Impact of Body Mass Index and the Metabolic Syndrome on the Risk of Cardiovascular Disease and Death in Middle-Aged Men

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Background—The purpose of this study was to investigate associations between combinations of body mass index (BMI) categories and metabolic syndrome (MetS) and the risk of cardiovascular disease and death in middle-aged men.

Methods and Results—At age 50 years, cardiovascular risk factors were assessed in 1758 participants without diabetes in the community-based Uppsala Longitudinal Study of Adult Men (ULSAM). According to BMI-MetS status, they were categorized as normal weight (BMI <25 kg/m^2) without MetS (National Cholesterol Education Program criteria; n=891), normal weight with MetS (n=64), overweight (BMI 25 to 30 kg/m^2) without MetS (n=582), overweight with MetS (n=125), obese (BMI >30 kg/m^2) without MetS (n=30), or obese with MetS (n=66). During follow-up (median 30 years), 788 participants died, and 681 developed cardiovascular disease (composite of cardiovascular death or hospitalization for myocardial infarction, stroke, or heart failure). In Cox proportional-hazards models that adjusted for age, smoking, and low-density lipoprotein cholesterol, an increased risk for cardiovascular disease was observed in normal-weight participants with MetS (hazard ratio 1.63, 95% confidence interval 1.11 to 2.37), overweight participants without MetS (hazard ratio 1.52, 95% confidence interval 1.28 to 1.80), overweight participants with MetS (hazard ratio 1.74, 95% confidence interval 1.32 to 2.30), obese participants without MetS (hazard ratio 1.95, 95% confidence interval 1.14 to 3.34), and obese participants with MetS (hazard ratio 2.55, 95% confidence interval 1.81 to 3.58) compared with normal-weight individuals without MetS. These BMI-MetS categories significantly predicted total mortality rate in a similar pattern.

Conclusions—Middle-aged men with MetS had increased risk for cardiovascular events and total death regardless of BMI status during more than 30 years of follow-up. In contrast to previous reports, overweight and obese individuals without MetS also had an increased risk. The present data refute the notion that overweight and obesity without MetS are benign conditions. **(*Circulation*. 2010;121:230-236.)**

Key Words: cardiovascular diseases ■ epidemiology ■ obesity ■ metabolic syndrome ■ insulin resistance

One reason for the major impact of obesity on the development of cardiovascular disease[1–4] is that it often is accompanied by the metabolic syndrome (MetS), a cluster of dyslipidemia, hyperglycemia, and hypertension.[5] The presence of the MetS is a strong predictor of future cardiovascular disease and death,[3,4,6–10] and the increase in risk begins with the presence of just 1 MetS component.[3] However, obese individuals without the MetS, sometimes referred to as metabolically healthy obese (MHO),[11–13] did not demonstrate an increased risk of cardiovascular disease in 2 previous prospective studies,[14,15] although an increased cardiovascular risk was seen in normal-weight individuals with the MetS,[4,14,15] a condition sometimes referred to as metabolically obese but normal weight.[16–20]

Clinical Perspective on p 236

In the 2 previous studies reporting the longitudinal associations between MHO, metabolically obese but normal weight, metabolically impaired obesity, and future cardiovascular events, the follow-up did not exceed 13 years.[14,15] Thus, there is a gap in previous literature with regard to the long-term impact of different body mass index (BMI)/MetS combinations. This could be important, because previous reports have suggested a time lag of 10 to 15 years before the full impact of the MetS on risk of death becomes evident.[10]

We hypothesized that the MetS is a risk factor for cardiovascular disease and death regardless of BMI status and that overweight/obesity without the MetS is not associated with higher cardiovascular risk. We tested our hypothesis by

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investigating the associations of combinations of BMI levels and presence/absence of the MetS with long-term risk of cardiovascular events and death using data from a cohort study of middle-aged men followed up for more than 30 years. As a secondary aim, we investigated the association between combinations of BMI levels and presence/absence of insulin resistance (IR) with future risk for cardiovascular disease or death, because some previous investigators have defined MHO as obesity in the absence of IR and "metabolically obese but normal weight" as normal weight with IR.[11,13,21]

Methods

Study Sample

In 1970–1973, all men born in 1920–1924 and residing in the county of Uppsala, Sweden, were invited to participate in a health survey (at age 50 years) aimed at identifying risk factors for cardiovascular disease; 82% of the invited men participated (n=2322). Of these, 564 participants were excluded for the following reasons: prior hospitalization for cardiovascular disease (n=9), diabetes mellitus at baseline (n=122), or unavailable covariates (n=433). This left 1758 as the present study sample. The design and selection criteria for the cohort have been described previously.[21,22] Written informed consent was obtained, and the Uppsala University Ethics Committee approved the study.

