 50–70 yr from Beijing and Shanghai in 2005 (16). Briefly, information on demographic characteristics, disease status, lifestyle practice, and physical activity (International Physical Activity Questionnaire short form last 7-d format) was collected using a standard questionnaire. Physical activity levels (low, moderate, and high) were evaluated according to the protocol for International Physical Activity Questionnaire short form (http://www.ipaq.ki.se). Body weight, height, waist circumference, hip circumference, and blood pressure were measured, and overnight fasting blood samples were collected in the local health station or the community clinic after the home interview (16). Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. A total of 1150 Shanghai participants (479 men and 671 women) with DXA and also cytokines measured were included in the current analyses. Study protocol was approved by the Institutional Review Board of the Shanghai Institute for Nutritional Sciences, and all participants provided written informed consents.

Assessment of body adiposity

Whole-body DXA scan was performed using Hologic QDR 4500W scanner (Hologic, Bedford, MA). Total body mass and fat mass of whole-body, trunk (including thorax, abdomen, and pelvis), and leg (sum of left leg and right leg) regions were analyzed with software provided by the manufacturer.

Laboratory measurement

Measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density cholesterol (LDL) cholesterol, triglycerides, glucose, hemoglobin A_{1c} (HbA_{1c}), adiponectin, RBP4, resistin, PAI-1, CRP, and IL-6 were described previously (16–20).

Definition of MetS

The MetS was defined by using the updated National Cholesterol Education Program Adult Treatment Panel III for Asian Americans as the presence of three or more of components: 1) waist circumference of at least 90 cm for men or at least 80 cm for women; 2) triglycerides of at least 1.7 mmol/liter; 3) HDL cholesterol lower than 1.03 mmol/liter for men or lower than 1.30 mmol/liter for women; 4) blood pressure of at least 130/85 mm Hg or current use of antihypertentive medications; and 5) fasting glucose of at least 5.6 mmol/liter, previously diagnosed type 2 diabetes, or on oral antidiabetic agents or insulin.

Statistical analysis

Analyses were performed in men and women separately as a result of gender differences of fat distribution. Residuals from regression of trunk or leg fat on total body mass were obtained and then rescaled by adding the expected trunk or leg fat for a person with mean total body mass (21). These body-size adjusted trunk fat mass (BATF) and leg fat mass (BALF) were used in subsequent analyses. Spearman's correlation analyses were performed to examine the association of BATF and BALF with metabolic features, adipokines, and inflammatory markers after adjustment for BATF or BALF (mutually adjusted for each other). Potential confounders included age, residence, educational attainment, alcohol drinking, smoking, physical activity, self reported CVD, and family history of diabetes and CVD. Multiple testing corrections were performed by the Benjamini and Hochberg procedure to determine the statistical significance of individual test. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for MetS and its components according to the tertiles of BATF and BALF, respectively. The confounders aforementioned were adjusted in the logistic regression models. In a secondary analyses, plasma adipokines and inflammatory markers were further adjusted to examine to what extent these biomarkers may explain the association of regional fat depot with MetS. To calculate the ORs for MetS according to the tertiles of BATF, a modified definition of MetS (two or more MetS components without central obesity) was used (16) because of the high correlation of trunk fat with waist circumference. Data were analyzed using Stata (version 9.2; StataCorp, College Station, TX). $P < 0.05$ (two sided) was considered statistically significant.

Results

Characteristics of participants

The characteristics of the study participants are shown in Table 1. As expected, women had significantly higher mean levels of BMI, hip circumference (both $P < 0.05$), more total body, trunk and leg fat mass, BATF, and BALF (all $P < 0.001$), whereas men had significantly higher mean levels of total body mass and larger waist circumference (both $P < 0.05$) and they were more likely to be alcohol drinkers and smokers. Women also had significantly higher levels of fasting plasma glucose, total cholesterol, LDL and HDL cholesterol, adiponectin, and lower RBP4 levels (all $P < 0.001$). The prevalence of MetS was 38.8% for women and 26.1% for men.

