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Cardiometabolic Risk

Risk of Myocardial Infarction and Heart Failure Among Metabolically Healthy But Obese Individuals

HUNT (Nord-Trøndelag Health Study), Norway

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Objectives This study sought to investigate whether obesity in the absence of metabolic abnormalities might be a relatively benign condition in relation to acute myocardial infarction (AMI) and heart failure (HF).

Background The results of previous studies are conflicting for AMI and largely unknown for HF, and the role of the duration of obesity has not been investigated.

Methods In a population-based prospective cohort study, a total of 61,299 men and women free of cardiovascular disease were classified according to body mass index (BMI) and metabolic status at baseline. BMI also was measured 10 and 30 years before baseline for 27,196 participants.

Results During 12 years of follow-up, 2,547 participants had a first AMI, and 1,201 participants had a first HF. Compared with being normal weight (BMI <25 kg/m^2) and metabolically healthy, the multivariable-adjusted hazard ratio (HR) for AMI was 1.1 (95% confidence interval [CI]: 0.9 to 1.4) among obese (BMI ≥ 30 kg/m^2) and metabolically healthy participants and 2.0 (95% CI: 1.7 to 2.3) among obese and metabolically unhealthy participants. We found similar results for severe (BMI ≥ 35 kg/m^2), long-lasting (>30 years), and abdominal obesity stratified for metabolic status. For HF, the HRs associated with obesity were 1.7 (95% CI: 1.3 to 2.3) and 1.7 (95% CI: 1.4 to 2.2) for metabolically healthy and unhealthy participants, respectively. Severe and long-lasting obesity were particularly harmful in relation to HF, regardless of metabolic status.

Conclusions In relation to AMI, obesity without metabolic abnormalities did not confer substantial excess risk, not even for severe or long-lasting obesity. For HF, even metabolically healthy obesity was associated with increased risk, particularly for long-lasting or severe obesity. (J Am Coll Cardiol 2014;63:1071–8) © 2014 by the American College of Cardiology Foundation

Obesity is associated with increased risk for acute myocardial infarction (AMI) and heart failure (HF) (1,2). It has adverse effects on metabolic components associated with cardiovascular disease, including blood pressure, glucose tolerance, and blood lipids (3). Manson et al. (4) suggested that most of the increased risk associated with obesity may be attributed to the adverse effect of these factors and that any effects beyond metabolic abnormalities are negligible. However, previous results concerning AMI are conflicting (5–13), and only a small study has investigated HF in this regard (14). Prior research also has limitations related to sample size and follow-up, as well as limited information on key covariates, including waist circumference and physical activity. In previous studies, obesity was measured only once and defined as body mass index (BMI) ≥ 30 kg/m^2, and there was no detailed analysis related to severity or duration of obesity.

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Differentiation between metabolically healthy and unhealthy obesity may be important for clinical management, and it could have direct implications for public health. Thus, the benefit of weight loss among obese individuals

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Abbreviations and Acronyms

AMI = acute myocardial infarction
BMI = body mass index
CI = confidence interval
HF = heart failure
HR = hazard ratio

who are metabolically healthy has been questioned (12) and even suggested to be potentially harmful (15).

In this prospective study of a large population-based cohort of men and women, we have assessed obesity in relation to the risks of AMI and HF, and we distinguished between metabolically healthy and unhealthy obesity. In a large proportion of participants, we had information on BMI from long before follow-up started, which allowed us to evaluate the role of duration of obesity.

Methods

Study population. Inhabitants 20 years of age and older in Nord-Trøndelag County in Norway were invited to participate in the second HUNT (Nord-Trøndelag health study) from August 1995 to June 1997. Briefly, 93,898 individuals were eligible to participate, and 64,726 (69%) accepted the invitation, filled in a questionnaire, and attended a clinical examination conducted by trained nurses. The HUNT study has been described in more detail by Holmen et al. (16). The present study was approved by the regional committee for ethics in medical research.

We excluded 480 participants with missing information on BMI and 2,947 individuals with a history of AMI, HF, or cerebral stroke at baseline. Thus, 61,299 participants (28,255 men and 33,044 women) were included in the main analyses of BMI and metabolic health with risk for AMI and HF.

