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ORIGINAL CONTRIBUTIONS

Association of Visceral Adipose Tissue with Incident Myocardial Infarction in Older Men and Women

The Health, Aging and Body Composition Study

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Assessment of body fat distribution, particularly visceral adipose tissue, may be important for accurate risk evaluation for cardiovascular disease in the elderly. This 1997–1998 US study examined the association of incident myocardial infarction (MI) with total adiposity (body mass index and fat mass) and body fat distribution (waist-to-thigh ratio, waist circumference, visceral and subcutaneous adipose tissue) in well-functioning men (n = 1,116) and women (n = 1,387) aged 70–79 years enrolled in the Health, Aging and Body Composition Study. There were 116 MI events (71 in men, 45 in women) during an average follow-up time of 4.6 (standard deviation, 0.9) years. No association was found between incident MI and the adiposity or fat distribution variables for men. For women, visceral adipose tissue was an independent predictor of MI (hazard ratio = 1.67, 95% confidence interval: 1.28, 2.17 per standard-deviation increase; $p < 0.001$). No association was found between body mass index or total fat mass and MI events in women. The association of visceral adipose tissue with MI in women was independent of high density lipoprotein cholesterol, interleukin-6 concentration, hypertension, and diabetes (hazard ratio = 1.79, 95% confidence interval: 1.24, 2.58 per standard-deviation increase; $p < 0.01$). The amount of adipose tissue stored in the intraabdominal cavity is an important, independent risk factor for MI in well-functioning, elderly women.

aged; body composition; myocardial infarction; obesity

Abbreviations: BMI, body mass index; CHD, coronary heart disease; Health ABC, Health, Aging and Body Composition; MI, myocardial infarction.

Obesity contributes to the risk of several chronic diseases, including coronary heart disease (CHD) (1–4). However, obesity is a heterogeneous disorder in that the storage depot for excess calories differs widely between persons, and these differences in fat distribution confer differential health risks. Prior studies designed to assess the health risks of body fat distribution have used anthropometric measures such as waist circumference, sagittal diameter, or waist-to-hip ratio to estimate the amount of adipose tissue stored specifically in the abdominal region. The majority of these findings show

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that abdominal fat measures are better predictors of incident CHD in both men and women than total adiposity assessed by body mass index (BMI) (5–11).

The association between these anthropometric measures of abdominal fat and CHD most likely is due to a preponderance of adipose tissue stored in and around the visceral organs. Associations between CHD risk factors and amount of visceral adipose tissue, measured directly with computed tomography or magnetic resonance imaging, are stronger than associations observed with indirect measures of visceral adipose tissue, such as waist and waist-hip ratio (12, 13). However, currently there are very few studies that show a cross-sectional association between directly measured visceral adipose tissue and actual coronary disease (14, 15), and, to our knowledge, only one examined the prospective association between visceral adipose tissue and incident CHD. This study showed that visceral adipose tissue was predictive of CHD onset, independently of BMI, in 175 middle-aged Japanese-American men (16). Data examining the association between visceral adipose tissue and onset of CHD in women or in elderly individuals were absent.

Previous data show that the relative risk of a greater BMI on all-cause mortality (17), cardiovascular disease mortality (18), and CHD (19) declines with age. The fact that the relative accumulation of visceral adipose tissue is higher in older persons (20, 21) may explain the lower disease risk associated with overall body mass with aging. Indeed, there does not appear to be a difference by age in the associations of surrogate measures of visceral adipose tissue with CHD morbidity and mortality (9, 19, 22, 23). While it is more practical to use a surrogate measure of visceral adipose tissue in the clinical setting to assess this risk factor, anthropometric measures provide poor estimates of visceral adipose tissue and are more reflective of total adiposity in older adults (24). Thus, direct assessment of visceral adipose tissue may be important for additional evaluation of CHD risk in an older population.