Baseline Examinations and MetS Definition

The examination at age 50 years has been described in detail previously.[21,22] Blood samples for fasting concentrations were drawn in the morning after an overnight fast. Cholesterol and triglyceride concentrations in serum and high-density lipoprotein cholesterol were assayed by enzymatic techniques. Fasting blood glucose was determined by an oxidase method and insulin by radioimmunoassay. The erythrocyte sedimentation rate was determined by Westergren's method.[23] Supine systolic and diastolic blood pressures were measured twice in the right arm after 10 minutes' rest, and means were calculated. Diabetes at baseline was defined according to the current World Health Organization definition (fasting blood glucose ≥6.1 mmol/L [which corresponds to fasting plasma glucose ≥7.0 mmol/L or 126 mg/dL] or the use of antidiabetic medication).[24]

In the present study, we used a modified version of the National Cholesterol Education Program definition of the MetS[5] (see Table I in the online-only Data Supplement for a detailed description of the criteria). Because waist circumference was only measured in a subsample of the participants (n=480), the National Cholesterol Education Program definition was modified by use of a BMI cut point instead of the National Cholesterol Education Program waist circumference criterion (>102 cm). In the subsample with data on waist circumference, a waist circumference of 102 cm corresponded to a BMI of 29.4 kg/m^2 in a linear regression analysis (regression equation: BMI [kg/m^2]=0.298×waist circumference [cm]−1.027). This BMI cut point is similar to BMI cut points used in previous modified National Cholesterol Education Program definitions of the MetS.[25] BMI did not differ between this subsample (25.2 kg/m^2, SD 3.1) and the rest of the cohort (25.0 kg/m^2, SD 3.3, P=0.32).

We used the homeostasis model[26] [(fasting glucose×fasting insulin)/22.5)] and defined IR as a homeostasis model assessment-IR level in the top quartile of the distribution in participants without diabetes (>3.43). By defining normal weight as BMI <25 kg/m^2, overweight as BMI 25 to 30 kg/m^2, and obesity as BMI >30 kg/m^2, we could categorize the participants as normal weight without MetS (n=891), normal weight with MetS (metabolically obese but normal weight; n=64), overweight without MetS (n=582), overweight with MetS (n=125), obese without MetS (MHO; n=30), and obese with MetS (n=66). In secondary analyses, we also categorized participants according to BMI-IR categories as normal weight without IR (n=681), normal weight with IR (n=277), overweight without IR (n=408), overweight with IR (n=296), obese without IR (n=24), and obese with IR (n=72).

End-Point Definitions

Deaths due to all causes and deaths due to cardiovascular disease (International Classification of Diseases [ICD], 8th Revision [ICD-8] codes 390 to 458; ICD, 9th Revision [ICD-9] codes 390 to 459; or ICD, 10th Revision [ICD-10] codes I00 to I99) were identified with the use of the Swedish Cause of Death Register. Noncardiovascular death was defined as all deaths due to noncirculatory causes listed in the Swedish Cause of Death Register. Major cardiovascular events were defined as a composite end point of death due to cardiovascular causes and hospitalization for acute myocardial infarction (ICD-8 code 410, ICD-9 code 310, or ICD-10 code I20), ischemic stroke (ICD-8 codes 433 to 434, ICD-9 code 434, or ICD-10 code I63), or heart failure by use of data from the Swedish Hospital Discharge Register. The combination of data from the Swedish Cause of Death Registry and the Swedish Hospital Discharge Register is an efficient, validated alternative to revised hospital discharge notes and death certificates for both coronary heart disease and stroke.[27] Previous studies suggest that the accuracy of the heart failure diagnosis in the Swedish Hospital Discharge Register may be lower when hospitalizations for heart failure in which heart failure was not the primary diagnosis are considered.[28] Therefore, we performed extensive medical chart review to promote the highest quality of the diagnosis of heart failure and to include as many correctly classified heart failure events as possible. The classification of heart failure events during follow-up has been described in detail previously.[28] In short, as a possible diagnosis of heart failure, we considered ICD heart failure codes 427.00, 427.10, 428.99 (ICD-8), 428 (ICD-9), and I50 (ICD-10) and hypertensive heart disease with heart failure, I11.0 (ICD-10), from the Swedish Hospital Discharge Register. The medical records from the relevant hospitalizations were reviewed by 2 physicians (E.I. and L.L.), who, blinded to the baseline data, classified the cases as definite, questionable, or miscoded. The classification relied on the definition proposed by the European Society of Cardiology.[1,14,15,29] Data on cancer incidence were retrieved from the Swedish Cancer Register. During follow-up, 7 individuals were lost to follow-up because they moved abroad from Sweden.