Body mass index. At the clinical examination, height and weight were measured with participants wearing light clothes without shoes; height was measured to the nearest centimeter, and weight was measured to the nearest one-half kilogram. BMI was calculated as body weight (kilograms) divided by the squared height (meters) and further subdivided into 3 categories: <25 kg/m^2 (normal), 25 to 29.9 kg/m^2 (overweight), and ≥ 30 kg/m^2 (obese).

For a large proportion of participants, height and weight had also been measured in a mandatory tuberculosis screening in the county between 1966 and 1969 and in the first HUNT study that was conducted between 1984 and 1986 (17). Just as in the main HUNT study, the weight and height measurements were standardized to the nearest one-half kilogram and the nearest centimeter. Among the 61,299 participants in HUNT-2 who were included in the main analyses, information on BMI from the tuberculosis screening and from HUNT-1 was available for 27,196 individuals. Thus, for the latter proportion of participants, BMI measurements were available approximately 10 and 30 years before baseline of the present study.

Metabolic status. At the clinical examination in HUNT-2, waist and hip circumferences were measured to the nearest centimeter with the participant standing and arms hanging relaxed (16). The waist circumference was measured at the height of the umbilicus, and the hip circumference was measured at the thickest part of the hip. Nonfasting serum samples were analyzed for glucose, triglycerides, and high-density lipoprotein cholesterol (16). Time since last meal (in hours) was recorded. Blood pressure was measured 3 times, and the average of the second and third measurement was used in the analysis (16). Information on previously diagnosed diabetes and use of blood pressure medication was collected from the self-administered questionnaire.

We used a modified definition of metabolic health based on the metabolic syndrome, as described by the International Diabetes Federation (3). Participants were categorized as metabolically unhealthy if they had elevated waist circumference (>94 cm for men, >80 cm for women) or BMI ≥ 30 kg/m^2 in addition to 2 or more of the following criteria: elevated nonfasting triglycerides (≥ 1.7 mmol/l), reduced high-density lipoprotein cholesterol (<1.03 mmol/l for men, <1.29 mmol/l for women), elevated blood pressure ($\geq 130/85$ mm Hg) or use of blood pressure medication, elevated nonfasting glucose (≥ 11.1 mmol/l), or diabetes diagnosis.

Measurements. Participants were asked about their smoking status (never, former, current) and the usual number of alcoholic drinks (beer, wine, and spirits) they consumed over a 2-week period. We categorized participants according to their alcohol consumption as abstainers, light drinkers (0 to 1 drinks per day), moderate drinkers (>1 but ≤ 2 drinks per day), or heavy drinkers (>2 drinks per day). From national registers, we had information on level of education (primary and secondary school, vocational school, high school, undergraduate and graduate school) and marital status (unmarried, married, widow[er], divorced, separated, live-in partner). The participants also were asked about their level of physical activity. Light physical activity was defined as activity that does not involve sweating or a feeling of breathlessness. The participants were classified as inactive if they reported <1 h of hard and <3 h of light physical activity per week, moderately active if they reported 1 to 3 h of hard or >3 h of light activity per week, and physically active if they reported >3 h of hard physical activity per week.

Endpoints. After participating at the baseline examination, the participants were followed up for a first AMI or for HF, identified by hospital admissions or the National Cause of Death Registry (18). Hospitalizations for AMI were identified through linkage with medical records from the 2 hospitals of Nord-Trøndelag County from the baseline examination to December 31, 2008. AMI was defined and diagnosed by practicing cardiologists according to the European Society of Cardiology/American College of Cardiology consensus guideline (19). Criteria for AMI included certain symptoms according to case history information, specified changes in blood levels of cardiac enzymes, and

specified electrocardiogram changes. Patients with AMI who did not reach the hospital before death were identified by the National Cause of Death Registry (International Classification of Diseases, 9th Revision, code 410; 10th Revision codes I21, I22, and I23).

