Visceral Adiposity and Risk of Type 2 Diabetes

A prospective study among Japanese Americans

EDWARD J. BOYKO, MD, MPH
WILFRED Y. FUJIMOTO, MD
DONNA L. LEONETTI, PHD
LAURA NEWELL-MORRIS, PHD

OBJECTIVE — We conducted a prospective study among Japanese Americans of diabetes incidence in relation to visceral and regional adiposity, fasting insulin and C-peptide, and a measure of insulin secretion, because little prospective data exist on these associations.

RESEARCH DESIGN AND METHODS — Baseline variables included plasma glucose, C-peptide, and insulin measured after an overnight fast and 30 and 120 min after a 75-g oral glucose tolerance test; abdominal, thoracic, and thigh fat areas by computed tomography (CT); BMI (kg/m^2); and insulin secretion (incremental insulin response [IIR]).

RESULTS — Study subjects included 290 second-generation (nisei) and 230 third-generation (sansei) Japanese Americans without diabetes, of whom 65 and 13, respectively, developed diabetes. Among nisei, significant predictors of diabetes risk for a 1 SD increase in continuous variables included intra-abdominal fat area (IAFA) (odds ratio, 95% CI) (1.6, 1.1–2.3), fasting plasma C-peptide (1.4, 1.1–1.8), and the IIR (0.5, 0.3–0.9) after adjusting for age, sex, impaired glucose tolerance, family diabetes history, and CT-measured fat areas other than intra-abdominal. Intra-abdominal fat area remained a significant predictor of diabetes incidence even after adjustment for BMI, total body fat area, and subcutaneous fat area, although no measure of regional or total adiposity was related to development of diabetes. Among sansei, all adiposity measures were related to diabetes incidence, but, in adjusted models, only IAFA remained significantly associated with higher risk (2.7, 1.4–5.4, BMI-adjusted).

CONCLUSIONS — Greater visceral adiposity precedes the development of type 2 diabetes in Japanese Americans and demonstrates an effect independent of fasting insulin, insulin secretion, glycemia, total and regional adiposity, and family history of diabetes.

Diabetes Care 23:465–471, 2000

A number of prospective and cross-sectional studies have shown a higher risk of diabetes in association with greater abdominal obesity usually assessed with surface measurements such as waist circumference, the ratio of waist-to-hip circumference, or skinfold thickness (1–4). A large study of insulin resistance in a multiethnic U.S. population demonstrated an inverse BMI-adjusted correlation between waist circumference and insulin sensitivity estimated from minimal model analysis (5), an important finding given the higher risk of type 2 diabetes associated with diminished insulin sensitivity (6,7).

Most research on the association between type 2 diabetes risk and regional adiposity argues that the intra-abdominal fat depot has the most detrimental metabolic effects (8–13). Body-surface measurements of abdominal adiposity, such as waist circumference, do not definitively measure intra-abdominal fat volume, because these measurements reflect not only intra-abdominal but also subcutaneous fat depots, and the relative contributions of each to the measurements vary by individual. Researchers have shown a wide range of the proportion of directly measured intra-abdominal fat area (IAFA) variance explained (0.38–0.87) in relation to surface measurements or BMI (14–18).

Despite the recognized importance of visceral fat with regard to abnormal glucose metabolism, little research has been performed on whether directly measured intra-abdominal fat is related to the incidence of diabetes. Most research on the association between directly measured visceral fat and glucose intolerance is cross-sectional in nature and, therefore, unable to demonstrate that visceral adiposity precedes rather than follows diabetes onset. Such a demonstration is necessary to establish visceral adiposity as a potential cause of type 2 diabetes. A publication in 1990 by our group of preliminary prospective data in Japanese-American men demonstrated that increasing computed tomography (CT)-measured IAFA was related to higher diabetes incidence, but this association disappeared after adjustment for glycemia (19). The findings of this previous analysis are further limited because of the absence of women and the small number of diabetes cases (n = 15) that impaired adjustment for potential confounding factors. Since the time of this analysis, many additional diabetes cases have developed. We therefore performed an analysis of the largest study known to us with measurements of overall and regional adipose tissue at baseline and follow-up over 6–10 years specifically targeted to detect incident cases of diabetes.

From the Epidemiologic Research and Information Center (E.J.B.), Veterans Affairs Puget Sound; and the Departments of Medicine (E.J.B., W.Y.F) and Anthropology (D.L.L., L.N.-M.), University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Edward J. Boyko, MD, MPH, Veterans Affairs Puget Sound (S-111-GIMC), 1660 S. Columbian Way, Seattle, WA 98108. E-mail: eboyko@u.washington.edu.

Received for publication 14 June 1999 and accepted in revised form 16 November 1999.