Statistical Analysis

We used the Mantel-Haenszel statistic or ANOVA to test differences in baseline characteristics across BMI-MetS categories. Thereafter, hazard ratios and 95% confidence intervals from Cox proportional-hazards regression models were used to estimate relative risks for incident major cardiovascular events by baseline BMI-MetS categories. These models were adjusted for age at baseline (continuous variable), smoking status (dichotomous variable), and low-density lipoprotein cholesterol (continuous variable).

Proportional hazards assumptions were confirmed by Schoenfeld tests.[30] The development of major cardiovascular events in the different BMI-MetS categories was depicted graphically by use of Kaplan-Meier survival curves. In secondary analyses, we also investigated the association between the BMI-MetS categories and total death, cardiovascular death, noncardiovascular death, and cancer incidence. In addition, the association between BMI-IR categories and the incidence of major cardiovascular events, cardiovascular death, and total death was investigated. In the analyses of total and cardiovascular deaths, the participants were not censored and were still considered at risk if they experienced a nonfatal major cardiovascular event during follow-up. In the analyses with major cardiovascular events, the individual was censored at the time of the first nonfatal or fatal cardiovascular event.

To investigate whether diabetes during follow-up was driving the associations between the overweight/obese without MetS and major cardiovascular events, we also performed the above analyses in participants who were still free from diabetes at the reexamination after 20 years (n=852). We also performed subgroup analyses in those who were still free from MetS at the reexamination after 20 years (n=720). To investigate the potential influence of inflammatory activity on our results, we added erythrocyte sedimentation rate to the multivariable model.

Table 1. Cardiovascular Risk Factors in Different BMI/MetS Categories

	Normal Weight Without MetS (n=891)	Normal Weight With MetS (n=64)	Overweight Without MetS (n=582)	Overweight With MetS (n=125)	Obese Without MetS (n=30)	Obese With MetS (n=66)	ANOVA *P*
Age, y	49.6 (0.6)	49.6 (0.5)	49.6 (0.6)	49.5 (0.6)	49.7 (0.4)	49.7 (0.6)	0.29
BMI, kg/m^2	22.6 (1.6)	23.2 (1.3)†	26.7 (1.3)‡	27.5 (1.4)‡	32.2 (2.1)‡	32.8 (2.6)‡	<0.001
Systolic blood pressure, mm Hg	129 (16)	137 (18)‡	134 (17)‡	142 (18)‡	139 (18)‡	148 (21)‡	<0.001
Diastolic blood pressure, mm Hg	80 (10)	86 (9)‡	84 (10)‡	89 (10)‡	90 (12)‡	95 (13)‡	<0.001
Fasting blood glucose, mmol/L	4.8 (0.5)	5.1 (0.6)‡	4.9 (0.5)†	5.2 (0.5)‡	4.8 (0.4)	5.2 (0.5)‡	<0.001
Fasting blood insulin, mU/L	10.5 (5.1)	13.1 (5.2)‡	13.5 (6.5)‡	16.4 (9.9)‡	15.6 (5.0)‡	24.1 (12.3)‡	<0.001
Serum low-density lipoprotein cholesterol, mmol/L	5.1 (1.2)	5.9 (1.4)‡	5.3 (1.2)†	5.9 (1.3)‡	4.8 (1.0)	5.6 (1.3)†	<0.001
Serum high-density lipoprotein cholesterol, mmol/L	1.5 (0.4)	1.0 (0.3)‡	1.4 (0.3)‡	1.0 (0.3)‡	1.4 (0.4)	1.2 (0.3)‡	<0.001
Serum triglycerides, mmol/L	1.6 (0.7)	2.8 (2.9)‡	1.9 (0.8)‡	2.9 (1.4)‡	1.5 (0.4)	3.1 (2.3)‡	<0.001
HOMA index, mU/L×mmol/L	2.3 (1.2)	3.0 (1.2)‡	2.9 (1.5)‡	3.8 (2.5)‡	3.4 (1.1)‡	5.6 (2.9)‡	<0.001
ESR, mm/h	7.5 (6.4)	10.6 (12.7)	7.4 (6.7)	9.3 (8.0)	7.2 (4.2)	7.3 (4.2)	0.55
Current smoking, n (%)	483 (54)	44 (69)*	264 (45)‡	70 (56)	10 (33)*	36 (55)	0.04
Hypertension, n (%)	218 (32)	28 (44)*	267 (46)‡	83 (66)‡	18 (60)‡	52 (79)‡	<0.001
Hypertension treatment, n (%)	22 (2)	1 (2)	19 (3)	12 (10)‡	3 (10)*	9 (14)‡	<0.001
Dyslipidemia, n (%)	380 (43)	61 (95)‡	346 (59)‡	116 (93)‡	12 (40)	51 (77)‡	<0.001
Lipid-lowering treatment, n (%)	6 (1)	0 (0)	10 (2)	2 (2)	0 (0)	0 (0)	0.39