Hospitalizations for HF were identified through linkage with medical records from the 2 hospitals of Nord-Trøndelag County from the baseline examination to December 31, 2008. HF was defined and diagnosed by practicing cardiologists according to the European Society of Cardiology guidelines (20). Criteria for HF included symptoms and signs of HF and objective evidence of cardiac dysfunction at rest. The overall quality of the hospital discharge diagnosis of HF is high in Nordic countries, and in the analysis, we used HF as the primary diagnosis at discharge, as recommended (21). Deaths due to HF were identified by the National Cause of Death Registry (International Classification of Diseases, 9th Revision, code 428; 10th Revision codes I50.0, I50.1, and I50.9).

During follow-up, 239 participants who emigrated from Norway or moved out of the county and 6,610 participants who died of other causes than AMI or HF were censored in the statistical analysis at the time of emigration or death.

Statistical analyses. We divided the participants into categories of BMI (<25, 25 to 29.9, and ≥30 kg/m^2) and as metabolically healthy or unhealthy, as defined in the "Metabolic Status" section. We calculated hazard ratios (HRs) for cardiovascular outcomes (i.e., AMI and HF) for a given stratum of BMI who were metabolically healthy or unhealthy, compared with participants with a BMI <25 kg/m^2 who were metabolically healthy (reference group). We also constructed Kaplan-Meier plots to compare the risk of cardiovascular outcomes between strata of BMI and metabolic status over time. In addition, we performed analyses using 6 categories of BMI (underweight <18.5 kg/m^2, normal weight 18.5 to 24.9 kg/m^2, overweight 25 to 29.9 kg/m^2, class I obese 30 to 34.9 kg/m^2, class II obese 35 to 39.9 kg/m^2, and class III obese ≥40 kg/m^2) stratified by metabolic health.

In a separate analysis, we assessed duration of obesity among participants for whom BMI measurements had been conducted in the tuberculosis screening in the 1960s, in HUNT-1 (1984 to 1986) and HUNT-2 (1995 to 1997, baseline). In this analysis, the participants were divided into 5 categories: long-term normal weight (BMI <25 kg/m^2 at all 3 measurements); long-term overweight (BMI 25 to 29.9 kg/m^2 at all 3 measurements); long-term obese (BMI ≥30 kg/m^2 at all 3 measurements); recent development of obesity (BMI <25 kg/m^2 in the tuberculosis survey or at HUNT-1, but BMI ≥30 g/m^2 in HUNT-2); and variable body mass (any other combination of BMI categories). We used metabolically healthy participants with long-term normal weight (BMI <25 kg/m^2) as the reference in the analysis.

In secondary analyses, we used abdominal obesity instead of general obesity as reflected by BMI. Abdominal obesity was defined as a waist–hip ratio >0.90 for men and >0.85 for women, as recommended (22).

We used the Cox proportional hazards model to adjust for potentially confounding factors. Adjustment for age was performed using polynomials and setting attained age as the underlying time scale; however, the results were identical to using age at baseline. The proportional hazards assumption was tested by comparing -ln-ln survival curves and by performing tests on Schoenfeld residuals for each of the predictors of the study. If a predictor did not satisfy the proportional hazards assumption, that predictor was specified as a time-varying covariate whenever relevant.

We conducted subgroup analyses to assess potential effect modification by sex and age (dichotomized at 65 years of attained age). We performed several sensitivity analyses presented in the Online Appendix. All statistical analyses were conducted using Stata software, release 12.1 for Windows (StataCorp LP, College Station, Texas).

Results

Acute myocardial infarction. During a median follow-up of 12.2 years (688,592 person-years), 2,547 participants had a first AMI (Table 1). Among 61,299 participants, 10,059 (16.4%) were classified as obese and 15,576 (25.4%) were classified as metabolically unhealthy. Among the obese, the proportion of metabolically healthy participants was 34.6%. Obese and metabolically healthy participants were more likely to be women, younger, and unmarried compared with obese and metabolically unhealthy participants.

