

Visceral Adiposity Is an Independent Predictor of Incident Hypertension in Japanese Americans

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Background: Visceral adiposity is generally considered to play a key role in the metabolic syndrome.

Objective: To examine the relationship between directly measured visceral adiposity and the risk for incident hypertension, independent of other adipose depots and fasting plasma insulin levels.

Design: Community-based prospective cohort study with 10- to 11-year follow-up.

Setting: King County, Washington.

Participants: 300 Japanese Americans with a systolic blood pressure less than 140 mm Hg and a diastolic blood pressure less than 90 mm Hg who were not taking antihypertensive medications, oral hypoglycemic medications, or insulin at study entry.

Measurements: Abdominal, thoracic, and thigh fat areas were measured by using computed tomography. Total subcutaneous fat area was calculated as the sum of these fat areas excluding the intra-abdominal fat area. Hypertension during follow-up was defined as having a systolic blood pressure of 140 mm Hg or greater, having a diastolic blood pressure of 90 mm Hg or greater, or taking antihypertensive medications.

Results: There were 92 incident cases of hypertension during the follow-up period. The intra-abdominal fat area was associated with an increased risk for hypertension. Multiple-adjusted odds ratios of hypertension for quartiles of intra-abdominal fat area (1 = lowest; 4 = highest) were 5.07 (95% CI, 1.75 to 14.73) for quartile 3 and 3.48 (CI, 1.01 to 11.99) for quartile 4 compared with quartile 1 after adjustment for age, sex, fasting plasma insulin level, 2-hour plasma glucose level, body mass index, systolic blood pressure, alcohol consumption, smoking status, and energy expenditure through exercise ($P = 0.003$ for quadratic trend). The intra-abdominal fat area remained a significant risk factor for hypertension, even after adjustment for total subcutaneous fat area, abdominal subcutaneous fat area, or waist circumference; however, no measure of these fat areas was associated with risk for hypertension in models that contained the intra-abdominal fat area.

Limitations: It is not known whether these results pertain to other ethnic groups.

Conclusions: Greater visceral adiposity increases the risk for hypertension in Japanese Americans.

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A central pattern of body fat distribution is now generally considered to play an important role in the metabolic syndrome, which involves obesity, insulin resistance, hyperinsulinemia, dyslipidemia, glucose intolerance, and hypertension (1, 2). In particular, visceral adiposity rather than regional or generalized obesity appears to play a key role in these diseases (3–7).

Several cross-sectional and prospective studies have examined associations between hypertension and greater central obesity, as measured by waist circumference, the ratio of waist-to-hip circumference, or the ratio of subscapular-to-triceps skinfold thickness (8–15). The cross-sectional studies have reported a positive association (8, 9), but the prospective studies have been inconclusive (10–15). These studies have posited that visceral adiposity and insulin resistance are the most important factors linking greater abdominal obesity (as assessed by surface measurements) and hypertension. Although visceral fat is thought to affect the prevalence of hypertension, only 3 cross-sectional studies have suggested a possible association between visceral adiposity (measured by using computed tomography [CT]) and blood pressure (3, 4, 16); however, the results of these studies were inconclusive. No prospective studies have examined whether directly measured visceral fat is associated with an increased risk for incident hypertension. Therefore, we prospectively examined the relationship between

directly measured visceral adiposity and the risk for incident hypertension, independent of other measurements of total and regional adiposity and fasting plasma insulin.

METHODS

Study Sample

Between 1983 and 1988, we enrolled 658 second- and third-generation Japanese Americans who were between 34 and 76 years of age (mean age, 54.2 years) into the Japanese American Community Diabetes Study (17, 18). Participants were chosen from volunteers through community-wide recruitment and were representative of Japanese-American residents of King County, Washington, in age distribution, residential distribution, and parental immigration pattern. A comprehensive mailing list and telephone directory that included almost 95% of the Japanese-American population of King County, Washington, was used. All participants were of 100% Japanese ancestry. Participants returned for follow-up examinations 5 to 6 and 10 to 11 years after a baseline evaluation.

For the current analysis, eligible participants had systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg and were not taking antihypertensive or oral hypoglycemic medications or insulin. We excluded 277 of the 658 participants in the origi-

nal cohort because they did not meet the inclusion criteria. We excluded an additional 67 persons because of death, loss to follow-up, or withdrawal from the study. Another 14 persons who completed follow-up but had missing covariate information were also excluded. The analytic cohort consisted of 300 persons (Figure). The follow-up rate in the present study was 91% (345 of 381) at the 5- to 6-year examination and 80% (304 of 381) at the 10- to 11-year examination (Figure).

