ARTICLE

Insulin resistance, beta cell dysfunction and visceral adiposity as predictors of incident diabetes: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study

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Abstract

Aims/hypothesis Central obesity, insulin resistance and beta cell dysfunction are independent risk factors for incident type 2 diabetes, although few studies have used detailed measures of these disorders. Our objective was to study the association of directly measured visceral and subcutaneous adipose tissue (VAT, SAT), insulin sensitivity (S_I) and the acute insulin response (AIR) with incident type 2 diabetes.

Methods Participants were 1,230 Hispanic-Americans and African-Americans in the Insulin Resistance Atherosclerosis Study (IRAS) Family Study who were free of type 2 diabetes at baseline (2000–2002). S_I and AIR were determined from frequently sampled IVGTTs with minimal model analysis. VAT and SAT were determined by computed tomography.

Impaired fasting glucose and type 2 diabetes were defined according to American Diabetes Association criteria.

Results Incident type 2 diabetes was diagnosed in 90 participants after 5 years. After adjustment for age, sex, ethnicity, centre, impaired fasting glucose, triacylglycerol, HDL-cholesterol and systolic BP, both S_I and AIR were inversely associated with type 2 diabetes (S_I, OR 0.53, 95% CI 0.39–0.73; AIR, OR 0.22, 95% CI 0.14–0.34 per SD; both $p<0.001$), while both VAT and SAT were positively associated with type 2 diabetes (VAT, OR 1.68, 95% CI 1.22–2.33; SAT, OR 1.49, 95% CI 1.13–1.99; both $p<0.01$). In a model including all four factors, S_I and AIR (S_I, OR 0.55, 95% CI 0.37–0.80; AIR, OR 0.21, 95% CI 0.13–0.33; both $p<0.01$) were significant predictors of type 2 diabetes, although associations with

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VAT and SAT were no longer significant. A significant sex × VAT interaction indicated a stronger association of VAT with type 2 diabetes in women than in men.

Conclusions/interpretation Insulin resistance, beta cell dysfunction and VAT predicted incident type 2 diabetes, with evidence of a stronger association of VAT with type 2 diabetes among women.

Abbreviations

AIR	Acute insulin response
GEE1	Generalised estimating equation
IFG	Impaired fasting glucose
IRAS	Insulin Resistance Atherosclerosis Study
SAT	Subcutaneous adipose tissue
S_I	Insulin sensitivity index
VAT	Visceral adipose tissue

Introduction

Obesity is a well established and extensively described risk factor for type 2 diabetes mellitus. In particular, the importance of body fat distribution in the aetiology of type 2 diabetes is now well understood, epidemiological studies often reporting stronger associations of anthropometric measures of central obesity, including waist circumference and waist-to-hip ratio, with incident type 2 diabetes compared with overall measures such as BMI [1–4]. It is hypothesised that the excess risk of metabolic disease in participants with a central pattern of obesity is due to the presence of larger amounts of intra-abdominal, or visceral, adipose tissue in these individuals [5, 6]. Visceral adipose tissue (VAT) has been demonstrated to be an important source of inflammatory cytokines and non-esterified fatty acids [7, 8], which have been shown to have a detrimental effect on insulin sensitivity and beta cell dysfunction.

Greater appreciation of the importance of VAT in metabolic disease has precipitated increasing use of imaging methods, including computed tomography and magnetic resonance imaging, to directly measure subcutaneous and VAT depots [9]. These approaches overcome some of the well documented limitations of surface measures of fat distribution, including their inability to distinguish the underlying distribution of various fat depots [10]. A number of cross-sectional studies using direct measures have reported that increased VAT is associated with an unfavourable metabolic profile, including insulin resistance, beta cell dysfunction and metabolic syndrome

[11–13]. In addition, it has been reported in cohorts of Japanese Americans and older whites and African-Americans that VAT predicts incident diabetes independently of covariates [14, 15]. These studies involved unique populations in terms of age and ethnicity, and, importantly, they did not include detailed measures of insulin sensitivity and secretion from clamps or intravenous glucose tolerance tests. The additional resolution provided by these methods is likely significant in understanding the relative importance of VAT and insulin sensitivity and secretion in the aetiology of type 2 diabetes [10].