HOMA indicates homeostasis model assessment; ESR, erythrocyte sedimentation rate.

Data are means (SDs). Normal weight was defined as BMI <25 kg/m^2; overweight, BMI 25–30 kg/m^2; obese, BMI >30 kg/m^2; and dyslipidemia, total cholesterol/HDL cholesterol ratio ≥5.0 or lipid-lowering treatment.

*P<0.05, †P<0.01, ‡P<0.001 for post hoc pairwise comparison with normal-weight participants without MetS.

Values of P<0.05 from 2-sided tests were considered statistically significant. The statistical software package STATA 10.0 (Stata Corp, College Station, Tex) was used.

Results

Baseline Data

Descriptive data on cardiovascular risk factors in the BMI-MetS categories are given in Table 1. Significant differences were found between the different BMI-MetS categories regarding all variables included in MetS, as well as low-density lipoprotein cholesterol, smoking status, and use of antihypertensive medication (see Table 1 for details). The age at baseline did not differ between the groups.

Major Cardiovascular Events

During follow-up (median 30 years, extremes 0.4 to 33 years, 42 374 person-years at risk), 681 participants experienced a major cardiovascular event (rate of 1.6 per 100 person-years at risk). Figure 1 shows the incidence rates in different BMI-MetS and BMI-IR categories. The risk of major cardiovascular events was higher with higher BMI categories and with prevalent MetS than in normal-weight individuals without the MetS in multivariable models that adjusted for age at baseline, smoking status, and low-density lipoprotein cholesterol (Table 2; Figure 2). Moreover, the risk for cardiovascular events was higher with higher BMI categories and with prevalent IR than for normal-weight individuals without IR (Table 3). The association between BMI-MetS, BMI-IR categories, and major cardiovascular events remained principally the same in subgroup analyses in participants who had not developed diabetes at the reexamination after 20 years and in participants without MetS at the reexamination after 20 years, although the confidence intervals became slightly wider owing to the lesser number of participants in these groups (online-only Data Supplement Tables II and III, respectively). Furthermore, the results remained the same after erythrocyte sedimentation rate was added to the multivariable model (data not shown).

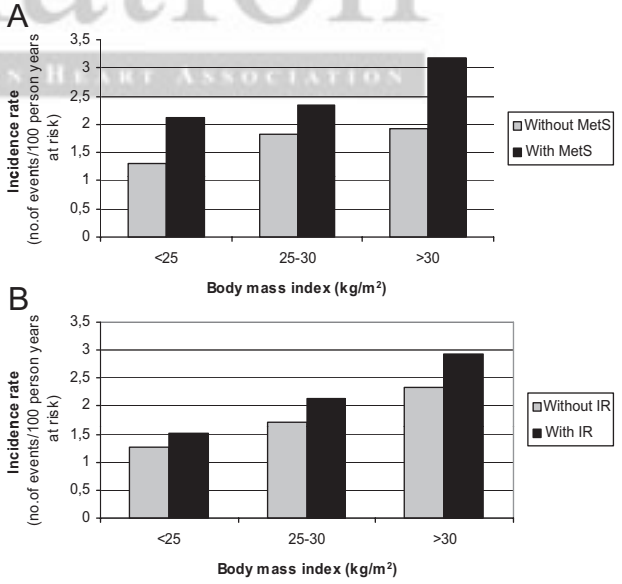

Figure 1. Incidence rates of major cardiovascular events in different combinations of BMI and MetS (A) and different combinations of BMI and IR (B).