Table 2 shows that the age- and sex-adjusted HR among obese (BMI ≥30 kg/m^2) men and women who were metabolically healthy was 1.0 (95% confidence interval [CI]: 0.8 to 1.2) compared with normal-weight (BMI <25 kg/m^2) and metabolically healthy participants. The corresponding HR for obese and metabolically unhealthy men and women was 1.7 (95% CI: 1.5 to 1.9).

In multivariable analyses, we evaluated whether smoking status, time since last meal, level of education, marital status, physical activity, and alcohol consumption could influence the results (Table 2). In general, the estimates became slightly stronger after adjustment for these factors.

Figure 1 shows the cumulative hazard for AMI during 12.2 years of follow-up and underlines the contrast in risk between participants with healthy and unhealthy metabolic status, regardless of BMI values.

Table 3 shows that the risk of AMI was consistently higher among metabolically unhealthy participants across the range of BMI, including the severely obese, compared with participants who were metabolically healthy.

Table 4 shows the results for the proportion (44.4%) of participants for whom we had complete longitudinal information on BMI. The results show that neither long-term obesity nor recently developed obesity was associated with substantial excess risk for AMI among metabolically healthy participants. In contrast, metabolically unhealthy participants had a consistently higher risk for AMI.

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Table 1 Baseline Characteristics of the Study Population, by Categories of BMI and Metabolic Status

	BMI <25.0 kg/m^2		BMI 25–29.9 kg/m^2		BMI ≥30.0 kg/m^2	
Metabolic Status	Healthy (n = 23,798)	Unhealthy (n = 1,032)	Healthy (n = 18,446)	Unhealthy (n = 7,964)	Healthy (n = 3,479)	Unhealthy (n = 6,580)
Age, y	44.3 ± 16.4	60.1 ± 16.9	48.0 ± 15.6	56.7 ± 16.0	50.6 ± 16.5	55.2 ± 15.9
Female, %	58.9%	71.2%	45.1%	48.9%	68.9%	55.9%
BMI, kg/m^2	22.6 ± 1.7	23.9 ± 0.9	26.9 ± 1.3	27.7 ± 1.4	32.9 ± 2.9	33.3 ± 3.2
SBP, mm Hg	130.2 ± 19.4	147.5 ± 22.6	136.1 ± 19.6	148.1 ± 21.0	139.8 ± 22.7	150.0 ± 22.5
DBP, mm Hg	76.2 ± 11.0	83.2 ± 11.9	80.0 ± 11.5	85.7 ± 11.5	82.1 ± 12.8	86.8 ± 12.3
Total cholesterol, mmol/l	5.5 ± 1.2	6.4 ± 1.3	5.9 ± 1.2	6.4 ± 1.3	6.0 ± 1.1	6.4 ± 1.2
HDL cholesterol, mmol/l	1.5 ± 0.4	1.2 ± 0.3	1.4 ± 0.3	1.2 ± 0.3	1.5 ± 0.3	1.1 ± 0.3
Triglycerides, mmol/l	1.3 ± 0.7	2.4 ± 1.1	1.6 ± 0.9	2.6 ± 1.3	1.4 ± 0.6	2.8 ± 1.4
Diabetes mellitus	240 (1)	82 (7)	179 (1)	479 (6)	10 (0)	579 (9)
Blood pressure medication	918 (4)	169 (16)	1,236 (7)	1,394 (18)	451 (13)	1,653 (25)
Time since last meal, h	2.1 ± 1.9	1.9 ± 1.5	2.2 ± 2.0	2.1 ± 1.7	2.6 ± 2.2	2.3 ± 1.9
Current smokers	8,344 (35)	367 (36)	4,838 (26)	2,173 (27)	763 (22)	1,536 (23)
Heavy drinkers	695 (3)	12 (1)	679 (4)	196 (2)	88 (3)	134 (2)
Graduate school	2,192 (9)	48 (5)	1,526 (8)	373 (5)	177 (5)	249 (4)
Unmarried	7,586 (32)	126 (12)	4,372 (24)	1,228 (15)	830 (24)	1,220 (19)
Physically inactive	7,431 (31)	422 (41)	6,015 (33)	3,176 (40)	1,430 (41)	2,814 (43)

Values mean ± SD or n (%) unless otherwise stated.
BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; SBP = systolic blood pressure.

