

# Impact of BMI and the Metabolic Syndrome on the Risk of Diabetes in Middle-Aged Men

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**OBJECTIVE** — The existence of an obese subgroup with a healthy metabolic profile and low diabetes risk has been proposed; yet long-term data are lacking. We aimed to investigate associations between combinations of BMI categories and metabolic syndrome and risk of type 2 diabetes in middle-aged men.

**RESEARCH DESIGN AND METHODS** — At age 50, cardiovascular risk factors were assessed in 1,675 participants without diabetes in the community-based Uppsala Longitudinal Study of Adult Men (ULSAM) study. According to BMI/metabolic syndrome status, they were categorized as normal weight (BMI <25 kg/m<sup>2</sup>) without metabolic syndrome (National Cholesterol Education Program criteria, *n* = 853), normal weight with metabolic syndrome (*n* = 60), overweight (BMI 25–30 kg/m<sup>2</sup>) without metabolic syndrome (*n* = 557), overweight with metabolic syndrome (*n* = 117), obese (BMI >30 kg/m<sup>2</sup>) without metabolic syndrome (*n* = 28), and obese with metabolic syndrome (*n* = 60). We investigated the associations between BMI/metabolic syndrome categories at baseline and diabetes incidence.

**RESULTS** — After 20 years, 160 participants had developed diabetes. In logistic regression models adjusting for age, smoking, and physical activity, increased risks for diabetes were observed in the normal weight with metabolic syndrome (odds ratio 3.28 [95% CI] 1.38–7.81; *P* = 0.007), overweight without metabolic syndrome (3.49 [2.26–5.42]; *P* < 0.001), overweight with metabolic syndrome (7.77 [4.44–13.62]; *P* < 0.001), obese without metabolic syndrome (11.72 [4.88–28.16]; *P* < 0.001), and obese with metabolic syndrome (10.06 [5.19–19.51]; *P* < 0.001) categories compared with the normal weight without metabolic syndrome category.

**CONCLUSIONS** — Overweight or obese men without metabolic syndrome were at increased risk for diabetes. Our data provide further evidence that overweight and obesity in the absence of the metabolic syndrome should not be considered a harmless condition.

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Higher BMI has consistently been associated with an increased risk for type 2 diabetes (1,2). One reason for the major impact of obesity on the development of type 2 diabetes is that it often is accompanied by the metabolic syndrome, a cluster of hyperglycemia, dyslipidemia, and hypertension (3).

It has been proposed that the association between BMI and the development of type 2 diabetes is more complex than a

mere a dose-response relationship (4,5). The existence of a metabolically healthy but obese phenotype (MHO) has been proposed, an obese subgroup with a healthy metabolic profile and with no increased risk for adverse outcomes such as diabetes or cardiovascular disease (4–6). It should, however, be noted that the MHO hypothesis is not undisputed; it was recently reported that both overweight and obese middle-aged men without the

metabolic syndrome were at increased risk for cardiovascular events and total mortality during 30 years of follow-up (7).

In a recent report from the Framingham Heart Study, overweight or obese individuals without the metabolic syndrome did not portray a significantly increased risk for diabetes, whereas participants with the metabolic syndrome were at substantially higher risk for diabetes regardless of BMI status (8). However, in this previous study, the follow-up did not exceed 7 years. Thus, data on the long-term impact of different BMI/metabolic syndrome combinations and the risk of diabetes are still lacking.

We hypothesized that overweight and obesity, regardless of metabolic syndrome status, as well as the metabolic syndrome, regardless of BMI status, would be associated with long-term increased risk for diabetes. We tested our hypothesis by investigating the associations of combinations of BMI categories and the presence or absence of the metabolic syndrome with long-term risk of type 2 diabetes using data from a cohort study of middle-aged men followed for 20 years. As a secondary aim, we investigated the association between combinations of BMI categories and the presence or absence of insulin resistance to future risk of diabetes as some previous investigators have defined MHO as obesity in the absence of insulin resistance (4,9,10).