The objective of the present study, therefore, was to investigate the association of directly measured visceral and subcutaneous adiposity, insulin sensitivity and beta cell dysfunction with the 5 year incidence of type 2 diabetes in 1,230 Hispanic- and African-American participants who were free of diabetes at baseline, using data from the Insulin Resistance Atherosclerosis (IRAS) Family Study.

Methods

The methods used in the IRAS Family Study have been described in detail [16, 17]. Briefly, the study was designed to explore genetic contributions to insulin resistance and visceral adiposity among Hispanic- and African-Americans using a family-based design [16]. Large families were recruited between 2000 and 2002 at centres in San Antonio, TX, San Luis Valley, CO, (Hispanic-Americans) and Los Angeles, CA (African-Americans), with probands identified from the parent study (IRAS) [16] as well as the general population. The present prospective analysis included 1,230 participants who were free of diabetes at the baseline examination (2000–2002) and who returned for the 5 year follow-up examination, representing a 77% participation rate at follow-up. Subjects who did not return at follow-up were more likely to be male and have slightly better health status than those that returned (including slightly lower levels of subcutaneous adipose tissue, VAT and acute insulin response and higher insulin sensitivity index). At baseline and follow-up examinations, diabetes was diagnosed as either fasting glucose ≥126 mg/dl (to convert to values in mmol/l, multiply by 0.0555) or use of antidiabetic medications. The institutional review boards at the respective institutions approved the protocol and informed consent was given by each participant.

Fat mass in the abdominal region was measured by computed tomography at both the L2/L3 and the L4/L5 vertebral region [16]. A standardised protocol was used at each of the three clinical centres. Scans were read centrally at the Department of Radiology of the University of Colorado Health Sciences Center for subcutaneous adipose tissue (SAT) and VAT, with bowel fat subtracted from the measure

of VAT. The L4/L5 measure was used in the present analysis. However, 45 participants had data for the L2/L3 region but not the L4/L5 region. Since adipose tissue areas at the L2/L3 and L4/L5 regions were highly correlated (Spearman correlation, 0.95 for SAT, 0.90 for VAT), data for these latter individuals for the L4/L5 region were imputed using a simple linear model [16, 17]. Insulin sensitivity was determined using a frequently sampled intravenous glucose tolerance test (FSIGTT), with two modifications to the original protocol [18]. First, an injection of insulin, rather than tolbutamide, was used to ensure adequate plasma insulin levels for the accurate computation of insulin sensitivity across a broad range of glucose tolerance [19]. Second, a reduced sampling protocol (with 12 rather than 30 samples) was employed for efficiency, given the large number of participants [20]. Insulin sensitivity, expressed as the insulin sensitivity index (S_I), was calculated using minimal model analysis [21, 22]. The acute insulin response (AIR), a measure of insulin secretion, was defined as the mean increment in the plasma insulin concentration above basal in the first 8 min after the administration of glucose.

Plasma glucose was measured using the glucose oxidase technique on an autoanalyser. Impaired fasting glucose was defined as fasting glucose ≥100 and <126 mg/dl (to convert to values in mmol/l, multiply by 0.0555). Plasma insulin was measured using the dextran-charcoal radioimmunoassay [23, 24], which has an interassay CV of 19%. Lipids were determined using standard laboratory procedures. Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. Waist circumference was measured at the natural indentation or at a level midway between the iliac crest and the lower edge of the rib cage if no natural indentation was present. Duplicate measures were made following a standardised protocol and averages were used in the analysis. Resting blood pressure (systolic and fifth phase diastolic) was recorded with a standard mercury sphygmomanometer after a 5 min rest. The average of the second and third measurements was used in the analysis. Ethnicity was assessed by self-report.

Statistical analysis SAS version 9.1 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. Data are presented as percentages for categorical variables and mean (SD) or median (interquartile range) for normally distributed and skewed continuous variables, respectively. Univariate comparisons of baseline variables across ethnic groups and follow-up diabetes status were calculated from generalised estimating equation (GEE1) models, adjusting for correlations within families. The cumulative incidence of type 2 diabetes at follow-up was compared across quartiles of SAT and VAT. GEE1 logistic regression models were used to test for associations of VAT, SAT, S_I and AIR with incident diabetes at the 5 year examination, while accounting for the familial correlations. Generalised estimating equations are a standard approach to the analysis of correlated data such as family data and are similar to logistic regression models except that they account for the correlation among pedigrees. Newly diagnosed diabetes at the 5 year follow-up examination was the dependent variable for all models. We first assessed the risk of type 2 diabetes across tertiles of SAT and VAT, adjusting for age, sex and ethnicity (tertiles rather than quartiles were used here since there were very few cases of diabetes mellitus in the lowest quartiles and thus effect estimates were imprecise). A multistage modelling approach was then used to investigate the relationships of visceral adiposity and insulin sensitivity/secretion, treated as continuous variables, with the risk of diabetes. The following transformations were used: the square root of VAT and SAT, the natural log of S_I, and the signed square root of AIR. Odds ratios were estimated per standard deviation increase

