Cardiovascular Disease Risk of Abdominal Obesity vs. Metabolic Abnormalities

Rachel P. Wildman[1], Aileen P. McGinn[1], Juan Lin[1], Dan Wang[1], Paul Muntner[2], Hillel W. Cohen[1], Kristi Reynolds[3], Vivian Fonseca[4] and MaryFran R. Sowers[5]

It remains unclear whether abdominal obesity increases cardiovascular disease (CVD) risk independent of the metabolic abnormalities that often accompany it. Therefore, the objective of this study was to evaluate the independent effects of abdominal obesity vs. metabolic syndrome and diabetes on the risk for incident coronary heart disease (CHD) and stroke. The Framingham Offspring, Atherosclerosis Risk in Communities, and Cardiovascular Health studies were pooled to assess the independent effects of abdominal obesity (waist circumference >102 cm for men and >88 cm for women) vs. metabolic syndrome (excluding the waist circumference criterion) and diabetes on risk for incident CHD and stroke in 20,298 men and women aged ≥45 years. The average follow-up was 8.3 (s.d. 1.9) years. There were 1,766 CVD events. After adjustment for demographic factors, smoking, alcohol intake, number of metabolic syndrome components, and diabetes, abdominal obesity was not significantly associated with an increased risk of CVD (hazard ratio (HR) (95% confidence interval): 1.09 (0.98, 1.20)). However, after adjustment for demographics, smoking, alcohol intake, and abdominal obesity, having 1–2 metabolic syndrome components, the metabolic syndrome and diabetes were each associated with a significantly increased risk of CVD (2.12 (1.80, 2.50), 2.82 (1.92, 4.12), and 5.33 (3.37, 8.41), respectively). Although abdominal obesity is an important clinical tool for identification of individuals likely to possess metabolic abnormalities, these data suggest that the metabolic syndrome and diabetes are considerably more important prognostic indicators of CVD risk.

Obesity (2011) **19,** 853–860. doi:10.1038/oby.2010.168

INTRODUCTION

Obesity is known to increase the risk of cardiovascular disease (CVD). However, we have recently shown that a substantial proportion (~30%) of obese US adults do not have the clustering of cardiometabolic abnormalities commonly associated with obesity including hypertension, dyslipidemia, and elevated levels of fasting glucose, insulin resistance, and systemic inflammation (1). Two prior studies suggest that obesity may increase the risk for CVD only among persons with hypertension, dyslipidemia, or type 2 diabetes (2,3). Additionally, new research suggests that the cardiovascular risk reduction of weight loss may differ in obese persons with vs. without cardiometabolic disturbances (4,5). Therefore, examination of the CVD risks associated with obesity independent of the cardiometabolic disturbances which often, but not always, accompany it is of considerable public health and clinical importance. Previous studies of the independent CVD risks associated with obesity have provided contradictory evidence (2,3,6–13), and have largely failed to directly examine whether CVD risk is elevated when obesity is unaccompanied by these cardiometabolic disturbances. Instead, most published studies used statistical adjustment to account for the effects of metabolic status. In addition, despite that abdominal obesity is known to confer greater risk of CVD than BMI-measured obesity, very few prior studies have addressed whether abdominal obesity is associated with increased risk of CVD even when it is unaccompanied by the cardiometabolic abnormalities thought to result from it. Therefore, the purpose of this study was to evaluate the independent effects of abdominal obesity and cardiometabolic abnormalities on the risk for incident CVD. Three large population-based cohort studies of men and women were pooled to obtain sufficient sample size and numbers of incident CVD events to assess the risk of CVD associated with obesity in those with and without cardiometabolic abnormalities, and to statistically evaluate whether metabolic status modifies the association between obesity and incident CVD.

[1]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, New York, USA; [2]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA; [3]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA; [4]Section of Endocrinology, Department of Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana, USA; [5]Department of Epidemiology, University of Michigan, Ann Arbor, Michigan, USA. Correspondence: Rachel P. Wildman (rachel.wildman@einstein.yu.edu)

Received 12 January 2010; accepted 8 June 2010; published online 19 August 2010. doi:10.1038/oby.2010.168

METHODS AND PROCEDURES

Study population

The population for these analyses is derived from the pooling of three large, limited-access public use databases from the following studies: the Framingham Offspring Study (FOS), the Atherosclerosis Risk in Communities Study (ARIC), and the Cardiovascular Health Study (CHS). Informed consent and appropriate institutional review board approval was obtained by each center for the three studies.

The FOS was initiated in 1971, and recruited 5,124 men and women aged 5–70 years who were children or spouses of participants in the Framingham Heart Study. As the FOS did not measure waist circumference until the 4th examination, this examination was used as the baseline visit for the current pooling of data. ARIC recruited 15,732 men and women aged 45–64 years in 1987–1989, and CHS initially recruited 5,201 participants aged ≥65 years in 1989–1990 using Medicare eligibility files. In 1992, an additional 687 black participants were recruited. Details regarding recruitment and study procedures for each of the three studies have been published previously (14–16).