The current study prospectively examined the associations of several adiposity measures including total adiposity (BMI and fat mass) and body fat distribution (waist-to-thigh ratio, waist circumference, visceral adipose tissue, subcutaneous abdominal adipose tissue, and visceral adipose tissue relative to subcutaneous adipose tissue and total fat mass) with incident fatal or nonfatal myocardial infarction (MI) in a large cohort of older (aged 70–79 years) men and women. We also examined whether the associations of incident MI with adiposity and body fat distribution variables differed by sex, race, or obesity status (BMI: ≤24.9 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2). We hypothesized that visceral adipose tissue would be the best predictor of incident MI among all subgroups and that this association would be independent of BMI and total fat mass.

MATERIALS AND METHODS

Study participants

Participants were well-functioning men and women aged 70–79 years enrolled in the Health, Aging and Body Composition (Health ABC) Study. They were recruited from April 1997 to June 1998 primarily from a random sample of Medicare beneficiaries residing in the areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Subjects were eligible for the study if they reported no difficulty walking a quarter mile (0.4 km), climbing 10 steps, or performing basic activities of daily living. They were ineligible if they reported having a life-threatening illness, had a history of active cancer in the 3 years prior to the study, did not plan to remain in the geographic area for at least 3 years, or were participating in another research study involving modification of their eating or exercise behavior. All participants signed an informed consent, approved by the institutional review boards of the clinical sites.

A total of 6,326 persons were screened by telephone. Of these, 1,885 were ineligible by phone screen, 1,179 refused the initial home visit, 41 were ineligible by home visit, and 146 refused the initial clinic visit. Thus, 3,075 persons (51 percent male, 42 percent Black, 0 percent Hispanic, mean age of 73.6 years) completed a baseline evaluation consisting of a medical questionnaire, health history, venipuncture for laboratory tests, and measurements of blood pressure, body composition, and body fat distribution. For the present analyses, we excluded 572 subjects with prevalent CHD at baseline. Evidence of baseline CHD was adjudicated according to disease algorithms by using self-reported health history (coronary artery bypass surgery, pacemaker, MI, or carotid endarterectomy), medication records (use of anti-angina medication), and electrocardiogram evidence of previous MI. Thus, the present study reports on data from 2,503 participants (1,116 men and 1,387 women).

Incident MI

Each participant was contacted every 6 months to ascertain data about hospitalizations or major outpatient procedures. If participants could not be interviewed, this information was ascertained from proxies. Records from all overnight hospitalizations were obtained and reviewed for evidence of incident MI, defined as death from MI or any overnight hospitalization for MI. All MI diagnoses were adjudicated by physicians at the clinical sites based on information from hospitalization and death records. Date of death was taken from the death certificate, and underlying and contributing causes of death were assigned by the study's death adjudication panel. Only those events confirmed by the Health ABC Disease Adjudication Committee were included in the analyses. The average follow-up time was calculated from the time of the baseline visit until the first event date (for those who had an event) or was censored at the last contact date (for those who did not have an event or were lost to follow-up) or the date of death.

Measures of obesity

Overall adiposity. BMI was calculated as body weight (measured on a standard balance beam scale to the nearest 0.1 kg) divided by height (measured barefoot to the nearest 0.1 cm by using a wall-mounted stadiometer) squared. Total fat mass was determined via a whole body dual energy x-ray absorptiometry scan performed by using the pencil beam

technology (QDR 00; Hologic, Waltham, Massachusetts). Baseline scan measurements were not available for 14 participants.

