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Abdominal Subcutaneous Fat: A Favorable or Nonfunctional Fat Depot for Glucose Metabolism in Chinese Adults?

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Abstract

Objective: The objective of this study was to assess the associations of abdominal visceral and subcutaneous adipose tissue with blood glucose and beta-cell function.

Methods: In this study, 11,223 participants without known diabetes were selected for this cross-sectional analysis. Visceral and subcutaneous fat area (VFA and SFA) were measured by magnetic resonance imaging. An oral glucose tolerance test was conducted, and beta-cell function was evaluated.

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*Xuhong Hou and Peizhu Chen contributed equally to this work.

Author contributions: WJ, XH, and YB conceptualized the study concept and design. WJ, XH, PC, YL, LW, LJ, and HW assisted in the acquisition, analysis, or interpretation of data. XH and PC performed statistical analysis. WJ, XH, PC, and GH drafted the manuscript. WJ and YB contributed to the administrative, technical, or material support. All the authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version.

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Additional Supporting Information may be found in the online version of this article.

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Results: Men had significantly larger VFA but smaller SFA than women. After controlling for age, linear regression showed that SFA was adversely associated with 0-minute, 30-minute, and 2-hour plasma glucose (PG) and early-, first- and second-phase disposition indices (DIs). After further adjustment for BMI and VFA, some associations of SFA with PG indices and DIs disappeared, while the other associations became significantly weaker in men (2-hour PG: 0.05 and DI_{2nd}: −0.05) or were reversed in women (0-minute, 30-minute, and 2-hour PG: from −0.07 to −0.04; DI_{1st}: 0.04, $P < 0.05$). After adjustment for age, BMI, and SFA, VFA was significantly and adversely associated with PG indices and DIs, with the largest standardized regression coefficients with 2-hour PG.

Conclusions: The associations of SFA with blood glucose and beta-cell function were clinically insignificant in Chinese adults. VFA had the strongest association with 2-hour PG.

Introduction

It has already been established that visceral adipose tissue is adversely associated with hyperglycemia (1–3), impaired glucose regulation (1,2,4), and decreased insulin function (5), whereas the association of abdominal subcutaneous adipose tissue with blood glucose and beta-cell function in human populations is still a controversial topic (1–3,5) in the context of subcutaneous adipose tissue as a natural storage depot of energy (6). Precision estimates of visceral adipose tissue and subcutaneous adipose tissue are dependent on dual-energy x-ray absorptiometry, magnetic resonance imaging (MRI), and computerized tomography (CT), which are difficult to perform in a large population-based study. Gender differences in the associations of visceral adipose tissue and subcutaneous adipose tissue with the blood glucose metabolism have also been reported (1,2). Thus, several previous relevant studies assessing the associations between abdominal adiposity distribution and glucose metabolism had some common limitations, like a very small sample size or a special population, which made them relatively ineffective in controlling confounding and sufficiently comparing gender differences (7–9). We have shown that visceral fat area (VFA) was strongly associated with newly diagnosed diabetes in both genders, whereas subcutaneous fat area (SFA) was negatively associated with newly diagnosed diabetes in women but not in men (P Chen, X Hou, and W Jia, unpublished data). In the present study, we further discussed whether there was any underlying association between adipose distributions and glucose metabolism that supported the above phenomenon.

Type 2 diabetes mellitus is characterized by impaired insulin secretion and beta-cell failure in the setting of insulin resistance (IR). Disposition indices (DIs), comprehensive indices of insulin secretion that are appropriately adjusted for insulin sensitivity, have been proven to be strong predictors of the development of diabetes (10–12). The aim of the present study was to assess the gender-specific associations of VFA and SFA measured by MRI with blood glucose and DIs derived from a three-time-point oral glucose tolerance test (OGTT) in a large population-based study of Chinese adults. To date, relevant studies are still scarce.

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Methods

Study population

A population-based prospective study has been designed to investigate the prevalence, incidence, and related factors of cardiometabolic diseases. A baseline survey for this study was completed between April 2013 and August 2014. A total of 21,408 adults 45 to 70 years old living in the Nicheng suburb of Shanghai, China, were invited to participate in the baseline survey, and 17,212 subjects completed the survey, yielding an 80.4% response rate. The present analyses included 11,223 subjects after excluding those without complete analysis data (n = 4,027), those with previously diagnosed diabetes (n = 1,048), and those with negative values of insulin secretion and IR according to their assay values (n = 914) (see Supporting Information Figure S1). The study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and written informed consent was obtained from each participant before the start of the study.

Baseline measurements

At the local community clinics, participants without any prior diagnosis of diabetes mellitus underwent a 75-g OGTT after an overnight fast of at least 10 hours. Venous blood samples were drawn at 0, 30, and 120 minutes following an OGTT. Fasting plasma glucose (FPG), 30-minute plasma glucose (PG), and 2-hour PG were assayed by a glucose oxidase method, and fasting, 30-minute, and 2-hour serum insulin concentrations were assayed by the electrochemiluminescence immunoassay method.

Information on demographics, history of diseases, medical history, leisure-time physical activity, smoking habits, and alcohol consumption was collected using a standard questionnaire. The participants were grouped into nonsmokers, ex-smokers, and current smokers according to smoking status and into nondrinkers, ex-drinkers, and current drinkers according to alcohol consumption. Leisure-time physical activity was categorized as 0min/d, 1 to 29 min/d, and ≥ 30 min/d. Education level was classified as primary school or less, middle school, and high school or more. Family history of diabetes was defined as having at least a first-degree relative (biological father, mother, siblings, and offspring) with diabetes.

Body weight and height were measured according to standard protocols (13). Height and weight were measured without shoes and with light clothing. BMI was calculated by dividing the weight by height squared. Waist circumference was measured at the horizontal plane between the inferior costal margin and the iliac crest on the midaxillary line (13).