Abbreviations: CT, computed tomography; IAFA, intra-abdominal fat area; IGT, impaired glucose tolerance; IIR, incremental insulin response; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; TFA, total body fat area.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Study subjects

The study population consisted of second-generation (nisei, mean age 61.8 years) and third-generation (sansei, mean age 40.1 years) Japanese-American men and women enrolled in the Japanese-American Community Diabetes Study. Details about the selection and recruitment of the sample population have been described previously (20). Briefly, subjects were chosen from a group of volunteers and were representative of the Japanese Americans in King County, Washington, in age distribution, residence, and parental immigration patterns. All subjects were of 100% Japanese ancestry. Nisei men returned for follow-up examinations 2.5, 5, and 10 years after a baseline evaluation. Nisei women returned at 2.5 and 6 years after a baseline evaluation. Sansei men and women underwent a baseline evaluation followed by one follow-up examination at 6 years. The originally intended 5-year follow-up could not be achieved in nisei women and sansei because of an interruption in grant support. The following proportion of subjects completed the most recent examination (10 years after baseline for nisei men and 6 years after baseline for the others): nisei men, 0.81; nisei women, 0.89; sansei men, 0.93; sansei women, 0.85. The remaining subjects were not followed up because of the subjects' death, the authors' inability to locate the subjects, or the subjects' withdrawal from the study.

Data collection

All evaluations were performed at a clinical research center. The research protocol was reviewed and approved by the institutional human subjects review committee, and signed informed consent was obtained from all participants. A 75-g oral glucose tolerance test (OGTT) was used to classify all subjects as having normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or type 2 diabetes based on the American Diabetes Association 1997 criteria (21). Subjects with impaired fasting glucose were included in the NGT category. Diabetes was deemed present if subjects reported a history of diabetes and were taking oral hypoglycemic medication or insulin, or if the fasting plasma glucose was $\geq$7.0 mmol/l or the 2-h value was $\geq$11.1 mmol/l. Subjects with a fasting plasma glucose $\leq$7.0 mmol but a 2-h value from $\geq$7.7 to $<$11.1 were defined as having IGT. Serum glucose was assayed by an automated glucose oxidase method at 0, 30, and 120 min during the OGTT. Plasma insulin and C-peptide levels were measured by radioimmunoassay at 0, 30, and 120 min during the OGTT. The intra- and interassay coefficients of variation were 5 and 8% for insulin and 7 and 11% for C-peptide, respectively. Fasting insulin level correlates well with insulin sensitivity measured using the clamp technique among nondiabetic subjects (22). To assess insulin secretion, we used the incremental insulin response (IIR) (30 min insulin – fasting insulin)/30 min glucose, which correlates well with direct measures of stimulated insulin secretion (23,24). Family history of diabetes was deemed positive when any first-degree relative had diabetes.

Measurement of BMI and body fat distribution

BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2). Single CT scans were obtained of the thorax, abdomen, and right thigh (25). Visceral obesity was measured as IAFA within the transversalis fascia in centimeters squared (cm^2) at the level of the umbilicus. A high correlation has been shown between this measurement and total abdominal fat volume as assessed in subjects undergoing complete abdominal CT consisting of 42 slices (r = 0.93) (14) or when comparing a single magnetic resonance image slice at a similar level with an intra-abdominal volume estimate of adipose tissue (r = 0.91) (26). Subcutaneous fat areas also were measured by CT scan in the abdomen, thorax, and thigh. Total body fat area (TFA) was calculated as the sum of intra- and subcutaneous abdominal, thorax, and twice the thigh depots. Our group has recently found that TFA correlates highly with fat mass as measured by hydrodensitometry among Japanese Americans (r = 0.89–0.94; M. McNeely, personal communication). A similar sum of CT scan areas correlated highly with body fat mass (r = 0.94) among premenopausal obese women (17). Nonintra-abdominal fat area was defined as TFA minus the intra-abdominal depot, and nonsubcutaneous abdominal fat area was defined as TFA minus the subcutaneous abdominal fat depot.

Statistical analysis

Only subjects without diabetes at baseline were included in this analysis. Because multiple evaluations of both exposures of interest and the outcome were available for the nisei at baseline, 2.5, 5 or 6, and 10 years (men only), a discrete-time proportional hazards model was used to estimate the incidence of diabetes in relation to independent variables (27). The likelihood for this model reduces to the conditional logistic model, which was used to estimate relative odds and 95% CI with Stata, version 5.0 (Stata Corp., College Station, TX). Each period of observation (0–2.5 years, 2.5–5 years, etc.) was used as the stratum variable in the conditional logistic model with the outcome occurring at any time during that period of observation (as opposed to failure times in the Cox proportional hazards model). This analytic method offers the advantage of using information collected during the follow-up examinations on exposure status, not just the baseline measurement. Nisei subjects who developed diabetes were excluded from the analysis from that time onward. Because only one follow-up examination was available for the sansei, logistic regression analysis was used to model diabetes incidence in relation to variables of interest (28). Also, nisei data were analyzed using the earliest baseline measure only of intra-abdominal fat in relation to diabetes occurring at any follow-up period to compare these results with the discrete-time model. Presence of effect modification was tested by the insertion of first-order interaction terms into appropriate regression models. Nonlinear effects of continuous independent variables were evaluated using quadratic and log transformations.