Regional fat depots, adipokines, inflammatory markers, and metabolic features

Table 2 displays the results of the associations of trunk and leg fat depots with metabolic parameters. After adjustment for BALF and potential confounders, BATF were significantly associated with most of metabolic risk factors (all $P < 0.05$) except fasting glucose in women and resistin in both genders. Conversely, increased BALF was significantly associated with lower levels of fasting glucose, HbA_{1c}, triglycerides, and diastolic blood pressure and higher levels of HDL cholesterol and adiponectin in both genders (all $P < 0.05$) and lower RBP4 and PAI-1 levels in men (both $P < 0.05$). All these correlations retained their significance even after multiple testing corrections by the

TABLE 1. Characteristics of study participants

	Men (n = 479)	Women (n = 671)	P
Total body mass (kg)	64.3 ± 10.1	56.7 ± 9.6	<0.001
Total body fat mass (kg)	13.5 ± 5.1	18.8 ± 5.6	<0.001
Trunk fat mass (kg)	7.57 ± 3.32	10.01 ± 3.45	<0.001
BATF (kg)	7.57 ± 1.76	10.01 ± 1.61	<0.001
Leg fat mass (kg)	3.64 ± 1.35	5.56 ± 1.73	<0.001
BALF (kg)	3.64 ± 0.75	5.56 ± 1.07	<0.001
BMI (kg/m^2)	23.5 ± 3.2	23.9 ± 3.5	0.046
Waist circumference (cm)	83.34 ± 10.39	80.00 ± 9.87	<0.001
Hip circumference (cm)	90.98 ± 5.79	91.90 ± 6.58	0.03
Age (yr)	59.0 ± 5.9	58.5 ± 6.1	0.21
Urban residents	210 (43.8)	310 (46.2)	0.43
Current smokers	342 (71.4)	9 (1.3)	<0.001
Alcohol use	193 (40.3)	30 (4.5)	<0.001
Education			<0.001
0–6 yr	221 (46.1)	374 (55.8)	
7–9 yr	139 (29.0)	176 (26.2)	
≥10 yr	119 (24.9)	121 (18.0)	
Physical activity			0.07
Low	30 (6.3)	42 (6.3)	
Moderate	198 (41.3)	322 (48.0)	
High	251 (52.4)	307 (45.8)	
Self-reported CVD[a]	27 (5.6)	34 (5.1)	0.68
Family history of diabetes[b]	48 (10.0)	83 (12.4)	0.35
Family history of CVD[b]	75 (15.7)	126 (18.8)	0.25
MetS	125 (26.1)	260 (38.8)	<0.001
Fasting glucose (mmol/liter)	5.68 ± 1.64	5.38 ± 1.08	<0.001
HbA_{1c} (%)	5.92 ± 1.03	5.88 ± 0.82	0.51
Triglycerides (mmol/liter)	0.94 (0.67–1.54)	1.09 (0.78–1.55)	0.38
Total cholesterol (mmol/liter)	4.20 ± 0.85	4.60 ± 0.84	<0.001
LDL cholesterol (mmol/liter)	2.79 ± 0.81	3.16 ± 0.85	<0.001
HDL cholesterol (mmol/liter)	1.20 ± 0.32	1.31 ± 0.32	<0.001
Systolic blood pressure (mm Hg)	135.07 ± 19.93	136.11 ± 22.62	0.22
Diastolic blood pressure (mm Hg)	80.85 ± 10.60	77.69 ± 10.42	<0.001
Adiponectin (μg/ml)	10.58 (6.21–17.36)	16.67 (10.18–24.94)	<0.001
RBP4 (μg/ml)	38.92 ± 10.84	36.64 ± 10.74	<0.001
Resistin (ng/ml)	8.26 (5.37–13.35)	8.55 (5.98–13.90)	0.29
PAI-1 (ng/ml)	4.35 (0.94–12.51)	5.39 (1.79–14.84)	0.30
CRP (mg/liter)	0.53 (0.28–1.18)	0.53 (0.28–1.19)	0.27
IL-6 (pg/liter)	0.94 (0.62–1.49)	0.95 (0.60–1.45)	0.94

Data are mean ± SD or median (interquartile range) for continuous variables depending on the distribution of these variables and number (%) for categorical variables; P values were adjusted for age and urban/rural residence (when appropriate).

[a] Self-reported CVD, including stroke and coronary heart disease.

