The cardiovascular metabolic syndrome
Rana, J.S.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Obesity and the Risk of Mortality
Following Acute Myocardial Infarction

Background:
In the general population, obesity is associated with an increased risk of all-cause mortality. However, the importance of obesity in patients with established coronary heart disease is less well defined.

Methods:
As part of the Determinants of Myocardial Infarction Onset Study, we performed a prospective cohort study of 1898 patients hospitalized with a confirmed acute myocardial infarction between 1989 and 1994, with a median follow-up of 3.8 years. We assessed all-cause mortality through December 1995 using the National Death Index. We categorized patients according to WHO criteria for body mass index (BMI). We compared long-term mortality according to BMI (kg/m²) using Cox proportional hazards regression.

Results:
Of the 1898 eligible patients, 607 (32%) were normal weight (18.5-24.9 kg/m²), 832 (44%) were overweight (25.0-29.9 kg/m²), 331 (17%) were Class I obese (30.0-34.9 kg/m²), and 128 (7%) were Class II or more obese (≥35.0 kg/m²). A total of 311 patients died during follow-up. After adjustment for potentially confounding risk factors and excluding patients with non-cardiac comorbidity, the risk for mortality appeared to increase linearly with increasing BMI across all categories (p-trend = 0.08). The relative risk of mortality in all obese patients (≥30 kg/m²) was 1.46 compared to those with normal weight (95% CI 0.98-2.17).

Conclusions:
We found that BMI appeared to have a positive, graded relationship with post-MI mortality. Whether weight reduction and secondary prevention strategies would reverse this effect in obese population remains to be seen.
Background

Obesity accounts for more than a quarter of a million deaths annually in the United States (1). Risks associated with overweight and obesity warrants more attention since, despite significant reductions in other risk factors for CHD and mortality (2) the prevalence of obesity continues to rise (1).

In the general population, higher body weight is associated with increased all-cause mortality and has been shown to markedly lessen life expectancy (3). However, the impact of obesity on mortality in patients following acute myocardial infarction (MI) or established coronary heart disease (CHD) is less well defined, with inconsistent results (4-7).

To assess the impact of overweight and obesity on mortality in patients following acute MI, we studied patients enrolled in the Determinants of Myocardial Infarction Onset Study (Onset Study) (8). This prospective, multicenter, inception cohort study included chart reviews and face-to-face interviews with hospitalized patients with confirmed acute MI.

Methods

The Onset Study was conducted in 45 community hospitals and tertiary care medical centers in the United States. Between August 1989 and September 1994, 1935 patients (601 women and 1334 men) were interviewed at a median of 4 days after sustaining acute MI. Trained research interviewers identified eligible patients by reviewing coronary care unit admission logs and patient charts. Thus our study does not include patients who died before hospitalization or did not go to a hospital with their AMI. For inclusion, patients were required to have a creatine kinase level above the upper limit of normal for each center, positive MB isoenzymes, an identifiable onset of symptoms of infarction, and the ability to complete a structured interview. For these analyses, we excluded 18 patients with missing information on BMI and 19 patients with BMI < 18.5 kg/m², because this small number of patients resulted in a lack of statistical
power to make inferences about this group. Thus, 1898 patients were included in the present study. The institutional review board of each center approved this protocol, and each patient gave informed consent.

Interviewers used a structured data abstraction and questionnaire form and recorded detailed medical histories (including self-reported height and weight). We derived BMI as the weight (in kilograms) divided by the square of the height (in meters) as an estimate of overweight and obesity (9). We categorized BMI according to WHO criteria (10) — normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²), and Obese (≥30.0 kg/m²). Obesity was further divided into obese class I (30.0-34.9 kg/m²), and obese class II or higher (≥35.0 kg/m²).

Other information collected from each interview and chart review included demographics, medical history, and medication use (both prescription and nonprescription). During the chart review, interviewers recorded complications of congestive heart failure and ventricular arrhythmias based on diagnoses recorded in the medical record. Interviewers also recorded all creatine kinase values available at the time of the interview.

We defined present aspirin use as the reported use of any aspirin or aspirin-containing product in the 4 days before the index MI, based on previous Onset Study analyses and the duration of its physiological effect (11). We used 1990 United States census data to derive median household income from United States Postal Service zip codes (12). We defined noncardiac comorbidity as a previous history of stroke, respiratory disease, renal disease, or cancer. We searched the National Death Index for deaths of Onset Study subjects through December 31, 1995 and requested death certificates from state offices of vital records for all probable matches, using a previously validated algorithm (13). Three physicians blinded to each participant’s BMI independently verified the determination of each death. Two physicians categorized each death as attributable to cardiovascular or non-cardiovascular causes. Disagreements among raters were resolved by discussion.