Pooling of the three longitudinal databases resulted in a data set with 26,744 individuals. Exclusion criteria from the pooled data set included missing age information or baseline age <45 years (total $n = 2,277$; missing = 1,198; <45 years = 1,079); BMI values in the underweight range (<18.5 kg/m^2; $n = 163$); missing data on waist circumference ($n = 85$); history of CVD (coronary heart disease (CHD), stroke, and peripheral vascular disease in all studies and heart failure for CHS and the FOS cohorts) at study baseline for ARIC and CHS, and at the original study baseline or at any time between baseline and the 4th follow-up visit for the FOS ($n = 3,158$); missing data on the four-level metabolic obesity variable ($n = 273$), and reported fasting <8 h before the study visit ($n = 490$), leaving data from 20,298 individuals for these analyses.

Blood pressure, anthropometrics, and questionnaire data

For each of the three studies, blood pressure was measured in the seated position after a short rest period and averaged across two readings. BMI was calculated as the weight in kilograms divided by height in meters squared, and categorized as normal weight (BMI <25 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), or obese (BMI ≥30 kg/m^2). Waist circumference was measured at the level of the umbilicus while the participant was standing, among all three studies. Abdominal obesity was defined as waist circumference >102 cm for men and >88 cm for women. Smoking and alcohol intake were assessed by questionnaire in each study. As the amount of alcohol consumed was not assessed identically across studies, participants were coded as current drinkers or not.

Laboratory measurements

Blood samples were obtained after an ≥8-h fast in each study. Laboratory methods have been previously reported for all three studies (17–22). Of relevance to these analyses, glucose was measured in serum with a Kodak Ektachem E-700 (Eastman Kodak, Rochester, NY) among CHS participants and by a hexokinase/glucose-6-phosphate dehydrogenase method among ARIC participants, and in plasma with a hexokinase reagent kit (A-gent glucose test; Abbott, South Pasadena, CA) among FOS participants. In all three studies, plasma triglycerides and high-density lipoprotein-cholesterol were measured enzymatically (high-density lipoprotein-cholesterol after precipitation of low- and very-low-density lipoproteins with dextran sulfate–magnesium ions sulfate).

Metabolic syndrome and diabetes definitions

Metabolic syndrome components were defined according to the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) revised recommendations (23): (i) fasting serum or plasma glucose ≥100 mg/dl, (ii) fasting serum triglycerides ≥150 mg/dl, (iii) fasting serum high-density lipoprotein-cholesterol <40 mg/dl for men and <50 mg/dl for women, and (iv) systolic/diastolic blood pressure ≥130/85 mm Hg or self-reported use of antihypertensive medications. The waist circumference criterion was not included as a metabolic syndrome component as it was used to define obesity. Diabetes was defined as a fasting serum or plasma glucose ≥126 mg/dl or self-reported use of antidiabetes medications. Participants were categorized into one of four metabolic abnormality groups: (i) no metabolic syndrome components or diabetes ("normal" metabolism), (ii) 1–2 metabolic syndrome components and no diabetes (1–2 components), (iii) ≥3 metabolic syndrome components and no diabetes (metabolic syndrome), and (iv) diabetes (diabetes).

CVD event ascertainment and follow-up time determination

To ensure consistency of event reporting across the three studies, these analyses are limited to probable and definite fatal and nonfatal CHD and stroke. In all three studies, CHD was defined as myocardial infarction, silent myocardial infarction, or CHD death and stroke included both hemorrhagic and ischemic subtypes. Event ascertainment has been previously reported for all studies (24–27). Briefly, each study obtained medical record data through chart abstraction for use in event classification, and utilized an adjudication committee to determine final event classification. Among all three studies, data abstracted for CHD determination included cardiac pain, electrocardiogram findings, and cardiac enzymes, and for stroke determination neurological evaluations, imaging studies, and pathology reports. Specific algorithms for event determination were similar, though not identical for all three studies, with the exception of myocardial infarction determination, for which CHS adopted the ARIC protocol identically.

As each of the three studies varied in the length of available follow-up, these analyses are limited to 9 years of follow-up to ensure adequate sample size throughout. Follow-up time for analyses of CVD (CHD and stroke considered together) was calculated as the time between the baseline visit (visit 4 for the FOS) and the first CHD or stroke event, or between the baseline visit and the last known contact with the participant for those without events.

Statistical methods

The distributions of demographic, anthropometric, and laboratory variables were compared across both abdominal obesity and metabolic status groupings using χ^2-tests for categorical variables and Kruskal–Wallis or Mann–Whitney *U* tests for continuous variables. Failure curves were generated using the Kaplan–Meier method for the eight metabolic categories (i.e., abdominal obesity crossclassified by metabolic abnormality grouping).