Table 1 Baseline demographic, anthropometric and metabolic characteristics of non-diabetic participants in the IRAS Family Study, stratified according to ethnicity

Data are mean ± SD for approximately normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables and proportion for categorical variables

[a] Calculated from GEE1 models, adjusting correlations within families

[b] To convert to values in min^{-1} $pmol^{-1}$ ml^{-1} multiply by 0.167

Variable	Ethnicity		p value[a]
	African-American (n=355)	Hispanic-American (n=875)	
Age (years)	42.4±13.4	41.2±13.5	0.4653
Sex (% males/females)	40.3/59.7	37.6/62.4	0.4367
BMI (kg/m^2)	29.4±6.5	28.6±5.9	0.1412
Waist circumference (cm)	90.2±14.7	88.5±13.6	0.2173
VAT (cm^2)	80.3 (45.3–119.0)	98.4 (65.3–140.7)	<0.0001
SAT (cm^2)	299.9 (216.4–442.8)	314.0 (229.2–427.7)	0.9867
Glucose (mmol/l)	5.3±0.5	5.2±0.5	0.0274
Insulin (pmol/l)	83.3 (55.6–125.0)	83.3 (55.6–132.0)	0.2957
S_I×10^{-4} (min^{-1} μU^{-1} ml^{-1})[b]	1.35 (0.77–2.15)	1.64 (0.81–2.84)	0.0005
AIR ($pmol$ ml^{-1} min^{-1})	750.1 (403.5–1256.6)	595.3 (351.0–955.6)	0.0006
Impaired fasting glucose (% yes/no)	29.0/71.0	21.7/78.3	0.0062

Table 2 Baseline demographic, anthropometric and metabolic characteristics of non-diabetic participants in the IRAS Family Study, stratified according to diabetes status at the 5 year follow-up examination

Variable	Diabetes status at 5 year follow-up examination		p value[a]
	Without diabetes ($n=1,140$)	Diabetes ($n=90$)	
Age (years)	40.8 ± 13.2	51.8 ± 12.8	<0.0001
Sex (% male/female)	38.3/61.8	40.0/60.0	0.7570
Ethnicity (% African-American/Hispanic-American)	29.0/71.0	26.7/73.3	0.4946
BMI (kg/m^2)	28.5 ± 5.9	33.0 ± 7.0	<0.0001
Waist circumference (cm)	88.2 ± 13.7	99.5 ± 13.5	<0.0001
VAT (cm^2)	89.3 (56.7–127.9)	155.8 (115.9–192.9)	<0.0001
SAT (cm^2)	305.5 (221.8–420.8)	402.8 (269.9–513.2)	<0.0001
Glucose (mmol/l)	5.2 ± 0.5	6.0 ± 0.6	<0.0001
Insulin (pmol/l)	83.3 (55.6–125.0)	138.9 (83.3–194.5)	<0.0001
$S_I \times 10^{-4}$ (min^{-1} μU^{-1} ml^{-1})[b]	1.6 (0.9–2.7)	0.7 (0.3–1.2)	<0.0001
AIR (pmol ml^{-1} min^{-1})	670.9 (398.2–1098.8)	164.3 (72.4–354.9)	<0.0001
Impaired fasting glucose (% yes/no)	19.7/80.3	76.7/23.3	<0.0001

Data are mean (SD) for approximately normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables and proportion for categorical variables

[a] Calculated from GEE1 models, adjusting correlations within families

[b] To convert to values in min^{-1} pmol^{-1} ml^{-1} multiply by 0.167

in the independent variable. We first determined the associations of VAT, SAT and insulin sensitivity/secretion measures with the risk of diabetes in individual models for each primary independent variable, with adjustment for covariates (described below). We next determined the joint effects of visceral adiposity and insulin sensitivity/secretion by modelling combinations of these variables simultaneously. Specifically, we constructed two analyses with the following independent variables: (1) SAT and VAT; and (2) SAT, VAT, S_I and AIR. We adjusted all models for age, sex and ethnicity (and S_I for models considering AIR as the main independent variable; model A) and additionally for impaired fasting glucose (IFG), triacylglycerol, HDL-cholesterol and systolic BP (model B). Finally, we tested for effect modification by sex and ethnicity on the associations of the main exposures (VAT, SAT, S_I and AIR) with incident diabetes.