Measurement of abdominal adipose tissue

Abdominal adiposity was detected using an MRI machine with an abdominal coil and a 3.0-T General Electric scanner (GE Healthcare, Milwaukee, Wisconsin). Participants were positioned supine and were scanned in cross-sectional planes. T1 axial images were centered at the navel and obtained with a slice thickness of 10.0 mm for eight slices. Fat area in a single umbilical slice image was separated into VFA and SFA and was manually measured by two trained observers using SliceOmatic image analysis software (version 5; Tomovision Inc., Montreal, Quebec, Canada). If results differed by more than 10%, a third observer who

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did not know the results reanalyzed the images. The average of two measures was then used in the analysis.

Assessment of beta-cell function based on OGTT test

Early-phase insulin secretion was evaluated using the insulinogenic index (14), the ratio of incremental insulin to incremental glucose responses during the first 30 minutes of the OGTT ($Ins_{30} - Ins_0$ / $Gluc_{30} - Gluc_0$). First and second phases of insulin secretion were estimated using the Stumvoll formula as follows: first-phase secretion (pmol/L) =1,283 +1.829 × Ins_{30} (mU/L) × 6.965 −138.7 ×$Gluc_{30}$ (mmol/L) +3.772×Ins_0 (mU/L)×6.965, and second-phase secretion (pmol/L) =393 +1.163 ×Ins_0 (mU/L) ×6.965 −40.72 ×$Gluc_{120}$ (mmol/L) +0.313 ×Ins_{120} (mU/L) ×6.965 (15,16). IR was evaluated using the homeostatic model assessment of IR (HOMA-IR): HOMA-IR=$Gluc_0$ × Ins_0 /22.5 (17). $Gluc_0$, Ins_0, $Gluc_{30}$, Ins_{30}, $Gluc_{120}$, and Ins_{120} refer to glucose and insulin levels at 0, 30, and 120 minutes, respectively. The early-phase DI (DI_{early}), first-phase DI (DI_{1st}), and second-phase DI (DI_{2nd}) were calculated, respectively, as insulin secretion indices of each phase (early-, first- and second-phase secretion), adjusted for HOMA-IR, to estimate relative insulin secretion.

Definitions of glucose regulation status

Glucose regulation statuses were categorized according to the World Health Organization criteria. Newly diagnosed diabetes was defined as FPG ≥7.0 mmol/L (126 mg/dL) or 2-hour PG ≥11.1 mmol/L (200 mg/dL); impaired glucose regulation was defined as FPG ≥6.1 mmol/L (110 mg/dL) and <7.0 mmol/L or 2-hour PG ≥7.8 mmol/L (140 mg/dL) and <11.1 mmol/L; and normal glucose was defined as FPG <6.1 mmol/L and 2-hour PG <7.8 mmol/L during an OGTT and without any diagnosis of diabetes prior to the time of this survey (18).

Statistical analysis

Descriptive statistics were reported as means (95% CIs), medians (interquartile ranges), geometric means (95% CIs), or frequencies (percentages). The differences in means, medians, or proportions between two groups were tested with the independent-sample *t* test, the Mann–Whitney *U* test, and the χ^2 test, as appropriate.

The adjusted means (95% CIs) were estimated using the general linear model, in which the covariates included age, BMI, and SFA or VFA, as appropriate. A linear trend test for adjusted means among multiple groups was tested by linear regression. The multiple linear regression analysis was used to assess the associations between the dependent variable and two or more independent variables. Here, the dependent variable was each one of blood glucose indices (FPG, 30-minute PG, and 2-hour PG) or log-transformed DIs ($lgDI_{early}$, $lgDI_{1st}$, and $lgDI_{2nd}$), and independent variables included two variables of age and VFA or SFA (in Model 1) or four variables of age, BMI, VFA, and SFA simultaneously (in Model 2). All statistical analyses were performed with SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, New York). P <0.05 (two-tailed) was considered to be statistically significant.

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Results

The characteristics of the study population are presented in Table 1. Out of the 11,223 middle-aged and elderly participants, 4,835 were men and 6,388 were women. Men and women had similar mean values of age. Men had very slightly higher mean values of FPG and 30-minute PG but had lower mean values of 2-hour PG than women. Men also had comparable median levels of DI_{early} and DI_{1st} but had a higher median DI_{2nd} level. There were significant gender differences in adipose distribution. Men had significantly larger mean values of VFA (122.0 cm^2 vs. 107.7 cm^2, $P<0.001$), BMI (24.9 kg/m^2 vs. 24.8 kg/m^2, $P=0.032$), and waist circumference (86.3 cm vs. 82.1 cm, $P<0.001$) but had a smaller mean value of SFA (127.1 cm^2 vs. 167.8 cm^2, $P<0.001$) than women. There was a difference in proportions of glucose regulation status between men and women. In addition, men were much more likely to be current smokers or drinkers compared with women.

Table 2 and Table 3 present the age-adjusted and multivariable-adjusted mean values (95% CIs) of blood glucose and log-transformed DIs across quartiles of VFA or SFA (also shown in Figures 1 and 2). The age-adjusted mean levels of FPG, 30-minute PG, and 2-hour PG all significantly linearly increased, whereas age-adjusted mean values of log-transformed DI_{early}, DI_{1st}, and DI_{2nd} significantly linearly decreased across quartiles of either VFA or SFA in both men and women (all $P<0.001$ for linear trend). After adjustment for age, BMI, and SFA, the increasing linear trends of FPG, 30-minute PG, and 2-hour PG and the decreasing linear trends of log-transformed DI_{early}, DI_{1st}, and DI_{2nd} across VFA remained significant, with a slightly flatter slope among both men and women (all $P<0.001$ for linear trend). However, after adjustment for age, BMI, and VFA, the increasing linear trends of FPG, 30-minute PG, and 2-hour PG with SFA and the decreasing linear trends of log-transformed DI_{early}, DI_{1st}, and DI_{2nd} with SFA disappeared or even changed directions in men and women.