After initial adjustment for demographic factors, smoking status, and alcohol intake, the independent effects of abdominal obesity and metabolic status on the risks of CVD, CHD, and stroke were examined by further adjustment of the Cox proportional hazard ratios (HRs) associated with abdominal obesity for metabolic status grouping; and further adjustment of the Cox proportional HRs associated with metabolic status grouping for abdominal obesity. A two-stage approach was used for all Cox proportional hazards regression modeling. First, study-specific HRs and 95% confidence intervals of each outcome were calculated. Pooled HRs were then calculated by combining the study-specific HRs, weighted by the inverse of their variance, using a random effects model. For CHD event analyses, individuals whose first event was a stroke were censored at the time of their stroke, whereas for stroke analyses, individuals whose first event was a CHD event were censored at the time of their CHD event. There were two cases where a CHD event and stroke event occurred on the same day, and these individuals were counted only once in total CVD analyses. Statistical interactions between abdominal obesity and metabolic status on the risk of CVD were tested *via* multiplicative interaction terms (i.e., abdominal obesity group × metabolic status and waist circumference, modeled as a continuous variable, × metabolic status). To ensure that covariability between abdominal obesity and metabolism was not affecting resulting estimates, analyses of abdominal obesity were stratified by metabolic status and *vice versa*. The proportional hazards assumption was evaluated by Schoenfeld residuals in all Cox models, and was not violated.

Sensitivity analyses were conducted by assessing the outcomes of fatal and nonfatal events, separately, by assessing outcomes in subgroups

defined by age (45–64 years and ≥65 years) and sex, and using BMI groups (<25 kg/m^2, 25–29.9 kg/m^2, and ≥30 kg/m^2) in place of abdominal obesity. Sensitivity analyses were also performed excluding events within the first 2 years in an attempt to remove the influence of subclinical disease at baseline on the results, and incorporating cholesterol-lowering medication use into the high-density lipoprotein-cholesterol criterion of the metabolic syndrome definition ($n = 637$). This lead to an additional 65 people recategorized as having 1–2 components, and 93 people recategorized as having metabolic syndrome. All analyses were conducted using STATA, version 10 (StataCorp, College Station, TX).

RESULTS

The average follow-up was 8.3 (s.d. 1.9) years, and over this time there were a total of 1,766 fatal or nonfatal incident CVD events (1,118 CHD events and 648 stroke events). Because two individuals had a CHD event and a stroke simultaneously, the number of events used for the combined CVD analyses was 1,764. Compared to nonobese individuals, those with abdominal obesity were more likely to be 45–64 years of age, women, African Americans, less educated, never smokers, never or former drinkers, to have metabolic syndrome or diabetes, and to have worse levels of metabolic syndrome components (**Table 1**). Compared to individuals without any metabolic syndrome components or diabetes, individuals with the metabolic syndrome or diabetes were older, and more likely to be men, African Americans, never smokers, less educated, never or former drinkers, obese, and to have worse levels of CVD risk factors (**Table 2**).

When abdominal obesity and metabolic categories were considered in combination, three groups of failure curves emerged corresponding to the metabolic categories (0 risk factors, 1–2 components or metabolic syndrome, and diabetes) (**Figure 1**).

After adjustment for age, sex, race, education, smoking status, and alcohol intake, abdominal obesity was associated with a 33% increased risk of total CVD (CHD and stroke) in pooled analyses (**Table 3**). However, after further adjustment for metabolic status, abdominal obesity was no longer significantly associated with increased risk of CVD. Metabolic syndrome and diabetes were associated with 100–400% increased risk of incident CVD events after initial adjustment for age, sex, race, education, smoking status, and alcohol intake, as well as after further adjustment for abdominal obesity. HRs for CHD and stroke showed similar patterns and effect magnitudes.

In stratified analyses, abdominal obesity was not significantly associated with an increased risk of incident CVD for participants with normal metabolism, metabolic syndrome or diabetes (**Figure 2**). However, an association was present between abdominal obesity and increased risk of incident CVD for those with 1–2 metabolic components. Among both nonobese and abdominally obese individuals, participants with 1–2 metabolic components, metabolic syndrome, and diabetes had an increased risk of incident CVD compared to those with normal metabolism. Results were similar when waist circumference was modeled as a continuous variable (data not shown). There was no significant statistical interaction between metabolic status and either abdominal obesity or waist circumference expressed as a continuous variable on the risks of CVD ($P = 0.48$ and $P = 0.49$, respectively).

