0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(8):2906–2912

doi: 10.1210/jc.2006-0594

Body Mass Index, Metabolic Syndrome, and Risk of Type 2 Diabetes or Cardiovascular Disease

James B. Meigs, Peter W. F. Wilson, Caroline S. Fox, Ramachandran S. Vasan, David M. Nathan, Lisa M. Sullivan, and Ralph B. D'Agostino

General Medicine Division and Department of Medicine (J.B.M.) and Diabetes Unit and Department of Medicine (D.M.N.), Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114; Department of Endocrinology, Diabetes, and Medical Genetics (P.W.F.W.), Medical University of South Carolina, Charleston, South Carolina 29403; The National Heart, Lung, and Blood Institute's Framingham Heart Study and the Division of Endocrinology, Diabetes, and Hypertension (C.S.F.), Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115; The National Heart, Lung, and Blood Institute's Framingham Heart Study and the Evans Department of Medicine, Whitaker Cardiovascular Institute, and Preventive Medicine Section (R.S.V.), Boston University School of Medicine, Boston, Massachusetts 02215; and Department of Mathematics, Statistics, and Consulting Unit (L.M.S., R.B.D.), Boston University, Boston, Massachusetts 02118

Context: Metabolic risk conferred by adiposity may be due to associated risk factor clustering.

Objective: The objective of this study was to assess risk for diabetes or cardiovascular disease (CVD) stratified by body mass index (BMI) and the presence or absence of metabolic syndrome (MetS) or insulin resistance (IR).

Design, Setting, and Participants: This was a community-based, longitudinal study of 2902 people (55% women, mean age 53 yr) without diabetes or CVD in 1989–1992 followed for up to 11 yr. We categorized subjects by normal weight (BMI < 25 kg/m^2), overweight (25–29.9 kg/m^2), or obese (>30 kg/m^2) and by the National Cholesterol Education Program's Adult Treatment Panel MetS or the top quartile of homeostasis model IR. We used proportional hazard models to estimate risk relative to normal weight and no MetS or IR.

Main Outcome Measure: Incident type 2 diabetes (treatment or fasting glucose ≥ 7 mmol/liter, 141 events) or CVD (myocardial infarction, stroke, or claudication, 252 events) were measured.

Results: Among 1056 normal-weight subjects, 7% had MetS and a risk factor-adjusted relative risk for diabetes of 3.97 (95% confidence interval, 1.35–11.6) and for CVD of 3.01 (1.68–5.41). Among 638 obese subjects, 37% did not have MetS or significantly increased risk. Obese subjects with MetS had an adjusted relative risk for diabetes of 10.3 (5.44–19.5) and for CVD of 2.13 (1.43–3.18). Results were similar in analyses of BMI-IR categories.

Conclusions: People with normal weight and MetS or IR or with obesity but no MetS or IR were not uncommon in our sample. Risk factor clustering or IR appear to confer much of the risk for diabetes or CVD commonly associated with elevated BMI. (***J Clin Endocrinol Metab* 91: 2906–2912, 2006**)

OBESITY IS A rapidly growing health problem in the United States, conferring substantial excess risk for morbidity and mortality, especially from type 2 diabetes and atherosclerotic cardiovascular disease (CVD) (1, 2). Obesity is a complex disorder, where genetic predisposition interacts with environmental exposures to produce a heterogeneous phenotype (3). Body mass index (BMI) has consistently been associated with adverse health outcomes, but subphenotypes of obesity have been recognized that appear to deviate from the apparent dose-response relationship between BMI and its consequences. Ruderman and others (4–8) identified metabolically obese normal-weight (MONW) individuals who, despite having a normal-weight BMI, demonstrate metabolic disturbances typical of obese individuals. These disturbances include insulin resistance (IR) and increased levels of central adiposity, low levels of high-density lipoprotein-cholesterol (HDL-C) and elevated levels of triglycerides, impaired fasting glucose, and hypertension. This clustering of risk factors has been called the metabolic syndrome (MetS) (9). Others have described metabolically healthy obese (MHO) individuals, who, despite having BMI exceeding 30 kg/m^2, are relatively insulin sensitive and lack most of the metabolic abnormalities typical of obese individuals (10–13). MONW and MHO individuals are interesting because these phenotypes separate obesity from its usual metabolic consequences, offering insight into risks associated with risk factor clustering or IR that are largely independent of overall obesity (MONW) or risks associated with obesity that are largely independent of adiposity's intermediate metabolic abnormalities (MHO).

Characteristics of BMI-metabolic risk subphenotypes have been described in selected study samples, but their prevalence in a community-based sample is not well established. Furthermore, both obesity and MetS or IR are strong risk

First Published Online May 30, 2006

Abbreviations: ATP3, Third Report of the National Cholesterol Education Program's Adult Treatment Panel; BMI, body mass index; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; FOS, Framingham Offspring Study; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; HOMA, homeostasis model assessment; IR, insulin resistance; LDL-C, low-density lipoprotein-cholesterol; MetS, metabolic syndrome; MHO, metabolically healthy obese; MONW, metabolically obese normal weight; OGTT, oral glucose tolerance test; RR, relative risk.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

factors for type 2 diabetes and CVD, but whether elevated BMI in their absence confers risk for type 2 diabetes or CVD is uncertain. In this study, we categorized subjects of the Framingham Offspring Study (FOS) into normal-weight, overweight, and obese BMI categories and with or without risk factor clustering (defined by the presence of MetS) or IR (using the homeostasis model) to describe the community prevalence of obesity subphenotypes. We then followed subjects for the development of type 2 diabetes or CVD to test the hypothesis that, relative to normal-weight individuals without MetS or IR, obese subjects without MetS or IR (resembling the MHO phenotype) were not at substantially increased risk, normal-weight individuals with MetS or IR were at intermediate risk (resembling MONW), and obese individuals with MetS or IR were at the highest risk for development of type 2 diabetes and/or CVD.