[b] First-degree relatives (parents or siblings) had a history of diabetes or CVD.

TABLE 2. Spearman's partial correlation coefficients of BALF and BATF with metabolic features and cytokines

	Men		Women	
	BATF	BALF	BATF	BALF
Waist circumference (cm)	0.34*	−0.11**	0.31*	−0.08
Hip circumference (cm)	0.10**	−0.04	0.09**	0.17*
Fasting glucose (mmol/liter)	0.12*	−0.18*	0.05	−0.19*
HbA_{1c} (%)	0.11**	−0.17*	0.15*	−0.15*
Triglycerides (mmol/liter)	0.37*	−0.19*	0.26*	−0.14*
Total cholesterol (mmol/liter)	0.20*	−0.00	0.11**	0.02
LDL cholesterol (mmol/liter)	0.22*	0.00	0.14*	0.01
HDL cholesterol (mmol/liter)	−0.22*	0.11**	−0.18*	0.16*
Systolic blood pressure (mm Hg)	0.16*	−0.07	0.08	−0.12**
Diastolic blood pressure (mm Hg)	0.19*	−0.12**	0.10**	−0.12**
Adiponectin (μg/ml)	−0.19*	0.19*	−0.15*	0.20*
RBP4 (μg/ml)	0.17*	−0.13**	0.12**	−0.05
Resistin (μg/ml)	0.05	0.04	0.05	0.01
PAI-1 (ng/ml)	0.31*	−0.17*	0.20*	−0.06
CRP (mg/liter)	0.28*	−0.08	0.27*	0.00
IL-6 (mg/liter)	0.16*	−0.05	0.12**	0.01

Adjusted for BATF or BALF (each other), additionally for age, residence, alcohol drinking, smoking, educational attainment, physical activity, self-reported CVD, and family history of diabetes and CVD. *, $P < 0.001$; **, $P < 0.05$.

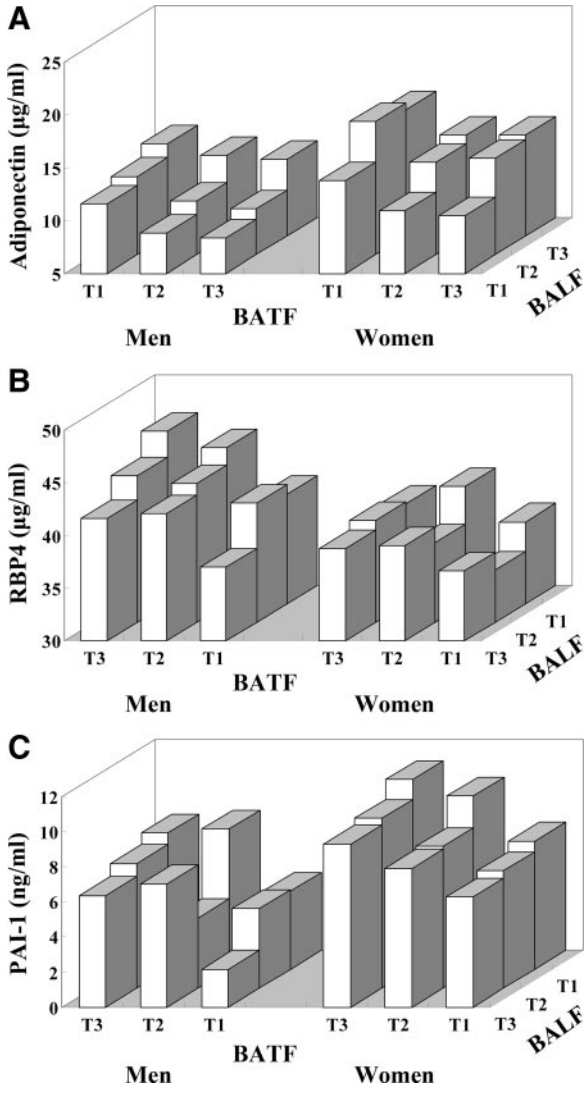

FIG. 1. Adjusted means of plasma adiponectin (A), RBP4 (B), and PAI-1 (C) according to the tertiles of BALF and BATF. Data are geometric means for adiponectin and PAI-1 and means for RBP4 after adjustment for age, residence, alcohol drinking, smoking, educational attainment, physical activity, self-reported CVD, and family history of diabetes and CVD.