In separate analyses, we used the waist–hip ratio to indicate abdominal obesity (Online Table 1). The results were similar to the primary analyses using BMI.

Heart failure. During a median follow-up of 12.3 years (720,759 person-years), 1,201 participants developed HF (Table 1). Table 2 shows that the age- and sex-adjusted HR among obese (BMI ≥30 kg/m^2) men and women who were metabolically healthy was 1.6 (95% CI: 1.3 to 2.0) compared with normal-weight (BMI <25 kg/m^2) and metabolically healthy participants. The corresponding HR for obese and metabolically unhealthy men and women was 1.7 (95% CI: 1.4 to 2.0).

In multivariable analyses, we evaluated whether smoking status, time since last meal, level of education, marital status, physical activity, and alcohol consumption could influence the results (Table 2). In general, the estimates did not change after adjustment for these factors.

Figure 1 shows the cumulative hazard for HF during 12.3 years of follow-up and illustrates the higher cumulative hazard in obese than in nonobese participants, with moderately higher hazards among those who were metabolically unhealthy.

As shown in Table 3, the risk of HF was positively associated with BMI, there was a particularly high risk among the severely obese, and the differences by metabolic status were negligible.

Table 4 shows the results for participants for whom we had complete longitudinal information on BMI. The results show a stronger risk of HF associated with long-lasting obesity, regardless of metabolic status, compared with normal-weight and metabolically healthy participants. There was also a higher risk of HF among metabolically healthy participants who had recently developed obesity.

In separate analyses, we used waist–hip ratio to indicate abdominal obesity (Online Table 1), and the results were similar to those obtained in the primary analyses using BMI.

Effect modification. The associations of obesity were substantially stronger before than after 65 years of attained

Table 2 Crude and Multivariable-Adjusted HRs of Acute Myocardial Infarction and Heart Failure, by Categories of BMI and Metabolic Status

		Myocardial Infarction					Heart Failure				
BMI (kg/m^2)	Metabolic Status	Events	HR*	95% CI	HR†	95% CI	Events	HR*	95% CI	HR†	95% CI
<25.0	Healthy	593	1.0	(Ref.)	1.0	(Ref.)	274	1.0	(Ref.)	1.0	(Ref.)
	Unhealthy	88	1.7	(1.4–2.1)	1.9	(1.4–2.5)	46	1.3	(0.9–1.8)	1.1	(0.7–1.7)
25.0–29.9	Healthy	663	1.1	(1.0–1.2)	1.3	(1.1–1.5)	262	1.0	(0.8–1.2)	1.0	(0.8–1.3)
	Unhealthy	616	1.6	(1.4–1.7)	1.7	(1.5–1.9)	268	1.2	(1.0–1.4)	1.4	(1.1–1.7)
≥30.0	Healthy	111	1.0	(0.8–1.2)	1.1	(0.9–1.4)	97	1.6	(1.3–2.0)	1.7	(1.3–2.3)
	Unhealthy	476	1.7	(1.5–1.9)	2.0	(1.7–2.3)	254	1.7	(1.4–2.0)	1.7	(1.4–2.2)

*Hazard ratio (HR) adjusted for age at baseline (continuous) and sex. †HR adjusted for age at baseline (continuous), smoking status (never, former, current), time since last meal (continuous), level of education (primary and secondary school, vocational school, high school, undergraduate school, graduate school), marital status (unmarried, married, widow[er], divorced, separated, partner, unknown), physical activity (physically active, moderately active, inactive), alcohol consumption (light drinkers, moderate drinkers, heavy drinkers), and sex.
BMI = body mass index; CI = confidence interval.