Subjects and Methods

Study sample

The FOS is a community-based prospective observational study of CVD (14). Offspring subjects are white, of mixed European ancestry. During the fifth examination cycle (1991–1995), 3799 participants fasted overnight and had a standardized medical examination, including a 2-h oral glucose tolerance test (OGTT). A total of 2902 subjects provided data for the present analysis, after exclusion of 659 with diabetes or CVD at the baseline exam, and 238 with missing baseline BMI or MetS characteristics. Subjects were followed from baseline over a mean of 6.8 yr for the incidence of diabetes and a mean of 11.4 yr for first CVD events. The Institutional Review Board of Boston University approved the study protocol, and all subjects gave informed consent at each examination.

Exposure and outcome definitions

We defined diabetes at the baseline exam as a fasting plasma glucose (FPG) level more than or equal to 7.0 mmol/liter, a 2-h OGTT glucose of more than or equal to 11.1 mmol/liter, or current use of hypoglycemic drug therapy. We defined diabetes at follow-up as development of a FPG level more than or equal to 7.0 mmol/liter or new use of hypoglycemic drug therapy. Over 98% of diabetes among Framingham Offspring is type 2 diabetes (15). We defined baseline and follow-up CVD by standard Framingham Heart Study criteria as any of the following: new-onset angina, fatal and nonfatal myocardial infarction or stroke, transient ischemic attack, heart failure, or intermittent claudication (16).

We defined MetS using the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP3) criteria as any three or more of: FPG, 5.6–6.9 mmol/liter; waist circumference more than 102 cm (in men) or more than 88 cm (in women); fasting triglycerides more than or equal to 1.7 mmol/liter; high-density lipoprotein-cholesterol (HDL-C) less than 1.0 mmol/liter (in men) or less than 1.3 mmol/liter (in women); and blood pressure (BP) more than or equal to 130/85 mm Hg or current treatment for hypertension (9). We used the homeostasis model [(fasting glucose $\times$ fasting insulin)/22.5)] and defined IR as a homeostasis model assessment (HOMA)-IR level in the top quartile of the distribution among subjects without diabetes (17, 18).

We measured height, weight, and waist circumference with the subject standing. We calculated BMI as weight in kilograms divided by the square of height in meters. We used BP as the mean of two measurements after the subject had been seated for at least 5 min. We considered subjects who reported smoking cigarettes regularly during the year before the exam to be current smokers. We estimated low-density lipoprotein-cholesterol (LDL-C) indirectly using the Friedewald formula (19). We based a positive parental history of diabetes on self-report of diabetes in one or both parents (20). We defined impaired glucose tolerance as a 2-h OGTT glucose level of 7.8–11.0 mmol/liter. Laboratory methods for glucose, insulin, and lipid assays have been published previously (21). The Framingham laboratory participates in the Centers for Disease Control lipoprotein cholesterol laboratory standardization program. Assay coefficients of variation were less than 3% for glucose and less than 10% for insulin.

Statistical analysis

We used the Mantel-Haenszel statistic or ANOVA to test trends in baseline characteristics across BMI-MetS or IR categories. We classified subjects into three BMI categories (normal weight, <25 kg/m^2; overweight, 25–29.9 kg/m^2; and obese, ≥ 30 kg/m^2) and with or without MetS or, in separate analyses, IR. Subjects were followed from baseline through the seventh exam (1998–2001) for diabetes and through December, 2004 for CVD events. Risk for diabetes or CVD was examined in separate analyses. We calculated the cumulative incidence of diabetes or CVD as the number of diabetes or CVD events divided by the number of subjects at risk in each category at baseline. For diabetes incidence, we used the exam visit date that a new case of diabetes was identified as the date of diagnosis. For CVD events, we used the actual date of the event as the date of diagnosis and for subjects without events, the date of their last follow-up exam as the censoring date. We used hazard ratios from proportional hazards regression models (accounting for interval censoring for diabetes events) to estimate relative risks (RRs) and 95% confidence intervals (CIs) for incident diabetes or CVD conditioned on baseline BMI and MetS or IR categories. Models were adjusted for age and sex, and we used those with BMI less than 25 kg/m^2 and without MetS or IR as the referent groups. Multivariable models predicting incident diabetes included covariates for age, sex, parental history of diabetes, and impaired glucose tolerance. Multivariable models predicting incident CVD included covariates for age, sex, LDL-C level, and smoking. We conducted a subsidiary analysis of CVD events that excluded incident cases of diabetes to ensure that risk was not a function of the concurrent development of diabetes. We did not conduct sex-specific analyses because there were too few events in some subgroups to calculate stable risk estimates. We estimated the population attributable fraction for diabetes or CVD associated with exposure categories (for instance, the normal weight with MetS category) as the proportion of cases in the exposure category $\times$ [$(RR_{\text{exposure category}} - 1)/RR_{\text{exposure category}})$] $\times$ 100 (22). We performed all analyses using SAS (SAS Institute, Cary, NC) and considered a two-sided value of $P < 0.05$ to be statistically significant.