Adjusted standardized linear regression coefficients of blood glucose and DIs with VFA and SFA are shown in Table 4. After controlling for age, either VFA or SFA was significantly and positively associated with all three blood glucose indices (the coefficients ranged from 0.16 to 0.31 for VFA and from 0.05 to 0.20 for SFA, all $P<0.001$) but inversely associated with the DIs (the coefficients ranged from −0.30 to −0.13 for VFA and −0.26 to −0.06 for SFA, all $P<0.001$) among men and women. After further adjustment for BMI and SFA, the positive associations of VFA with blood glucose indices and inverse associations of VFA with DIs in both genders still remained significant but attenuated in association strength (the regression coefficients ranged from 0.10 to 0.25 and from −0.21 to −0.11, respectively, all $P<0.001$). After further adjustment for BMI and VFA, the positive association of SFA with blood glucose indices and the inverse association of SFA with DIs in men mostly disappeared or were still statistically significant but not clinically significant, with the absolute values of regression coefficients less than 0.1; in women, the associations mostly reversed and became favorable, but not to clinical significance (the absolute values of regression coefficients being less than 0.1). Further adjustment for smoking, drinking, physical activity, and family history of diabetes made little difference in the above results (data not shown).

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Discussion

The main findings of the present study in Chinese men and women included the following aspects. (1) After adjustment for age, BMI, and VFA, some adverse associations of SFA with blood glucose indices and DIs disappeared, whereas in the rest, the associations became significantly weaker in men (2-hour PG: 0.05 and DI_{2nd}: −0.05) or were even reversed in women (PG: from −0.07 to −0.04; DI_{1st}: 0.04) (all P <0.05). (2) After adjustment for age, BMI, and SFA, VFA was positively associated with indicators of blood glucose at three time points and inversely associated with DIs of three phases; of note, VFA had the strongest positive association with 2-hour PG (0.25 in men and 0.24 in women) and the strongest inverse association with DI_{2nd} (−0.19 in men and −0.21 in women), far beyond BMI.

Some studies have suggested that there are some limitations in reporting beta-cell function in isolation (19) and that insulin secretion should be adjusted by insulin sensitivity (20). Under normal physiological conditions, circulating insulin concentrations are reciprocally related to insulin sensitivity, expressed as the body's capacity for glucose disposal and ability to suppress hepatic glucose production in response to insulin (12,21). DIs (11,12,20,21), which are derived from an OGTT and incorporate a measurement of insulin sensitivity into assessments of beta-cell responses, have been widely used. Both basic and population studies have proven that defects in early- or first-phase insulin secretion lead to hyperglycemia (22) and type 2 diabetes (10,11,23–25). In addition, DI_{early} has been reported as the strongest metabolic predictor of subsequent diabetes (10,11). Thus, in the present study, DIs were used to reflect insulin function instead.

The positive associations of visceral adipose tissue with FPG and 2-hour PG have been consistently found in multiple ethnicities, such as white Americans (1), African Americans (2), Greenland Inuit (26), and Caucasians in Denmark (27) (visceral adipose tissue was measured by CT in the former two populations and by ultrasound in the latter two populations). To our knowledge, no population-based studies have examined the associations of visceral adipose tissue with DIs evaluated by a three-time-point OGTT. The inverse association of visceral adipose tissue (measured by MRI or CT) with insulin-mediated glucose disposal rate (measured during euglycemic, hyperinsulinemic, and glucose clamp) has been uniformly reported in some small sample studies reviewed by Garg (28). The present study first reported a positive association of VFA with 0-minute, 30-minute, and 2-hour blood glucose and an inverse association of VFA with the early-, first-, and second-phase DIs in Chinese men and women, independent of SFA and BMI. Moreover, VFA showed a stronger positive association with 2-hour PG than with FPG and 30-minute PG and had a stronger inverse association with DI_{2nd} than with DI_{early} and DI_{1st}, far beyond BMI, which is supported by the viewpoint that obesity is more intimately associated with post-prandial blood glucose.

The above studies conducted in multiple ethnicities (1,2,26,27) have also examined the association of subcutaneous adipose tissue with FPG and 2-hour PG, but the results are inconsistent, mainly due to different confounding factors being controlled for in each study. The study in African Americans (2) has elucidated a positive association of subcutaneous adipose tissue with FPG without adjustment for BMI and waist circumference, and the

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other three studies (1,26,27) indicated that the positive association of subcutaneous adipose tissue with glucose intolerance and IR tended toward the inverse or even disappeared after adjustment for BMI and/or waist circumference. Meanwhile, one review (28) including several studies with small study sample sizes indicated that there were inconsistent conclusions regarding the association of subcutaneous adipose tissue with glucose disposal rate and that no significant association of subcutaneous adipose tissue with glucose disposal rate was found in men and women with obesity (7–9).

The present study found that after controlling for age, SFA was positively associated with three blood glucose indices (the standardized coefficients ranged from 0.05 to 0.20, all P <0.001) and inversely associated with DIs (the standardized coefficients ranged from −0.26 to −0.06, all P<0.001) among men and women. After further adjustment for BMI and VFA, most of the positive associations of SFA with blood glucose indices and the inverse associations of SFA with DIs disappeared, the strength of the other associations became significantly weaker in men (2-hour PG: 0.05 and DI_{2nd}: −0.05), or the associations were even reversed in women (PG: from −0.07 to −0.04; DI_{1st}: 0.04) (all P<0.05). The reason for this gender-specific difference in associations of SFA with blood glucose and beta-cell function is unclear, but the significant gender differences in abdominal adipose distribution, in which men had significantly higher VFA (122.0 cm^2 vs. 107.7 cm^2, P< 0.001) but significantly lower SFA (127.1 cm^2 vs. 167.8 cm^2, P<0.001), may be one explanation. In addition, estrogen receptors expressed in adipose tissue with variation in density may be another reason (6). The clinically insignificant but favorable association between SFA and glucose metabolism may to some extent explain the inverse association between SFA and newly diagnosed diabetes in women (P Chen, X Hou, and W Jia, unpublished data). The present study provided strong evidence that VFA and BMI severely confounded the associations of SFA with blood glucose and DIs, according to the changes in regression coefficients before and after additional adjustment for BMI and VFA (29). The associations of SFA with blood glucose and DIs were not independent of VFA and BMI. The study conducted by Ross et al. also showed that the correlations between subcutaneous adipose tissue and glucose disposal were close to zero (0.06 in men and 0.02 in women) (7,8), which is in agreement with our findings regarding associations between SFA and DIs.