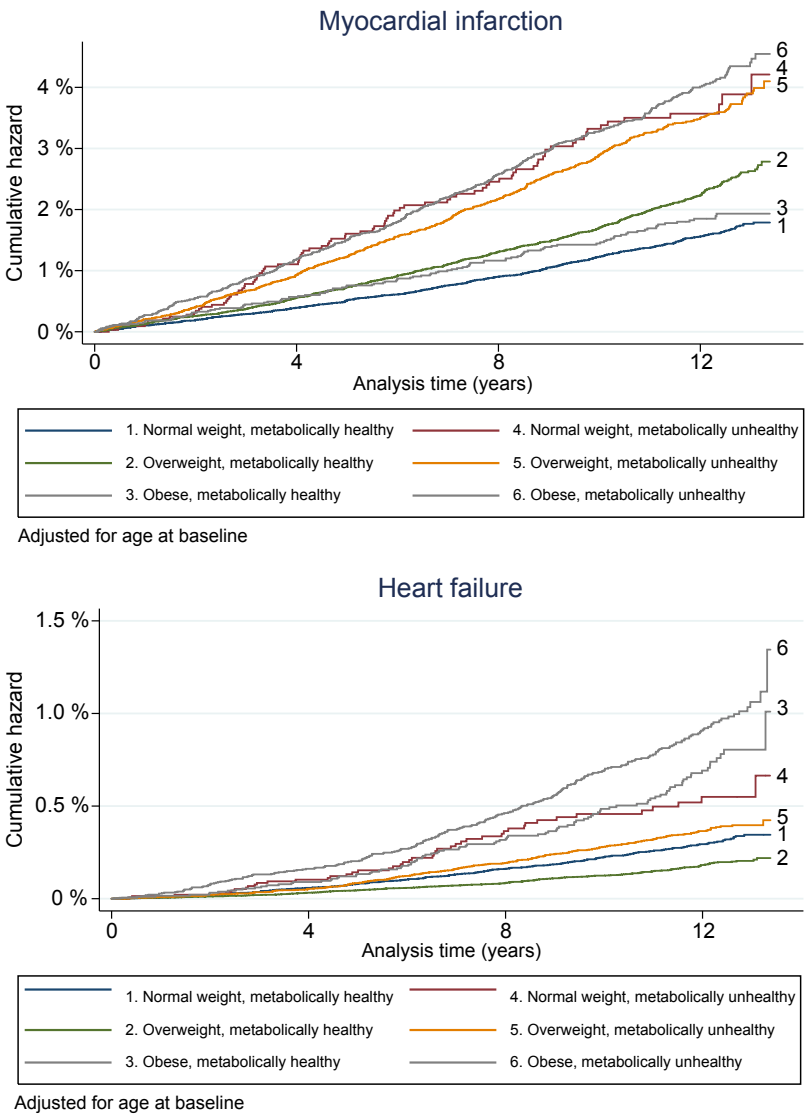

Figure 1 **Cumulative Hazard of Acute Myocardial Infarction and Heart Failure**

Cumulative hazard is based on Kaplan-Meier estimates during follow-up, by categories of body mass index (BMI) and metabolic status.

age. For AMI risk, the contrast between metabolically healthy and unhealthy obesity was present in both age groups. On the other hand, in both age groups the relative risk of HF did not differ between metabolically healthy and unhealthy obese participants (Online Table 2). For both AMI and HF, most of the sex-specific results were similar to those obtained in the combined analyses (Online Table 3).

Sensitivity analyses. As shown in Online Tables 4 to 8, our results were robust in different sensitivity analyses.

Discussion

In this prospective study of 61,299 men and women who were free of known cardiovascular disease at baseline, we assessed the risk of AMI and HF related to obesity and distinguished between healthy and unhealthy metabolic status.

Acute myocardial infarction. We found that the risk of AMI among obese and metabolically healthy individuals was not substantially increased compared with normal-weight and metabolically healthy individuals. The results associated with long-term and recently developed obesity were similar in this regard. In contrast, the risk of AMI in metabolically unhealthy individuals was higher and did not substantially differ across categories of BMI.