Data Collection

All measurements were made in the General Clinical Research Center at the University of Washington, Seattle, Washington. The Human Subjects Review Committee at the University of Washington approved the protocol for this research, and we obtained signed informed consent from all participants. At all examinations, blood pressure was measured to the nearest 2 mm Hg with a mercury sphygmomanometer while the participant was in a recumbent position. Systolic blood pressure was determined by the first perception of sound, and diastolic blood pressure was determined at the disappearance of sounds (fifth-phase Korotkoff). Average blood pressure was calculated from the second and third of 3 consecutive measurements. We diagnosed hypertension at baseline or follow-up if the average systolic blood pressure was 140 mm Hg or greater, the average diastolic blood pressure was 90 mm Hg or greater, or the participant was receiving antihypertensive medications. We classified participants as hypertensive if they met these criteria at the follow-up examination at 5 to 6 years or 10 to 11 years (Figure). All patients received a 75-g oral glucose tolerance test after a 10-hour fast. We then used the American Diabetes Association criteria (19) to classify patients as having normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes mellitus. Blood samples were drawn after an overnight 10-hour fast and during an oral glucose tolerance test for measurement of plasma glucose and insulin levels. We used an automated glucose oxidase method to assay plasma glucose. Fasting plasma insulin was measured by radioimmunoassay, as reported previously (5, 7). We measured triglyceride and high-density lipoprotein cholesterol levels in the Northwest Lipid Research Laboratory, according to modified procedures of the Lipid Research Clinics (20).

We calculated body mass index (BMI) as the weight in kilograms divided by height in meters squared. For CT scans, we used single slices of the thorax, abdomen (at the umbilicus), and mid-thigh to measure cross-sectional subcutaneous thoracic, abdominal, and right thigh and intra-abdominal fat areas (measured in cm^2), as described elsewhere (21). We directly estimated visceral adiposity from the intra-abdominal fat area. This measurement has been reported to have a high correlation with directly ascertained total visceral fat volume measured by using CT or magnetic resonance imaging (22, 23). We calculated total subcutaneous fat area as the sum of subcutaneous thoracic

Context

Central obesity and hypertension are well-established components of the metabolic syndrome, but what exactly is the relationship between visceral adiposity and hypertension?

Contribution

This prospective study used computed tomography to measure multiple body fat areas of 300 middle-aged, normotensive Japanese Americans. Ninety-two participants developed hypertension within 10 to 11 years. Greater visceral adiposity, independent of other measures of body fat and other risk factors, such as plasma insulin and glucose levels, was associated with increased risk for hypertension.

Cautions

Relationships between visceral adiposity and the development of hypertension may vary in different ethnic groups.