Table 1 Baseline characteristics of study participants by abdominal obesity groups

	Nonobese ($n = 10,357$)	Abdominally Obese ($n = 9,941$)	*P* value
Age group, %			
45–64.9 years	7,858 (75.9%)	7,740 (77.9%)	0.001
≥65 years	2,499 (24.1%)	2,201 (22.1%)	
Sex, %			<0.001
Women	4,590 (44.3%)	6,826 (68.7%)	
Men	5,767 (55.7%)	3,115 (31.3%)	
Race, %			<0.001
White	8,744 (84.4%)	7,536 (75.8%)	
African American	1,613 (15.6%)	2,405 (24.2%)	
High school education, %			<0.001
≤High school	5,229 (50.5%)	5,966 (60.0%)	
>High school	5,128 (49.5%)	3,975 (40.0%)	
Cigarette smoking, %			
Never	3,931 (38.6%)	4,570 (46.4%)	<0.001
Current	2,491 (24.5%)	1,994 (20.3%)	
Former	3,766 (37.0%)	3,283 (33.3%)	
Alcohol consumption, %			<0.001
Never or Former	3,801 (36.8%)	4,868 (49.2%)	
Current	6,541 (63.3%)	5,032 (50.8%)	
Cardiometabolic status, %			
Normal	2,752 (26.6%)	1,159 (11.7%)	<0.001
1–2 Components	5,773 (55.7%)	4,941 (49.7%)	
Metabolic syndrome	1,249 (12.1%)	2,322 (23.4%)	
Diabetes	583 (5.6%)	1,519 (15.3%)	
Systolic BP, mm Hg	123.4 (20.4)	127.6 (19.8)	<0.001
Diastolic BP, mm Hg	73.2 (11.4)	74.9 (11.1)	<0.001
HDL cholesterol, mmol/l	1.41 (0.45)	1.30 (0.40)	<0.001
Triglycerides, mmol/l[a]	1.12 (0.82–1.57)	1.40 (1.02–1.98)	<0.001
Glucose, mmol/l[a]	5.34 (5.02–5.72)	5.61 (5.22–6.20)	<0.001
Waist circumference, cm	86.6 (9.0)	104.4 (10.7)	<0.001

Values in table are *n* (%) or mean (standard deviation) unless otherwise indicated.
BP, blood pressure; HDL, high-density lipoprotein.
[a]Values are median (interquartile range).

Sensitivity analyses

The results were markedly similar after excluding events that occurred within the first 2 years of follow-up (data not shown). Additionally, the associations were also similar when analyses were conducted stratified by sex, age group, and by fatal vs. nonfatal event status, and considering cholesterol-lowering medication use in the metabolic syndrome definition (data

Table 2 Baseline characteristics of study participants by metabolic syndrome and diabetes status

	Normal (*n* = 3,911)	1–2 Components (*n* = 10,714)	Metabolic syndrome (*n* = 3,571)	Diabetes (*n* = 2,102)	*P* value
Age group, %					
45–64.9 years	3,354 (85.8%)	8,119 (75.8%)	2,670 (74.8%)	1,455 (69.2%)	<0.001
≥65 years	557 (14.2%)	2,595 (24.2%)	901 (25.2%)	647 (30.8%)	
Sex, %					
Women	2,589 (66.2%)	5,941 (55.5%)	1,740 (48.7%)	1,146 (54.5%)	<0.001
Men	1,322 (33.8%)	4,773 (44.6%)	1,831 (51.3%)	956 (45.5%)	
Race, %					
White	3,362 (86.0%)	8,479 (79.1%)	3,019 (84.5%)	1,420 (67.6%)	<0.001
African American	549 (14.0%)	2,235 (20.9%)	552 (15.5%)	682 (32.5%)	
≥High school education, %					
<High school	1,813 (46.4%)	5,828 (54.4%)	2,161 (60.5%)	1,393 (66.3%)	<0.001
≥High school	2,098 (53.6%)	4,886 (45.6%)	1,410 (39.5%)	709 (33.7%)	
Cigarette smoking, %					
Never	1,769 (45.9%)	4,432 (42.0%)	1,357 (38.4%)	943 (45.3%)	0.001
Current	821 (21.3%)	2,412 (22.8%)	850 (24.1%)	402 (19.3%)	
Former	1,268 (32.9%)	3,720 (35.2%)	1,324 (37.5%)	737 (35.4%)	
Alcohol consumption, %					
Never or former	1,391 (35.7%)	4,455 (41.7%)	1,557 (43.7%)	1,266 (60.5%)	<0.001
Current	2,511 (64.4%)	6,230 (58.3%)	2,004 (56.3%)	828 (39.5%)	
Abdominal obesity, %					
Nonobese	2,752 (70.4%)	5,773 (53.9%)	1,249 (35.0%)	583 (27.7%)	<0.001
Obese	1,159 (29.6%)	4,941 (46.1%)	2,322 (65.0%)	1,519 (72.3%)	
BMI group, %					
Normal weight	2,239 (57.3%)	3,850 (36.0%)	615 (17.2%)	338 (16.1%)	<0.001
Overweight	1,318 (33.7%)	4,560 (42.6%)	1,610 (45.1%)	807 (38.5%)	
Obese	353 (9.0%)	2,299 (21.5%)	1,343 (37.6%)	954 (45.5%)	
Systolic BP, mm Hg	110.8 (10.4)	126.6 (20.3)	132.9 (19.0)	134.2 (21.5)	<0.001
Diastolic BP, mm Hg	68.5 (8.0)	74.7 (11.5)	77.3 (11.1)	75.4 (11.9)	<0.001
HDL cholesterol, mmol/l	1.63 (0.39)	1.40 (0.42)	1.03 (0.26)	1.18 (0.36)	<0.001
Triglycerides, mmol/l[a]	0.90 (0.70–1.15)	1.19 (0.89–1.54)	2.06 (1.73–2.60)	1.68 (1.18–2.46)	<0.001
Glucose, mmol/l[a]	5.11 (4.86–5.29)	5.40 (5.08–5.77)	5.83 (5.56–6.16)	8.38 (7.22–11.38)	<0.001
Waist circumference, cm	87.7 (11.7)	94.5 (12.6)	101.2 (11.8)	103.9 (13.0)	<0.001
BMI, kg/m^2	24.9 (3.8)	27.0 (4.6)	29.2 (4.8)	30.1 (5.4)	<0.001