In a number of previous smaller studies, ranging from 780 to 25,626 participants with 3 to 15 years of follow-up, the reported results were similar to our findings (5–9). In those studies, obese or overweight individuals who were

Table 3 HRs of AMI and HF, by Categories of BMI and Metabolic Status

		Myocardial Infarction			HF		
BMI (kg/m^2)	Metabolic Status	Events	HR	95% CI	Events	HR	95% CI
<18.5	Healthy	13	1.2	(0.7–2.1)	9	1.4	(0.7–2.7)
	Unhealthy	0	—	—	0	—	—
18.5–24.9	Healthy	580	1.0	(Ref.)	265	1.0	(Ref.)
	Unhealthy	88	1.7	(1.4–2.1)	46	1.3	(1.0–1.8)
25.0–29.9	Healthy	663	1.1	(1.0–1.2)	262	1.0	(0.9–1.2)
	Unhealthy	616	1.6	(1.4–1.7)	268	1.2	(1.0–1.4)
30.0–34.9	Healthy	90	1.0	(0.8–1.2)	80	1.7	(1.3–2.1)
	Unhealthy	386	1.7	(1.5–1.9)	179	1.4	(1.2–1.8)
35.0–39.9	Healthy	18	1.2	(0.8–1.9)	8	0.9	(0.5–1.9)
	Unhealthy	75	1.8	(1.4–2.3)	54	2.5	(1.9–3.4)
≥40.0	Healthy	3	0.9	(0.3–2.9)	9	5.0	(2.5–9.7)
	Unhealthy	15	1.8	(1.1–3.1)	21	4.9	(3.1–7.7)

HRs adjusted for age at baseline (continuous) and sex.
AMI = acute myocardial infarction; other abbreviations as in Table 2.

metabolically healthy had a risk of fatal or nonfatal cardiovascular disease that was similar to that of normal weight and metabolically healthy individuals. The relative risks when these 2 categories were compared ranged from 0.7 to 1.7. The corresponding relative risks for metabolically unhealthy individuals ranged from 1.6 to 2.5 (5–9).

On the other hand, the investigators of a relatively small Swedish study of 1,758 men with a long-term follow-up found that obese but metabolically healthy men were at increased risk of cardiovascular events (HR: 2.0; 95% CI: 1.1 to 3.3) compared with normal-weight men with healthy metabolic status (11).

In contrast to other investigators, we had a unique possibility to investigate both recently developed and long-term obesity. We found that in metabolically healthy individuals, even long-lasting obesity was a rather benign condition in relation to AMI. We also investigated risk of AMI across the whole spectrum of BMI and found only a modestly increased risk among severely obese participants with healthy metabolic status.

The observed associations of obesity were consistently and substantially stronger before than after 65 years of age, but the contrast according to metabolic health status was present in both age groups.

It has been suggested that measures of abdominal obesity, such as the waist–hip ratio or waist circumference, may be better predictors of ischemic heart disease than measures of general adiposity, such as BMI (23). Therefore, we also conducted analyses using waist–hip ratio, but the results were similar to our main findings using BMI as indicator of obesity.

Heart failure. Risk of HF was similarly increased in metabolically healthy and unhealthy obese participants compared with normal-weight participants with healthy metabolic status. The association with HF was especially pronounced for severe obesity (>40 kg/m^2) and long-term obesity, and did not differ substantially by metabolic status, suggesting that metabolic health may not play a central role for these associations.

As for AMI, the relative risks associated with HF were generally stronger before than after 65 years of attained age.

Table 4 HRs of AMI and HF, by Trajectories of BMI and by Metabolic Status

		Myocardial Infarction			HF		
BMI (kg/m^2)	Metabolic Status	Events	HR	95% CI	Events	HR	95% CI
Long-term BMI <25.0*	Healthy	341	1.0	(Ref.)	159	1.0	(Ref.)
	Unhealthy	40	1.6	(1.1–2.2)	17	1.0	(0.6–1.7)
Long-term BMI 25.0–29.9*	Healthy	165	1.1	(0.9–1.4)	85	1.1	(0.8–1.4)
	Unhealthy	201	1.5	(1.3–1.8)	95	1.1	(0.9–1.5)
Long-term BMI ≥30.0*	Healthy	19	1.0	(0.6–1.5)	26	1.9	(1.2–2.9)
	Unhealthy	92	1.7	(1.3–2.1)	78	2.2	(1.7–2.9)
Recently developed BMI ≥30.0†	Healthy	16	1.2	(0.7–1.9)	10	2.0	(1.0–3.7)
	Unhealthy	70	2.0	(1.5–2.5)	16	1.3	(0.8–2.1)
Varying body mass	Healthy	451	1.1	(1.0–1.3)	223	1.2	(1.0–1.4)
	Unhealthy	487	1.5	(1.3–1.7)	244	1.4	(1.1–1.7)