There are many differences between visceral adipose tissue and subcutaneous adipose tissue, including anatomical (subcutaneous vs. abdominal cavity), cellular (different number of larger adipocytes), molecular (receptor and adipokines), physiological, and metabolic differences (6). Subcutaneous adipose tissue is a natural depot for energy, whereas visceral adipose tissue is considered to be a more pathogenic adipose tissue compartment (6). Compared with those in subcutaneous adipose tissue, adipocytes in visceral adipose tissue are more metabolically active, more sensitive to lipolysis, and are more insulin resistant. Subcutaneous adipose tissue secretes or expresses more favorable adipokines than visceral adipose tissue, and excess visceral adipose tissue is correlated with higher levels of free fatty acid overflow, inflammatory biomarkers, adipocytokines, and proteins (6). These differences may partly explain the different associations of VFA and SFA with glucose metabolism.

Our present study has some advantages. First, to our knowledge, this was the first population-based study with large samples, which let us explore gender-specific weak

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associations after controlling for confounders. Second, VFA and SFA were accurately measured by MRI, with a higher resolution, and can thus more clearly show fat depots than when measured by CT. Third, blood glucose and insulin were measured at three time points (0 minutes, 30 minutes, and 2 hours) after an OGTT test, which allowed us to have a more comprehensive estimation of beta-cell function in different phases. The limitations were the cross-sectional study format and the single-slice estimates of VFA and SFA by MRI.

Conclusion

The associations of SFA with blood glucose and beta-cell function were clinically insignificant (slightly favorable in women but not in men); VFA was adversely associated with blood glucose and beta-cell function and was most strongly associated with 2-hour PG. Our population-based findings support the hypothesis that SFA is a natural fat depot, but VFA is a pathogenic fat depot and mainly affects 2-hour PG; these findings are very important in guiding the population toward a healthy weight.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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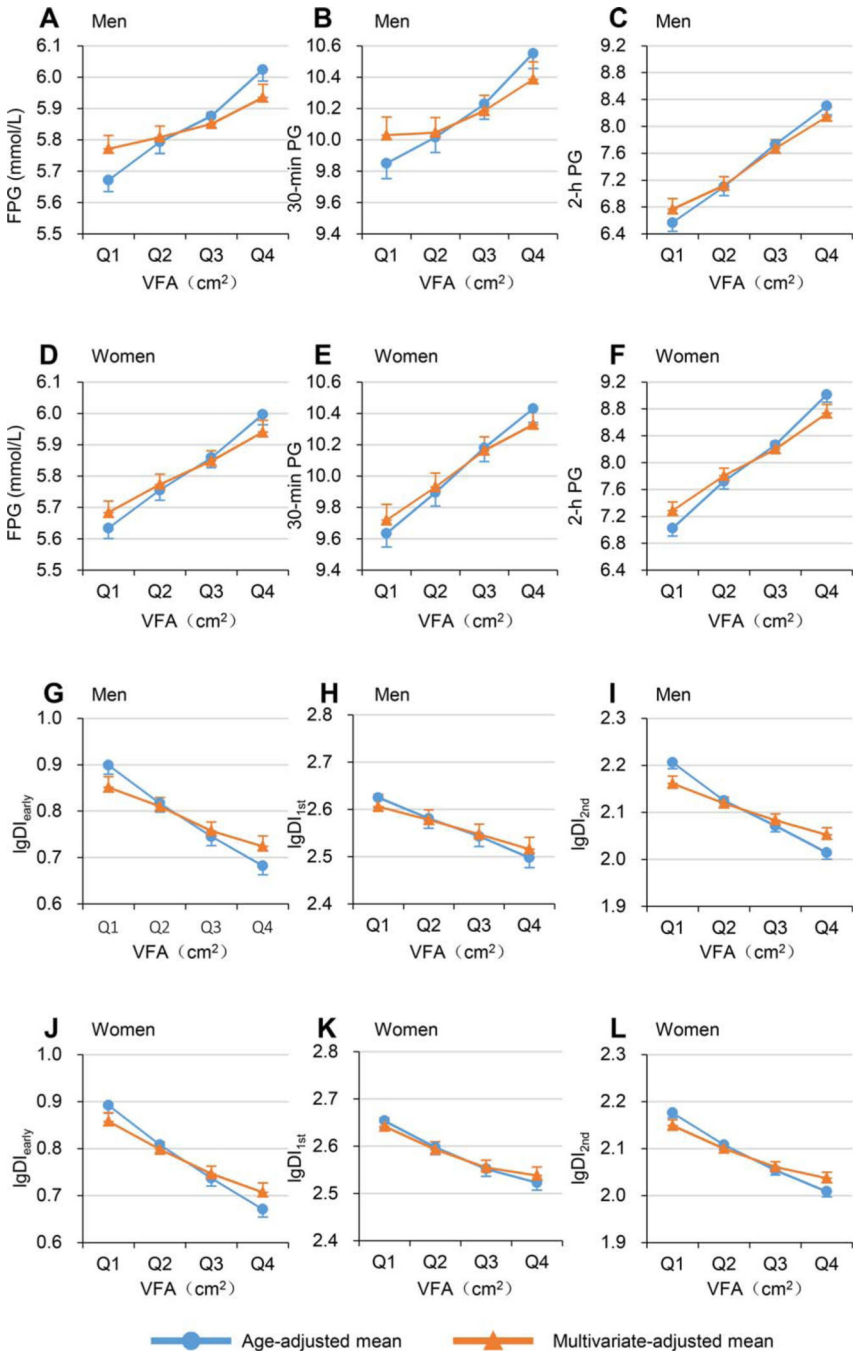

Figure 1.