RESULTS — Study sample sizes at baseline and the number and proportion for which follow-up information is available from any subsequent examination are as follows: nisei men, 151/146 (97%); nisei women, 139/130 (94%); sansei men, 115/107 (93%); and sansei women 115/98 (85%). Of the 146 nisei men, 40 developed diabetes (27.4%) for an annual incidence of 3.2%. Among the 130 nisei women, 25 developed diabetes (19.2%) for an annual incidence of 3.5%. Among the 107 sansei men followed for 6 years, 10 developed diabetes (9.3%), equivalent to an annual incidence rate of 1.6%, while 3 of 98 sansei women (3.1%) developed diabetes over the same time frame, for an annual incidence of 0.5%. Study subjects overall were not obese, with a mean BMI of 24.3 in nisei and 23.9 in sansei. The following proportion of subjects

Table 1—*Characteristics of study subjects at baseline according to whether diabetes developed at the end of follow-up*

Characteristic	Second-generation (nisei)				Third-generation (sansei)			
	Did not progress to diabetes	Progressed to diabetes	OR (95% CI)	*P*	Did not progress to diabetes	Progressed to diabetes	OR (95% CI)	*P*
n	211	65	—	—	192	13	—	—
Age (years)	61.1 (5.8)	63.3 (5.8)	1.7 (1.2–2.3)	0.003	40.0 (4.2)	43.1 (5.0)	1.9 (1.1–3.2)	0.015
Female sex (%)	105 (50)	25 (39)	1.2 (0.7–2.1)	0.593	95 (50)	3 (23)	0.3 (0.1–1.2)	0.079
Family history of diabetes (%)	74 (35)	34 (52)	2.2 (1.3–3.6)	0.004	60 (31)	8 (62)	3.5 (1.1–11.2)	0.033
IGT at baseline (%)	82 (39)	53 (82)	6.5 (3.4–12.5)	<0.001	41 (21)	11 (85)	20.3 (4.3–95.0)	<0.001
Fasting insulin (nmol/l)	74.0 (33.0)	78.3 (34.7)	1.3 (1.0–1.6)	0.067	83.7 (47.7)	140.8 (70.4)	2.0 (1.3–2.9)	0.001
Fasting C-peptide (pmol/l)	0.86 (0.26)	0.98 (0.28)	1.3 (1.0–1.6)	0.022	0.80 (0.26)	1.17 (0.29)	2.7 (1.7–4.4)	<0.001
IIR	46.7 (34.6)	32.4 (24.7)	0.4 (0.2–0.7)	0.003	57.8 (42.2)	68.9 (45.9)	1.2 (0.8–2.0)	0.365
Fasting glucose (mmol/l)	5.3 (0.5)	5.8 (0.6)	2.8 (2.0–3.9)	<0.001	4.9 (0.5)	5.5 (0.4)	3.9 (1.9–8.0)	<0.001
Intra-abdominal fat (cm^2)	96.5 (46.8)	115.9 (52.9)	1.4 (1.1–1.8)	0.018	56.3 (35.4)	117.5 (57.5)	3.4 (1.9–5.9)	<0.001
Subcutaneous abdominal fat (cm^2)	163.1 (78.2)	160.2 (65.4)	1.0 (0.8–1.3)	0.887	149.5 (80.1)	205.9 (63.0)	1.7 (1.1–2.8)	0.018
Non–intra-abdominal fat (cm^2)	395.6 (66.2)	384.5 (145.4)	1.0 (0.7–1.3)	0.758	337.3 (178.2)	498.6 (186.3)	1.8 (1.1–2.8)	0.019
Total fat (cm^2)	494.1 (187.6)	500.7 (166.0)	1.0 (0.8–1.4)	0.780	427.3 (195.8)	616.0 (214.5)	2.1 (1.3–3.3)	0.002
BMI (kg/cm^2)	24.1 (3.1)	24.9 (3.3)	1.1 (0.8–1.4)	0.664	23.7 (3.2)	27.7 (3.4)	2.8 (1.6–4.7)	<0.001

Data are *n*, means (SD), or *n* (%). Odds ratios (ORs) for continuous variables reflect a 1 SD magnitude increase. Nonabdominal fat and total abdominal fat areas represent sums of adipose tissue areas as determined by multiple CT slices as defined in the text.