Benjamini and Hochberg procedure. The correlation coefficients for percentage of trunk fat and leg fat were similar to those of absolute fat mass (data not shown). In addition, the leg fat/trunk fat ratio (LTR) was observed to be strongly correlated with a favorable profile of the MetS traits, adipokines, and inflammatory markers (all $P < 0.05$), except total cholesterol in women and resistin in both genders. After isolating nine groups of participants with different fat distribution types according to the tertiles of BATF and BALF (Fig. 1), increasing BALF tertiles were associated with higher adiponectin and lower PAI-1 and RBP4 levels at a given tertile of BATF.

MetS and regional fat depots

As indicated in Table 3, the MetS risk monotonically increased from lowest to highest tertiles of BATF (P for trend <0.001 in both genders) after adjustment for age, residence, educational attainment, alcohol drinking, smoking, physical activity, self-reported CVD, family history of diabetes and CVD (model 1), and BALF (model 2). Larger trunk fat was also significantly associated with elevated triglycerides and reduced HDL cholesterol in both genders (all P for trend <0.05) and elevated fasting glucose (P for trend $=0.03$) and blood pressure (P for trend <0.001) in men. The significant associations were dramatically attenuated or even abolished after additional adjustment for inflammatory markers (CRP and IL-6) and adipokines (adiponectin, RBP4, resistin, and PAI-1) in model 3.

In contrast, corresponding to increased BALF from the lowest to the highest tertiles (Table 4), the MetS risk was significantly reduced with the ORs (95% confidence interval) 0.33 (0.18–0.62) for men and 0.43 (0.28–0.65) for women, respectively, in the highest tertile of BALF (P for trend <0.001, model 2). For the components of MetS, increased BALF tertiles were also associated with lower risks for elevated fasting glucose, triglycerides, and blood pressure and reduced HDL cholesterol (all P for trend <0.05, model 2). Similar to the results for BATF, after

TABLE 3. Adjusted ORs and 95% confidence intervals for MetS and its components according to BATF tertiles

	Men				Women			
	T1 (n = 159)	T2 (n = 160)	T3 (n = 160)	P for trend	T1 (n = 223)	T2 (n = 224)	T3 (n = 224)	P for trend
MetS								
Model 1[a]	1.0	1.93 (1.06–3.52)	4.00 (2.22–7.20)	<0.001	1.0	2.02 (1.32–3.08)	2.90 (1.87–4.49)	<0.001
Model 2[b]	1.0	2.62 (1.38–4.94)	6.38 (3.28–12.4)	<0.001	1.0	1.98 (1.29–3.05)	3.82 (1.81–4.40)	<0.001
Model 3[c]	1.0	1.63 (0.82–3.22)	3.40 (1.66–7.00)	0.002	1.0	1.34 (0.82–2.19)	1.72 (1.04–2.87)	0.04
Elevated fasting glucose								
Model 1[a]	1.0	0.76 (0.46–1.25)	1.19 (0.72–1.97)	0.48	1.0	0.86 (0.53–1.40)	1.06 (0.65–1.71)	0.78
Model 2[b]	1.0	0.98 (0.57–1.67)	1.84 (1.05–3.22)	0.03	1.0	0.82 (0.50–1.34)	1.00 (0.62–1.63)	0.95
Model 3[c]	1.0	0.88 (0.50–1.53)	1.58 (0.86–2.90)	0.12	1.0	0.75 (0.44–1.25)	0.76 (0.45–1.29)	0.33
Elevated triglycerides								
Model 1[a]	1.0	1.76 (0.90–3.45)	2.97 (1.54–5.73)	<0.001	1.0	2.12 (1.25–3.62)	2.40 (1.38–4.17)	0.002
Model 2[b]	1.0	2.14 (1.06–4.33)	4.00 (1.95–8.20)	<0.001	1.0	2.08 (1.21–3.56)	2.36 (1.35–4.10)	0.003
Model 3[c]	1.0	1.34 (0.64–2.94)	2.14 (0.95–4.73)	0.05	1.0	1.42 (0.78–2.59)	1.55 (0.83–2.90)	0.19
Reduced HDL cholesterol								
Model 1[a]	1.0	1.38 (0.81–2.35)	2.36 (1.39–3.99)	0.001	1.0	1.98 (1.34–2.91)	1.69 (1.13–2.52)	0.01
Model 2[b]	1.0	1.66 (0.95–2.89)	3.08 (1.72–5.51)	<0.001	1.0	1.93 (1.31–2.87)	1.63 (1.09–2.45)	0.02
Model 3[c]	1.0	1.34 (0.74–2.41)	2.13 (1.13–4.00)	0.02	1.0	1.47 (0.96–2.25)	1.15 (0.74–1.80)	0.54
Elevated blood pressure								
Model 1[a]	1.0	1.65 (1.04–2.62)	2.44 (1.48–4.01)	<0.001	1.0	1.20 (0.81–1.80)	1.42 (0.92–2.19)	0.11
Model 2[b]	1.0	1.93 (1.18–3.16)	3.11 (1.80–5.36)	<0.001	1.0	1.18 (0.79–1.77)	1.38 (0.89–2.13)	0.15
Model 3[c]	1.0	1.73 (1.03–2.89)	2.71 (1.50–4.89)	0.001	1.0	1.00 (0.65–1.53)	1.08 (0.68–1.71)	0.77