Age-adjusted and multivariable-adjusted means (95% CIs) of blood glucose and log-transformed disposition indices across increasing VFA quartiles. Dots or triangles represent means, and bars represent 95% CI of the upper or lower bound. Line with dots indicates age-adjusted means. Line with triangles indicates multivariable-adjusted means (adjusted for age, SFA, and BMI). Mean values of FPG, 30-minute PG, and 2-hour PG, in (**A-C**) men and (**D-F**) women. Mean values of $lgDI_{early}$, $lgDI_{1st}$, and $lgDI_{2nd}$ in (**G-I**) men and (**J-L**) women. DI_{early}, early-phase disposition index; DI_{1st}, first-phase disposition index;

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DI_{2nd}, second-phase disposition index; FPG, fasting plasma glucose; lg, log-transformed; PG, plasma glucose; SFA, subcutaneous fat area; VFA, visceral fat area. [Color figure can be viewed at wileyonlinelibrary.com]

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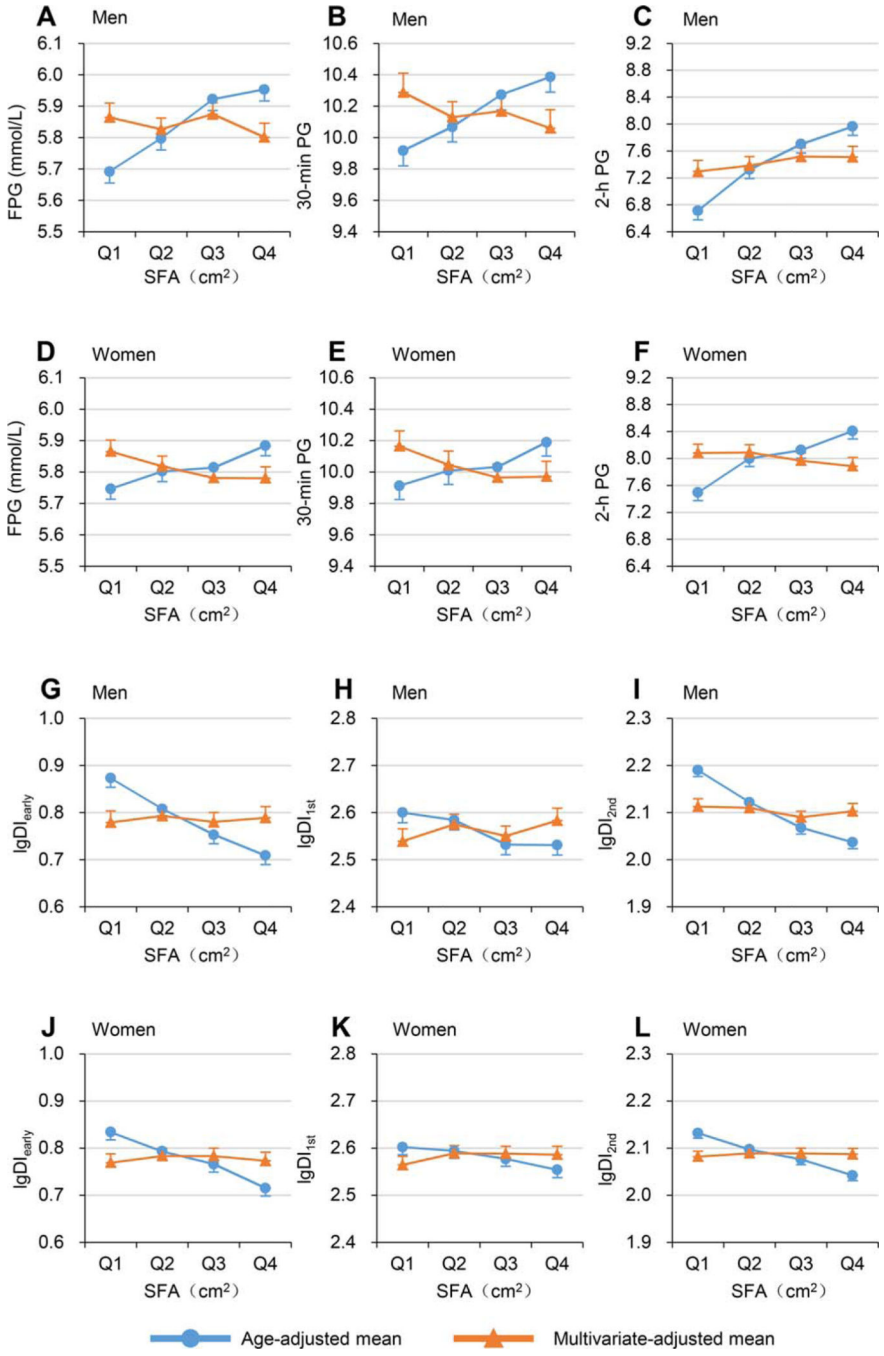

Figure 2.