—The Editors

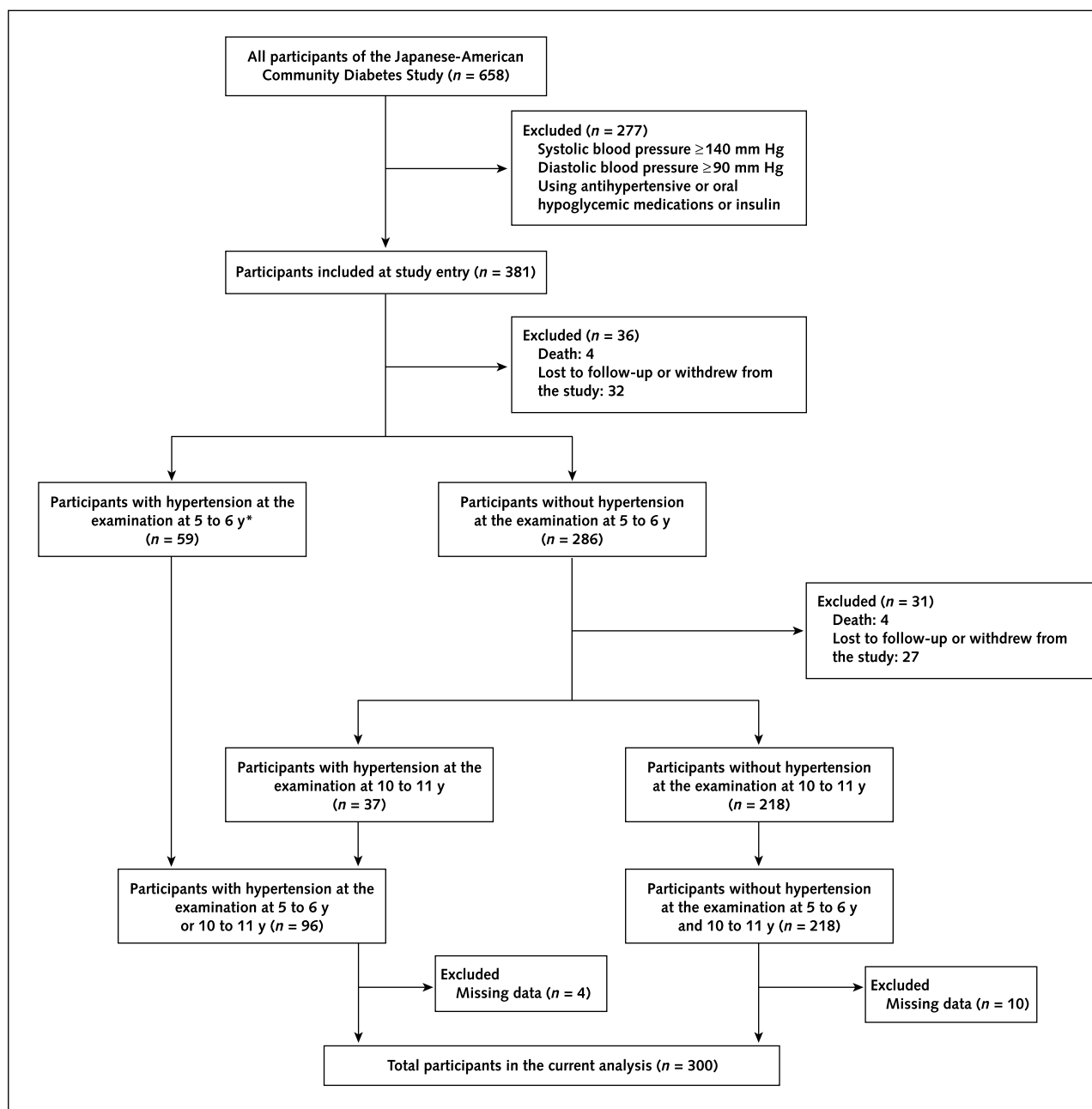
and abdominal fat areas and twice the right thigh subcutaneous fat area. We defined total fat area as total subcutaneous fat area plus intra-abdominal fat area. Among Japanese Americans, total fat area correlates highly with fat mass, as measured by hydrodensitometry ($r = 0.89$ to 0.94) (24). Waist circumference was measured at the level of the umbilicus to the nearest tenth of a centimeter.

Participants were questioned about current use of cigarettes and daily consumption of alcoholic beverages, which was converted into grams of alcohol consumed per day. Usual weekly energy expenditure in kilocalories was estimated from questionnaire data on work and recreational activities, strenuous exercise, distance walked, and stairs climbed, as described elsewhere (25).

Statistical Analysis

We used multiple logistic regression analysis to estimate the odds ratio for incident hypertension in relation to an increase of 1 SD in baseline variables. For rare outcomes, the odds ratio will approximately equal the relative risk. For more frequent outcomes, such as hypertension, the odds ratio will overestimate the relative risk (26). We evaluated nonlinear effects of continuous independent variables by using quadratic and log transformations (27). The linear trends in odds were evaluated by using the median value for each quartile category of continuous variables. To assess departure from linearity, we included linear and quadratic terms (the median and the value squared) in the model (28). To determine whether interaction was present (that is, the relationship between the risk factor and the outcome varied depending on the value of a third variable) (27, 29, 30), we inserted first-order interaction terms into appropriate regression models. We assessed interaction to

Figure. Flow of participants through the study.



*Of the 59 participants with hypertension at the 5- to 6-year examination, 2 died and 8 were lost to follow-up before the 10- to 11-year examination.

determine whether the relationship between hypertension status at follow-up and baseline adipose variables, such as intra-abdominal fat area, subcutaneous abdominal fat area, total subcutaneous fat area, BMI, or waist circumference, differed according to the level of an additional variable (for example, sex) in the model. We used the likelihood ratio test to determine the statistical significance of nonlinear effects of continuous independent variables and interaction terms in the logistic regression models. Multicollinearity was assessed by using the variance inflation factor (31). A variance inflation factor exceeding 10 is regarded as indi-

cating serious multicollinearity, and values greater than 4.0 may be a cause for concern (31). We calculated the 95% CI for each odds ratio. *P* values were 2-tailed. We performed statistical analyses using Stata SE, version 8.0 (Stata Corp., College Station, Texas).