Body fat distribution. Visceral adipose tissue and subcutaneous abdominal adipose tissue at the L4–L5 level were measured via a Somatom Plus 4 (Siemens, Erlangen, Germany) or a Picker PQ 2000S (Marconi Medical Systems, Cleveland, Ohio) computed tomography scanner in Memphis and a 9800 Advantage scanner (General Electric, Milwaukee, Wisconsin) in Pittsburgh. The scans were conducted at 120 kVp, 200–250 mA/second, at a slice thickness of 10 mm. Subjects were placed in the supine position with their arms above their head and legs elevated with a cushion to reduce the curve in the back. Areas were calculated by multiplying the number of pixels for a given tissue type by the pixel area using ILD development software (RSI Systems, Boulder, Colorado). The external contours of the waist were determined by using a threshold of –224 Hounsfield Units, and the external bone contours were determined at 150 Hounsfield Units. Visceral fat was manually distinguished from subcutaneous fat by tracing along the fascial plane defining the internal abdominal wall. Baseline measurement of visceral and subcutaneous adipose tissue areas was not available for 40 participants.

Waist and thigh circumferences were measured with a flexible plastic tape measure to the nearest 0.1 cm. Waist circumference was taken at the largest abdominal circumference, and thigh circumference was measured midway between the inguinal crease and the proximal border of the patella.

Covariates

Confounding variables. Potential confounder variables of the association between overall adiposity or body fat distribution and incident MI included sociodemographic factors (age, sex, race, study site, education), comorbidity (as assessed by the presence of diabetes, hypertension, chronic obstructive pulmonary disease, stroke, congestive heart failure, or cancer obtained by self-report and medication usage), as well as smoking status, alcohol intake, and medication use. Medications used in the past 2 weeks were brought in at the yearly clinic visit, recorded by research staff, and coded according to the Iowa Drug Information System. The present analyses included data on prevalent use of antihypertensive drugs, statins, antidiabetic drugs, systemic corticosteroids, and hormone replacement therapy.

Explanatory variables. Potential explanatory variables that may causally explain an association of adiposity or body fat distribution with incident MI were also assessed. Concentrations of total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, glucose, insulin, interleukin-6, and C-reactive protein were measured from blood collected by venipuncture after an overnight fast at baseline. Samples were obtained in the morning (mean time, 9:25 a.m.; 50 percent of the participants underwent blood sampling between 8:55 a.m. and 9:58 a.m.); after processing, the specimens were aliquotted into cryovials, were frozen at –70°C, and were shipped to the Health ABC Core Laboratory at the University of Vermont. Lipoprotein lipids were measured by a colorimetric technique on a Vitros 950 analyzer (Johnson & Johnson, New Brunswick, New Jersey). Plasma glucose was measured by using an automated glucose oxidase reaction (YSI 2300 STAT Plus Glucose & Lactate Analyzer; YSI Life Sciences, Inc., Yellow Springs, Ohio), and serum insulin was measured by using a commercially available radioimmunoassay kit (Pharmacia, Uppsala, Sweden). Interleukin-6 was measured in duplicate with an enzyme-linked immunosorbent assay kit from R&D Systems (Minneapolis, Minnesota). The detectable limit for interleukin-6 (by HS600 Quantikine kit; R&D Systems, Inc.) was 0.10 pg/ml. Plasma C-reactive protein concentrations were measured in duplicate by enzyme-linked immunoassay (Calbiochem; EMD Biosciences, Inc., Darrnstadt, Germany). The C-reactive protein assay was standardized according to the World Health Organization First International Reference Standard with a sensitivity of 0.08 μg/ml.

Statistical analyses

Differences in proportions or means of variables between persons with and without incident MI during follow-up were assessed by using chi-square and *t*-test statistics, respectively. Persons for whom values for any of the adiposity variables were missing were excluded from the analyses. Cox proportional hazards analyses were performed to assess the relative risks of a new MI event. Hazard ratios for the onset of MI were calculated per sample standard-deviation increase to permit comparison between all adiposity variables. We also examined whether the associations of incident MI with adiposity and body fat distribution variables differed by sex, race, or obesity status (BMI: ≤24.9 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2) by including an interaction term in the models. In this paper, hazard ratios and 95 percent confidence intervals are reported after adjustments for age, race, and other covariates that had a significant univariate association with onset of MI (table 1). Variables that could potentially explain the association between MI onset and visceral adipose tissue were entered as covariates in separate models in a stepwise fashion, and new hazard ratios were assessed. The nominal level of statistical significance used was $p < 0.05$.