Results

At baseline, African-American participants had significantly less VAT compared with Hispanic-American participants (90 vs 108 cm^2, $p<0.001$; Table 1), although the two groups did not differ in other anthropometric variables. Hispanic-American participants were more insulin sensitive and had lower insulin secretion compared with African-American participants (both $p<0.001$). Participants who

developed incident diabetes at the 5 year follow-up examination had significantly lower baseline S_I and AIR as well as higher glucose and insulin concentrations and were more likely to have had IFG at baseline (all $p<0.0001$; Table 2). In addition, these participants were older and had higher BMI, waist circumference, VAT and SAT at baseline compared with those who remained free of diabetes at follow-up (all $p<0.0001$; Table 2). The incidence of diabetes increased across quartiles of both SAT and VAT
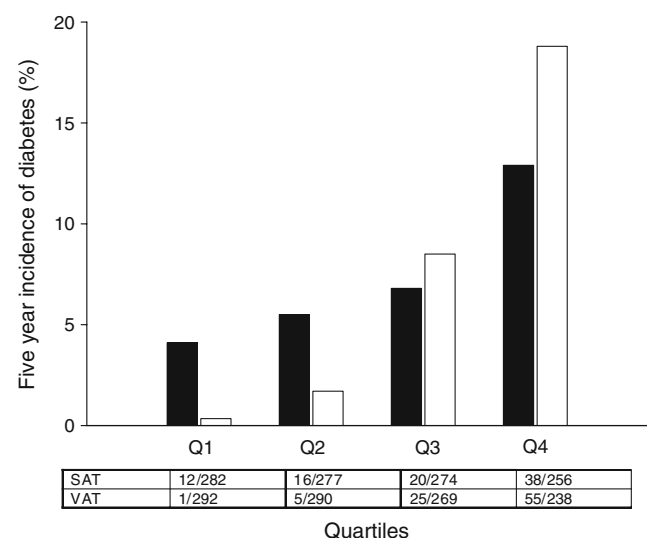

	Q1	Q2	Q3	Q4
SAT	12/282	16/277	20/274	38/256
VAT	1/292	5/290	25/269	55/238

Fig. 1 Incidence of type 2 diabetes according to quartiles (Q) of SAT (black columns) and VAT (white columns)
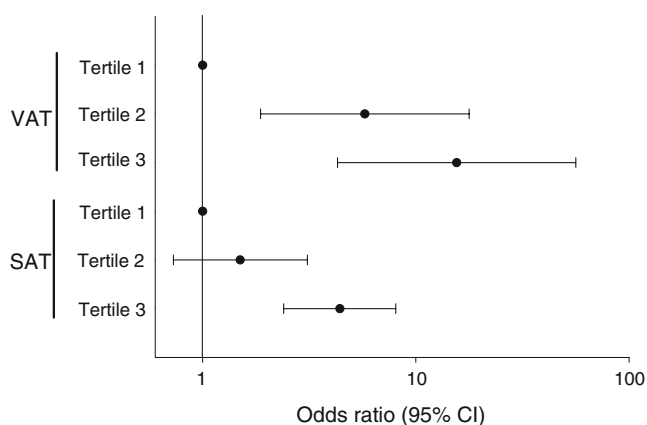
Fig. 2 Associations of tertiles of VAT and SAT with incident diabetes mellitus at the 5 year follow-up examination. Odds ratios (with 95% CI) were adjusted for age, sex, ethnicity and clinic, and indicate the risk of diabetes mellitus among subjects in the 2nd and 3rd tertiles of VAT or SAT compared with those in the 1st tertile (serving as the reference category)