met National Center for Health Statistics criteria for obesity (BMI >27.7 for men or >27.3 for women): nisei men, 17.9%; nisei women, 8.6%; sansei men, 14.8%; sansei women, 8.7% (29). Nisei subjects were on average ~21 years older than the sansei subjects. As expected, nisei subjects with IGT had greater BMI (24.7 vs. 23.9), TFA (454.2 vs. 417.9 cm^2), IAFA (115.1 vs. 100.0 cm^2), and fasting insulin (77.1 vs. 73.9 nmol/l) and had lower IIR (351.7 vs. 455.6) than those with NGT. The same associations were seen among sansei.

A number of characteristics were significantly related to higher diabetes incidence among nisei and sansei (Table 1). Family history of diabetes and presence of IGT at baseline were associated with higher diabetes incidence in both generations. Fasting C-peptide and glucose, but not insulin level, were positively associated with diabetes incidence in nisei, although all three were associated with higher risk in sansei. Higher IIR was related to lower diabetes incidence in nisei but not in sansei. Of the measures of regional and overall adiposity, only IAFA was related to higher diabetes incidence in nisei, although all such measures were related to higher diabetes incidence in sansei. Correlations between IAFA and TFA, non–intra-abdominal fat area, and BMI were less strong among nisei (correlation coefficients = 0.51, 0.27, 0.54, respectively) compared with sansei (correlation coefficients = 0.57, 0.41, 0.67, respectively). An additional logistic model among nisei of the earliest IAFA measured in relation to diabetes at any follow-up examination revealed a significant effect of similar magnitude to that obtained from the proportional hazards model (odds ratio = 1.5, 95% CI 1.1–2.0).

A number of regression models were tested to assess the effects of body fat distribution on diabetes incidence. Among nisei, a positive association between this outcome and IAFA was seen with adjustment for age, sex, IGT, family history of diabetes, non–intra-abdominal fat area, fasting C-peptide, and the IIR (model 1, Table 2). Similar results were seen when fasting insulin was substituted for C-peptide in this regression model (model 2). Of note, fasting C-peptide was more strongly related to diabetes incidence than fasting insulin and was entered into all other nisei models (models 3–7). Models 3–5 are identical to model 1, with the exception that a different adipose variable is used in place of non–intra-abdominal fat area. In all of these models, the significant positive association between IAFA and diabetes incidence persists. Also, none of the other measures of regional or total adiposity emerges as being significantly related to diabetes incidence. In model 6, subcutaneous abdominal fat area was tested in relation to diabetes incidence in place of IAFA, adjusted for remaining fat areas and the other covariates shown in model 1. No significant association was seen between the subcutaneous fat depot and diabetes incidence. Adjustment for glycemia (model 7) in addition to the other covariates in model 1 similarly does not result in a substantial change in the magnitude or significance of the association between IAFA and diabetes incidence, although fasting C-peptide and the IIR become insignificant in this regression model. Insertion of quadratic or log transformations of IAFA [x^2, Ln(x)] into model 1 did not result in an improvement in fit compared with the linear model (data not shown). Similarly, first-order interaction terms between IAFA and sex, family history, and IGT at baseline when inserted into model 1 did not result in a significant improvement in fit (data not shown).

Regression analysis among sansei was limited by the small number of subjects who experienced the outcome (*n* = 13), thereby limiting the number of independent variables inserted into each model. In eight separate models of the association between IAFA and diabetes risk, the magnitude of this association was not appreciably changed by adjustment for age, sex, family history of diabetes, or BMI; TFA, abdominal subcutaneous, or nonabdominal subcuta-

Table 2—*Multivariate models of the incidence of diabetes in relation to intra-abdominal fat area among second-generation (nisei, models 1–7) and third-generation (sansei, models 8–10) Japanese Americans*