RESULTS

Baseline characteristics

During an average follow-up time of 4.6 (standard deviation, 0.9) years, 116 MI events (4.6 percent of the sample) occurred. Of these MI events, 46 (39.7 percent) were fatal. Table 1 shows baseline characteristics of these 116 participants compared with those for participants without an MI event (n = 2,387). Participants who experienced an MI were more likely to be male, be a former or current smoker, have less education, have chronic obstructive pulmonary disease, and, among women, to not use hormone replacement therapy at baseline. There was no significant age or racial difference between subjects with or without incident MI. Incident MI was associated with higher blood pressure, fasting glucose,

TABLE 1. Baseline participant characteristics* according to incident MI,† The Health, Aging and Body Composition Study, United States, 1997–1998

	No MI event (n = 2,387)	MI event (n = 116)	p value
Sociodemographic variables			
Age in years	74.1 (2.8)	74.3 (3.1)	0.36
Female sex	56.2	38.8	<0.001
White race	57.7	55.2	0.59
Clinical site: Memphis, Tennessee	50.9	52.6	0.73
Potential confounding variables			
Education			0.05
Less than high school	24.7	34.2	
High school	33.2	32.5	
Postsecondary	42.1	33.3	
Smoking			0.001
Never	46.8	31.3	
Former	43.0	49.6	
Current	10.2	19.1	
Alcohol intake			0.61
Never	50.2	56.0	
Occasional	20.4	19.0	
1–7 drinks/week	21.6	17.0	
≥8 drinks/week	7.8	7.8	
Chronic obstructive pulmonary disease	8.5	17.2	0.001
Hormone replacement therapy‡	13.2	6.0	0.02
Corticosteroids	2.1	3.4	0.35
Stroke	6.0	5.2	0.70
Cancer	18.4	16.4	0.58
Potential explanatory variables			
Hypertension	58.8	62.1	0.48
Congestive heart failure	0.7	1.7	0.19
Diabetes	13.5	19.0	0.10
Antihypertensive drugs	50.4	50.0	0.93
Statins	9.8	7.8	0.48
Antidiabetic drugs	11.0	15.5	0.13
Total cholesterol (mg/dl)	204.8 (37.9)	204.3 (37.4)	0.88
HDL† cholesterol (mg/dl)	55.4 (17.0)	49.7 (14.2)	<0.001
LDL† cholesterol (mg/dl)	122.7 (34.3)	127.3 (34.5)	0.17
Triglyceride (mg/dl)§	117.0 (88.0–160.0)	118.0 (89.5–163.5)	0.49
Systolic blood pressure (mmHg)	135.6 (20.5)	140.9 (23.5)	0.007
Diastolic blood pressure (mmHg)	71.5 (11.7)	74.7 (12.1)	0.004
Fasting glucose (mg/dl)	102.4 (31.5)	111.5 (47.1)	0.004
Fasting insulin (IU†/ml)§	6.8 (4.8–10.1)	7.9 (5.4–10.5)	0.06
C-reactive protein (μg/ml)§	1.7 (1.0–3.1)	1.7 (1.0–3.2)	0.36
Interleukin-6§	1.7 (1.2–2.7)	2.2 (1.4–3.8)	<0.001

* Unless otherwise noted, values are expressed as % or mean (standard deviation).
† MI, myocardial infarction; HDL, high density lipoprotein; LDL, low density lipoprotein; IU, International Units.
‡ A total of 319 (23.1%) of the 1,387 women were taking hormone replacement therapy; 312 (23.4%) had no MI, and seven (15.6%) had MI; p = 0.22.
§ Median (25%–75%).