($p_{trend} < 0.001$), although the increase was much more pronounced across VAT quartiles (Fig. 1). Notably, only 1 of 292 participants (0.3%) in the lowest quartile of VAT developed diabetes, compared with 12 of 282 participants (4%) in the lowest quartile of SAT. Similarly, after adjustment for age, sex and ethnicity, participants in the second and third tertiles of VAT were at significantly increased risk of diabetes mellitus (tertile 2 [T2] vs T1, OR 5.8, 95% CI 1.9–17.7; T3 vs T1, OR 15.6, 95% CI 4.3–56.3 respectively), while the magnitude of risk across tertiles of SAT was more modest (T2 vs T1, OR 1.5, 95% CI 0.7–3.1; T3 vs T1, OR 4.4, 95% CI 2.4–8.1; Fig. 2).

After adjustment for age, sex and ethnicity, individual GEE logistic regression models indicated that baseline VAT and SAT were associated with increased risk of incident diabetes mellitus (VAT, OR 2.7, 95% CI 2.0–3.6; SAT, OR 2.1, 95% CI 1.6–2.7 per SD increase; $p<0.0001$), while baseline S_I and AIR were associated with decreased risk (OR 0.4, 95% CI 0.3–0.5; OR 0.2, 95% CI 0.1–0.3; per SD increase, respectively; all $p<0.0001$; Table 3, model A). The significant inverse association of AIR with incident diabetes mellitus remained largely unchanged with additional adjustment for IFG, triacylglycerol, HDL-cholesterol and systolic BP, while the inverse association of S_I with diabetes mellitus was attenuated slightly, suggesting that these variables accounted for some of the variance in S_I (Table 3, model B). In contrast, the associations of VAT and SAT with incident diabetes mellitus showed more marked attenuation in the fully adjusted model, although the associations remained statistically significant (VAT, OR 1.7, 95% CI 1.2–2.3; SAT, OR 1.5, 95% CI 1.1–2.0; Table 3, model B).

To evaluate the combined effects of the different adipose tissue depots, we included VAT and SAT in the same model, with covariate adjustment as described above. In both minimally and fully adjusted models, VAT, but not SAT, was independently associated with incident diabetes mellitus (Table 4, analysis 1, models A and B). VAT, S_I and AIR (but not SAT) were significantly associated with incident diabetes mellitus when modelled together and adjusted for age, sex and ethnicity (Table 4, analysis 2, model A). However, with additional adjustment of these primary exposure combinations for IFG, triacylglycerol, HDL-cholesterol and systolic BP, the magnitude of the association of VAT was reduced and no longer statistically significant, while the inverse associations with measures of insulin sensitivity and secretion were attenuated only slightly and remained highly significant (Table 4, model B).

Table 3 Multivariate associations of baseline VAT, SAT, S_I and AIR with incident diabetes mellitus at the 5 year follow-up examination in the IRAS Family Study

Analysis[a]	Independent variable	Model A			Model B		
		OR[b]	95% CI[b]	p value	OR[b]	95% CI[b]	p value
1	VAT	2.65	1.97–3.56	<0.0001	1.68	1.22–2.33	0.002
2	SAT	2.06	1.60–2.65	<0.0001	1.49	1.12–1.99	0.007
3	S_I	0.37	0.28–0.50	<0.0001	0.53	0.39–0.73	<0.0001
4	AIR	0.17	0.11–0.28	<0.0001	0.22	0.14–0.34	<0.0001

Model A was adjusted for age, sex, ethnicity (+ S_I for AIR model)

Model B was adjusted for age, sex, ethnicity, IFG, triacylglycerol, HDL-cholesterol, systolic BP (+ S_I for AIR model)

[a] Each analysis (row) represents an individual model, with adjustments as indicated; outcome variable for each model is incident diabetes at the 5 year follow-up examination.