Model	Variables in the model	OR (95% CI)	*P*
1	Age	1.4 (1.0–2.0)	0.065
	Female sex	1.8 (0.8–4.2)	0.176
	IGT at baseline	4.5 (2.3–9.0)	<0.001
	Family history of diabetes	1.9 (1.0–3.3)	0.040
	Intra-abdominal fat area	1.6 (1.1–2.3)	0.019
	Non–intra-abdominal fat area	0.7 (0.5–1.0)	0.064
	Fasting C-peptide level	1.4 (1.1–1.8)	0.016
	IIR	0.5 (0.3–0.9)	0.022
2	Same variables as model 1, except fasting insulin substituted for fasting C-peptide		
	Fasting insulin	1.3 (0.9–1.7)	0.165
	Intra-abdominal fat area	1.6 (1.1–2.3)	0.022
3	Same variables as model 1, except BMI substituted for non–intra-abdominal fat area		
	BMI	0.8 (0.5–1.2)	0.251
	Intra-abdominal fat area	1.6 (1.1–2.4)	0.023
4	Same variables as model 1, except total fat area substituted for non–intra-abdominal fat area		
	Total fat	0.7 (0.4–1.0)	0.064
	Intra-abdominal fat area	1.8 (1.1–2.8)	0.012
5	Same variables as model 1, except subcutaneous abdominal fat substituted for non–intra-abdominal fat		
	Intra-abdominal fat area	1.6 (1.1–2.3)	0.013
	Subcutaneous abdominal fat area	0.7 (0.5–1.0)	0.078
6	Same variables as model 1, except subcutaneous abdominal fat and nonsubcutaneous abdominal fat areas substituted for intra-abdominal and non–intra-abdominal fat areas		
	Subcutaneous abdominal fat area	0.7 (0.4–1.1)	0.128
	Nonsubcutaneous abdominal fat area	1.4 (0.8–2.3)	0.249
7	Age	1.3 (1.0–1.9)	0.100
	Female sex	3.1 (1.3–7.9)	0.014
	IGT at baseline	3.8 (1.9–7.7)	<0.001
	Family history of diabetes	1.9 (1.0–3.4)	0.039
	Intra-abdominal fat area	1.5 (1.0–2.3)	0.033
	Non–intra-abdominal fat area	0.7 (0.4–1.0)	0.065
	Fasting C-peptide level	1.2 (0.9–1.6)	0.204
	IIR	0.6 (0.4–1.0)	0.072
	Fasting glucose	2.3 (1.5–3.5)	<0.001
8	IGT at baseline	13.2 (2.6–65.9)	0.002
	Intra-abdominal fat area	2.7 (1.5–4.9)	0.001
9	Fasting C-peptide	2.0 (1.1–3.7)	0.024
	Intra-abdominal fat area	2.8 (1.4–5.5)	0.004
10	Fasting glucose	3.0 (1.4–6.7)	0.007
	Intra-abdominal fat area	3.0 (1.6–5.7)	0.001

OR, odds ratio.

neous fat areas; or fasting insulin and IIR (data not shown). Of note, only three variables were significantly associated with diabetes incidence among sansei when adjusting for IAFA: IGT at baseline, fasting C-peptide, and fasting glucose (Table 2, models 8–10). Adjustment for these variables similarly did not result in appreciable change in the magnitude of the association between IAFA and diabetes risk. Because of the small number of outcomes, testing for the significance of nonlinear transformations of IAFA or first-order interactions between IAFA and covariates could not be performed. In models containing IAFA and either IGT or fasting glucose, fasting C-peptide was no longer significantly associated with diabetes incidence (data not shown).

CONCLUSIONS — This analysis confirms an important role for visceral adiposity in the development of type 2 diabetes. In both generations, this effect was independent of other measures of total and regional adiposity, diabetes family history, sex, correlates of insulin resistance (fasting C-peptide) and secretion (IIR), and glycemia (IGT, fasting glucose). A linear association between IAFA area and diabetes incidence best fit the nisei data. The association between IAFA and diabetes incidence among nisei did not significantly vary by sex, IGT at baseline, or family history of diabetes. Because of the small number of sansei cases, assessment of nonlinear effects and interaction was not possible.

Among nisei, no measure of overall or regional adiposity was predictive of diabetes incidence except for IAFA. In fat-adjusted models (Table 2), the significant association between IAFA and diabetes incidence persisted. Greater subcutaneous abdominal fat area was unrelated to a higher diabetes incidence in univariate analysis, and models adjusted for intra-abdominal (model 5) or non–intra-abdominal (model 6) fat area and other covariates reinforced this conclusion. Although there exist cross-sectional reports of an association between greater truncal subcutaneous fat area and insulin resistance (30,31), no report to our knowledge has prospectively shown that this fat depot leads to higher risk of diabetes. Total and non–intra-abdominal fat area measurements were similarly not significantly related to diabetes incidence among nisei in multivariate models.

Among sansei, all measures of total and regional adiposity were positively associated with diabetes incidence in univariate models (Table 1). In models adjusted for IAFA, the associations between other adiposity measures declined substantially in both magnitude and significance, although in these same models a significant association remained between the visceral depot measurement and diabetes incidence (data not shown).

These results are consistent with a previous 1990 report based on a mean 2.5-year follow-up of the nisei men only (19). In particular, the association between IAFA

in the 1990 study diminished with adjustment for glycemia. In the present analysis, IAFA remained significantly associated with diabetes incidence after adjustment for fasting glucose and IGT, reflecting the 2-h glucose, in the nisei (model 7) and sansei (model 8). Differences in the results of this study compared with its predecessor are likely explained by the development of additional cases with the passage of time among nisei men (40 compared with 15 in 1990) and the inclusion of nisei women, thereby boosting statistical power. It is also possible that glycemia plays an earlier role in the prediction of diabetes risk than IAFA.