Results

Characteristics of the study subjects, stratified by BMI and MetS categories, are displayed in Table 1. The prevalence of most MetS traits and other diabetes or CVD risk factors increased with increasing BMI in subjects with or without MetS, although the trend for increasing risk factors was more prominent across BMI categories among subjects without MetS. Thirty-two percent of those with MetS and normal weight were insulin resistant, 34% of obese subjects without MetS were insulin resistant, and 68% of obese subjects with MetS were insulin resistant.

The distributions of study subjects and incident diabetes or CVD events, stratified by BMI and IR categories, are displayed in Table 2. Overall, of 2902 subjects, 2.6% were normal weight with MetS (resembling the MONW phenotype), and 8.1% were obese without MetS (resembling the MHO phenotype). Only 33.8% of the sample was normal weight and without MetS, and 13.9% were obese with MetS. Among normal-weight subjects, 7.1% had MetS, and among obese subjects, 37.0% did not have MetS. The distribution of BMI-risk categories was similar using IR instead of MetS. For instance, among normal-weight subjects, 7.7% were insulin resistant, and among obese subjects, 44.3% were insulin sensitive.

Over a mean of 7-yr follow-up, 141 subjects developed type 2 diabetes, and over a mean of 11-yr follow-up, 252

TABLE 1. Characteristics of 2902 study subjects at baseline, stratified by BMI and MetS category

	No MetS				Yes MetS			
	BMI < 25	BMI 25–29.9	BMI ≥ 30	P^a	BMI < 25	BMI 25–29.9	BMI ≥ 30	P^a
N	981	881	236		75	327	402	
Mean age (yr)	52	53	52	0.3	59	57	56	0.0006
Sex (% women)	72.6	44.7	48.7	<0.0001	61.3	44.7	46.5	0.2
Waist > 88 cm (women) or >102 (men) (%)	3.5	18.6	75.4	<0.0001	18.7	54.7	95.3	<0.0001
HDL < 1.3 mmol/liter (women) or <1.0 (men) (%)	18.6	24.9	22.9	0.008	82.7	74.3	68.7	0.007
Triglycerides ≥ 1.7 mmol/liter (%)	10.3	18.7	9.8	0.02	77.3	79.8	67.7	0.001
BP ≥ 130/85 mm Hg or treatment (%)	22.6	30.8	34.3	<0.0001	89.3	81.4	82.1	0.3
Fasting glucose, 5.6–6.9 mmol/liter (%)	12.7	16.9	14.8	0.07	56.0	56.0	57.7	0.7
IR (HOMA-IR ≥ 75th percentile; %)	5.8	14.9	34.1	<0.0001	32.4	47.4	68.4	<0.0001
2-h Postchallenge glucose, 7.8–10.9 mmol/liter (%)	5.2	5.9	10.2	0.01	24.0	22.3	25.6	0.4
Parental history of diabetes mellitis (%)	16.5	16.0	16.5	0.9	13.3	18.7	21.4	0.1
LDL-C (mean mmol/liter)	3.07	3.30	3.37	<0.0001	3.45	3.48	3.43	0.5
Smoking (%)	21.8	16.5	11.1	<0.0001	24.0	18.7	18.2	0.3

[a] *P* for trend across BMI categories within MetS category.

experienced a first CVD event, giving an overall cumulative incidence of 4.9% for diabetes and 8.7% for CVD (Table 2). Among 1056 normal-weight subjects, there were 17 incident diabetes and 63 first CVD events, giving cumulative incidence of 1.6% for diabetes and 6.0% for CVD. Likewise, among overweight subjects, the cumulative incidence was 4.1% for diabetes and 9.4% for CVD and for obese subjects, 11.6% for diabetes and 11.8% for CVD. Unadjusted cumulative incidences of diabetes and CVD in each category are shown in Table 2, and age-sex-adjusted cumulative incidences of diabetes or CVD stratified by BMI and MetS are shown in Fig. 1. At each level of BMI, MetS conferred greater risk of diabetes or CVD.

Age-sex-adjusted and multivariable-adjusted RRs for incident type 2 diabetes or CVD associated with BMI, MetS, IR, and their joint effects are displayed in Tables 3 and 4. Overweight, obesity, MetS, or IR all increased the multivariable RR for incident diabetes by approximately 5- to 7-fold relative to those without these conditions (Table 3). Subjects with MetS or IR, regardless of level of BMI, were at a significant approximately 4- to 11-fold increased multivariable RR of incident diabetes relative to normal-weight subjects without MetS or IR. Overweight or obese subjects without MetS and overweight, insulin-sensitive subjects were not at increased risk for diabetes. Interestingly, obese, insulin-sensitive subjects were at about 3-fold increased risk of diabetes relative to normal-weight subjects without IR, suggesting that obesity is diabetogenic even in the absence of IR.

Obesity, MetS, or IR increased the multivariable RR for incident CVD by approximately 1.6- to 2-fold relative to those without these conditions (Table 4). Subjects with MetS or IR, regardless of obesity category, were at about 2-fold increased risk for CVD relative to normal-weight subjects without MetS or IR. Normal-weight subjects with MetS or IR subjects were at 2- to 3-fold increased risk for CVD events. Subjects without MetS or IR, regardless of BMI category (including obese subjects), were not at increased risk for incident CVD relative to normal-weight subjects without MetS or IR.