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Among the 300 eligible men and women followed for 10 to 11 years, there were 92 incident cases of hypertension. In univariate logistic regression analysis, intra-abdominal fat area, abdominal subcutaneous fat area, total subcutaneous fat area, total fat area, BMI, and waist circumference were associated with a higher incidence of hypertension. Fasting plasma insulin level, fasting plasma glucose level, 2-hour plasma glucose level, and high-density lipoprotein cholesterol level were also associated with incidence of hypertension (Table 1). We also compared the baseline characteristics of participants included in the present analyses (Table 1) with baseline characteristics of persons with inadequate follow-up (data not shown). Baseline characteristics by follow-up status did not differ significantly, except that participants who completed follow-up had on average slightly higher diastolic blood pressure than those who missed a follow-up examination (73.4 mm Hg vs. 71.4 mm Hg; $P = 0.047$).

To further assess the effect of intra-abdominal fat area on the incidence of hypertension, independent of the effects of regional or total adiposity, we stratified participants according to median values of total fat area, subcutaneous abdominal fat area, total subcutaneous fat area, BMI, or

waist circumference. All values showed that greater visceral adiposity was associated with a higher incidence of hypertension (Table 2). On the other hand, after participants were stratified according to tertiles of intra-abdominal fat area, the relationship between a higher incidence of hypertension and total fat area, subcutaneous abdominal fat area, total subcutaneous fat area, BMI, or waist circumference was not consistent or was of small magnitude (Table 2).

In multiple logistic regression analysis, insertion of quadratic or log transformations of all continuous variables except intra-abdominal fat area into all models without systolic blood pressure (Table 3) did not result in an improvement in fit compared with the linear model that did not include the quadratic or log transformation. Because the linear and quadratic transformation of intra-abdominal fat area was significant in all models ($P < 0.05$), only intra-abdominal fat area showed a nonlinear association with the incidence of hypertension. Therefore, we fit a model by using intra-abdominal fat area categorized by quartiles to account for this nonlinearity (Table 3). The relative odds of hypertension in relation to quartiles of intra-abdominal fat area demonstrated a leveling off and slight decrease beyond the median value. Nonlinear trends in the relative

Table 1. Characteristics of Study Participants at Baseline according to Whether Hypertension Developed after the 10- to 11-Year Follow-up*

Characteristic	Total (n = 300)	Hypertension Status after Follow-up		Crude Odds Ratio (95% CI)†	P Value‡
		Normotension (n = 208)	Hypertension (n = 92)		
Age, y	49.6 ± 11.8	47.3 ± 11.3	54.7 ± 11.3	1.91 (1.47–2.47)	<0.001
Women, %	50	52.4	44.6	0.73 (0.45–1.20)	>0.2
Systolic blood pressure, mm Hg	120.7 ± 10.1	118.7 ± 9.7	125.3 ± 9.4	2.10 (1.57–2.80)	<0.001
Diastolic blood pressure, mm Hg	73.4 ± 7.6	72.5 ± 7.6	75.6 ± 7.1	1.56 (1.19–2.03)	0.001
Metabolic variables					
Fasting plasma insulin level, pmol/L	77.4 ± 38.1	74.1 ± 35.9	84.8 ± 42.0	1.31 (1.03–1.66)	0.028
Fasting plasma glucose level, mmol/L (mg/dL)	5.23 ± 1.10 (94.2 ± 19.8)	5.10 ± 1.01 (91.9 ± 18.2)	5.53 ± 1.23 (99.6 ± 22.1)	1.50 (1.18–2.00)	0.007
2-h plasma glucose level, mmol/L (mg/dL)	7.53 ± 2.98 (135.6 ± 53.7)	7.17 ± 2.65 (129.1 ± 47.8)	8.35 ± 3.49 (150.4 ± 62.9)	1.46 (1.14–1.88)	0.003
Triglyceride level, mmol/L (mg/dL)	1.46 ± 1.22 (129.2 ± 108.1)	1.44 ± 1.37 (128.0 ± 121.4)	1.49 ± 0.78 (132.0 ± 69.5)	1.04 (0.82–1.32)	>0.2
High-density lipoprotein cholesterol, mmol/L (mg/dL)	1.55 ± 0.43 (59.8 ± 16.8)	1.58 ± 0.46 (61.1 ± 17.9)	1.47 ± 0.35 (56.8 ± 13.6)	0.77 (0.5–0.99)	0.044
Adipose variables					
Intra-abdominal fat area, cm ²	70.9 ± 43.7	63.6 ± 42.9	87.5 ± 40.9	See quartile model below	
Intra-abdominal fat area quartiles, n					
Quartile 1	75	68	7	1.00	
Quartile 2	75	56	19	3.30 (1.29–8.40)	0.013
Quartile 3	76	42	34	7.86 (3.20–19.34)	<0.001
Quartile 4	74	42	32	7.40 (3.00–18.27)	<0.001
Abdominal subcutaneous fat area, cm ²	152.2 ± 73.3	143.9 ± 69.2	171.0 ± 78.9	1.44 (1.13–1.84)	0.004
Total subcutaneous fat area, cm ² §	382.1 ± 170.0	366.4 ± 160.2	417.5 ± 186.3	1.34 (1.05–1.71)	0.018
Total fat area, cm ² §	453.0 ± 191.6	430.0 ± 184.2	505.0 ± 198.7	1.47 (1.15–1.88)	0.002
Body mass index, kg/m ²	23.7 ± 3.1	23.5 ± 3.2	24.4 ± 3.0	1.35 (1.05–1.72)	0.019
Waist circumference, cm	84.5 ± 8.3	83.4 ± 8.3	87.1 ± 7.8	1.58 (1.22–2.04)	0.001
Daily alcohol consumption, g/d	5.1 ± 11.0	5.9 ± 12.3	3.6 ± 7.1	0.78 (0.58–1.05)	0.105
Weekly energy expenditure, kcal/wk	6562 ± 6829	6960 ± 7292	5661 ± 5575	0.81 (0.62–1.07)	0.132
Cigarette use, %	14.7	15.9	12.0	0.72 (0.35–1.50)	>0.2