Age-adjusted and multivariable-adjusted means (95% CIs) of blood glucose and log-transformed disposition indices across increasing SFA quartiles. Dots or triangles represent means, and bars represent 95% CI of the upper or lower bound. Line with dots indicates age-adjusted means. Line with triangles indicates multivariable-adjusted means (adjusted for age, VFA, and BMI). Mean values of FPG, 30-minute PG, and 2-hour PG in (**A-C**) men and (**D-F**) women. Mean values of $lgDI_{early}$, $lgDI_{1st}$, and $lgDI_{2nd}$ in (**G-I**) men and (**J-L**) women. DI_{early}, early-phase disposition index; DI_{1st}, first-phase disposition index;

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DI_{2nd}, second-phase disposition index; FPG, fasting plasma glucose; lg, log-transformed; PG, plasma glucose; SFA, subcutaneous fat area; VFA, visceral fat area. [Color figure can be viewed at wileyonlinelibrary.com]

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TABLE 1

Characteristics of study participants by gender

	Men	Women	P^a
No. of participants	4,835	6,388	
Age (y)	56.6 ± 6.5	56.6 ± 6.6	0.76
Glucose and insulin indices			
Fasting plasma glucose (mmol/L)	5.84 ± 0.66	5.81 ± 0.68	0.019
30-min plasma glucose (mmol/L)	10.2 ± 1.73	10.0 ± 1.82	< 0.001
2-h plasma glucose (mmol/L)	7.43 ± 2.42	8.01 ± 2.46	< 0.001
Fasting serum insulin (uU/mL)	6.36 (4.38–9.13)	7.52 (5.47–10.5)	< 0.001
30-min serum insulin (uU/mL)	47.4 (32.3–71.4)	54.3 (37.9–77.5)	< 0.001
2-h serum insulin (uU/mL)	35.4 (20.2–59.8)	49.9 (32.2–78.1)	< 0.001
HOMA-IR	1.63 (1.10–2.41)	1.92 (1.36–2.74)	< 0.001
Insulinogenic index	9.65 (6.08–16.0)	11.4 (7.33–17.8)	< 0.001
First-phase secretion	693 (408–1,046)	822 (541–1,174)	< 0.001
Second-phase secretion	208 (149–290)	239 (178–319)	< 0.001
Early-phase disposition index	6.18 (3.79–10.1)	6.03 (3.64–9.56)	0.21
First-phase disposition index	420 (251–634)	429 (272–612)	0.20
Second-phase disposition index	130 (91.5–183)	126 (89.1–171)	0.018
Variables from MRI			
Visceral fat area (cm^2)	122.0 ± 53.1	107.7 ± 41.2	< 0.001
Subcutaneous fat area (cm^2)	127.1 ± 46.3	167.8 ± 57.2	< 0.001
Anthropometric variables			
BMI (kg/m^2)	24.9 ± 3.0	24.8 ± 3.2	0.032
Waist circumference (cm)	86.3 ± 9.0	82.1 ± 9.0	< 0.001
Glucose regulation status			< 0.001
Normal glucose regulation, *n* (%)	2,491 (51.5)	3,046 (47.7)	
Impaired glucose regulation, *n* (%)	1,873 (38.7)	2,581 (40.4)	
Newly diagnosed diabetes, *n* (%)	471 (9.7)	761 (11.9)	
Demographic variables			

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	Men	Women	*P* [a]
Education levels, *n* (%)			< 0.001
Primary school or less	1,921 (40.3)	3,405 (53.9)	
Middle school	2,343 (49.1)	2,420 (38.3)	
High school or more	508 (10.6)	491 (7.8)	
Smoking status, *n* (%)			< 0.001
Nonsmokers	2,055 (42.5)	6,372 (99.7)	
Ex-smokers	290 (6.0)	7 (0.1)	
Current smokers	2,490 (51.5)	9 (0.1)	
Alcohol consumption, *n* (%)			< 0.001
Nondrinkers	3,142 (65)	6,352 (99.4)	
Ex-drinkers	124 (2.6)	3 (0.05)	
Current drinkers	1,569 (32.5)	33 (0.5)	
Leisure-time physical activity, *n* (%)			0.12
0 min/d	4,577 (94.7)	5,999 (93.9)	
1–29 min/d	117 (2.4)	158 (2.5)	
≥ 30 min/d	141 (2.9)	231 (3.6)	
Family history of diabetes, *n* (%)	603 (12.5)	869 (13.6)	0.08

Data are presented as means ± SD, medians (interquartile range), or frequencies (percentage). To convert values for insulin to pmol/L, multiply by 6.965.

[a] *P* values from *t* test for difference in means, Mann–Whitney *U* test for difference in medians, or χ^2 test for difference in proportions between two groups. HOMA-IR, homeostatic model assessment of insulin resistance; MRI, magnetic resonance imaging.

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TABLE 2

Adjusted means (95% CIs) of blood glucose and log-transformed disposition indices across increasing VFA quartiles