Table 2. Deaths and Major Cardiovascular Events in Groups With Different Combinations of BMI and MetS

	Normal Weight Without MetS	Normal Weight With MetS	Overweight Without MetS	Overweight With MetS	Obese Without MetS	Obese With MetS
Total death						
No. of events/No. at risk	391/891	34/64	276/582	76/125	18/30	50/66
Multivariable hazard ratio	Referent	1.28 (0.90–1.82)	1.21 (1.03–1.40)*	1.53 (1.19–1.96)‡	1.65 (1.03–2.66)*	2.43 (1.81–3.27)‡
Cardiovascular death						
No. of events/No. at risk	155/891	20/64	133/582	46/125	5/30	27/66
Multivariable hazard ratio	Referent	1.77 (1.11–2.83)*	1.44 (1.14–1.83)†	2.19 (1.57–3.06)‡	1.20 (0.49–2.93)	3.20 (2.12–4.82)‡
Major cardiovascular events						
No. of events/No. at risk	287/891	30/64	250/582	62/125	14/30	38/66
Multivariable hazard ratio	Referent	1.63 (1.11–2.37)*	1.52 (1.28–1.80)‡	1.74 (1.32–2.30)‡	1.95 (1.14–3.34)*	2.55 (1.82–3.58)‡

Multivariable model adjusted for age, smoking status, and LDL cholesterol.
*$P<0.05$, †$P<0.01$, ‡$P<0.001$.

Mortality Rate

During the follow-up, 845 participants died (rate of 1.8 per 100 person-years at risk); 386 deaths were due to cardiovascular disease (rate of 0.8 per 100 person-years at risk). The risk for total death was higher with higher BMI categories and with prevalent MetS than for normal-weight individuals without MetS after adjustment for age, smoking, and low-density lipoprotein cholesterol (Table 2). A similar pattern was seen in the prediction of cardiovascular death, with the exception that the moderately increased risk estimate for the

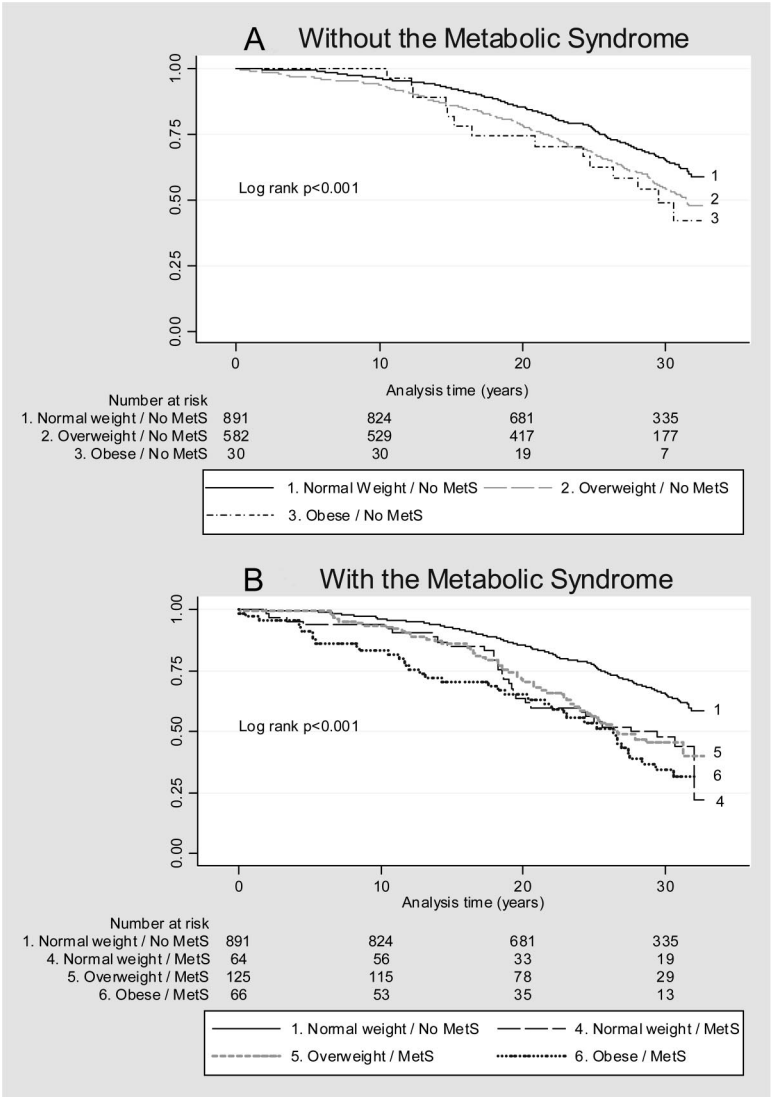

Figure 2. Kaplan-Meier curves for major cardiovascular events in different BMI categories in individuals without MetS (A) and with MetS (B).