## RESEARCH DESIGN AND METHODS

— In 1970–1973, all men born in 1920–1924 and residing in the county of Uppsala were invited to a health survey (at age 50) aimed to identify risk factors for cardiovascular disease; 82% of the invited men participated (*n* = 2,322). The cohort was reinvestigated after 10 and 20 years when the subjects were ~60 and 70 years old, respectively. The design and selection criteria for the cohort have been described previously (11). Participants were excluded for the following reasons: diabetes at baseline (*n* = 124) or unavailability of data on metabolic syndrome components or covariates (*n* = 523), leaving 1,675 men as the present

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**Table 1—Modified NCEP Adult Treatment Panel III metabolic syndrome definition used in the present study**

Metabolic syndrome present if $\geq 3$ of the following criteria are fulfilled:
● Fasting blood glucose $\geq 5.6$ mmol/l (100 mg/dl)*
● Blood pressure $\geq 130/85$ mmHg or treatment
● Triglycerides $\geq 1.7$ mmol/l (150 mg/dl)
● HDL cholesterol $< 1.04$ mmol/l (40 mg/dl)
● BMI $\geq 29.4$ kg/m <sup>2</sup>

\*Corresponds to plasma glucose  $\geq 6.1$  mmol/l (110 mg/dl) (14).

study sample. Of these, 1,375 participants had available data on insulin resistance. The baseline characteristics and the event rates of diabetes in the present study sample were similar to those for participants who were excluded because of missing data at baseline (data not shown). Informed written consent was obtained, and the Uppsala University Ethics Committee approved the study.

**Baseline examinations and metabolic syndrome definition**

The examination at age 50 has been described in detail previously (11). Blood samples for fasting concentrations were drawn in the morning after an overnight fast. Cholesterol and triglyceride concentrations in serum were assayed by enzymatic techniques. Fasting blood glucose was determined by an oxidase method

and insulin by radioimmunoassay. Supine systolic and diastolic blood pressures were measured twice in the right arm after a 10-min rest, and means were calculated.

In the present study we used a modified version of the National Cholesterol Education Program (NCEP) definition of the metabolic syndrome (3) (Table 1). Because waist circumference was only measured in a subsample of the participants ( $n = 480$ ), the NCEP definition was modified by using a BMI cut point instead of the NCEP 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<sup>2</sup> in a linear regression analysis (regression equation: BMI [weight in kilograms divided by the square of height in meters] = 0.298  $\times$  waist circumference [centimeters] - 1.027). This BMI cut point is similar to BMI cut points used in previous modified NCEP definitions of the metabolic syndrome (12) BMI did not differ between this subsample ( $25.2 \pm 3.1$  kg/m<sup>2</sup>, mean  $\pm$  SD) and the rest of the cohort ( $25.0 \pm 3.3$  kg/m<sup>2</sup>;  $P = 0.32$ ).

We used the homeostasis model (HOMA) [fasting glucose  $\times$  fasting insulin]/22.5) (13) and defined insulin resistance (IR) as HOMA-IR in the top quartile of the distribution in participants without diabetes ( $> 3.43$ ). Leisure time physical activity was estimated using a questionnaire containing four physical activity categories: sedentary, moderate, regular, and athletic (11).

By defining normal weight as BMI

$< 25$  kg/m<sup>2</sup>, overweight as BMI 25–30 kg/m<sup>2</sup>, and obesity as BMI  $> 30$  kg/m<sup>2</sup>, we could categorize the participants as normal weight without metabolic syndrome ( $n = 853$ ), normal weight with metabolic syndrome ( $n = 60$ ), overweight without metabolic syndrome ( $n = 557$ ), overweight with metabolic syndrome ( $n = 117$ ), obese without metabolic syndrome (MHO,  $n = 28$ ), and obese with metabolic syndrome ( $n = 60$ ). In secondary analyses, we also categorized participants according to BMI/insulin resistance categories: normal weight without insulin resistance ( $n = 652$ ), normal weight with insulin resistance ( $n = 103$ ), overweight without insulin resistance ( $n = 389$ ), overweight with insulin resistance ( $n = 172$ ), obese without insulin resistance ( $n = 21$ ), and obese with insulin resistance ( $n = 48$ ).

**End point definitions**

Diabetes was defined according to current World Health Organization criteria using fasting concentrations of glucose (fasting blood glucose  $\geq 6.1$  mmol/l at the baseline investigation and 10-year reinvestigation, which corresponds to fasting plasma glucose  $\geq 7.0$  mmol/l) or fasting plasma glucose  $\geq 7.0$  mmol/l at the 20-year reinvestigation) or the use of antidiabetes medication at any investigation (14). Of the present study sample, 1,364 participants attended the 10-year reinvestigation and 967 participants attended the 20-year reinvestigation. In those who did not attend the reinvestigations, the Swed-