	VFA (cm^2)				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for linear trend**
Men					
Age-adjusted means					
Fasting plasma glucose (mmol/L)	5.67 (5.64–5.71)	5.79 (5.76–5.83)	5.88 (5.84–5.91)	6.02 (5.99–6.06)	< 0.001
30-min plasma glucose (mmol/L)	9.85 (9.75–9.95)	10.0 (9.92–10.1)	10.2 (10.1–10.3)	10.6 (10.5–10.6)	< 0.001
2-h plasma glucose (mmol/L)	6.57 (6.44–6.70)	7.10 (6.97–7.23)	7.73 (7.60–7.86)	8.30 (8.17–8.43)	< 0.001
$lgDI_{early}$	0.90 (0.88–0.92)	0.82 (0.80–0.84)	0.75 (0.73–0.76)	0.68 (0.66–0.70)	< 0.001
$lgDI_{1st}$	2.63 (2.60–2.65)	2.58 (2.56–2.60)	2.54 (2.52–2.56)	2.50 (2.48–2.52)	< 0.001
$lgDI_{2nd}$	2.21 (2.19–2.22)	2.13 (2.11–2.14)	2.07 (2.06–2.08)	2.01 (2.00–2.03)	< 0.001
Multivariable-adjusted means[a]					
Fasting plasma glucose (mmol/L)	5.77 (5.73–5.81)	5.81 (5.77–5.84)	5.85 (5.81–5.89)	5.94 (5.89–5.98)	< 0.001
30-min plasma glucose (mmol/L)	10.0 (9.91–10.1)	10.1 (9.95–10.1)	10.2 (10.1–10.3)	10.4 (10.3–10.5)	< 0.001
2-h plasma glucose (mmol/L)	6.77 (6.61–6.92)	7.12 (6.99–7.25)	7.67 (7.54–7.80)	8.15 (7.99–8.30)	< 0.001
$lgDI_{early}$	0.85 (0.83–0.87)	0.81 (0.79–0.83)	0.76 (0.74–0.78)	0.72 (0.70–0.75)	< 0.001
$lgDI_{1st}$	2.61 (2.58–2.63)	2.58 (2.56–2.60)	2.55 (2.53–2.57)	2.52 (2.49–2.54)	< 0.001
$lgDI_{2nd}$	2.16 (2.15–2.18)	2.12 (2.11–2.13)	2.08 (2.07–2.10)	2.05 (2.04–2.07)	< 0.001
Women					
Age-adjusted means					
Fasting plasma glucose (mmol/L)	5.63 (5.60–5.67)	5.76 (5.72–5.79)	5.86 (5.83–5.89)	6.00 (5.96–6.03)	< 0.001
30-min plasma glucose (mmol/L)	9.64 (9.55–9.72)	9.90 (9.81–9.98)	10.2 (10.1–10.3)	10.4 (10.3–10.5)	< 0.001
2-h plasma glucose (mmol/L)	7.02 (6.91–7.14)	7.72 (7.61–7.83)	8.26 (8.15–8.38)	9.01 (8.90–9.13)	< 0.001
$lgDI_{early}$	0.89 (0.88–0.91)	0.81 (0.79–0.82)	0.74 (0.72–0.75)	0.67 (0.65–0.69)	< 0.001
$lgDI_{1st}$	2.65 (2.64–2.67)	2.60 (2.58–2.61)	2.55 (2.54–2.57)	2.52 (2.51–2.54)	< 0.001
$lgDI_{2nd}$	2.18 (2.17–2.19)	2.11 (2.10–2.12)	2.05 (2.04–2.07)	2.01 (2.00–2.02)	< 0.001
Multivariable-adjusted means[a]					
Fasting plasma glucose (mmol/L)	5.68 (5.65–5.72)	5.77 (5.74–5.81)	5.85 (5.82–5.88)	5.94 (5.90–5.98)	< 0.001

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	VFA (cm^2)				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for linear trend**
30-min plasma glucose (mmol/L)	9.72 (9.62–9.82)	9.93 (9.84–10.0)	10.2 (10.1–10.3)	10.3 (10.2–10.4)	< 0.001
2-h plasma glucose (mmol/L)	7.28 (7.15–7.41)	7.80 (7.69–7.92)	8.20 (8.09–8.32)	8.74 (8.60–8.87)	< 0.001
lgDI$_{early}$	0.86 (0.84–0.88)	0.80 (0.78–0.81)	0.75 (0.73–0.76)	0.71 (0.69–0.73)	< 0.001
lgDI$_{1st}$	2.64 (2.62–2.66)	2.59 (2.58–2.61)	2.56 (2.54–2.57)	2.54 (2.52–2.56)	< 0.001
lgDI$_{2nd}$	2.15 (2.14–2.16)	2.10 (2.09–2.11)	2.06 (2.05–2.07)	2.04 (2.02–2.05)	< 0.001

Cut points of VFA (cm^2) are 83.5, 117.8, and 155.5 in men and 78.4, 103.3, and 131.8 in women. Linear trend test tested by linear regression.

[a]Adjusted for age, BMI, and subcutaneous fat area.

DI_{early}, early-phase disposition index; DI_{1st}, first-phase disposition index; DI_{2nd}, second-phase disposition index; lg, log-transformed; VFA, visceral fat area.

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TABLE 3

Adjusted means (95%CIs) of blood glucose and log-transformed disposition indices across increasing SFA quartiles

	Abdominal SFA				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for linear trend**
Men					
Age-adjusted means					
Fasting plasma glucose (mmol/L)	5.69 (5.66–5.73)	5.80 (5.76–5.83)	5.92 (5.89–5.96)	5.95 (5.92–5.99)	< 0.001
30-min plasma glucose (mmol/L)	9.92 (9.82–10.0)	10.1 (9.97–10.2)	10.3 (10.2–10.4)	10.4 (10.3–10.5)	< 0.001
2-h plasma glucose (mmol/L)	6.71 (6.58–6.85)	7.32 (7.19–7.45)	7.70 (7.57–7.84)	7.96 (7.83–8.10)	< 0.001
lgDI$_{early}$	0.87 (0.85–0.89)	0.81 (0.79–0.83)	0.75 (0.73–0.77)	0.71 (0.69–0.73)	< 0.001
lgDI$_{1st}$	2.60 (2.58–2.62)	2.58 (2.56–2.61)	2.53 (2.51–2.55)	2.53 (2.51–2.55)	< 0.001
lgDI$_{2nd}$	2.19 (2.18–2.20)	2.12 (2.11–2.14)	2.07 (2.05–2.08)	2.04 (2.02–2.05)	< 0.001
Multivariable-adjusted means[a]					
Fasting plasma glucose (mmol/L)	5.86 (5.82–5.91)	5.83 (5.79–5.86)	5.87 (5.84–5.91)	5.80 (5.76–5.85)	0.040
30-min PG (mmol/L)	10.3 (10.2–10.4)	10.1 (10.0–10.2)	10.2 (10.1–10.3)	10.1 (9.94–10.2)	0.10
2-h plasma glucose (mmol/L)	7.30 (7.13–7.46)	7.38 (7.25–7.52)	7.52 (7.38–7.65)	7.51 (7.35–7.67)	0.24
lgDI$_{early}$	0.78 (0.76–0.80)	0.79 (0.77–0.81)	0.78 (0.76–0.80)	0.79 (0.77–0.81)	0.74
lgDI$_{1st}$	2.54 (2.51–2.57)	2.58 (2.55–2.60)	2.55 (2.53–2.57)	2.58 (2.56–2.61)	0.043
lgDI$_{2nd}$	2.11 (2.10–2.13)	2.11 (2.10–2.12)	2.09 (2.08–2.10)	2.10 (2.09–2.12)	0.12
Women					
Age-adjusted means					
Fasting plasma glucose (mmol/L)	5.75 (5.71–5.78)	5.80 (5.77–5.83)	5.81 (5.78–5.85)	5.88 (5.85–5.92)	< 0.001
30-min plasma glucose (mmol/L)	9.91 (9.82–10.0)	10.0 (9.92–10.1)	10.0 (9.94–10.1)	10.2 (10.1–10.3)	< 0.001
2-h plasma glucose (mmol/L)	7.49 (7.38–7.61)	8.00 (7.88–8.12)	8.12 (8.01–8.24)	8.41 (8.29–8.53)	< 0.001
lgDI$_{early}$	0.83 (0.82–0.85)	0.79 (0.78–0.81)	0.77 (0.75–0.78)	0.72 (0.70–0.73)	< 0.001
lgDI$_{1st}$	2.60 (2.59–2.62)	2.59 (2.58–2.61)	2.58 (2.56–2.59)	2.55 (2.54–2.57)	< 0.001
lgDI$_{2nd}$	2.13 (2.12–2.14)	2.10 (2.09–2.11)	2.08 (2.07–2.09)	2.04 (2.03–2.05)	< 0.001
Multivariable-adjusted means[a]					
Fasting plasma glucose (mmol/L)	5.87 (5.83–5.90)	5.82 (5.79–5.85)	5.78 (5.75–5.81)	5.78 (5.74–5.82)	0.006