* Values expressed with a plus/minus sign are the mean ± SD.

† Odds ratios for continuous variables reflect a 1-SD magnitude increase.

‡ For univariate logistic regression analysis.

§ Represents sums of adipose tissue areas, as determined by multiple computed tomography slices (described in the text).

Table 2. Incidence of Hypertension according to Intra-Abdominal Fat Area, Total Fat Area, Abdominal Subcutaneous Fat Area, Total Subcutaneous Fat Area, Body Mass Index, and Waist Circumference

Variable	Hypertension according to Tertile of Intra-Abdominal Fat Area		
	Tertile 1	Tertile 2	Tertile 3
	←————— <i>n/n (%)</i> —————→		
Total fat area			
≤424 cm ²	9/83 (10.8)	15/44 (34.1)	11/23 (47.8)
>424 cm ²	5/17 (29.4)	21/56 (37.5)	31/77 (40.3)
Abdominal subcutaneous fat area			
≤139 cm ²	8/74 (10.8)	15/42 (35.7)	16/34 (47.1)
>139 cm ²	6/26 (23.1)	21/58 (36.2)	26/66 (39.4)
Total subcutaneous fat area			
≤351 cm ²	7/66 (10.6)	14/42 (33.3)	17/42 (40.5)
>351 cm ²	7/34 (20.6)	22/58 (37.9)	25/58 (43.1)
Body mass index			
≤23.4 kg/m ²	11/81 (13.6)	17/46 (37.0)	11/23 (47.8)
>23.4 kg/m ²	3/19 (15.8)	19/54 (35.2)	31/77 (40.3)
Waist circumference			
≤84.4 cm	14/91 (15.4)	16/45 (35.6)	6/14 (42.9)
>84.4 cm	0/9 (0)	20/55 (36.4)	36/86 (41.9)

odds of hypertension in relation to quartiles of intra-abdominal fat area were significant in all models of **Table 3**, although linear trends were not significant. In all models without systolic blood pressure, we examined the significance of the first-order interaction terms between intra-abdominal fat area and the other variables. None of these interactions was significant. Correlation coefficients between intra-abdominal fat area and BMI, total fat area, abdominal subcutaneous fat area, total subcutaneous fat area, or waist circumference were 0.665, 0.581, 0.491, 0.398, and 0.745, respectively; however, evidence for multicollinearity was absent because the variance inflation factor for independent variables in all models in **Table 3** was less than 4.0. Because the variance inflation factor between the highest quartile of intra-abdominal fat area and total body fat area was 4.2, we did not adjust for this covariate in the models.