**Table 2—Cardiovascular risk factors in different BMI/metabolic syndrome categories**

	Normal weight		Overweight		Obese	
	Without MetS	With MetS	Without MetS	With MetS	Without MetS	With MetS
<i>n</i>	853	60	557	117	28	60
Age (years)	49.6 $\pm$ 0.6	49.6 $\pm$ 0.5	49.6 $\pm$ 0.6	49.5 $\pm$ 0.6	49.7 $\pm$ 0.4	49.7 $\pm$ 0.6
BMI (kg/m <sup>2</sup> )	22.6 $\pm$ 1.6	23.3 $\pm$ 1.3	26.7 $\pm$ 1.3	27.5 $\pm$ 1.4	32.2 $\pm$ 2.2	32.9 $\pm$ 2.7
Systolic blood pressure (mmHg)	129 $\pm$ 16	135 $\pm$ 17	134 $\pm$ 17	142 $\pm$ 18	139 $\pm$ 17	148 $\pm$ 21
Diastolic blood pressure (mmHg)	80 $\pm$ 10	86 $\pm$ 9	84 $\pm$ 10	89 $\pm$ 10	90 $\pm$ 12	95 $\pm$ 12
Fasting blood glucose (mmol/l)	4.8 $\pm$ 0.5	5.1 $\pm$ 0.6	4.9 $\pm$ 0.5	5.2 $\pm$ 0.5	4.9 $\pm$ 0.4	5.2 $\pm$ 0.5
Fasting blood insulin (mU/l)	10.5 $\pm$ 5.2	12.9 $\pm$ 4.8	13.5 $\pm$ 6.5	16.4 $\pm$ 10.0	16.1 $\pm$ 4.8	24.5 $\pm$ 12.5
Serum HDL cholesterol (mmol/l)	1.5 $\pm$ 0.4	1.0 $\pm$ 0.2	1.4 $\pm$ 0.3	1.0 $\pm$ 0.3	1.4 $\pm$ 0.4	1.2 $\pm$ 0.3
Serum triglycerides (mmol/l)	1.6 $\pm$ 0.7	2.9 $\pm$ 3.0	1.9 $\pm$ 0.8	2.9 $\pm$ 1.4	1.5 $\pm$ 0.4	3.1 $\pm$ 2.4
HOMA index (mU/l $\cdot$ mmol/l)	2.3 $\pm$ 1.2	3.0 $\pm$ 1.2	2.9 $\pm$ 1.5	3.9 $\pm$ 2.5	3.5 $\pm$ 1.1	5.7 $\pm$ 2.9
Current smoking	463 (54)	42 (70)	253 (45)	66 (56)	9 (32)	33 (55)
Hypertension	273 (32)	24 (40)	259 (46)	79 (68)	17 (61)	46 (77)
Hypertension treatment	21 (3)	1 (2)	20 (4)	12 (10)	3 (11)	9 (15)
Dyslipidemia*	366 (43)	58 (97)	331 (59)	108 (92)	12 (43)	46 (77)
Lipid-lowering treatment	6 (1)	0 (0)	11 (2)	2 (2)	0 (0)	0 (0)

Data are means  $\pm$  SD or *n* (%). Normal weight, BMI  $< 25$  kg/m<sup>2</sup>; overweight, BMI 25–30 kg/m<sup>2</sup>; obese, BMI  $> 30$  kg/m<sup>2</sup>. MetS, metabolic syndrome. \*Dyslipidemia: total cholesterol-to-HDL cholesterol ratio  $\geq 5.0$  or lipid-lowering treatment.

ish national hospital discharge register was used to identify additional participants who developed diabetes during the 20-year follow-up (ICD-9 code 250 or ICD-10 codes E10–E14).

**Statistical analysis**

We investigated the associations of baseline BMI/metabolic syndrome status with the incidence of diabetes using crude and multivariable logistic regression. These multivariable models were adjusted for age at baseline (continuous), smoking status (dichotomous), and level of physical activity (ordinal). In addition, the association between BMI/insulin resistance categories and the incidence of diabetes was investigated in a similar manner.

To elucidate whether participants with impaired fasting glucose at baseline were driving the associations, we performed secondary analyses in which participants with impaired fasting glucose at baseline were excluded (fasting blood glucose >5.6–6.1 mmol/l, n = 134).

P < 0.05 from two-sided tests was considered statistically significant. The statistical software package Stata 10.0 (StataCorp, College Station, TX) was used.