In addition, this analysis confirmed that correlates of insulin resistance (fasting C-peptide) and secretion (IIR) were related to diabetes incidence as previously demonstrated, with higher resistance and lower secretion associated with greater risk of this outcome (6,7). Furthermore, these effects are shown by our data to be independent of directly measured visceral adiposity, a finding not previously demonstrated to our knowledge. This raises the possibility that visceral obesity may contribute to the development of diabetes through actions independent of its effects on insulin sensitivity, such as a direct effect on glucose effectiveness, although previous studies have not demonstrated an association between glucose effectiveness and BMI or body circumference measurements (32). Fasting C-peptide was used in these models in place of the insulin measurement among nisei for empiric reasons, because C-peptide proved to be a stronger predictor of diabetes occurrence in univariate (Table 1) and multivariate (Table 2 and models 1 and 2) analyses. C-peptide may better reflect insulin level than the fasting insulin measurement, because the latter undergoes hepatic extraction dependent on body fat distribution that may confound the association between diabetes risk and insulinemia (33). Of note, adjustment for fasting glucose results in a reduction in the magnitude of the odds ratios for both C-peptide and IIR among nisei (model 7), probably because abnormal insulin sensitivity and secretion would serve to increase the plasma glucose level (34,35). The sansei analysis confirms the independent effects of IAFA and fasting C-peptide on diabetes incidence. The IIR is not significantly associated with diabetes incidence, possibly because of reduced statistical power or a different role for insulin secretion in the pathogenesis of diabetes in these younger subjects.

The higher risk of type 2 diabetes in relation to IGT or family history of diabetes has been shown in previous prospective studies (36–38). This analysis demonstrated that these effects were independent of visceral fat area, fasting C-peptide, and the IIR among nisei. Among sansei, this finding was true for IGT only, which independently predicted diabetes incidence after adjustment for IAFA (model 8). A higher risk of diabetes was related to female sex among nisei only (model 7) for unknown reasons and will require further investigation.

Several potential sources of bias exist in this study. No direct measurement of total body fat mass was made, although it has been shown that the sum of CT-slice areas used in this analysis correlated very highly with this measure in this (M. McNeely, personal communication) and other populations (17). Visceral fat volume was represented with a single CT-scan slice of the abdomen at the L4-L5 level. A very high correlation exists between this measurement and directly ascertained total visceral fat volume, thereby diminishing the potential for bias (14,26). Indirect measurements that imperfectly reflect insulin sensitivity (fasting C-peptide) and insulin secretory capacity (IIR) were used as well (22,24). Any error that occurred as a result of these indirect measures was most likely random as opposed to systematic in nature, thereby biasing study results toward the null value (28). Therefore, significant differences probably reflect underestimates of the true effect, although no differences might be explained by this random misclassification bias, insufficient sample size, or absence of a true effect. Because a single ethnic group was included, results may not be generalizable to other ethnic groups or populations with a higher prevalence of obesity. The 100% Japanese origin of the subjects provides high assurance that confounding of study findings by ethnic admixture is unlikely. It is also unlikely that loss to follow-up resulted in bias, because complete follow-up was high, ranging from, depending on the study group, a low of 81% (nisei men) to a high of 93% (sansei men). Although most subjects in this study were nonobese by BMI, it has been shown that Asians have a higher percent body fat at the same BMI level than Caucasians (39). Autoantibodies to GAD were not measured in this study, but it is unlikely that the inclusion of subjects with type 1 diabetes in our sample caused important bias. The proportion of falsely classified type 1 subjects is likely to be low, given that the prevalence of anti-GAD autoantibodies is low in Japanese (2.2%), and Japanese have nearly the lowest incidence and prevalence of type 1 diabetes in the world (40,41).

Regional adipose tissue depots are known to vary in terms of physiology, which helps to explain the different associations noted in this study between diabetes incidence and fat location. Visceral fat is lipolytically more active and less sensitive to the antilipolytic effects of insulin (42). Visceral fat may result in hepatic delivery of excessive amounts of free fatty acids via the portal vein (43), which may further accentuate insulin resistance (44). Although this is one potential mechanism for the association between visceral fat and diabetes risk, it has been shown that higher insulin resistance and lower secretion precede intra-abdominal fat accumulation in a subsegment of this population (nisei men) (45). More research is needed to confirm the results of this study and help to establish the sequence of events underlying the development of type 2 diabetes.