MetS, Modified defined as the presence of two or more MetS components without central obesity; Elevated fasting glucose, fasting glucose of at least 5.6 mmol/liter or previously diagnosed type 2 diabetes or on oral antidiabetic agents or insulin; Elevated triglycerides, triglycerides of at least 1.7 mmol/liter; Reduced HDL cholesterol, HDL cholesterol less than 1.03 mmol/liter for men or less than 1.30 mmol/liter for women; Elevated blood pressure, blood pressure of at least 130/85 mm Hg or current use of antihypertentive medications.

[a] Model 1 adjusted for age, residence, education attainment, alcohol drinking, smoking, physical activity, self-reported CVD, and family history of diabetes and CVD.

[b] Model 2 further adjusted for BALF.

[c] Model 3 further adjusted for adipokines (adiponectin, RBP4, resistin, and PAI-1) and inflammatory markers (CRP and IL-6).

TABLE 4. Adjusted ORs and 95% confidence intervals for MetS and its components according to BALF tertiles

	Men				Women			
	T1 (n = 159)	T2 (n = 160)	T3 (n = 160)	P for trend	T1 (n = 223)	T2 (n = 224)	T3 (n = 224)	P for trend
MetS								
Model 1[a]	1.0	0.84 (0.50–1.43)	0.66 (0.38–1.12)	0.12	1.0	0.44 (0.29–0.65)	0.42 (0.28–0.63)	<0.001
Model 2[b]	1.0	0.51 (0.29–0.90)	0.33 (0.18–0.62)	<0.001	1.0	0.44 (0.29–0.67)	0.43 (0.28–0.65)	<0.001
Model 3[c]	1.0	0.68 (0.37–1.28)	0.55 (0.28–1.09)	0.09	1.0	0.54 (0.34–0.86)	0.50 (0.31–0.81)	0.004
Elevated fasting glucose								
Model 1[a]	1.0	0.75 (0.46–1.20)	0.37 (0.22–0.63)	<0.001	1.0	0.53 (0.34–0.84)	0.41 (0.25–0.66)	<0.001
Model 2[b]	1.0	0.66 (0.40–1.09)	0.30 (0.17–0.54)	<0.001	1.0	0.53 (0.34–0.84)	0.41 (0.25–0.66)	<0.001
Model 3[c]	1.0	0.71 (0.42–1.19)	0.35 (0.19–0.62)	0.001	1.0	0.56 (0.35–0.91)	0.41 (0.25–0.68)	<0.001
Elevated triglycerides								
Model 1[a]	1.0	0.88 (0.49–1.59)	0.78 (0.43–1.42)	0.41	1.0	0.49 (0.30–0.80)	0.52 (0.32–0.84)	0.006
Model 2[b]	1.0	0.62 (0.33–1.17)	0.48 (0.25–0.93)	0.03	1.0	0.50 (0.31–0.82)	0.53 (0.33–0.86)	0.008
Model 3[c]	1.0	0.74 (0.37–1.48)	0.74 (0.35–1.56)	0.43	1.0	0.58 (0.33–1.02)	0.67 (0.39–1.14)	0.12
Reduced HDL cholesterol								
Model 1[a]	1.0	0.87 (0.53–1.43)	0.77 (0.46–1.27)	0.30	1.0	0.50 (0.34–0.74)	0.54 (0.36–0.80)	0.002
Model 2[b]	1.0	0.65 (0.38–1.10)	0.52 (0.29–0.90)	0.02	1.0	0.52 (0.35–0.76)	0.55 (0.37–0.82)	0.003
Model 3[c]	1.0	0.75 (0.43–1.30)	0.64 (0.35–1.15)	0.14	1.0	0.59 (0.39–0.90)	0.63 (0.41–0.98)	0.04
Elevated blood pressure								
Model 1[a]	1.0	1.04 (0.65–1.67)	0.80 (0.50–1.29)	0.37	1.0	0.66 (0.43–1.01)	0.52 (0.34–0.80)	0.002
Model 2[b]	1.0	0.77 (0.46–1.27)	0.52 (0.31–0.89)	0.02	1.0	0.67 (0.44–1.02)	0.53 (0.34–0.80)	0.003
Model 3[c]	1.0	0.88 (0.52–1.49)	0.60 (0.35–1.04)	0.07	1.0	0.80 (0.51–1.26)	0.62 (0.40–0.96)	0.03