**RESULTS** — Baseline characteristics for the different BMI/metabolic syndrome categories are shown in Table 2.

**BMI/metabolic syndrome categories and type 2 diabetes incidence**

During the 20-year follow-up, 160 participants had developed type 2 diabetes. The risk of diabetes was higher in the overweight and obesity categories and with prevalent metabolic syndrome compared with that for normal-weight individuals without the metabolic syndrome in both crude and multivariable models with adjustment for age at baseline, smoking status, and physical activity (Table 3). Obese participants, regardless of metabolic syndrome status, had a >10-fold increased risk for diabetes compared with normal-weight individuals without the metabolic syndrome. Interestingly, the associations were similar when participants with impaired fasting glucose at baseline were excluded (Table 3).

**BMI/insulin resistance categories and type 2 diabetes incidence**

The risk of diabetes during follow-up was higher in the overweight and obesity categories and with prevalent insulin resistance compared with that in normal-

weight individuals without insulin resistance, both in crude and multivariable models (Table 4). The obese participants with insulin resistance were at highest risk for diabetes at the investigation after 20 years compared with the normal-weight individuals without insulin resistance (Table 4); however the obese participants without insulin resistance also had a >11-fold increased diabetes risk. Moreover, the associations were similar when participants with impaired fasting glucose at baseline were excluded (Table 4).

**CONCLUSIONS**

**Principal findings**

In the present study, middle-aged men with metabolic syndrome or insulin resistance had an increased risk of type 2 diabetes, regardless of BMI status during 20 years of follow-up, compared with normal-weight men without metabolic syndrome or insulin resistance. The highest risk estimate was seen in obese participants with insulin resistance. In contrast to previous studies, overweight and obese men without metabolic syndrome or without insulin resistance had a markedly increased diabetes risk. Thus, our data provide further evidence that opposes the notion of overweight and obesity without metabolic derangements as harmless conditions. Interestingly, the associations between BMI/metabolic syndrome categories, BMI/insulin resistance categories, and diabetes incidence were independent of the level of physical activity.

**Comparisons with the literature**

Although numerous studies have reported the separate associations between BMI, metabolic syndrome, insulin resistance, and the risk for type 2 diabetes (1,2,15), we are aware of only one study that has investigated associations between BMI/metabolic syndrome categories, BMI/insulin resistance categories, and diabetes risk (8). In the previous study by Meigs et al. (8), all participants with metabolic syndrome or insulin resistance were at higher risk for diabetes regardless of BMI status, whereas overweight/obese individuals without the metabolic syndrome were at no increased risk. Moreover, obese participants without insulin resistance were at a threefold higher risk for diabetes relative to normal-weight participants without insulin resistance, whereas overweight individuals without insulin resistance were at no increased

**Table 3—Diabetes incidence during 20-year follow-up in groups with different combinations of BMI and metabolic syndrome in the whole sample and in participants with normal fasting blood glucose at baseline (<5.6 mmol/l)**

	Normal weight		Overweight		Obese	
	Without Mets	With Mets	Without Mets	With Mets	Without Mets	With Mets
Whole sample (n = 1,675)						
No. of events/no. at risk	32/853	7/60	67/557	27/117	9/28	18/60
Crude odds ratio	Referent	3.39 (1.43–8.04)†	3.51 (2.27–5.42)†	7.70 (4.41–13.43)†	12.15 (5.10–28.96)†	11.00 (5.71–21.18)†
Multivariable odds ratio	Referent	3.28 (1.38–7.81)†	3.50 (2.26–5.42)†	7.77 (4.44–13.62)†	11.73 (4.88–28.16)†	10.06 (5.19–19.51)†
Normal fasting glucose (n = 1,541)						
No. of events/no. at risk	28/817	4/44	60/529	15/78	9/28	9/45
Crude odds ratio	Referent	2.82 (0.94–8.42)	3.60 (2.27–5.73)†	6.71 (3.41–13.21)†	13.35 (5.55–32.11)†	7.04 (3.10–18.03)†
Multivariable odds ratio	Referent	2.77 (0.92–8.33)	3.64 (2.28–5.81)†	6.87 (3.46–13.64)†	13.19 (5.42–32.09)†	6.37 (2.77–14.64)†

Data are odds ratios (95% CI). Multivariable models were adjusted for age, smoking status, and level of physical activity. Normal weight, BMI <25 kg/m<sup>2</sup>; overweight, BMI 25–30 kg/m<sup>2</sup>; obese, BMI >30 kg/m<sup>2</sup>. Mets, metabolic syndrome. †P < 0.01; ‡P < 0.001.