Table 3. Deaths and Major Cardiovascular Events in Groups With Different Combinations of BMI and IR

	Normal Weight Without IR	Normal Weight With IR	Overweight Without IR	Overweight With IR	Obese Without IR	Obese With IR
Total death						
No. of events/No. at risk	290/681	137/277	196/408	154/296	17/24	51/72
Multivariable hazard ratio	Referent	1.06 (0.86–1.31)	1.22 (1.02–1.46)*	1.30 (1.06–1.59)†	2.04 (1.25–3.32)†	2.21 (1.64–2.99)‡
Cardiovascular death						
No. of events/No. at risk	112/681	65/277	86/408	91/296	6/24	26/72
Multivariable hazard ratio	Referent	1.23 (0.90–1.69)	1.36 (1.02–1.80)*	1.88 (1.42–2.50)‡	1.80 (0.79–4.08)	2.87 (1.87–4.42)‡
Major cardiovascular events						
No. of events/No. at risk	214/681	104/277	166/408	145/296	12/24	40/72
Multivariable hazard ratio	Referent	1.15 (0.90–1.46)	1.44 (1.18–1.77)‡	1.73 (1.39–2.14)‡	1.91 (1.07–3.41)*	2.56 (1.83–3.60)‡

IR was defined as the top quartile of homeostasis model of assessment of IR (>3.43).
Multivariable model adjusted for age, smoking status, and LDL cholesterol.
*$P<0.05$, †$P<0.01$, ‡$P<0.001$.

obese without MetS did not reach statistical significance (Table 2). However, because there were few participants in this group, and consequently, there was limited statistical power, no firm conclusions regarding this nonsignificant association should be drawn. In secondary analyses, obesity regardless of the presence or absence of MetS was associated with an increased risk for noncardiovascular death (multivariable hazard ratio for obese participants without MetS 1.94, 95% confidence interval 1.23 to 3.63, $P=0.02$; hazard ratio for obese participants with MetS 1.91, 95% confidence interval 1.24 to 2.94, $P=0.003$) and for cancer incidence (multivariable hazard ratio for obese participants without MetS 1.82, 95% confidence interval 1.04 to 3.20, $P=0.04$; multivariable hazard ratio for obese participants with MetS 1.72, 95% confidence interval 1.10 to 2.70, $P=0.02$) compared with normal-weight participants without MetS (see online-only Data Supplement Table IV for risk estimates for noncardiovascular death and cancer incidence in all BMI-MetS and BMI-IR categories). The BMI-IR categories predicted total death, cardiovascular death, noncardiovascular death, and cancer incidence in a similar fashion as the BMI-MetS categories (Table 3; online-only Data Supplement Table IV).

Discussion

Principal Findings

In the present study, we hypothesized that the MetS would be a major risk factor for cardiovascular disease regardless of obesity status and that overweight and obesity without the MetS would not be associated with higher cardiovascular risk. Our hypothesis was only partly confirmed. Middle-aged men with MetS had an increased risk of cardiovascular events, regardless of BMI status, and the highest risk estimates were seen in obese participants with MetS during the 30 years of follow-up. However, in contrast to previous studies, the overweight and obese participants without MetS or without IR also had an increased risk for cardiovascular events and total death compared with normal-weight men without MetS or IR. Moreover, obesity, regardless of presence or absence of MetS, was associated with a higher risk for noncardiovascular death and cancer incidence. Thus, the present data argue against the notion that overweight and obesity without metabolic derangements are benign conditions.

Comparisons With the Literature

The finding that men with MetS are at higher risk for cardiovascular events regardless of their BMI status is in accordance with previous longitudinal community-based data.[4,14,15] In contrast, overweight and obese individuals without MetS or IR previously have been reported not to be at an increased cardiovascular risk.[14,15] These conflicting results between the present study and prior studies may be explained by the fact that the present study had almost 3 times as many cardiovascular events during follow-up and consequently a better statistical power to discriminate moderate differences in risk between the BMI-MetS groups. Moreover, we had up to 3 times longer follow-up. Interestingly, there appeared to be a lag time of approximately 10 years before the Kaplan-Meier curves for the overweight or obese participants without MetS started to diverge from the curve of the normal-weight participants without MetS (Figure 2A). This could be important, because it is possible that the transition from overweight/obesity without metabolic derangements to overt cardiovascular disease is a pathological process that spans several decades. This is further supported by prior community-based studies with lengthy follow-up in which BMI has been shown to be an independent predictor of cardiovascular events.[31,32]

We cannot exclude the possibility that the present results could be explained by the fact that some of the overweight/obese men without MetS or diabetes at baseline developed MetS or diabetes during follow-up, which in turn led to a cardiovascular event. However, the fact that the association between overweight/obesity without MetS, overweight/obesity without IR, and major cardiovascular events remained essentially unaltered in subsamples of participants free from diabetes or MetS during the initial 20 years of follow-up suggests that this is not the sole explanation for our findings. The increased risk for total death, noncardiovascular death, and cancer incidence in the overweight and obese, regardless

of the presence or absence of MetS, has not been reported previously to the best of our knowledge.