Elevated fasting glucose, Fasting glucose of at least 5.6 mmol/liter or previously diagnosed type 2 diabetes or on oral antidiabetic agents or insulin; Elevated triglycerides, triglycerides of at least 1.7 mmol/liter; Reduced HDL cholesterol, HDL cholesterol less than 1.03 mmol/liter for men or less than 1.30 mmol/liter for women; Elevated blood pressure, blood pressure of at least 130/85 mm Hg or current use of antihypertentive medications.

[a] Model 1 adjusted for age, residence, education attainment, alcohol drinking, smoking, physical activity, self-reported CVD, and family history of diabetes and CVD.

[b] Model 2 further adjusted for BATF.

[c] Model 3 further adjusted for adipokines (adiponectin, RBP4, resistin, and PAI-1) and inflammatory markers (CRP and IL-6).

additional adjustment for inflammatory markers and adipokines (model 3), the association between BALF and MetS was attenuated (*P* for trend =0.09 for men and *P* for trend =0.004 for women). Moreover, the significant associations of BALF with elevated triglycerides and blood pressure and reduced HDL cholesterol were either dramatically attenuated or disappeared in model 3, except for elevated fasting glucose. Meanwhile, we also found that the MetS risk was significantly declined across the tertile of LTR. Compared with the lowest LTR tertile, ORs (95% confidence interval) were 0.20 (0.11–0.35) for men and 0.20 (0.13–0.31) for women in the highest tertile.

As shown in Figure 2, the risk for MetS increased remarkably among participants with less leg fat and more trunk fat depots for men and women. Interestingly, even among participants in the lowest tertile of BATF, the ORs for MetS were much higher in the lowest BALF tertile (OR = 1.89 in men and OR = 1.68 in women) compared with those in the highest tertile BALF.