TABLE 2. Baseline total adiposity and body fat distribution* according to incident MI† in men and women, The Health, Aging and Body Composition Study, United States, 1997–1998

	Women			Men		
	No MI event (n = 1,342)	MI event (n = 45)	p value	No MI event (n = 1,045)	MI event (n = 71)	p value
Total adiposity						
Body mass index (kg/m^2)	27.6 (5.5)	28.6 (6.7)	0.22	27.1 (4.0)	26.8 (3.9)	0.57
Fat mass (kg)	28.4 (9.1)	29.0 (10.0)	0.62	23.3 (7.2)	22.9 (7.2)	0.69
Body fat distribution						
Waist (cm)	98.0 (13.8)	100.0 (16.8)	0.36	100.9 (12.3)	98.9 (15.3)	0.21
Waist-thigh ratio	1.9 (0.2)	1.9 (0.3)	0.27	2.0 (0.2)	2.0 (0.2)	0.73
VAT† area (cm^2)	128.1(58.5)	163.2 (85.7)	<0.001	153.1 (70.7)	155.4 (79.3)	0.80
SAT† area (cm^2)	336.6 (126.4)	331.1 (130.0)	0.78	233.5 (91.2)	229.1 (88.4)	0.70
VAT/SAT	0.4 (0.2)	0.5 (0.3)	0.002	0.7 (0.3)	0.7 (0.4)	0.44
VAT/fat mass	4.6 (1.7)	5.4 (2.0)	0.003	6.5 (2.2)	6.7 (2.7)	0.43

* Values are expressed as mean (standard deviation).
† MI, myocardial infarction; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

and interleukin-6 concentrations and with lower high density lipoprotein cholesterol concentrations.

Baseline adiposity and body fat distribution in men and women

Women who had an MI during follow-up (n = 45) had a greater absolute amount of visceral adipose tissue at baseline as well as a higher amount of such tissue relative to subcutaneous adipose tissue (visceral adipose tissue/subcutaneous adipose tissue) and to total fat mass (visceral adipose tissue/fat mass) compared with women without an incident MI (n = 1,342) (table 2). No differences in baseline measures of total obesity or body fat distribution were found between men who experienced an MI (n = 71) and those who did not (n = 1,045).

Hazard ratios associated with total adiposity and body fat distribution

In the entire study sample, Cox proportional hazards analyses (with adjustment for confounders) showed that visceral adipose tissue (hazard ratio = 1.24, 95 percent confidence interval: 1.04, 1.47) and visceral adipose tissue/fat mass (hazard ratio = 1.21, 95 percent confidence interval: 1.00, 1.46) were significant predictors of the onset of MI but that there was no association between total adiposity (BMI and fat mass) and incident MI (table 3). We next examined whether these associations were different between men and women, between Blacks and Whites, or between classes of obesity status by entering interaction terms into the models. We found no statistically significant interactions for race or obesity status with any of the independent variables (all $p >$ 0.10). However, there was a significant interaction of sex on the association between visceral adipose tissue and incident MI ($p < 0.01$), so we reperformed our analyses stratified by sex (table 3). These analyses showed no association between any of the adiposity or body fat distribution variables and incident MI in men.

For women, absolute visceral adipose tissue, visceral adipose tissue/subcutaneous adipose tissue, and visceral adipose tissue/fat mass were significant predictors of incident MI in a model adjusted for age, race, education, smoking, chronic obstructive pulmonary disease, and hormone replacement therapy use (table 3). We found no association of BMI and total fat mass with MI events in women. In an adjusted model that included both visceral adipose tissue and BMI as independent variables, visceral adipose tissue was associated with incident MI (hazard ratio = 1.85, 95 percent confidence interval: 1.31, 2.62 per standard-deviation increase; $p < 0.001$), but BMI was not (hazard ratio = 0.84, 95 percent confidence interval: 0.58, 1.23). In a model that included both visceral adipose tissue and fat mass, visceral adipose tissue was highly predictive of MI (hazard ratio = 1.98, 95 percent confidence interval: 1.42, 2.75 per standard-deviation increase; $p < 0.001$), but fat mass did not predict MI (hazard ratio = 0.73, 95 percent confidence interval: 0.49, 1.22).