[b] Odds ratios and 95% confidence intervals were calculated from multivariate GEE1 models, adjusting correlations within families; odds ratios refer to risk associated with SD increases in the square root transformations of VAT and SAT, the natural log transformation of S_I, the signed square root transformations of AIR. SDs were as follows: VAT. 2.78; SAT, 4.42; S_I, 0.51; AIR, 11.27

Table 4 Combined effect of adiposity and insulin sensitivity and secretion on incident diabetes mellitus at the 5 year follow-up examination in the IRAS Family Study

Analysis[a]	Independent variable	Model A			Model B		
		OR[b]	95% CI[b]	p value	OR[b]	95% CI[b]	p value
1	VAT	2.32	1.61–3.33	<0.0001	1.52	1.03–2.25	0.04
	SAT	1.32	0.94–1.86	0.11	1.22	0.85–1.75	0.27
2	VAT	1.61	1.05–2.47	0.03	1.33	0.86–2.05	0.20
	SAT	1.41	0.92–2.14	0.12	1.38	0.89–2.14	0.15
	S_I	0.47	0.33–0.66	0.0001	0.55	0.37–0.80	0.0.002
	AIR	0.16	0.10–0.27	0.0001	0.21	0.13–0.33	<0.0001

Model A was adjusted for age, sex, ethnicity

Model B was adjusted for age, sex, ethnicity, IFG, triacylglycerol, HDL-C, systolic BP

[a] Combinations of VAT and insulin sensitivity and secretion measures, with adjustments as indicated; outcome variable, incident diabetes at the 5 year follow-up examination. Each analysis (group of rows) represents an individual model, with adjustments as indicated

[b] Odds ratios and 95% confidence intervals calculated from multivariate GEE1 models, adjusting correlations within families; odds ratios refer to risk associated with SD increases in the square root transformations of VAT and SAT, the natural log transformation of S_I, the signed square root transformations of AIR. SDs were as follows: VAT, 2.78; SAT, 4.42; S_I, 0.51; AIR, 11.27

Ethnicity did not modify the associations of adipose tissue depots or glucose homeostasis measures with the risk of diabetes mellitus (all $p_{interaction} > 0.25$). Sex did not modify the associations of SAT, S_I or AIR with the risk of diabetes mellitus (all $p_{interaction} > 0.13$), although there was strong effect modification of sex on the association of VAT with incident diabetes mellitus ($p_{interaction} = 0.0006$). Specifically, the association of VAT with the risk of diabetes was much stronger among women than men (Fig. 3).
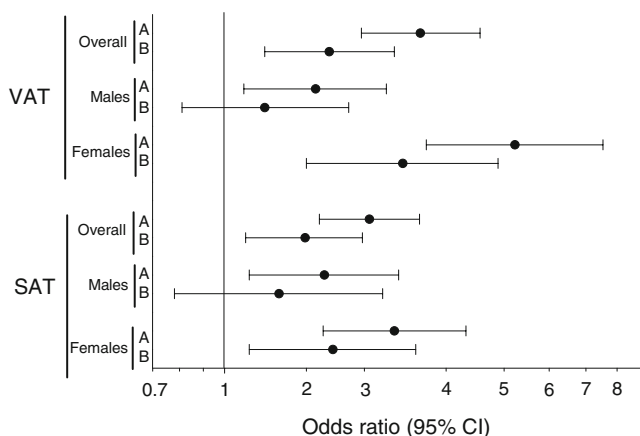

Fig. 3 Associations of baseline VAT and SAT with incident diabetes mellitus at the 5 year follow-up examination, overall and stratified by sex, in the IRAS Family Study. Odds ratios (with 95% CI) refer to 1 SD changes. Overall models were adjusted for age, sex and ethnicity (minimally adjusted, model A); and age, sex, ethnicity, IFG, triacylglycerol, HDL-cholesterol and systolic BP (fully adjusted, model B). Sex-specific models were adjusted for age and ethnicity (minimally adjusted, model A); and age, ethnicity, IFG, triacylglycerol, HDL-cholesterol and systolic BP (fully adjusted, model B)

Discussion

In this prospective study of non-diabetic African-American and Hispanic-American participants, we found that increased VAT and SAT, as well as reduced insulin sensitivity and secretion, were significantly associated with progression to type 2 diabetes in individual models after adjustment for age, sex, ethnicity, IFG, triacylglycerol, HDL-cholesterol and systolic BP. Furthermore, in models including both VAT and SAT, only VAT was a significant risk factor for diabetes. However, when adipose tissue depots and glucose homeostasis measures were modelled together, only decreased insulin sensitivity and secretion remained significantly related to the incidence of diabetes. Assessment of effect modification revealed a substantially stronger effect of VAT on diabetes risk among women.