The normal weight with MetS phenotype was associated with a small age-sex-adjusted population attributable fraction for adverse outcomes, accounting for 2.9% (95% CI, 1.6–3.3%) of diabetes risk in the population and for 4.4%

TABLE 2. Numbers of type 2 diabetes and CVD events over follow-up according to BMI and ATP3 MetS or IR category

	No. with diabetes events	No. without diabetes events	Events in category (cumulative incidence) (%)	No. with CVD events	No. without CVD events	Events in category (cumulative incidence) (%)	Total no.	Overall prevalence	MetS or IR in BMI category (%)
Total	141	2761		252	2650		2902		
No MetS									
BMI < 25 kg/m^2	12	969	1.2	47	934	4.8	981	33.8	
BMI 25–29.9 kg/m^2	13	868	1.5	69	812	7.8	881	30.4	
BMI ≥ 30 kg/m^2	7	229	3.0	19	217	8.1	236	8.1	
MetS									
BMI < 25 kg/m^2	5	70	6.7	16	59	21.3	75	2.6	7.1
BMI 25–29.9 kg/m^2	37	290	11.3	45	282	13.8	327	11.3	27.1
BMI ≥ 30 kg/m^2	67	335	16.7	56	346	13.9	402	13.9	63.0
HOMA-IR quartiles 1–3 (insulin sensitive)[a]									
BMI < 25 kg/m^2	11	927	1.2	48	890	5.1	938	32.3	
BMI 25–29.9 kg/m^2	20	875	2.2	71	824	7.9	895	30.8	
BMI ≥ 30 kg/m^2	12	259	4.4	24	247	8.9	271	9.3	
HOMA-IR quartile 4 (insulin resistant)									
BMI < 25 kg/m^2	6	72	7.7	10	68	12.8	78	2.7	7.7
BMI 25–29.9 kg/m^2	29	251	10.4	41	239	14.6	280	9.6	23.8
BMI ≥ 30 kg/m^2	57	284	16.7	46	295	13.5	341	11.8	55.7

[a] For outcomes conditioned on IR, 2803 subjects contributed 135 diabetes events and 240 CVD events due to missing values for HOMA-IR.

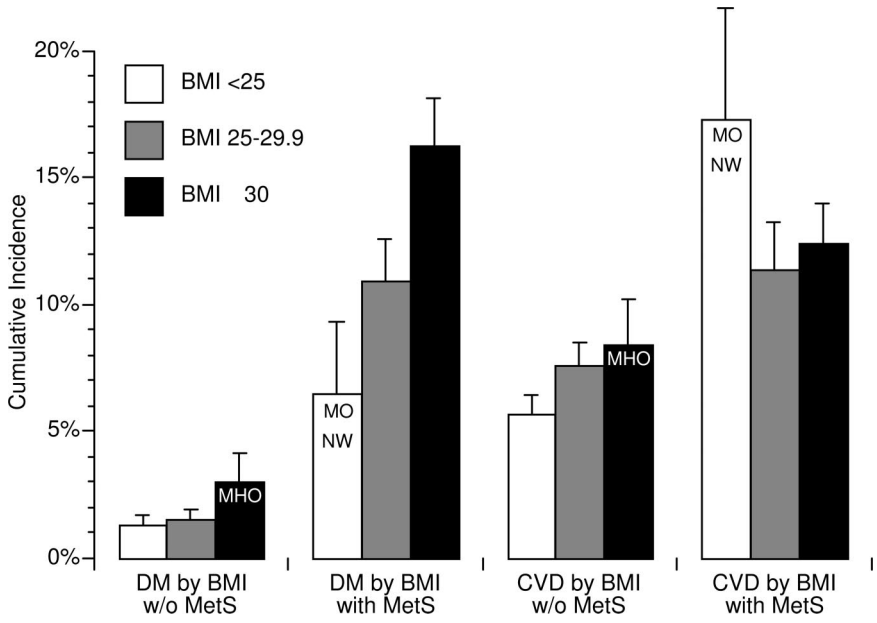

FIG. 1. Seven-year age-sex-adjusted cumulative incidence of type 2 diabetes (DM, *left bars*) and 11-yr adjusted cumulative incidence CVD (*right bars*) stratified by BMI and the absence of ATP3 MetS. Obese subjects without MetS (MHO phenotype) and normal-weight subjects with MetS (MONW phenotype) are indicated.

(3.0–5.3%) of CVD risk. The obese with MetS phenotype accounted for 44.1% (41.2–45.7%) of diabetes risk in the population and for 12.5% (7.8–15.6%) of CVD risk.

In a subsidiary analysis that excluded all cases of incident diabetes occurring over follow-up, associations of obesity and MetS or IR with incident CVD remained very similar. For instance, the multivariable risk factor-adjusted RRs for incident CVD after exclusion of incident diabetes were 3.09 (95% CI, 1.69–5.66; $P = 0.0003$) for normal-weight subjects with MetS and 1.56 (0.90–2.68; $P = 0.1$) for obese subjects without MetS relative to normal-weight subjects without MetS. Finally, P values for first order BMI-by-MetS or BMI-by-IR interaction terms were all $P \geq 0.3$, suggesting that MetS or IR did not appear to have more than additive effects on the association of obesity with risk of diabetes or CVD.