We tested several regression models to assess the effects of body fat distribution on incident hypertension (**Table 3**). After adjustment for age, sex, fasting plasma insulin level, 2-hour plasma glucose level, BMI, systolic blood pressure, alcohol consumption, smoking status, and energy expenditure through exercise, intra-abdominal fat area was associated with an increased risk for incident hypertension (model 1, **Table 3**). Models 2 to 4 of **Table 3** were identical to model 1, with the exception that a different adiposity variable was used in place of BMI. In all models, the association between intra-abdominal fat area and incident hypertension did not change (models 2 to 4, **Table 3**). Also, none of the other measures of regional or total adiposity emerged as being significantly related to incident hypertension (models 1 to 4, **Table 3**). In all models, age and systolic blood pressure were associated with an increased incidence of hypertension, but fasting plasma insulin and 2-hour plasma glucose values were not. Substitution of diastolic blood pressure for systolic blood pressure

did not change these results. Diastolic blood pressure was also significantly related to the risk for hypertension in all models (data not shown). Further adjustment of models with systolic blood pressure or diastolic blood pressure for serum triglyceride or high-density lipoprotein cholesterol levels did not influence the relative odds estimates of incident hypertension in relation to intra-abdominal fat area (data not shown).

We examined the association between total fat area and the risk for hypertension in a model that did not include intra-abdominal fat area. After adjustment for age, sex, fasting plasma insulin level, 2-hour plasma glucose level, systolic blood pressure, alcohol consumption, smoking status, and energy expenditure through exercise, total fat area was not associated with the risk for hypertension. Multiple-adjusted odds ratios of hypertension for quartiles of total fat area (1 = lowest; 4 = highest) were 1.45 (95% CI, 0.62 to 3.37) for quartile 2, 1.46 (CI, 0.63 to 3.39) for quartile 3, and 1.92 (CI, 0.73 to 4.97) for quartile 4 compared with quartile 1.

DISCUSSION

These prospective data demonstrate that greater visceral adiposity was associated with an increased risk for incident hypertension. This finding was independent of fasting plasma insulin level; 2-hour plasma glucose level; age; sex; alcohol consumption; smoking status; energy expenditure through exercise; and other measures of total and regional adiposity, such as BMI, total subcutaneous fat area, abdominal subcutaneous fat area, or waist circumference. On the other hand, no measure of these fat areas other than intra-abdominal fat area was associated with incident hypertension after adjustment for baseline intra-abdominal fat area.

Only a few cross-sectional epidemiologic studies that

Table 3. Multivariate Models of the Incidence of Hypertension in Relation to Baseline Values of Intra-Abdominal Fat Area and Other Adipose Depots*