Analyses adjusted for explanatory variables

In an attempt to identify the potential metabolic explanatory variables linking visceral adipose tissue to incident MI in elderly women, we performed a series of Cox proportional hazards analyses (table 4). High density lipoprotein cholesterol concentration, interleukin-6 concentration, hypertension-related variables (adjudicated prevalent disease, antihypertensive medication use, or blood pressure), and diabetes-related variables (adjudicated prevalent disease, fasting glucose, and use of antidiabetic drugs) were entered in a stepwise fashion into a model that included visceral adipose tissue, BMI, age, race, education, smoking, chronic

TABLE 3. Hazard ratios and 95% confidence intervals for an incident MI* event associated with total adiposity and body fat distribution (per standard-deviation increase) in men (*n* = 71 events) and in women (*n* = 45 events), The Health, Aging and Body Composition Study, United States, 1997–1998

	Women†			Men†		
	HR*	95% CI*	*p* value	HR	95% CI	*p* value
Total adiposity						
Body mass index (per 4.90-kg/m^2 increase)	1.15	0.88, 1.51	0.31	1.00	0.75, 1.35	0.98
Fat mass (per 8.74-kg increase)	1.06	0.78, 1.42	0.72	1.01	0.76, 1.36	0.93
Body fat distribution						
Waist (per 13.37-cm increase)	1.13	0.85, 1.51	0.40	0.87	0.67, 1.12	0.27
Waist-thigh ratio (per 0.22 increase)	1.19	0.90, 1.58	0.22	1.03	0.79, 1.35	0.83
VAT* area (per 66.23-cm^2 increase)‡	1.67	1.28, 2.17	<0.001	1.05	0.83, 1.31	0.70
VAT/SAT* area (per 0.30 increase)	1.42	1.08, 1.87	0.01	1.03	0.83, 1.27	0.82
VAT/fat mass (per 2.17 increase)	1.67	1.20, 2.31	0.002	1.08	0.86, 1.37	0.52

* MI, myocardial infarction; HR, hazard ratio; CI, confidence interval; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

† Values were adjusted for age, race, education, smoking, chronic obstructive pulmonary disease, and, for women, hormone replacement therapy.

‡ Significant interaction of sex for the association between VAT and incident MI ($p < 0.01$).

obstructive pulmonary disease, and hormone replacement therapy use. Of the explanatory variables, high density lipoprotein cholesterol concentration accounted for the most variation in incident MI, and adding high density lipoprotein cholesterol to the model reduced the risk of incident MI related to a high level of visceral adipose tissue; however, visceral adipose tissue remained a significant predictor of MI ($p < 0.01$; table 4). Adding diabetes-related and blood pressure–related variables reduced the risk of an MI event associated with a high level of visceral adipose tissue, but, again, visceral adipose tissue remained an independent predictor of incident MI ($p < 0.01$). Adding interleukin-6 concentration did not reduce the visceral adipose tissue-associated relative risk of MI.

DISCUSSION

The Health ABC Study population provides a unique cohort of men and women aged 70–79 years who underwent state-of-the-art measures of body composition and fat distribution at baseline and biannual adjudicated assessments of disease status. This cohort allowed us to examine the association of total adiposity and body fat distribution with development of the definitive CHD endpoint of MI. We found that the visceral adipose tissue area, measured directly via computed tomography, is an independent risk factor for MI in older women but not in older men. Moreover, measures of total adiposity (BMI and fat mass) and surrogate measures of visceral fat (waist circumference and waist-thigh ratio) were not associated with incident MI in men or women. Thus, the absolute and relative amount of adipose tissue stored in the intraabdominal cavity was the only adiposity-related risk factor for MI in these older women, whereas, in older men, there was no additional risk of MI due to greater total or abdominal adiposity.