Discussion

In this study, we addressed the hypothesis that there is heterogeneity in the metabolic risk status of individuals with normal weight, overweight, or obesity. We observed in our community-based sample that there were small numbers of men and women with normal weight who had MetS or IR, resembling the MONW phenotype described by Ruderman and others (4–8) and modest numbers with obesity but without MetS or IR, resembling the MHO phenotype described by

TABLE 3. Adjusted RRs for incident type 2 diabetes according to BMI and metabolic obesity phenotypes (ATP3 MetS or IR)

	Age-sex-adjusted			Multivariable-adjusted[a]		
	RR	95% CI	*P*	RR	95% CI	*P*
MetS[b]	9.22	6.15–13.8	<0.0001	6.98	4.58–10.6	<0.0001
IR (HOMA-IR ≥ 75th percentile)[b]	6.45	4.44–9.36	<0.0001	4.78	3.24–7.05	<0.0001
BMI < 25 kg/m^2	1.00			1.00		
BMI 25–29.9 kg/m^2	2.35	1.34–4.11	0.003	2.12	1.21–3.73	0.009
BMI ≥ 30 kg/m^2	7.12	4.16–12.2	<0.0001	5.28	3.07–9.1	<0.0001
No MetS[b]						
BMI < 25 kg/m^2	1.00			1.00		
BMI 25–29.9 kg/m^2	1.13	0.51–2.49	0.8	1.11	0.50–2.44	0.8
BMI ≥ 30 kg/m^2	2.40	0.94–6.12	0.07	2.19	0.85–5.60	0.1
MetS						
BMI < 25 kg/m^2	5.32	1.84–15.4	0.002	3.97	1.35–11.6	0.01
BMI 25–29.9 kg/m^2	8.88	4.54–17.4	<0.0001	6.77	3.43–13.4	<0.0001
BMI ≥ 30 kg/m^2	14.1	7.53–26.4	<0.0001	10.3	5.44–19.5	<0.0001
Insulin sensitive (HOMA-IR < 75th percentile)						
BMI < 25 kg/m^2	1.00			1.00		
BMI 25–29.9 kg/m^2	1.84	0.87–3.87	0.1	1.77	0.84–3.73	0.1
BMI ≥ 30 kg/m^2	3.79	1.66–8.62	0.002	3.28	1.44–7.50	0.005
IR (HOMA-IR ≥ 75th percentile)[b]						
BMI < 25 kg/m^2	6.28	2.30–17.2	0.0003	4.81	1.74–13.3	0.002
BMI 25–29.9 kg/m^2	8.28	4.06–16.9	<0.0001	6.08	2.94–12.6	<0.0001
BMI ≥ 30 kg/m^2	15.1	7.81–29.3	<0.0001	10.7	5.43–20.9	<0.0001

[a] RRs for diabetes adjusted for age, sex, family history of diabetes, and impaired glucose tolerance.
[b] RRs for diabetes associated with MetS use those without MetS as the referent, risk associated with IR use those without IR as the referent, and risk associated with obesity-metabolic obesity phenotypes use those with BMI < 25 kg/m^2 and without MetS (or IR) as the referent.

TABLE 4. Adjusted RRs for incident CVD according to BMI and metabolic obesity phenotypes (ATP3 MetS or IR)

	Age-sex-adjusted			Multivariable-adjusted[a]		
	RR	95% CI	*P*	RR	95% CI	*P*
MetS[b]	1.86	1.45–2.40	<0.0001	1.83	1.42–2.36	<0.0001
IR (HOMA-IR ≥ 75th percentile)[b]	1.77	1.36–2.29	<0.0001	1.77	1.35–2.31	<0.0001
BMI < 25 kg/m^2	1.00			1.00		
BMI 25–29.9 kg/m^2	1.26	0.92–1.73	0.1	1.27	0.93–1.75	0.1
BMI ≥ 30 kg/m^2	1.63	1.16–2.29	0.005	1.60	1.13–2.26	0.008
No MetS[b]						
BMI < 25 kg/m^2	1.00			1.00		
BMI 25–29.9 kg/m^2	1.34	0.92–1.95	0.1	1.30	0.89–1.90	0.2
BMI ≥ 30 kg/m^2	1.46	0.85–2.49	0.2	1.48	0.87–2.55	0.2
MetS						
BMI < 25 kg/m^2	3.31	1.87–5.86	<0.0001	3.01	1.68–5.41	0.0002
BMI 25–29.9 kg/m^2	2.02	1.33–3.06	0.001	2.08	1.37–3.16	0.0006
BMI ≥ 30 kg/m^2	2.28	1.54–3.38	<0.0001	2.13	1.43–3.18	0.0002
Insulin sensitive (HOMA-IR < 75th percentile)						
BMI < 25 kg/m^2	1.00			1.00		
BMI 25–29.9 kg/m^2	1.28	0.88–1.86	0.2	1.25	0.86–1.81	0.2
BMI ≥ 30 kg/m^2	1.49	0.91–2.43	0.1	1.42	0.87–2.33	0.2
IR (HOMA-IR ≥ 75th percentile)[b]						
BMI < 25 kg/m^2	2.09	1.06–4.14	0.03	1.89	0.93–3.85	0.08
BMI 25–29.9 kg/m^2	2.11	1.38–3.24	0.001	2.18	1.41–3.35	0.0004
BMI ≥ 30 kg/m^2	2.14	1.41–3.23	0.0003	2.06	1.35–3.14	0.0008

[a] RRs for CVD adjusted for age, sex, LDL-C, and smoking. The multivariate BMI-MetS model predicts 169 CVD events, and the BMI-HOMA-IR model predicts 160 events due to missing data for some covariates.

[b] RRs for CVD associated with MetS use those without MetS as the referent, risks associated with IR use those without IR as the referent, and risks associated with obesity-metabolic obesity phenotypes use those with BMI < 25 kg/m^2 and without MetS (or IR) as the referent.