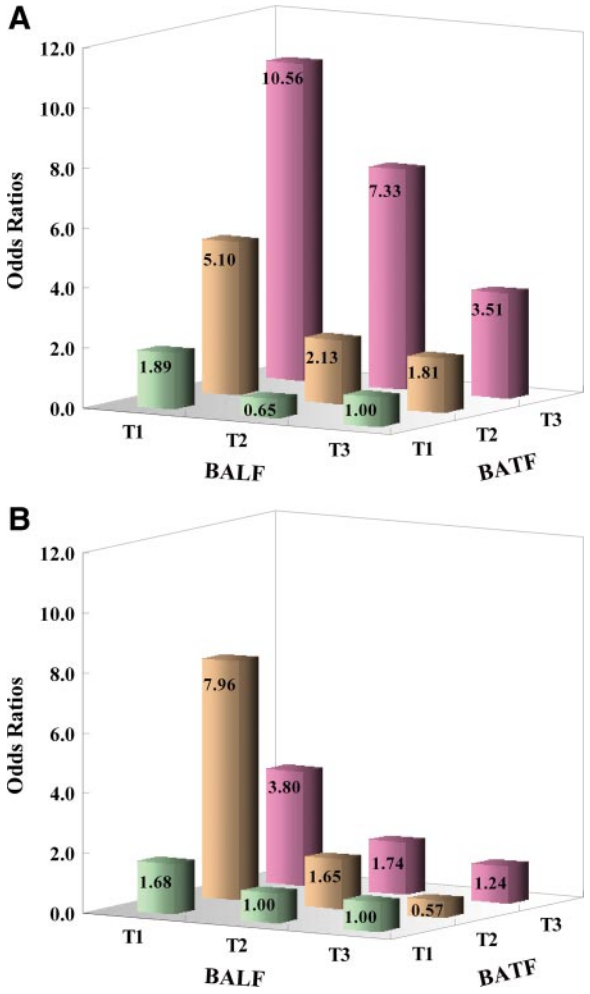

FIG. 2. Adjusted ORs for MetS according to the tertiles of BALF and BATF in men (A) and women (B). Adjusted for age, residence, alcohol drinking, smoking, educational attainment, physical activity, self-reported CVD, and family history of diabetes and CVD (*P* = 0.76 and 0.35 for interaction in men and women, respectively).

Discussion

To our knowledge, this is the first study that simultaneously investigated trunk and leg fat depots in relation to adipokines, inflammatory markers, and MetS. In contrast to the adverse effects of excess truck fat, the leg fat accumulation was associated with a favorable profile of adipokines and inflammatory markers, as well as lower MetS risk. Our data also suggested that opposite associations of trunk and leg fat with metabolic outcomes may be partially mediated by adipokines and inflammatory markers.

In the current study, consistent with the findings from the studies in other ethnicities, we have confirmed the adverse effect of trunk fat on most of the cardiometabolic risks in the Chinese population. More importantly, we also revealed a favorable impact of leg fat on MetS, an important risk factor of diabetes and CVD, although it was observed previously that leg fat depots reduced individual risks of diabetes and CVD, such as fasting glucose (5, 6), triglycerides levels (2–4, 6, 8), HDL cholesterol levels (2, 3, 6, 8), and blood pressure (2–4, 7, 8) among whites and Japanese. Notably, the opposite associations of trunk fat and leg fat observed were independent of each other in our study, and larger leg fat appeared to counteract the adverse effects of trunk fat on MetS even in the highest levels of trunk fat. These results suggested that leg adiposity accumulation might have a protective effect against metabolic disease risk rather than simply being less harmful. The finding of the protective role of leg fat in our study, therefore, is particularly crucial for Asians who are known to have a greater amount of abdominal adipose tissue than Europeans at a given BMI. Compelling studies have documented that excess abdominal fat was a well established risk factor for pathogenesis of type 2 diabetes and CVD (22). Thus, our results support the notion that leg fat accumulation bears protective effects on metabolic risk factors in Chinese and possibly in Asians who suffer high prevalence of the "metabolically obese" phenotype (11).

Paralleling the significant opposite associations of trunk and leg fat with MetS risk, we also observed that leg fat was associated with a favorable profile of adipokines (higher adiponectin and lower PAI-1 and RBP4 levels), whereas trunk fat was associated with the unfavorable status of adipokines (lower adiponectin and higher RBP4 and PAI-1 levels) and inflammatory markers (higher CRP and IL-6 levels), which have been found to be the risk factors of MetS in this population previously (17–19). Despite the fact that studies from other ethnic populations have documented adverse impact of abdominal fat or trunk fat depot on circulating adiponectin (13, 15, 23) and PAI-1 (10, 24), RBP4 (25, 26), CRP (23), and IL-6 (24), only two studies thus far showed a positive association