Although very few previous studies included persons older than age 70 years, the lack of an association between total adiposity and incident MI in this age group is not surprising. Results of studies that include a wide age range of persons, including those older than 70 years, show that the relative risk of a greater BMI on all-cause mortality (17), cardiovascular disease mortality (18), and CHD (19) declines with age. In addition, studies examining the association between BMI and mortality or CHD in a strictly elderly cohort often show an inverse association or no association (4, 10, 22, 25–27). One of the postulated reasons for the lower CHD risk attributed to obesity in elderly persons is that BMI, the

TABLE 4. Hazard ratios and 95% confidence intervals* for an incident MI† event associated with VAT† area in women, with successive adjustment for explanatory variables, The Health, Aging and Body Composition Study, United States, 1997–1998

Explanatory variables	HR†	95% CI†
VAT	1.85	1.31, 2.61
VAT + HDL† cholesterol	1.77	1.24, 2.53
VAT + HDL cholesterol + diabetes‡	1.70	1.18, 2.46
VAT + HDL cholesterol + diabetes + blood pressure§	1.71	1.19, 2.47
VAT + HDL cholesterol + diabetes + blood pressure + interleukin-6 (log value)	1.79	1.24, 2.58

* Values were adjusted for age, race, body mass index, education, smoking, chronic obstructive pulmonary disease, and hormone replacement therapy.

† MI, myocardial infarction; VAT, visceral adipose tissue; HR, hazard ratio; CI, confidence interval; HDL, high density lipoprotein.

‡ Diabetes-related variables include adjudicated diabetes, fasting glucose, and antidiabetic drugs.

§ Blood pressure-related variables include adjudicated hypertension, systolic and diastolic blood pressure, and antihypertensive drugs.

measure most often used to quantify obesity in epidemiologic studies, is a poor measure of actual fat mass (28). However, in the current study, we directly measured fat mass via dual energy x-ray absorptiometry and found no association between total fat mass and incident MI for either sex. Thus, total adiposity is not a risk factor for MI in men and women in their eighth decade of life.

Another possibility for the lack of association between total adiposity and MI in the elderly is that location, rather than amount, of body fat may be a better predictor of disease onset. Anthropometric measures of abdominal fat often provide a better assessment of CHD risk than total body fat does (5–11). The underlying assumption is that these associations likely result from an excess accumulation of adipose tissue stored in the visceral region. However, very few epidemiologic studies, especially prospective studies, include a direct measurement of this fat depot. To our knowledge, only one previous longitudinal study (16) reported that visceral adipose tissue is a prospective risk factor for CHD (defined as MI, angina, cardiac death, coronary artery bypass, or coronary angioplasty). This study was small (n = 175, 50 incident cases) and included only middle-aged Japanese-American men, but it had a longer follow-up time (10 years). Our findings confirmed the risk prediction of visceral adipose tissue in older women but did not show an association between visceral adipose tissue and incident MI in older men. Whether our results for men differ from those of this previous study because of the dissimilar age or race of the two study samples is not obvious.

Our findings showed that the association between visceral adipose tissue and incident MI does not differ between racial groups or by obesity status but that there is a definite sex difference in the association between visceral adipose tissue and incident MI. Although our hypothesis was that visceral adipose tissue would best predict incident MI in both men and women, results showed that visceral adipose tissue is a risk factor for only women. It is possible that this sex difference is due to selective mortality attributed to greater visceral adipose tissue in men less than age 70 years. From adolescence to middle age, there are obvious sex differences in body fat distribution (29); on average, men store 21 percent of their total body fat in the visceral region compared with only 8 percent in women (30, 31). In some studies, this sex difference in fat distribution totally accounted for sex differences in CHD risk factors and incident MI (32–34). Consequently, it is likely that a high amount of visceral adipose tissue represents a greater risk of CHD in middle-aged compared with older men.