Prevalence of Obesity and the MetS

In a previous report from the Framingham Study, the prevalence of MHO and obese persons with MetS was higher than in the present study.[14] Calendar period and cultural differences that result in different lifestyle behaviors, together with different sex distributions, might explain these discrepancies, because the mean age of the populations was rather similar. A recent analysis of data from the National Health and Nutrition Examination Survey also reported the prevalence of MHO but unfortunately used other definitions of metabolic abnormalities, so the prevalence cannot be compared easily.[33]

Clinical Implications

The differentiation of MHO individuals and metabolically impaired obesity has been suggested to have important implications for therapeutic medical decision making,[11] and given the favorable metabolic profile of MHO individuals, the benefits of weight loss in this subgroup has been questioned.[12] In fact, some investigators have even suggested that weight loss in these individuals potentially could be harmful.[34] However, because the present data show that the overweight and obese are at higher cardiovascular risk regardless of metabolic status, the potential benefits of diagnosing MHO in clinical practice appears limited.

Strength and Limitations of the Study

The major strength of the present study is the long follow-up period in a well-characterized population-based sample, which resulted in a large number of incident cases of major cardiovascular disorders. Another strength of the study is the completeness of ascertainment and the accuracy of classification in the nationwide compulsory Swedish Cause of Death Registry and Swedish Hospital Discharge Register.[27,35] The major limitation is that the study was performed in middle-aged males of northern European ethnicity, which limits its generalizability to women and other age and ethnic groups. Another limitation is that we used a modified version of the National Cholesterol Education Program criteria. Instead of waist circumference, BMI was used to define central obesity. The usefulness of waist circumference was not evident in the early 1970s, and therefore, it was only measured in a small proportion of the sample. However, because the results were similar when BMI-IR categories were used, it is not likely that the potential misclassification of participants had a major impact on the results of the present study.

Moreover, even though the present data were essentially unaltered after inflammation, as evaluated by erythrocyte sedimentation rate, was taken into account, it is not possible to fully evaluate the potential influence of specific inflammatory pathways or adipokine activity on the present results, because these data were not available at baseline. Finally, the present study was also limited by the fact that there were few participants in some of the BMI-MetS and BMI-IR categories. Ideally, our results should be validated in larger study populations.

Conclusions

In the present study, middle-aged men with MetS had an increased risk of major cardiovascular events, regardless of BMI status. Moreover, both overweight and obesity in the absence of MetS or IR also placed individuals at higher risk for major cardiovascular events, as well as for total death, compared with normal-weight men without metabolic derangements. Thus, the present study data do not support the existence of a healthy obese phenotype based on the definition of absence of MetS or IR.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Previous studies suggested that overweight and obese individuals without the metabolic syndrome do not have an increased risk of cardiovascular disease. Consequently, the existence of a "metabolically healthy" obese phenotype has been proposed. However, there is a gap in previous literature with regard to the long-term impact on cardiovascular risk of these different combinations of body mass index categories and the metabolic syndrome. Accordingly, we investigated the associations of combinations of body mass index levels and presence/absence of the metabolic syndrome with long-term risk of cardiovascular events and total death using data from a cohort study of middle-aged men followed up for more than 30 years. In multivariable Cox proportional-hazards models, both overweight and obese men without the metabolic syndrome had an increased risk for cardiovascular disease and total death compared with normal-weight men without the metabolic syndrome. Thus, our data refute the notion that overweight and obesity without the metabolic syndrome are benign conditions.

Impact of Body Mass Index and the Metabolic Syndrome on the Risk of Cardiovascular Disease and Death in Middle-Aged Men

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Supplemental material

Supplementary Table 1 Modified National Cholesterol Education Program Adult Treatment Pane III metabolic syndrome definition used in the present study

Metabolic syndrome present if 3 or more of the following criteria is fulfilled:
- Fasting blood glucose ≥5.6 mmol/l (100 mg/dl)*
- Blood pressure ≥130/85 mm Hg or treatment
- Triglycerides ≥1.7 mmol/l (150 mg/dl)
- High density lipoprotein cholesterol <1.04 mmol/l (40 mg/dl)
- Body mass index ≥29.4 kg/m^2

* Corresponds to plasma glucose ≥ 6.1 mmol/l (110 mg/dl)[24]

Supplementary Table 2 The association between BMI/MetS-, BMI/IR-categories and major cardiovascular events in participants without diabetes at baseline and at the reinvestigation after 20 years.