In conclusion, this study identified visceral fat or an unmeasured correlate as having a key role in the development of type 2 diabetes in Japanese Americans. The higher diabetes incidence with increasing visceral adiposity is independent of measures of insulin resistance and secretion, suggesting that the effect of visceral fat on diabetes risk may be mediated by mechanisms not reflected by fasting C-peptide level or the IIR. Given that fasting C-peptide and the IIR have been shown to predict visceral fat accumulation, it is possible that visceral fat, fasting C-peptide, and the IIR are all related to an antecedent event not measured in this study that increases diabetes risk. Further research on these associations is needed to confirm these findings and may offer new insights into the sequence of metabolic events that eventuate in type 2 diabetes.

Acknowledgments — This research was supported by National Institutes of Health Grants DK-31170 and HL-49293 and by facilities and services provided by the Diabetes and Endocrinology Research Center (DK-17047), Clinical Nutrition Research Unit (DK-35816), and the General Clinical Research Center (RR-00037) at the University of Washington.

References

1. Wei M, Gaskill SP, Haffner SM, Stern MP: Waist circumference as the best predictor of

noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans: a 7-year prospective study. *Obes Res* 5:16–23, 1997
2. Dowse GK, Zimmet PZ, Gareeboo H, George K, Alberti MM, Tuomilehto J, Finch CF, Chitson P, Tulsidas H: Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. *Diabetes Care* 14:271–282, 1991
3. Cassano PA, Rosner B, Vokonas PS, Weiss ST: Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus: a prospective cohort study of men in the normative aging study. *Am J Epidemiol* 136:1474–1486, 1992
4. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE: Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women: the Nurses' Health Study. *Am J Epidemiol* 145:614–619, 1997
5. Karter AJ, Mayer-Davis EJ, Selby JV, D'Agostino RB Jr, Haffner SM, Sholinsky P, Bergman R, Saad MF, Hamman RF: Insulin sensitivity and abdominal obesity in African-American, Hispanic, and non-Hispanic white men and women: the Insulin Resistance and Atherosclerosis Study. *Diabetes* 45:1547–1555, 1996
6. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. *Ann Intern Med* 113:909–915, 1990
7. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 329:1988–1992, 1993
8. Bjorntorp P: Metabolic implications of body fat distribution. *Diabetes Care* 14:1132–1143, 1991
9. Bjorntorp P: Regional obesity and NIDDM. *Adv Exp Med Biol* 334:279–285, 1993
10. Despres JP: Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition* 9:452–459, 1993
11. Kissebah AH: Intra-abdominal fat: is it a major factor in developing diabetes and coronary artery disease? *Diabetes Res Clin Pract* 30 (Suppl. 30):25–30, 1996
12. Boyko EJ, Leonetti DL, Bergstrom RW, Newell-Morris L, Fujimoto WY: Visceral adiposity, fasting plasma insulin, and blood pressure in Japanese-Americans. *Diabetes Care* 18:174–181, 1995
13. Boyko EJ, Leonetti DL, Bergstrom RW, Newell-Morris L, Fujimoto WY: Visceral adiposity, fasting plasma insulin, and lipid and lipoprotein levels in Japanese Americans. *Int J Obes Relat Metab Disord* 20: 801–808, 1996
14. Schoen RE, Thaete FL, Sankey SS, Weissfeld JL, Kuller LH: Sagittal diameter in comparison with single slice CT as a predictor of total visceral adipose tissue volume. *Int J Obes Relat Metab Disord* 22: 338–342, 1998
15. Kekes-Szabo T, Hunter GR, Nyikos I, Williams M, Blaudeau T, Snyder S: Anthropometric equations for estimating abdominal adipose tissue distribution in women. *Int J Obes Relat Metab Disord* 20:753–758, 1996
16. Weits T, van der Beek EJ, Wedel M, Ter Haar Romeny BM: Computed tomography measurement of abdominal fat deposition in relation to anthropometry. *Int J Obes Relat Metab Disord* 12:217–225, 1988
17. Ferland M, Despres JP, Tremblay A, Pinault S, Nadeau A, Moorjani S, Lupien PJ, Theriault G, Bouchard C: Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. *Br J Nutr* 61:139–148, 1989
18. Despres JP, Prud'homme D, Pouliot MC, Tremblay A, Bouchard C: Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. *Am J Clin Nutr* 54:471–477, 1991
19. Bergstrom RW, Newell-Morris LL, Leonetti DL, Shuman WP, Wahl PW, Fujimoto WY: Association of elevated fasting C-peptide level and increased intra-abdominal fat distribution with development of NIDDM in Japanese-American men. *Diabetes* 39: 104–111, 1990
20. Fujimoto WY, Leonetti DL, Kinyoun JL, Shuman WP, Stolov WC, Wahl PW: Prevalence of complications among second-generation Japanese-American men with diabetes, impaired glucose tolerance, or normal glucose tolerance. *Diabetes* 36: 730–739, 1987
21. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
22. Laakso M: How good a marker is insulin level for insulin resistance? *Am J Epidemiol* 137:959–965, 1993
23. Phillips DI, Clark PM, Hales CN, Osmond C: Understanding oral glucose tolerance: comparison of glucose or insulin measurements during the oral glucose tolerance test with specific measurements of insulin resistance and insulin secretion. *Diabet Med* 11:286–292, 1994
24. Wareham NJ, Phillips DI, Byrne CD, Hales CN: The 30 minute insulin incremental response in an oral glucose tolerance test as a measure of insulin secretion (Letter). *Diabet Med* 12:931, 1995
25. Shuman WP, Morris LL, Leonetti DL, Wahl PW, Moceri VM, Moss AA, Fujimoto WY: Abnormal body fat distribution detected by computed tomography in diabetic men. *Invest Radiol* 21:483–487, 1986
26. Han TS, Kelly IE, Walsh K, Greene RM, Lean ME: Relationship between volumes and areas from single transverse scans of intra-abdominal fat measured by magnetic resonance imaging. *Int J Obes Relat Metab Disord* 21:1161–1166, 1997
27. Prentice R, Gloeckler L: Regression analysis of grouped survival data with application to breast cancer data. *Biometrics* 34:57–67, 1978
28. Rothman KJ, Greenland S: Introduction to regression models. In *Modern Epidemiology* Philadelphia, Lippincott-Raven, 1998, p. 127–399
29. Najjar MF, Rowland M: Anthropometric reference data and prevalence of overweight, United States, 1976–80. Vital and Health Statistics–Series 11: Data From the National Health Survey, 1987, p. 1–73
30. Goodpaster BH, Thaete FL, Simoneau JA, Kelley DE: Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 46:1579–1585, 1997
31. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM: Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 96:88–98, 1995
32. Clausen JO, Borch-Johnsen K, Ibsen H, Bergman RN, Hougaard P, Winther K, Pedersen O: Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians: analysis of the impact of gender, body fat, physical fitness, and life-style factors. *J Clin Invest* 98:1195–1209, 1996
33. Peiris AN, Mueller RA, Smith GA, Struve MF, Kissebah AH: Splanchnic insulin metabolism in obesity: influence of body fat distribution. *J Clin Invest* 78:1648–1657, 1986
34. Bergman RN: Toward physiological understanding of glucose tolerance: minimal model approach. *Diabetes* 38:1512–1527, 1989
35. O'Rahilly S, Hattersley A, Vaag A, Gray H: Insulin resistance as the major cause of impaired glucose tolerance: a self-fulfilling prophesy? *Lancet* 344:585–589, 1994
36. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 46:701–710, 1997
37. Ohlson LO, Larsson B, Bjorntorp P, Eriksson H, Svardsudd K, Welin L, Tibblin G, Wilhelmsen L: Risk factors for type 2 (non-insulin-dependent) diabetes mellitus: thir-