The major strengths of this study include its prospective assessment of a large, well characterised cohort of individuals from two ethnic groups at high risk of type 2 diabetes, and the characterisation of participants using detailed measures of adipose tissue depots and insulin sensitivity/secretion. To our knowledge, this is the only prospective study to date with detailed measures of both of these major diabetes risk factors. The most significant limitation of this study is the absence of oral glucose tolerance testing, and the consequent reliance on fasting glucose measures to diagnose diabetes.

Although cross-sectional data are available on associations of SAT and VAT with metabolic variables [12, 13, 23–26], to our knowledge only two other cohorts contain both direct measures of visceral fat and information on incident glucose intolerance. The Health, Aging and Body Composition (Health ABC) Study, a cohort study of older

African-American and white participants, reported that VAT predicted incident diabetes mellitus after adjustment for age, sex and race. However, the association with VAT was partially explained by adipokines, particularly plasminogen activator inhibitor 1 [15]. In the Japanese-American Community Diabetes Study, VAT predicted diabetes mellitus and impaired glucose tolerance independently of covariates, including OGTT-based indices of insulin resistance and beta cell function [14, 27]. In the present study, the association of VAT with incident diabetes was independent of SAT as well as a number of conventional diabetes risk factors. However, the association with VAT was attenuated and became non-significant after adjustment for S_I and AIR. There are a number of possible explanations for differences in findings between our study and those of the Japanese-American study [14, 27]. First, indirect, OGTT-based measures of insulin sensitivity and secretion were used in the Japanese-American cohort, resulting perhaps in lower accuracy in the measures of these disorders relative to the characterisation of VAT, which was measured directly. Second, in the Japanese-American study, glucose intolerance was classified based on OGTT results, while in the present study only fasting glucose measures were available, resulting in the misclassification of participants who would have been diagnosed with diabetes based on post-challenge glucose alone. If elevated VAT is especially related to post-challenge hyperglycaemia, the association of VAT with incident diabetes mellitus in our study would have been attenuated. Third, the period of follow-up was longer in the Japanese-American cohort (6–11 years) compared with that in the present study (5 years). It is possible that VAT would be independently associated with diabetes mellitus incidence with longer follow-up. Finally, the marked ethnic differences between the two cohorts raise the possibility of differences in the relative importance of underlying pathophysiological traits in the aetiology of type 2 diabetes between these populations.

Although there were significant baseline differences in VAT between Hispanic- and African-Americans in the present study, ethnicity did not modify the association of VAT with incident diabetes. In contrast, the association of VAT with diabetes mellitus was notably stronger in women compared with men. A similar finding was reported from a case–control analysis in the Health ABC study; specifically, there was a stronger association of VAT with type 2 diabetes in women, as well as less attenuation of this VAT–diabetes association by adipokines in women compared with men [28]. Furthermore, the same study team has reported a stronger association of VAT with incident myocardial infarction in women [29]. The explanation for this sex difference in the metabolic impact of VAT is unclear. Women typically carry lower amounts of VAT

compared with men, and it is therefore possible that increases in VAT in women reflect a more insidious or advanced state of metabolic deterioration.

Our results showing a substantial and significantly reduced risk of progression to diabetes among those with higher levels of insulin sensitivity and secretion is consistent with previous studies that have used similarly detailed physiological measures [30–34]. Taken together, the findings of these studies highlight the fundamental role of insulin sensitivity and secretion disorders in the pathogenesis of type 2 diabetes. Our results extend these observations by showing that the detrimental effect of reduced insulin sensitivity and secretion is independent of directly quantified VAT and SAT, and is present in multiple high-risk populations, including African- and Hispanic-Americans. The lack of a significant association of VAT with diabetes mellitus independently of insulin sensitivity and secretion may indicate that a portion of the association of VAT with diabetes mellitus operates through these disorders. In a previous paper from this study, for example, we reported that VAT was inversely and significantly associated with S_I and S_I-adjusted AIR in cross-sectional analysis [11]. Thus, when S_I is added to logistic models containing VAT, the insulin sensitivity and secretion variances are removed from VAT, attenuating its association with diabetes mellitus.

In conclusion, increased VAT and SAT and reduced insulin sensitivity and secretion were significantly associated with incident diabetes mellitus after adjustment for multiple confounders. Although VAT continued to predict diabetes with adjustment for SAT, the association was attenuated with further adjustment for insulin sensitivity and secretion. There were notable sex differences in the VAT–diabetes mellitus association, suggesting that visceral fat accumulation may be particularly detrimental among women.

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