Variable	Odds Ratio (95% CI) for Hypertension in Multivariate Model without Systolic Blood Pressure	P Value	Odds Ratio (95% CI) for Hypertension in Multivariate Model with Systolic Blood Pressure	P Value
Model 1				
Intra-abdominal fat area				
Quartile 2 vs. quartile 1	2.64 (0.98–7.12)		2.78 (1.01–7.61)	
Quartile 3 vs. quartile 1	5.11 (1.80–14.48)	0.003†	5.07 (1.75–14.73)	0.003†
Quartile 4 vs. quartile 1	3.50 (1.04–11.73)		3.48 (1.01–11.99)	
Body mass index	0.94 (0.65–1.34)	>0.2	0.87 (0.60–1.26)	>0.2
Fasting plasma insulin level	1.21 (0.87–1.68)	>0.2	1.13 (0.81–1.57)	>0.2
Age	1.62 (1.16–2.26)	0.005	1.44 (1.02–2.04)	0.039
Female sex	0.72 (0.37–1.38)	>0.2	0.88 (0.44–1.74)	>0.2
2-h plasma glucose level	1.15 (0.87–1.53)	>0.2	1.14 (0.85–1.52)	>0.2
Current smoking vs. nonsmoking	0.68 (0.31–1.49)	>0.2	0.78 (0.35–1.74)	>0.2
Daily alcohol consumption	0.74 (0.52–1.05)	0.090	0.73 (0.51–1.03)	0.074
Weekly energy expenditure	1.02 (0.75–1.38)	>0.2	1.03 (0.75–1.41)	>0.2
Systolic blood pressure	–	–	1.68 (1.22–2.32)	0.002
Model 2				
Intra-abdominal fat area				
Quartile 2 vs. quartile 1	2.37 (0.86–6.52)		2.42 (0.87–6.77)	
Quartile 3 vs. quartile 1	4.29 (1.46–12.62)	0.006†	4.04 (1.34–12.17)	0.008†
Quartile 4 vs. quartile 1	2.73 (0.78–9.51)		2.51 (0.70–8.98)	
Abdominal subcutaneous fat area	1.11 (0.77–1.60)	>0.2	1.10 (0.76–1.60)	>0.2
Fasting plasma insulin level	1.16 (0.84–1.60)	>0.2	1.06 (0.76–1.48)	>0.2
Age	1.64 (1.17–2.29)	0.004	1.48 (1.05–2.09)	0.027
Female sex	0.68 (0.34–1.37)	>0.2	0.87 (0.42–1.79)	>0.2
2-h plasma glucose level	1.17 (0.88–1.55)	>0.2	1.16 (0.87–1.55)	>0.2
Current smoking vs. nonsmoking	0.71 (0.32–1.58)	>0.2	0.81 (0.36–1.83)	>0.2
Daily alcohol consumption	0.74 (0.52–1.06)	0.099	0.74 (0.52–1.04)	0.084
Weekly energy expenditure	1.02 (0.75–1.38)	>0.2	1.03 (0.75–1.40)	>0.2
Systolic blood pressure	–	–	1.66 (1.20–2.29)	0.002
Model 3				
Intra-abdominal fat area				
Quartile 2 vs. quartile 1	2.36 (0.86–6.47)		2.42 (0.87–6.72)	
Quartile 3 vs. quartile 1	4.28 (1.47–12.42)	0.006†	4.04 (1.36–11.99)	0.007†
Quartile 4 vs. quartile 1	2.69 (0.78–9.31)		2.48 (0.70–8.81)	
Total subcutaneous fat area	1.13 (0.77–1.66)	>0.2	1.12 (0.76–1.66)	>0.2
Fasting plasma insulin level	1.16 (0.84–1.59)	>0.2	1.06 (0.76–1.47)	>0.2
Age	1.65 (1.18–2.31)	0.004	1.49 (1.05–2.11)	0.025
Female sex	0.65 (0.30–1.38)	>0.2	0.83 (0.38–1.83)	>0.2
2-h plasma glucose level	1.17 (0.88–1.55)	>0.2	1.16 (0.87–1.55)	>0.2
Current smoking vs. nonsmoking	0.71 (0.32–1.57)	>0.2	0.81 (0.36–1.82)	>0.2
Daily alcohol consumption	0.74 (0.52–1.06)	0.098	0.73 (0.52–1.04)	0.083
Weekly energy expenditure	1.02 (0.75–1.38)	>0.2	1.03 (0.75–1.41)	>0.2
Systolic blood pressure	–	–	1.65 (1.20–2.28)	0.002
Model 4				
Intra-abdominal fat area				
Quartile 2 vs. quartile 1	2.52 (0.92–6.93)		2.64 (0.94–7.36)	
Quartile 3 vs. quartile 1	4.80 (1.62–14.28)	0.004†	4.71 (1.55–14.34)	0.005†
Quartile 4 vs. quartile 1	3.16 (0.88–11.34)		3.08 (0.83–11.36)	
Waist circumference	0.98 (0.66–1.45)	>0.2	0.94 (0.63–1.41)	>0.2
Fasting plasma insulin level	1.21 (0.87–1.68)	>0.2	1.11 (0.79–1.56)	>0.2
Age	1.63 (1.17–2.28)	0.004	1.47 (1.04–2.08)	0.028
Female sex	0.73 (0.39–1.38)	>0.2	0.92 (0.47–1.79)	>0.2
2-h plasma glucose level	1.15 (0.87–1.53)	>0.2	1.14 (0.86–1.52)	>0.2
Current smoking vs. nonsmoking	0.70 (0.32–1.53)	>0.2	0.79 (0.35–1.77)	>0.2
Daily alcohol consumption	0.75 (0.53–1.07)	0.114	0.74 (0.52–1.05)	0.091
Weekly energy expenditure	1.02 (0.75–1.38)	>0.2	1.03 (0.75–1.40)	>0.2
Systolic blood pressure	–	–	1.65 (1.20–2.28)	0.002

* Odds ratios for continuous variables reflect a 1-SD magnitude increase, except where indicated otherwise. Multiple-adjusted odds ratio for quartiles 3 and 4 of the intra-abdominal fat area were 4.79 (95% CI, 1.65 to 13.89) for model 1, 3.78 (CI, 1.26 to 11.39) for model 2, 3.78 (CI, 1.27 to 11.24) for model 3, and 4.52 (CI, 1.48 to 13.82) for model 4 compared with quartile 1 after adjustment for age, sex, fasting plasma insulin level, 2-hour plasma glucose level, body mass index, systolic blood pressure, alcohol consumption, smoking status, and energy expenditure through exercise.