HRs adjusted for age at baseline (continuous) and sex. *Consistent BMI category from tuberculosis survey, HUNT-1, and HUNT-2. †Change in BMI category from <25 kg/m^2 in the tuberculosis survey or HUNT-1 to ≥30 kg/m^2 in HUNT-2.
Abbreviations as in Tables 2 and 3.

However, unlike for AMI, relative risks of HF associated with obesity did not differ between metabolically healthy and unhealthy participants in any age groups. In the analyses using waist–hip ratio, the results were similar to our main findings using BMI as indicator for obesity.

To our knowledge, only a small study (14) has investigated the risk of HF in relation to metabolically healthy obesity. In that study, 550 participants were followed for a median of 6 years (14). In contrast to our study, the investigators found that metabolic health was a stronger determinant of HF risk than obesity.

Study strengths and limitations. Compared with prior research, our study had ample statistical power to address the role of obesity with and without metabolic abnormalities in relation to the risk of AMI and HF. The population-based nature of the study, the stability and homogeneity of the study population, the high attendance at the baseline examination, and the reliable and carefully revised diagnostic information from hospitals and information from the National Cause of Death Registry ensured close to complete follow-up and minimized the possibility for selection bias or misclassification of endpoints.

The blood samples were nonfasting; therefore, our criteria for metabolically healthy status were generally less strict than in some other studies (5,6,8,11,13). For example, individuals with nonfasting glucose levels between 7.8 and 11.0 mmol/l were classified as free of glucose intolerance in our study, but nonetheless, it is likely that some of them may have impaired glucose tolerance. This misclassification of blood glucose most likely resulted in an overestimation of risk among participants who were classified as obese but metabolically healthy, because some of them probably were metabolically unhealthy. Despite this, we found only a moderate risk increase for AMI in this group. Triglyceride levels are also affected by nonfasting, whereas high-density lipoprotein cholesterol is largely resilient to food intake (24). Overall, it is remarkable that despite the misclassification of metabolic status due to nonfasting, our results suggest that metabolic status and not obesity was the main determinant of risk for AMI. On the other hand, the misclassification of metabolic status also may have contributed to the relative unimportance of metabolic status that we observed in relation to HF risk. Nevertheless, the contrast between AMI and HF in this regard was clear and could not be explained by the nonfasting measures. In addition, the inclusion of time since last meal in the statistical analysis did not change the results.

Of note, BMI does not differentiate between fat tissue and muscle mass, and thus it is not clear whether the distribution of fat tissue and muscle mass is different among metabolically healthy and unhealthy obese individuals. We have stratified on abdominal obesity (Online Table 4), and the results were similar to the main analyses.

We did not have data on inflammation in this study, which could have provided important information on metabolic health (2). Finally, we shall note that our data on physical activity was self-reported, and we were unable to assess directly the role of cardiorespiratory fitness in relation to metabolically healthy obesity (2,10).

Conclusions

Obesity combined with healthy metabolic status does not confer substantial excess risk for AMI, not even for long-lasting or severe obesity. On the other hand, risk of AMI among metabolically unhealthy individuals seems to be increased across the whole range of BMI. In contrast to the risk of AMI, obesity may be more important than metabolic factors for the development of HF. Accordingly, even metabolically healthy obesity is mostly associated with increased risk for HF, and this is particularly true for long-lasting and severe obesity.

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Key Words: epidemiology ■ heart failure ■ myocardial infarction ■ obesity.

APPENDIX

For supplemental tables on the study protocol, please see the online version of this article.