Values in table are n (%) or mean (standard deviation) unless otherwise indicated.
BP, blood pressure; HDL, high-density lipoprotein.
[a]Values are median (interquartile range).

not shown). Finally, all analyses were repeated using BMI categories (normal weight, overweight, obese) rather than waist circumference, and analyses were also similar (data not shown). When analyses were conducted for each of the three studies separately, a significant effect of abdominal obesity on risk for CVD (HR for total CVD events 1.17; 95% confidence interval 1.01–1.37) was present after adjustment for metabolic status in the ARIC study, but not in the CHS or FOS (HR 1.01 (0.87–1.18) and 1.06 (0.73–1.54) respectively) (see **Supplementary Table S1** online). However, this difference between studies was not statistically significant, as indicated by a nonsignificant study × abdominal obesity interaction term ($P = 0.52$). Similar to the pooled analysis, within each of the three studies, abdominal obesity was not statistically significantly associated with increased risk of CVD within metabolic status categories, but 1–2 metabolic components, metabolic syndrome, and diabetes were each associated with incident CVD events among both abdominally obese

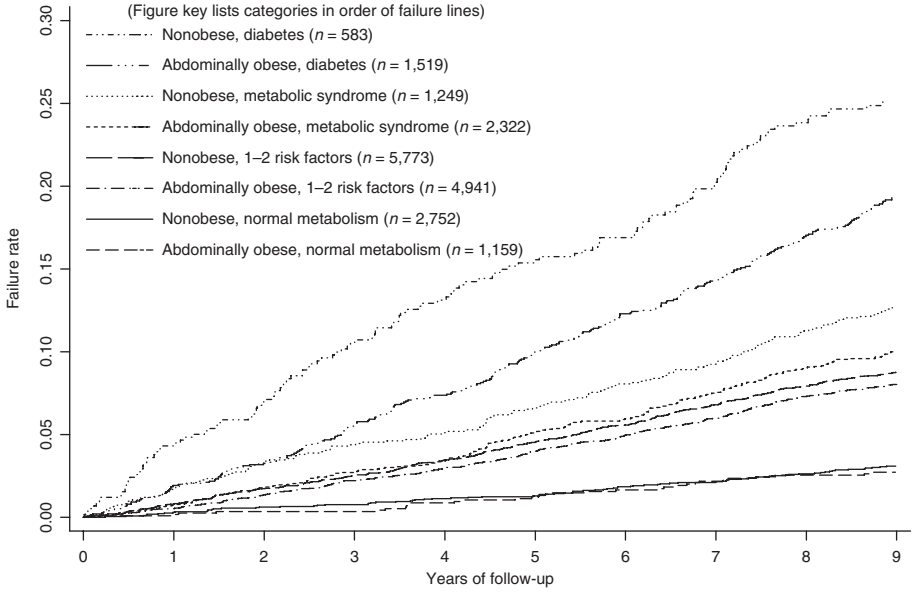

Figure 1 Kaplan–Meier plot of cardiovascular disease event rates by the eight joint obesity/metabolic abnormality categories.