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	Abdominal SFA				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for linear trend**
30-min plasma glucose (mmol/L)	10.2 (10.1–10.3)	10.1 (9.96–10.1)	9.96 (9.88–10.1)	9.97 (9.87–10.1)	0.027
2-h plasma glucose (mmol/L)	8.08 (7.96–8.21)	8.09 (7.97–8.20)	7.97 (7.85–8.08)	7.89 (7.76–8.01)	0.12
lgDI$_{early}$	0.77 (0.75–0.79)	0.78 (0.77–0.80)	0.78 (0.77–0.80)	0.77 (0.75–0.79)	0.52
lgDI$_{1st}$	2.56 (2.55–2.58)	2.59 (2.57–2.61)	2.59 (2.57–2.60)	2.59 (2.57–2.60)	0.17
lgDI$_{2nd}$	2.08 (2.07–2.09)	2.09 (2.08–2.10)	2.09 (2.08–2.10)	2.09 (2.07–2.10)	0.78

Cut points of SFA (cm^2) are 94.9, 124.0, and 155.6 in men and 127.5, 162.0, and 201.6 in women. Linear trend test tested by linear regression.

[a]Adjusted for age, BMI, and visceral fat area.

DI_{early}, early-phase disposition index; DI_{1st}, first-phase disposition index; DI_{2nd}, second-phase disposition index; lg, log-transformed; SFA, subcutaneous fat area.

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TABLE 4

Adjusted regression coefficients of blood glucose and log-transformed disposition indices with visceral fat area, subcutaneous fat area, and BMI

	Men				Women			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
Independent variable	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Blood glucose								
Fasting plasma glucose								
Visceral fat area	0.22	< 0.001	0.13	< 0.001	0.23	< 0.001	0.19	< 0.001
Subcutaneous fat area	0.18	< 0.001	−0.002	0.92	0.07	< 0.001	−0.07	< 0.001
BMI	0.22	< 0.001	0.13	< 0.001	0.17	< 0.001	0.10	< 0.001
30-min plasma glucose								
Visceral fat area	0.16	< 0.001	0.10	< 0.001	0.17	< 0.001	0.14	< 0.001
Subcutaneous fat area	0.12	< 0.001	−0.02	0.38	0.05	< 0.001	−0.06	< 0.001
BMI	0.16	< 0.001	0.11	< 0.001	0.13	< 0.001	0.08	< 0.001
2-h plasma glucose								
Visceral fat area	0.28	< 0.001	0.25	< 0.001	0.31	< 0.001	0.24	< 0.001
Subcutaneous fat area	0.20	< 0.001	0.05	0.015	0.14	< 0.001	−0.04	0.008
BMI	0.22	< 0.001	0.001	0.97	0.25	< 0.001	0.13	< 0.001
Disposition indices								
$lgDI_{early}$								
Visceral fat area	−0.24	< 0.001	−0.15	< 0.001	−0.25	< 0.001	−0.19	< 0.001
Subcutaneous fat area	−0.20	< 0.001	−0.02	0.40	−0.13	< 0.001	0.01	0.37
BMI	−0.23	< 0.001	−0.11	< 0.001	–0.21	< 0.001	−0.10	< 0.001
$lgDI_{1st}$								
Visceral fat area	−0.13	< 0.001	−0.11	< 0.001	−0.15	< 0.001	−0.13	< 0.001
Subcutaneous fat area	−0.09	< 0.001	0.02	0.42	−0.06	< 0.001	0.04	0.030
BMI	−0.11	< 0.001	−0.05	0.030	−0.12	< 0.001	−0.06	0.004
$lgDI_{2nd}$								
Visceral fat area	−0.30	< 0.001	−0.19	< 0.001	−0.29	< 0.001	−0.21	< 0.001
Subcutaneous fat area	−0.26	< 0.001	−0.05	0.030	−0.15	< 0.001	0.02	0.21

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	Men				Women			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
Independent variable	*β*	*P*	*β*	*P*	*β*	*P*	*β*	*P*
BMI	−0.29	< 0.001	−0.13	< 0.001	−0.25	< 0.001	−0.13	< 0.001

[a] In Model 1, dependent variables were each one of blood glucose indices or log-transformed DIs; independent variables included age and a single one of the obesity indices (visceral fat area, subcutaneous fat area, or BMI).

[b] In Model 2, dependent variables were each one of blood glucose indices or log-transformed DIs; independent variables included age, visceral fat area, subcutaneous fat area, and BMI simultaneously.

DI_{early}, early-phase disposition index; DI_{1st}, first-phase disposition index; DI_{2nd}, second-phase disposition index; lg, log-transformed.