	BMI / MetS categories					
	Normal weight without MetS	**Normal weight with MetS**	**Overweight without MetS**	**Overweight with MetS**	**Obese without MetS**	**Obese with MetS**
No. of events/ no. at risk	127/478	8/24	92/283	13/43	4/9	9/15
Hazard ratio (95 % CI)	(referent)	1.10 (0.54-2.26)	1.35 (1.03-1.77)*	1.16 (0.65-2.07)	2.11 (0.78-5.72)	2.68 (1.36-5.72)†

	BMI / IR categories					
	Normal weight without IR	**Normal weight with IR**	**Overweight without IR**	**Overweight with IR**	**Obese without IR**	**Obese with IR**
No. of events/ no. at risk	93/373	42/131	63/205	42/119	5/9	8/15
Hazard ratio (95 % CI)	(referent)	1.20 (0.83-1.76)	1.37 (0.99-1.89)§	1.44 (0.99-2.09)§	2.54 (1.03-6.25)*	2.66 (1.28-5.50)†

Data are multivariable hazard ratios for major cardiovascular events adjusted for age, smoking status, LDL-cholesterol.
BMI –body mass index, MetS –Metabolic Syndrome, IR –insulin resistance
† $p<0.01$, * $p<0.05$, § $p=0.055$ compared to normal weight without MetS

Supplementary Table 3. The association between overweight/obesity without MetS at baseline and major cardiovascular events in participants without MetS at the re-examination after 20 years.

	BMI/MetS-categories			
	Normal weight without MetS	**Overweight without MetS**	**Obese without MetS**	**P for trend**
No. of events/ No. at risk	115/435	77/226	3/6	
Hazard ratio (95 % CI)	(referent)	1.41 (1.05-1.88)*	2.39 (0.76-7.54)	0.01

Data are multivariable hazard ratios for major cardiovascular events adjusted for age, smoking status, LDL-cholesterol.
* $p<0.05$ compared to Normal weight without MetS
BMI –body mass index, MetS –Metabolic Syndrome

Supplementary Table 4 The association between BMI/MetS-, BMI/IR-categories, non-CVD mortality, and cancer incidence: Cox regression

	BMI / MetS-categories					
	Normal weight without MetS	**Normal weight with MetS**	**Overweight without MetS**	**Overweight with MetS**	**Obese without MetS**	**Obese with MetS**
Non-CVD mortality						
No. of events/ no. at risk	236/891	14/64	143/582	30/125	13/30	23/66
Hazard ratio (95 % CI)	(referent)	0.93 (0.54-1.60)	1.04 (0.85-1.29)	1.05 (0.72-1.55)	1.94 (1.11-3.40)*	1.91 (1.24-2.94)†
Cancer incidence						
No. of events/ no. at risk	249/891	20/64	159/582	32/125	13/30	21/66
Hazard ratio (95 % CI)	(referent)	1.30 (0.82-2.06)	1.09 (0.89-1.33)	1.07 (0.74-1.55)	1.82 (1.04-3.20)*	1.73 (1.11-2.70)*

	BMI / IR-categories					
	Normal weight without IR	**Normal weight with IR**	**Overweight without IR**	**Overweight with IR**	**Obese without IR**	**Obese with IR**
Non-CVD mortality						
No. of events/ no. at risk	178/681	72/277	110/408	63/296	11/24	25/72
Hazard ratio (95 % CI)	(referent)	0.96 (0.72-1.27)	1.14 (0.89-1.44)	0.91 (0.68-1.23)	2.24 (1.22-4.11)†	1.79 (1.18-2.73)†
Cancer incidence						
No. of events/ no. at risk	186/681	83/277	116/408	75/296	11/24	23/72
Hazard ratio (95 % CI)	(referent)	1.05 (0.80-1.37)	1.15 (0.91-1.44)	1.01 (0.77-1.33)	2.40 (1.31-4.42)†	1.56 (1.01-2.41)*

Data are multivariable hazard ratios for major cardiovascular events adjusted for age, smoking status, LDL-cholesterol

† $p<0.01$, * $p<0.05$ compared to normal weight without MetS

BMI –body mass index, MetS –Metabolic Syndrome, IR –insulin resistance