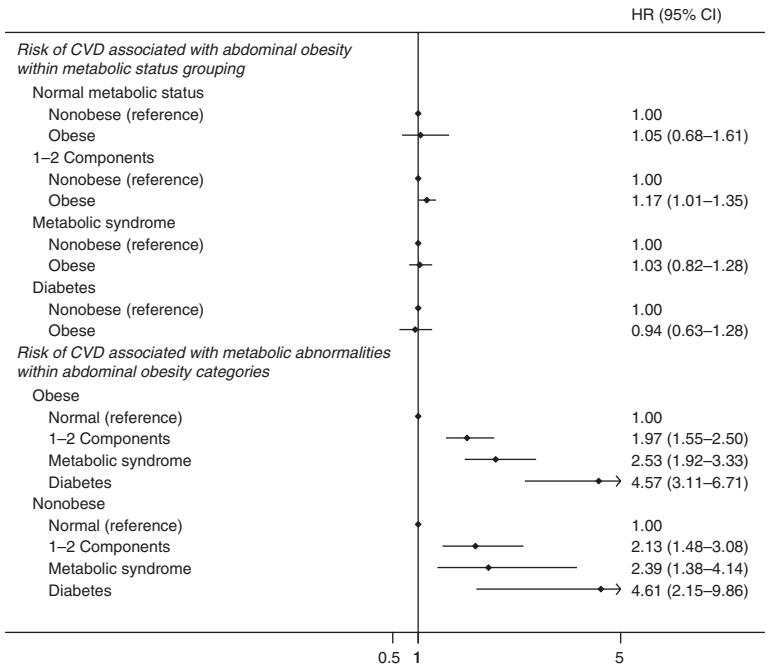

Figure 2 Forest plot of pooled adjusted[a] hazard ratios (95% confidence intervals) for incident CVD events associated with metabolic status stratified by abdominal obesity (top) and associated with abdominal obesity stratified by metabolic status (bottom). CVD, cardiovascular disease. [a]Adjusted for age, sex, race, education, smoking status, and alcohol intake.

and nonobese participants (see **Supplementary Table S2** online).

DISCUSSION

The present analyses of data pooled from three large cohort studies showed that after accounting for metabolic status, abdominal obesity was not associated with a significantly increased risk for CHD or stroke in nearly every case, the one exception being among those with 1–2 metabolic components. However, the presence of metabolic syndrome components, metabolic syndrome, or diabetes were each associated with ~2–5 times increased risk for CHD or stroke over an average follow-up of 8 years, even after accounting for abdominal obesity.

In this study, we assessed the independent effects of abdominal obesity and metabolism by two different methods. After statistical adjustment for metabolic status, abdominal obesity was not associated with a statistically significantly increased risk for CVD. Similarly, stratified analyses of the association between abdominal obesity and CVD within metabolic status

Table 3 Pooled HRs (95% CIs) for incident CVD events associated with abdominal obesity and metabolic status

	CHD	Stroke	Total CVD
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Abdominal obesity			
Model 1[a]			
Nonobese (reference)	1.00	1.00	1.00
Obese	1.40 (1.10–1.79)	1.18 (1.00–1.39)	1.33 (1.09–1.63)
P value	<0.01	0.05	<0.01
Model 1[a] + adjustment for metabolic status grouping			
Nonobese (reference)	1.00	1.00	1.00
Obese	1.13 (0.99–1.29)	1.00 (0.85–1.19)	1.09 (0.98–1.20)
P value	0.06	0.97	0.12
Metabolic status			
Model 1[a]			
Normal (reference)	1.00	1.00	1.00
1–2 Components	2.20 (1.70–2.84)	1.84 (1.34–2.52)	2.09 (1.71–2.54)
Metabolic syndrome	2.92 (1.89–4.53)	1.86 (1.29–2.64)	2.67 (1.79–3.98)
Diabetes	5.19 (3.22–8.36)	4.20 (2.38–7.40)	5.14 (3.13–7.76)
P value	<0.001	<0.001	<0.001
Model 1[a] + adjustment for abdominal obesity			
Normal (reference)	1.00	1.00	1.00
1–2 Components	2.15 (1.66–2.78)	1.86 (1.31–2.64)	2.05 (1.68–2.50)
Metabolic syndrome	2.77 (1.90–4.03)	1.86 (1.29–2.68)	2.56 (1.78–3.69)
Diabetes	4.90 (3.25–7.39)	4.22 (2.35–7.59)	4.91 (3.11–7.76)
P value	<0.001	<0.001	<0.001

CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.
[a]Adjusted for age, sex, race, education, smoking status, and alcohol intake.

group showed that abdominal obesity was not significantly associated with CVD among those with 0 components, metabolic syndrome, or diabetes. However, those with 1–2 metabolic syndrome components had an increased risk for CVD associated with abdominal obesity that was statistically significant. Although this latter result raises the possibility that abdominal obesity may increase the risk of CVD independent of metabolic abnormalities, this increased risk was modest (HR 1.17) compared with the increased risk associated with varying degrees of metabolic abnormalities (HRs ranging from 1.97 to 4.61), and was not found among those with 0 components, metabolic syndrome, or diabetes. **Figure 2** presents a striking visual illustration of the strong risks of CVD associated with metabolic abnormalities compared with the lack of an association between abdominal obesity and CVD. Therefore, these analyses support previous studies showing that the risk of CVD commonly associated with obesity is largely driven by concomitant metabolic abnormalities (2,3,6–8).