† P value for quadratic trend.

have related CT-measured intra-abdominal fat area to blood pressure and hypertension are available, and the results are inconsistent (3, 4, 16). In one of these studies (3), we reported that among participants who did not have type 2 diabetes and were not taking antihypertensive medication, visceral adiposity (measured by CT) was not independently related to blood pressure after adjustment for age, fasting plasma insulin level, and BMI. In another study (4), we recently reported that among participants not taking oral hypoglycemic medications or insulin, greater visceral adiposity was associated with a higher prevalence of hypertension, independent of other measures of total and regional adiposity, fasting plasma insulin level, 2-hour plasma glucose level, age, and sex. In the study published in 1995 (3), we did not include patients who were taking antihypertensive medication or had type 2 diabetes. This resulted in excluding patients with higher blood pressure values, which may have limited the ability to detect significant relationships between visceral adiposity and hypertension. In a study focused on relatively young men (mean age, 36 years), Johnson and colleagues (16) found no independent effect of CT-measured intra-abdominal fat area on blood pressure. In another study of severely obese women in Japan (mean BMI, 33.6 kg/m²), Kanai and colleagues (32) showed that the ratio of CT-measured intra-abdominal fat area to subcutaneous fat area was related to blood pressure, independent of age and BMI. Because this study focused on a highly select population subsample, the results cannot be generalized to Japanese or other ethnic groups. In all of these studies, conclusions could not be drawn about cause-and-effect relationships because of the cross-sectional nature of the data. To our knowledge, our study is the first prospective study to evaluate the relationship of directly measured visceral adiposity to incident hypertension, independent of other measures of total and regional adiposity and fasting plasma insulin level.

In the present study, we did not identify why visceral fat increases the risk for hypertension. Fasting plasma insulin level was associated with an increased risk for hypertension in univariate analysis, but this association was not significant after adjustment for intra-abdominal fat area. Relationships between visceral fat and incidence of hypertension may be partly mediated by insulin resistance (33–36). On the other hand, adjustment for fasting plasma insulin level did not remove a significant relationship between intra-abdominal fat area and incident hypertension. Furthermore, this association was independent of total body fat and regional fat depots. Therefore, visceral adiposity may affect hypertension through mechanisms unrelated to insulin level or sensitivity. Recently, adipocytes have been recognized as an endocrine gland and have been reported to synthesize and release various peptide and non-peptide compounds (37). Some of these, such as adiponectin and plasminogen-activator inhibitor, have been reported to be related to blood pressure (38, 39). Of interest, some studies have reported that visceral fat produced

considerably more of these peptides than did subcutaneous fat (40–42). Therefore, the function of adipocytes as an endocrine gland may have a key role in relating visceral fat to the risk for hypertension. The role of visceral adiposity in the pathogenesis of hypertension requires further investigation.

Our study has several limitations. First, we used the sum of the areas from a limited number of CT scans to estimate total body fat mass. However, our group has found that this measurement correlates highly with fat mass, as measured by hydrodensitometry, among Japanese Americans ($r = 0.89$ to 0.94) (24). Visceral fat volume was estimated with a single CT scan at the L4–L5 level. This measurement has been reported to highly correlate with directly ascertained volume of total visceral fat (22, 23).

Second, because we studied a single ethnic group, our results may not be representative of the general population but may apply to native Japanese and possibly other Asian Americans. It is clear that measures of adiposity differ in Asian persons compared with white persons. Asian and Asian-American persons have been reported to have a lower prevalence of obesity, as measured by BMI, than white persons but a higher percentage of body fat at the same BMI level as white persons (43, 44). Whether such differences also exist in relationships between adiposity and incidence of hypertension by ethnicity is not known.

Third, we adjusted our analysis for multiple potential confounding variables, including age, sex, 2-hour plasma glucose level, fasting plasma insulin level, measures of total and regional adiposity, blood pressure, daily alcohol consumption, smoking habit, weekly energy expenditure, and lipid levels. However, other unknown or unmeasured confounding variables might explain the associations we observed between incident hypertension and visceral adiposity.

Fourth, because our definition of hypertension was based in part on the measurement of blood pressure at a single visit, it is possible that measurement error exists regarding the presence or absence of our primary outcome. Fifth, a high proportion of eligible participants completed adequate follow-up for this study, given its duration and time demands. Nonetheless, it is possible that a small degree of incomplete follow-up may have led to bias if attrition was strongly associated with both body fat distribution and risk for hypertension. Because we saw no major differences between participants who did and did not complete follow-up at baseline, except for diastolic blood pressure, we do not believe that there is a high likelihood for bias due to differential loss to follow-up.

In conclusion, these results demonstrate that visceral fat is a significant risk factor for the development of incident hypertension in Japanese Americans. This finding is independent of fasting plasma insulin level, which suggests that the effect of visceral fat on the incidence of hypertension may be mediated by mechanisms not reflected by fasting plasma insulin level. The mechanism by which visceral

fat is associated with incident hypertension remains to be determined. To confirm these findings, further research on these associations is needed.

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