between leg fat and adiponectin (14, 15), whereas only one report suggested an inverse relationship between leg fat and PAI-1 (10). Given a systematical investigation in the current study, we have first evidenced opposite influences of regional fat distributions on multiple adipokines and inflammatory marker in a single population. Furthermore, we also discovered a novel inverse association of leg fat with RBP4 levels, particularly in men. Moreover, compared with trunk fat, it seems that leg fat was more closely associated with adipokines than inflammatory factors. Indeed, we only detected a tendency that leg fat was associated with lower CRP and IL-6 levels in men, whereas trunk fat was significantly associated with these inflammatory factors in both sexes, which are in consistent with the results from a recent study that reported an opposite association of trunk fat and lower-body fat with CRP levels from a large cohort in the European population (27). The mechanisms for these apparently opposite effects of trunk and leg fat on these cytokines still remain to be clarified. Previous studies have showed that visceral and sc adipose tissues have different gene expression characteristics, especially in those of adipokine-related genes (28–30). Compared with sc fat, visceral adipose tissue has lower adiponectin gene expression and secretion rate (29, 30) but higher PAI-1 expression and production (28) and contains more macrophages (31), which actively secrete IL-6 and TNF-α, consequently stimulating secretion of CRP.

Another interesting finding of the present study is that the opposite associations of trunk and leg fat depots with MetS were attenuated after adjustment for various adipokines and inflammatory markers. Although the roles of obesity and certain cytokines in the pathogenesis of MetS, type 2 diabetes, and CVD have been extensively investigated (32, 33), few studies have systematically evaluated adipokines and inflammatory factors, as determinates, in the associations between regional fat depots and metabolic diseases, except one study that reported that adiponectin partially explained the association of lower body fat mass with an advantageous blood lipid profile (14). Notably, our data further showed that the association between regional fat depots and MetS was explained more by adipokines than by inflammatory markers, and this was more apparent in the leg fat when the adipokines and inflammatory markers were separately controlled in logistic regression models (data not shown). This observation is in line with the association patterns of trunk fat and leg fat with adipokines and inflammatory markers as mentioned above. The less attenuation may also be attributable to the lower number of inflammatory markers used in the current analyses compared with adipokines. Certainly, additional studies with prospective designs are needed to elucidate this aspect.

It should be noted from our data that adipokines and inflammatory markers could only partially explain the relationship between region fat depots and metabolic risks, implicating that other depot-specific properties of adipose tissue may also account for these opposite effects. For instance, besides the genes for adipocytokines, genes encoding metabolic enzymes and related signaling proteins, and the adipogenic factors were reported to be expressed differently in abdominal and sc adipocytes (34). In addition, compared with abdominal sc and visceral adipose tissues, femoral/gluteal sc adipose tissues were reported to have lower rates of basal and catecholamine-stimulated lipolysis (35, 36). Existing studies suggested that sc adipose tissue plays an important role of buffering fluxes of free fatty acid in the circulation. Lower-body obese women, despite having greater upper-body fat mass, were found to have lower free fatty acid release than their non-obese counterparts (37). These specific characteristics may help prevent ectopic fat accumulation in liver, muscle, and pancreatic β-cells and lead to a decreased metabolic disease risk. Nevertheless, more studies are needed to clarify the underlying precise molecular mechanisms.

The current study is subject to a few limitations. Because of the cross-sectional nature, we could not establish the causal association of leg fat depot with these cytokines and metabolic risk, highlighting the necessity of longitudinal studies. Another limitation is that DXA could not separate visceral and sc fat in the trunk, as well as sc and intramuscular fat in the legs. However, it still remains controversial whether abdominal sc and/or visceral fats have adverse effects on metabolic risk. Vega *et al.* (38) reported that trunk, abdominal sc, and visceral fat showed similar associations with most metabolic risk factors. Moreover, the associations between leg fat and MetS and its components observed in the current study are most likely attributable to the sc fat, which account for most of the fat located in the legs, whereas im fat only attributed for 2–6% (39).

In summary, we have found that larger leg fat, in contrast to trunk fat, was associated with a favorable profile of adipokines and inflammatory markers and a reduced risk of MetS in Chinese. Although prospective studies are required, the findings from the present study provide novel insights regarding the potential mechanisms of obesity-related cytokines in mediating the opposite effects of regional fat depots on metabolic diseases.

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