The current results contradict some prior studies which have suggested the possibility that metabolic status may modify the obesity–CVD relationship (2,3). In the Aerobics Center Longitudinal Study (ACLS), abdominal obesity was associated with incident CVD events over 10–11 years of follow-up among middle-aged men who had hypertension, dyslipidemia, or diabetes but not among those without these factors (2). Similar results were reported for obesity defined by BMI among middle-aged women in the Women's Health Study (3). However, in our stratified analyses, the HR for CVD events associated with abdominal obesity was 1.03 among those with metabolic syndrome and 0.94 among those with diabetes, suggesting that even in the presence of multiple metabolic abnormalities or diabetes, abdominal obesity was not significantly associated with elevated risk of CVD. The interaction term (abdominal obesity × metabolic status) was not statistically significant, further confirming the lack of effect modification in this study.

BMI-defined obesity and abdominal obesity have been found to impart significantly increased risk of CVD independent of standard risk factors and diabetes in some studies (9–11,13). Notably, significant associations with obesity appear to be more frequently observed in studies of longer duration, raising the possibility that obesity increases long-term (20–25 years) risk of CVD, perhaps due to enhanced subclinical atherosclerosis in obese individuals. Obese, metabolically healthy individuals have been shown to have impaired endothelial dysfunction and greater carotid intima–media thickness (ref. 28 and U. Khan, D. Wang, and R. Thurston *et al.*, unpublished

data). However, all but one of the incident CVD studies with long-term follow-up used statistical adjustment to account for metabolic abnormalities, rather than stratification, and none accounted for the development of cardiometabolic abnormalities across follow-up. Therefore, it remains unclear whether obesity without concomitant metabolic abnormalities is associated with elevated long-term risk of CVD.

In stratified analyses, individuals who were abdominally obese but did not have any of the metabolic syndrome components or diabetes were not at significantly increased risk for CHD or stroke over an average follow-up of 8 years compared to similar individuals without obesity. However, stratified analyses also showed that individuals without abdominal obesity had a substantially increased risk for CHD or stroke over 8 years if they possessed metabolic syndrome components or diabetes compared to individuals without these factors. Similar results were found in sensitivity analyses among normal-weight individuals, as defined by BMI. Therefore, in addition to highlighting the need for risk stratification *via* assessment of metabolic abnormalities among obese individuals, these data suggest that the metabolic syndrome may confer an approximate threefold increase in risk of incident CVD even in normal-weight individuals.

The results of this study must be viewed within the context of its limitations. As indicated previously, measurement protocols were not identical for certain laboratory and questionnaire data across the three studies. However, we analyzed data in two stages and present both study-specific and pooled results. Results were similar for each of the three studies. There were insufficient numbers of African Americans to stratify results by race. The frequency and extent of assessment of body size and metabolic changes across follow-up were not uniform for all three studies and comparable data on physical activity was not available at baseline for each study, and therefore, these could not be taken into account in the statistical analyses. Additionally, in order to maintain sufficient numbers of events in all three studies across the follow-up period, we were limited to 9 years of follow-up. Longer follow-up is needed to examine whether the effect of obesity is more pronounced when risk of CVD is examined over an extended time frame.

However, this study also has a number of strengths. With the large sample size resulting from the pooling of longitudinal databases, substantial numbers of CHD and stroke events occurred, permitting the investigation of the independent risks of CVD associated with obesity and abnormal metabolism in important population subgroups. The large sample size also afforded us the power to assess independence of abdominal obesity from metabolic status *via* stratification, as well as to formally assess effect modification. Each of the three studies pooled in these analyses followed standardized data collection protocols for measurement of the variables included here-in, and each performed active follow-up for CVD events with formal adjudication of events.

In conclusion, these analyses of individuals from three large, longitudinal population-based studies, suggest that the presence of metabolic abnormalities is a substantially stronger predictor than abdominal obesity of incident CHD and stroke over an average of 8 years. Although abdominal obesity and body size remain important clinical tools for identification of individuals likely to possess metabolic abnormalities, metabolic syndrome and diabetes are considerably more important prognostic indicators of CVD risk. These data underscore the need for close monitoring and treatment of adverse levels of blood pressure, lipids, and glucose even among normal-weight or nonobese individuals.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

ACKNOWLEDGMENTS

The Cardiovascular Health Study (CHS), Atherosclerosis Risk in Communities Study (ARIC), and Framingham Offspring Study (FOS) are conducted and supported by the NHLBI in collaboration with the CHS, ARIC, and FOS investigators, respectively. The article was prepared using a limited-access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the CHS, ARIC, or FOS or the NHLBI. This study was supported by the following grant from the National Heart, Lung, and Blood Institute of the NIH: R21-HL089625 (R.P.W.). The sponsor had no role in the design, conduct, or reporting of the study.