Table 4—Diabetes incidence during 20-year follow-up in groups with different combinations of BMI and insulin resistance in the whole sample and in participants with normal fasting blood glucose at baseline (<5.6 mmol/l)

	Normal weight		Overweight		Obese	
	Without IR	With IR	Without IR	With IR	Without IR	With IR
Whole sample (n = 1,385)	17/652	13/103	38/389	28/172	5/21	16/48
No. of events/no. at risk	Referent	5.40 (2.54–11.48)†	4.04 (2.25–7.27)†	7.26 (3.87–13.63)†	11.67 (3.83–35.55)†	18.68 (8.65–40.32)†
Crude odds ratio	Referent	5.24 (2.46–11.16)†	4.09 (2.72–7.37)†	7.29 (3.87–13.72)†	11.22 (3.67–34.35)†	17.06 (7.84–37.14)†
Multivariable odds ratio						
Normal fasting glucose (n = 1,269)	15/622	9/87	31/360	19/143	5/19	9/38
No. of events/no. at risk	Referent	4.66 (1.98–11.03)†	3.81 (2.03–7.17)†	6.20 (3.07–12.54)†	14.46 (4.61–45.30)†	12.56 (5.07–31.09)†
Crude odds ratio	Referent	4.55 (1.92–10.77)†	3.87 (2.05–7.29)†	6.28 (3.09–12.78)†	13.80 (4.38–43.41)†	11.70 (4.68–29.25)†
Multivariable odds ratio						

Data are odds ratios (95% CI). Multivariable models adjusted for age, smoking status, and level of physical activity. Normal weight, BMI <25 kg/m<sup>2</sup>; overweight, BMI 25–30 kg/m<sup>2</sup>; obese, BMI >30 kg/m<sup>2</sup>. IR, insulin resistance defined as the top quartile of HOMA insulin resistance >3.43. †P < 0.001.

risk. There are several differences that may explain the partly conflicting results between the present and this prior study: The baseline of the present study was ~20 years earlier than that for the study by Meigs et al. (8). Our study sample consisted of men only with a very narrow age span, and the percentage of overweight and obese participants was substantially lower compared with that in the previous study. Moreover, our study had a longer follow-up and a somewhat different approach of identifying diabetes case subjects and control subjects during follow-up that may explain the higher event rates in the present study.

**Clinical implications**

Given the favorable metabolic profile of the MHO individuals, the benefits of weight loss in this subgroup has been questioned (5,14,16), and some small scale intervention studies have suggested that weight loss in this group may lead to a worsened risk profile (17,18). However, based on our observational data, overweight or obese persons without the metabolic syndrome or insulin resistance should be considered to have a substantially higher risk for diabetes compared with normal-weight individuals without the metabolic syndrome. The influence of weight loss on risk in such individuals needs to be determined in intervention studies with predefined metabolic syndrome/insulin resistance subgroups and hard end points. Until such studies are available, our data oppose the concept that individuals who are overweight/obese without the metabolic syndrome should not be offered weight loss interventions.

**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. The major limitation is that the study was performed in middle-aged men of Northern European ethnicity, limiting the generalizability to women and other age- and ethnic groups. Another limitation is that we used a modified version of the NCEP 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 was only measured in a small proportion of the sample. However, because the results were similar when BMI/insulin resistance categories were used, it is not likely that the potential misclassifi-

cation of participants has had a major impact on our results. Moreover, our study was also limited by the fact that there were few participants in some of the BMI/metabolic syndrome and BMI/insulin resistance categories, leading to wider CIs and consequently a higher uncertainty regarding the level of the risk estimate. Accordingly, no firm conclusions should be drawn regarding a potential dose-response relationship between the BMI/metabolic syndrome and BMI/insulin resistance categories. Ideally, our results should be validated in study populations with larger numbers of obese participants. Finally, for those who did not attend the reinvestigation we used the Swedish Hospital Discharge Register to identify participants who developed diabetes during follow-up. Because not all patients with diabetes are hospitalized, it is likely that some participants who developed diabetes during follow-up were incorrectly classified as not having diabetes in our analyses. However, any such misclassification would conservatively bias the risk estimates.

In summary, the increased risk for type 2 diabetes in overweight/obese men without the metabolic syndrome or insulin resistance in the present study provides additional evidence that opposes the existence of a healthy obese phenotype based on the definition of absence of the metabolic syndrome or insulin resistance.

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J.Å. researched data and wrote the manuscript. J.S. contributed to discussion and reviewed/edited the manuscript. E.I. contributed to discussion and reviewed/edited the manuscript. L.L. researched data, contributed to discussion, and reviewed/edited the manuscript.

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