teen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia*31:798–805, 1988
38. Stern MP, Morales PA, Valdez RA, Monterrosa A, Haffner SM, Mitchell BD, Hazuda HP: Predicting diabetes: moving beyond impaired glucose tolerance. *Diabetes*42: 706–714, 1993
39. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN: Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. *Am J Clin Nutr*60:23–28, 1994
40. Karvonen M, Tuomilehto J, Libman I, LaPorte R: A review of the recent epidemiological data on the worldwide incidence of type 1 (insulin-dependent) diabetes mellitus: World Health Organization DIAMOND Project Group [Erratum in *Diabetologia*38:642, 1994]. *Diabetologia*36: 883–892, 1993
41. Tsuruoka A, Matsuba I, Toyota T, Isshiki G, Nagataki S, Ikeda Y: Antibodies to GAD in Japanese diabetic patients: a multicenter study. *Diabetes Res Clin Pract*28:191–199, 1995
42. Bolinder J, Kager L, Ostman J, Arner P: Differences at the receptor and postreceptor levels between human omental and subcutaneous adipose tissue in the action of insulin on lipolysis. *Diabetes*32:117–123, 1983
43. Bjorntorp P: Regional fat distribution: implications for type II diabetes. *Int J Obes Relat Metab Disord*16 (Suppl. 4):S19–S27, 1992
44. Randle PJ, Garland PB, Hales CN, Newsholme EA: The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet*i: 785–789, 1963
45. Boyko EJ, Leonetti DL, Bergstrom RW, Newell-Morris L, Fujimoto WY: Low insulin secretion and high fasting insulin and C-peptide levels predict increased visceral adiposity: 5-year follow-up among initially nondiabetic Japanese-American men. *Diabetes*45:1010–1015, 1996