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES

1. Wildman RP, Muntner P, Reynolds K *et al*. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* 2008;168:1617–1624.
2. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair SN. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. *Diabetes Care* 2006;29:404–409.
3. Song Y, Manson JE, Meigs JB *et al*. Comparison of usefulness of body mass index versus metabolic risk factors in predicting 10-year risk of cardiovascular events in women. *Am J Cardiol* 2007;100:1654–1658.
4. Shin MJ, Hyun YJ, Kim OY *et al*. Weight loss effect on inflammation and LDL oxidation in metabolically healthy but obese (MHO) individuals: low inflammation and LDL oxidation in MHO women. *Int J Obes (Lond)* 2006;30:1529–1534.
5. Karelis AD, Messier V, Brochu M, Rabasa-Lhoret R. Metabolically healthy but obese women: effect of an energy-restricted diet. *Diabetologia* 2008;51:1752–1754.
6. Kip KE, Marroquin OC, Kelley DE *et al*. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Circulation* 2004;109:706–713.
7. Schulte H, Cullen P, Assmann G. Obesity, mortality and cardiovascular disease in the Münster Heart Study (PROCAM). *Atherosclerosis* 1999;144:199–209.
8. Meigs JB, Wilson PW, Fox CS *et al*. Body mass index, metabolic syndrome, and risk of type 2 diabetes or cardiovascular disease. *J Clin Endocrinol Metab* 2006;91:2906–2912.
9. Hu G, Tuomilehto J, Silventoinen K *et al*. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. *Arch Intern Med* 2007;167:1420–1427.
10. Rosengren A, Wilhelmsen L, Lappas G, Johansson S. Body mass index, coronary heart disease and stroke in Swedish women. A prospective 19-year follow-up in the BEDA study. *Eur J Cardiovasc Prev Rehabil* 2003;10:443–450.
11. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up

of participants in the Framingham Heart Study. *Circulation* 1983;67:968–977.
12. St-Pierre AC, Cantin B, Mauriège P *et al*. Insulin resistance syndrome, body mass index and the risk of ischemic heart disease. *CMAJ* 2005;172:1301–1305.
13. Flint AJ, Hu FB, Glynn RJ *et al*. Excess weight and the risk of incident coronary heart disease among men and women. *Obesity (Silver Spring)* 2010;18:377–383.
14. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. *Am J Epidemiol* 1979;110:281–290.
15. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol* 1989;129:687–702.
16. Fried LP, Borhani NO, Enright P *et al*. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol* 1991;1:263–276.
17. Ettinger WH, Wahl PW, Kuller LH *et al*. Lipoprotein lipids in older people. Results from the Cardiovascular Health Study. The CHS Collaborative Research Group. *Circulation* 1992;86:858–869.
18. Shahar E, Chambless LE, Rosamond WD *et al*.; Atherosclerosis Risk in Communities Study. Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2003;34:623–631.
19. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes* 2000;49:2201–2207.
20. Kannel WB, Vasan RS, Keyes MJ, Sullivan LM, Robins SJ. Usefulness of the triglyceride-high-density lipoprotein versus the cholesterol-high-density lipoprotein ratio for predicting insulin resistance and cardiometabolic risk (from the Framingham Offspring Cohort). *Am J Cardiol* 2008;101:497–501.
21. Atherosclerosis Risk in Communities Limited Access Data. 2008. <www.cscc.unc.edu/aric> 16 Jun 2008. Ref Type: Internet Communication.
22. Meigs JB, Nathan DM, Wilson PW, Cupples LA, Singer DE. Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance. The Framingham Offspring Study. *Ann Intern Med* 1998;128:524–533.
23. Grundy SM, Cleeman JI, Daniels SR *et al*.; American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735–2752.
24. Rosamond WD, Folsom AR, Chambless LE *et al*. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke* 1999;30:736–743.
25. White AD, Folsom AR, Chambless LE *et al*. Community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) Study: methods and initial two years' experience. *J Clin Epidemiol* 1996;49:223–233.
26. Ives DG, Fitzpatrick AL, Bild DE *et al*. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. *Ann Epidemiol* 1995;5:278–285.
27. Stokes J 3rd, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. *Circulation* 1987;75:V65–V73.
28. Oflaz H, Ozbey N, Mantar F *et al*. Determination of endothelial function and early atherosclerotic changes in healthy obese women. *Diabetes Nutr Metab* 2003;16:176–181.