Brochu, Karelis, and others (10–13). The presence of metabolic risk factors typically associated with obesity augmented risk for incident type 2 diabetes or CVD, regardless of obesity status. It has thus far only been hypothesized that the MONW or MHO phenotypes exist in the community and have differential associations with diabetes or CVD (23). We observed that the MONW-like phenotype was associated with a 3- to 4-fold risk factor-adjusted RR for diabetes or CVD events, accounting for 2–3% of these events in the population. Not surprisingly, obese individuals with MetS or IR were at the highest RR for type 2 diabetes, were also at risk for CVD, and accounted for 13–44% of these events in the population. Subjects with the MHO-like phenotype did not appear to be at significantly increased risk for CVD and were at lesser risk for diabetes. Overweight conferred risk intermediate between that of normal weight and obesity but only increased risk in the presence of MetS or IR. The results of this study establish that there are BMI-metabolic risk subphenotypes in the community and that the metabolic consequences of elevated BMI are the critical factors that confer risk for type 2 diabetes or CVD associated with fatness. In the presence of the metabolic consequences of obesity, increasing levels of overall obesity added incremental risk for type 2 diabetes, although not for CVD. Conversely, in the absence of metabolic abnormalities, obesity itself did not increase risk for CVD and was a relatively weak risk factor for incident diabetes.

We defined metabolic risk as the presence of the cluster of risk factors defining ATP3 MetS or by the presence of IR. These characteristics are those typically described to be present in MONW subjects and absent in MHO (23). ATP3 MetS includes visceral adiposity (assessed by a large waist circumference), which has long been known to confer risk for type 2 diabetes or CVD independent of BMI and to be a key determinant of IR and risk factor clustering (24–35). However, only 19% of normal-weight subjects with MetS had a large waist circumference and were at increased risk for diabetes or CVD, whereas 75% of obese subjects without MetS subjects had a large waist circumference and were not at increased risk. Conversely, the other recognized diabetes and CVD risk factors that cluster with central adiposity (including low levels of HDL-C and elevated levels of triglycerides, impaired fasting glucose, and hypertension) occurred with relatively high frequency in normal-weight subjects with MetS but not in obese subjects without MetS. This suggests either that these individual traits were responsible for elevated risk or that their aggregate clustering was the risk factor. The latter interpretation is supported by our observation that the prevalence of BMI-metabolic risk subphenotypes and the magnitude of their associated risks for diabetes or CVD were very similar when metabolic risk was defined by the presence of IR rather than MetS (6, 7, 10, 11). This interpretation is qualified to some degree by the fact that only 32–68% of FOS subjects with ATP3 MetS were insulin resistant. However, IR at any given degree of obesity has been associated with elevated levels of diabetes and CVD risk factors (36), and dysmetabolism (MetS and diabetes combined) also confers risk for subsequent CVD events independent of BMI (37). Whether IR underlies the risk factor clustering embodied in ATP3 MetS is the subject of debate (38). Nonetheless, our data demonstrate that the presence of metabolic risk defined either by risk factor clusters or IR identifies BMI subphenotypes with substantially different levels of risk for consequences traditionally considered to have a simple dose-response relationship with increasing BMI.

Population-based data on the prevalence of BMI subphenotypes are sparse, and different definitions for metabolic

risk allow only indirect comparisons. Some data suggest that the MONW-like phenotype is reasonably common, with a prevalence of 3–28% that depends on the specific definition of metabolic risk and the population source (8, 11, 23, 39). Our data show that in a white community, the prevalence of a MONW-like phenotype is about 3% overall and 7% among those with BMI less than 25 kg/m^2. The MHO-like phenotype also appears in other studies to be reasonably common, with a prevalence of 11–28% (10, 11, 40, 41). Our data are consistent, with 8% of the Framingham community overall and 37% of obese individuals having the obese-no MetS phenotype. We extend these data to show that, as hypothesized, normal-weight subjects with MetS but not obese subjects without MetS individuals were at substantially elevated risk for both type 2 diabetes or CVD over 7–11 yr of follow-up. The interpretation that obese subjects without MetS are really obese and healthy needs to be made with caution, however. Apparently healthy obese subjects may have subclinical vascular disease (42, 43) so that longer follow-up or more careful evaluation of vascular phenotypes may be required for MHO-like subjects to develop adverse health outcomes, including those not considered in this analysis (2). Furthermore, given that MHO-like subjects were younger than obese subjects with MetS, as these subjects age, they may transition from obese and apparently healthy to obese with risk factor clustering with accompanying increased risk. In addition, we had limited statistical power in the obese-without MetS group to detect small differences. Because of our sample size, we had only 30–40% power to detect a difference in the observed proportions at $P = 0.05$. Although our sample may have had only enough power to detect large risks in the obese-without MetS group, it is clear that these subjects were at substantially lower risk for diabetes or CVD than any of the metabolically higher risk subgroups. Perhaps the greater significance of the prevalence of the obese-without MetS phenotype is its converse—that most overweight and obese individuals are metabolically high risk and at substantially elevated risk for diabetes or CVD. Physiological data confirm that the combination of obesity and IR confer the greatest elevations in metabolic risk factors and the greatest degree of risk factor clustering (44, 45). Our findings have one apparent clinical implication. The clinical role of risk factor clustering as codified in the MetS has thus far been unclear (46), but one use for MetS may be to discriminate the obese high-risk phenotype from the background population of apparently healthy people at all levels of BMI for purposes of diabetes and CVD prevention.