In our study, there was a sex difference in the absolute amount of visceral adipose tissue in participants who did not experience an MI; women had less despite a higher fat mass and subcutaneous adipose tissue, which is consistent with the sex differences normally seen for the relative amount of fat stored in the visceral region. However, we found no differences in visceral adipose tissue (absolute or relative) between men and women with incident MI. Thus, men with high levels of visceral adipose tissue may have experienced earlier CHD mortality; for women, the risk associated with visceral adipose tissue may become more apparent in older age, after a menopause-related increase in such tissue (35). This hypothesis is supported by data showing that total cholesterol and systolic blood pressure are also more predictive of CHD risk for older women than for men (36). In addition to possible selective mortality, the interaction of visceral adipose tissue and sex may be present in this age group only, suggesting that unmeasured variables may interact with visceral adipose tissue in women to cause an effect, but not in elderly men. Further studies are needed to determine the exact nature of this interaction and to assess whether this finding is age-group specific.

We hypothesized that, because abdominal obesity is a component of the metabolic syndrome (37), the association of visceral adipose tissue with CHD in older women would be mediated by other components of this syndrome associated with CHD (high density lipoprotein cholesterol, diabetes, hypertension, inflammation). Although adding these variables attenuated the relative risk attributed to a high level of visceral adipose tissue, it remained an independent predictor of incident MI. These results are consistent with those from the study of Japanese-American men in which visceral adipose tissue remained an independent risk factor for incident CHD, even after accounting for the effects of high density lipoprotein cholesterol, fasting glucose, and systolic blood pressure (16). Thus, it appears that the association of visceral adipose tissue with CHD cannot be accounted for by these other components of the metabolic syndrome.

There are several potential underlying anatomic, physiologic, and molecular mechanisms by which an excess of adipose tissue stored in the visceral region could affect the risk of experiencing an MI for older women. First, the vascular anatomy of visceral fat is unique in that it is connected via the portal venous system to the liver, allowing direct free fatty acid flux into the liver. This elevation in fatty acids can lead to suppression of hepatic glucose production, hyperinsulinemia, and accelerated synthesis and secretion of triglyceride particles, as well as increased hepatic lipase activity (38). In addition, there are notable differences in metabolism between visceral and subcutaneous adipocytes (38–40). Compared with subcutaneous cells, visceral cells are associated with higher rates of catecholamine-stimulated lipolysis because of an increased function of beta-adrenergic receptors and a decreased function of antilipolytic receptors (41). This difference results in higher systemic and portal free fatty acid concentrations in persons with larger amounts of visceral adipose tissue. Moreover, visceral adipocytes differ from subcutaneous adipocytes in their release of secretory proteins that are known or potential CHD risk factors. In at least one study, visceral fat, compared with subcutaneous fat, expressed and released more plasminogen activator inhibitor-1, an inhibitor of fibrinolysis (42). Expression of angiotensinogen, a potential regulator of blood pressure, is also higher in visceral adipose tissue (43). Finally, proteins potentially protective for diabetes and CHD (adiponectin, leptin, glycogen synthase, and peroxisome proliferator activated receptor-gamma) show lower expression levels in visceral than in subcutaneous adipocytes (44–46).

It is important to note that the association between visceral adipose tissue and MI for the women in this study was independent of the amount of total body fat. This finding was the

case whether BMI or the actual total amount of adipose tissue (fat mass) was added to the analyses. Previous studies show that a high amount of visceral fat contributes to CHD risk in healthy, nonobese as well as obese persons (15, 47). In addition, obese persons who are "metabolically healthy" have very little visceral fat accumulation (48). Collectively, our findings, along with those from these previous studies, demonstrate that, although the absolute volume of visceral fat may be relatively small, it is the best obesity-related predictor of MI in elderly, well-functioning women.

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