Strengths of our analysis include the examination of a large, community-based sample of men and women across a broad age spectrum and standardized assessment of diabetes and CVD risk factors and outcomes, but there are limitations of our study in addition to those addressed above. We used a definition of metabolic risk restricted to traditional diabetes or CVD risk factors. In the obese-without MetS phenotype, in particular, measurement of subclinical inflammation, endothelial dysfunction, or adiponectin (13, 43, 47, 48) might reveal less than perfect metabolic health. In addition, follow-up longer than 7–11 yr might be required to be certain that obese subjects without risk factors are indeed low risk. Our observation that BMI incrementally increased risk among subjects with MetS or IR suggests that additional factors associated with obesity, but not measured in this study, further account for risk of adverse health consequences associated with increased BMI. In addition, the criteria defining ATP3 MetS are arbitrary; alternate schemes to define metabolic risk may be equally valid and could produce different results (5, 7, 23). However, analyses using IR to define metabolic obesity gave essentially similar results as for MetS, suggesting that our findings were not an artifact imposed by the ATP3 MetS criteria. Finally, our data cannot be readily generalized to other communities because the distribution of obesity, MetS, and IR is known to vary substantially across different race/ethnicity groups (49).

In summary, we used normal-weight, overweight, and obese BMI categories and risk factor clustering or IR to define the prevalence of BMI-metabolic risk subphenotypes in a community-based sample. We found that MONW-like and obese-high-risk phenotypes exist and confer increased risk for incident diabetes or CVD. A MHO-like phenotype was also moderately common and did not confer marked increased risk. Risk factor clustering or IR appear to confer the risk for diabetes or CVD commonly associated with elevated BMI. Assessment of metabolic risk, regardless of BMI, appears to identify individuals at increased risk for future development of type 2 diabetes or CVD and who may benefit from interventions to reduce risk.

Acknowledgments

Received March 16, 2006. Accepted May 18, 2006.

Address all correspondence and requests for reprints to: James B. Meigs, M.D., M.P.H., General Medicine Division, Massachusetts General Hospital, 50 Staniford Street, 9th Floor, Boston, Massachusetts 02114. E-mail: jmeigs@partners.org.

This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and by Grant 2K24 HL04334 (to R.S.V.) from the National Heart, Lung, and Blood Institute. J.B.M. is supported by an American Diabetes Association Career Development Award. D.M.N. is supported by the Ida Charlton Charitable Trust. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have nothing to disclose.

References

1. **Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP** 1999 The spread of the obesity epidemic in the United States, 1991–1998. JAMA 282:1519–1522
2. **Willett WC, Dietz WH, Colditz GA** 1999 Guidelines for healthy weight. N Engl J Med 341:427–434
3. **Comuzzie AG, Williams JT, Martin LJ, Blangero J** 2001 Searching for genes underlying normal variation in human adiposity. J Mol Med 79:57–70
4. **Ruderman NB, Schneider SH, Berchtold P** 1981 The "metabolically-obese," normal-weight individual. Am J Clin Nutr 34:1617–1621
5. **Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S** 1998 The metabolically obese, normal-weight individual revisited. Diabetes 47:699–713
6. **Zavaroni I, Bonora E, Pagliara M, Dall'Aglio E, Luchetti L, Buonanno G, Bonati PA, Bergonzani M, Gnudi L, Passeri M** 1989 Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 320:502–506
7. **Dvorak RV, DeNino WF, Ades PA, Poehlman ET** 1999 Phenotypic characteristics associated with insulin resistance in metabolically obese but normal-weight young women. Diabetes 48:2210–2214
8. **St-Onge MP, Janssen I, Heymsfield SB** 2004 Metabolic syndrome in normal-weight Americans: new definition of the metabolically obese, normal-weight individual. Diabetes Care 27:2222–2228
9. **Grundy SM, Brewer Jr HB, Cleeman JI, Smith Jr SC, Lenfant C** 2004 Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood

Institute/American Heart Association conference on scientific issues related to definition. Circulation 109:433–438
10. **Ferrannini E, Natali A, Bell P, Cavallo-Perin P, Lalic N, Mingrone G** 1997 Insulin resistance and hypersecretion in obesity. European Group for the Study of Insulin Resistance (EGIR). J Clin Invest 100:1166–1173
11. **Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G, Alberiche M, Bonadonna RC, Muggeo M** 1998 Prevalence of insulin resistance in metabolic disorders. Diabetes 47:1643–1649
12. **Brochu M, Tchernof A, Dionne IJ, Sites CK, Eltabbakh GH, Sims EA, Poehlman ET** 2001 What are the physical characteristics associated with a normal metabolic profile despite a high level of obesity in postmenopausal women? J Clin Endocrinol Metab 86:1020–1025
13. **Karelis AD, Faraj M, Bastard JP, St-Pierre DH, Brochu M, Prud'homme D, Rabasa-Lhoret R** 2005 The metabolically healthy but obese individual presents a favorable inflammation profile. J Clin Endocrinol Metab 90:4145–4150
14. **Kannel WB, Feinleib M, McNamara JR, Garrison RJ, Castelli WP** 1979 An investigation of coronary heart disease in families: the Framingham Offspring Study. Am J Epidemiol 110:281–290
15. **Meigs JB, Cupples LA, Wilson PWF** 2000 Parental transmission of type 2 diabetes mellitus: the Framingham Offspring Study. Diabetes 49:2201–2207
16. **Cupples LA, D'Agostino RB** 1988 Section 34: some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements: Framingham Heart Study, 30-year followup. In : Kannel W, Wolf P, Garrison R, eds. The Framingham Study: an epidemiological investigation of cardiovascular disease. Washington, DC: U.S. Department of Commerce
17. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
18. **Balkau B, Charles MA** 1999 Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med 16:442–443
19. **Friedewald WT, Levy RI, Fredrickson DS** 1972 Estimation of the concentration of low density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin Chem 18:499–502
20. **Murabito JM, Nam BH, D'Agostino Sr RB, Lloyd-Jones DM, O'Donnell CJ, Wilson PW** 2004 Accuracy of offspring reports of parental cardiovascular disease history: the Framingham Offspring Study. Ann Intern Med 140:434–440
21. **Meigs JB, Mittleman MA, Nathan DM, Tofler GH, Singer DE, Murphy-Sheehy PM, Lipinska I, D'Agostino RB, Wilson PWF** 2000 Hyperinsulinemia, hyperglycemia, and impaired hemostasis: the Framingham Offspring Study. JAMA 283:221–228
22. **Rockhill B, Newman B, Weinberg C** 1998 Use and misuse of population attributable fractions. Am J Public Health 88:15–19
23. **Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET** 2004 Metabolic and body composition factors in subgroups of obesity: what do we know? J Clin Endocrinol Metab 89:2569–2575
24. **Kannel WB, Cupples LA, Ramaswami R, Stokes 3rd J, Kreger BE, Higgins M** 1991 Regional obesity and risk of cardiovascular disease; the Framingham Study. J Clin Epidemiol 44:183–190
25. **Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE** 1998 Abdominal adiposity and coronary heart disease in women. JAMA 280:1843–1848
26. **Rexrode KM, Buring JE, Manson JE** 2001 Abdominal and total adiposity and risk of coronary heart disease in men. Int J Obes Relat Metab Disord 25:1047–1056
27. **Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, Willett WC** 1995 Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 141: 1117–1127
28. **Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC** 1994 Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 17:961–969
29. **Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE** 1997 Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 145:614–619
30. **Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjostrom L** 1989 Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. Int J Obes 13:413–423
31. **Ohlson LO, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G** 1985 The influence of body fat distribution on the incidence of diabetes mellitus: 13.5 years of follow-up of the participants in the study of men born in 1913. Diabetes 34:1055–1058
32. **Wei M, Gaskill SP, Haffner SM, Stern MP** 1997 Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans: a 7-year prospective study. Obes Res 5:16–23
33. **Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB** 2005 Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr 81:555–563
34. **Carr DB, Utzschneider KM, Hull RL, Kodama K, Retzlaff BM, Brunzell JD, Shofer JB, Fish BE, Knopp RH, Kahn SE** 2004 Intra-abdominal fat is a major determinant of the National Cholesterol Education Program Adult Treatment Panel III criteria for the metabolic syndrome. Diabetes 53:2087–2094
35. **Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A, Kritchevsky SB, Simonsick EM, Nevitt M, Holvoet P, Newman AB** 2005 Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. Arch Intern Med 165:777–783
36. **Abbasi F, Brown Jr BW, Lamendola C, McLaughlin T, Reaven GM** 2002 Relationship between obesity, insulin resistance, and coronary heart disease risk. J Am Coll Cardiol 40:937–943
37. **Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, Rogers WJ, Reis SE** 2004 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 109:706–713
38. **Kahn R, Buse J, Ferrannini E, Stern M** 2005 The metabolic syndrome: time for a critical appraisal Joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 48:1684–1699
39. **McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G** 2004 Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. Metabolism 53:495–499
40. **Karelis AD, Brochu M, Rabasa-Lhoret R** 2004 Can we identify metabolically healthy but obese individuals (MHO)? Diabetes Metab 30:569–572
41. **Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F** 2005 Prevalence of uncomplicated obesity in an Italian obese population. Obes Res 13:1116–1122
42. **Oflaz H, Ozbey N, Mantar F, Genchellac H, Mercanoglu F, Sencer E, Molvalilar S, Orhan Y** 2003 Determination of endothelial function and early atherosclerotic changes in healthy obese women. Diabetes Nutr Metab 16:176–181
43. **Benjamin EJ, Larson MG, Keyes MJ, Mitchell GF, Vasan RS, Keaney Jr JF, Lehman BT, Fan S, Osypiuk E, Vita JA** 2004 Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. Circulation 109:613–619
44. **Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Vessby B, Basu S, Tracy R, Jacobs Jr DR** 2005 Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. Circulation 111:1985–1991
45. **Piche ME, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J, Lemieux S** 2005 Contribution of abdominal visceral obesity and insulin resistance to the cardiovascular risk profile of postmenopausal women. Diabetes 54:770–777
46. **Meigs JB** 2004 Metabolic syndrome: in search of a clinical role. Diabetes Care 27:2761–2763
47. **Festa A, D'Agostino Jr R, Howard G, Mykkanen L, Tracy RP, Haffner SM** 2000 Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 102: 42–47
48. **Meigs JB, Hu FB, Rifai N, Manson JE** 2004 Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. JAMA 291:1978–1986
49. **Meigs JB, Williams K, Sullivan LM, Hunt KJ, Haffner SM, Stern MP, Gonzalez Villalpando C, Perhanidis JS, Nathan DM, D'Agostino Jr RB, D'Agostino Sr RB, Wilson PW** 2004 Using metabolic syndrome traits for efficient detection of impaired glucose tolerance. Diabetes Care 27:1417–1426

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.