Statistical Analysis
We analyzed continuous and binary variables using ANOVA and Fisher’s exact tests, respectively. We used Cox proportional-hazards models to examine the association of
BMI with survival after adjustment for potentially confounding factors. The covariates included in the multivariate model were age, sex, race, current smoking, former smoking, noncardiac comorbidity (a previous history of stroke, cancer, gastro-intestinal disease, renal disease, or respiratory disease), use of thrombolytic therapy, episodes/week of exertion ≥6 METs (<1, 1-4, ≥5), usual alcohol consumption in servings/week (none, <7, ≥7), usual tea consumption in cups/week (none, <14, ≥14), educational attainment (< high school, high school, some college), and median household income in the zip code of residence. For test for trend, we derived P-values for linear trend, using the mean BMI within categories. We also treated the categories of BMI as continuous variable, with increment of 1 and 5 kg/m². To explore possible effect modification, we repeated adjusted analyses within strata of age, sex, and smoking status. We performed sensitivity analyses that included diabetes, hypertension, and prior history of CHD to assess mediating effects of these variables. We repeated our analyses after excluding patients with noncardiac comorbidity (a previous history of stroke, cancer, gastro-intestinal disease, renal disease, or respiratory disease) to minimize bias caused by disease-related changes in weight. We used SAS statistical software version 8 (SAS Institute Inc, Cary, NC) for all analyses.

Results

The characteristics of the Onset Study participants have been previously reported (8). Table 1 shows characteristics of the patient population according to BMI category. The mean BMI ranged from 22.7 kg/m² in patients in the normal weight category, to 39.3 kg/m² in obesity class ≥II. Higher BMI was associated with younger age, diabetes, and hypertension. Minorities also tended to be more likely to be obese (p-value = 0.07). Gender, abstention from alcohol, and presence of non-cardiac co-morbidities were associated with significant variability across BMI categories. Current and past history of smoking, a past history of CHD, and socioeconomic status were similar across BMI categories.
## Table 1. Characteristics of the Onset Study Participants According to their BMI (kg/m²) category.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (18.5-24.9)</th>
<th>Overweight (25.0-29.9)</th>
<th>Obesity Class I (30.0-34.9)</th>
<th>Obesity Class II (≥35.0)</th>
<th>P* value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>607 (32)</td>
<td>832 (44)</td>
<td>331 (17)</td>
<td>128 (7)</td>
<td></td>
</tr>
<tr>
<td>Mean BMI</td>
<td>22.7</td>
<td>27.3</td>
<td>32.0</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>Age † (years)</td>
<td>65.3 (12.9)</td>
<td>60.6 (12.9)</td>
<td>58.0 (11.9)</td>
<td>57.5 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (%)</td>
<td>237 (39)</td>
<td>184 (22)</td>
<td>109 (33)</td>
<td>51 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race (%)</td>
<td>549 (91)</td>
<td>754 (92)</td>
<td>286 (87)</td>
<td>112 (88)</td>
<td>0.07</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>198 (33)</td>
<td>279 (34)</td>
<td>105 (32)</td>
<td>43 (34)</td>
<td>0.93</td>
</tr>
<tr>
<td>Former smoker (%)</td>
<td>239 (40)</td>
<td>347 (42)</td>
<td>145 (44)</td>
<td>51 (41)</td>
<td>0.62</td>
</tr>
<tr>
<td>No alcohol (%)</td>
<td>366 (60)</td>
<td>436 (52)</td>
<td>211 (64)</td>
<td>88 (69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No Tea (%)</td>
<td>311 (52)</td>
<td>432 (53)</td>
<td>185 (57)</td>
<td>74 (59)</td>
<td>0.24</td>
</tr>
<tr>
<td>No Exertion § (%)</td>
<td>509 (84)</td>
<td>656 (79)</td>
<td>268 (81)</td>
<td>110 (86)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Education:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Less than high school (%)</td>
<td>149 (25)</td>
<td>173 (21)</td>
<td>86 (26)</td>
<td>38 (31)</td>
<td></td>
</tr>
<tr>
<td>Complete High school (%)</td>
<td>218 (37)</td>
<td>339 (42)</td>
<td>144 (44)</td>
<td>62 (50)</td>
<td></td>
</tr>
<tr>
<td>Some College (%)</td>
<td>218 (37)</td>
<td>301 (37)</td>
<td>96 (29)</td>
<td>24 (19)</td>
<td></td>
</tr>
<tr>
<td>Income † # (dollars)</td>
<td>38628 (13325)</td>
<td>38603 (13481)</td>
<td>38011 (12304)</td>
<td>36164 (12255)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>83 (14)</td>
<td>145 (17)</td>
<td>97 (29)</td>
<td>33 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Noncardiac Comorbidity‡ (%)</td>
<td>168 (28)</td>
<td>190 (23)</td>
<td>67 (20)</td>
<td>32 (25)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Past Cardiac History</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>166 (27)</td>
<td>229 (28)</td>
<td>98 (30)</td>
<td>39 (31)</td>
<td>0.72</td>
</tr>
<tr>
<td>Angina (%)</td>
<td>149 (25)</td>
<td>210 (25)</td>
<td>90 (27)</td>
<td>32 (25)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>241 (40)</td>
<td>358 (43)</td>
<td>171 (52)</td>
<td>68 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>25 (4)</td>
<td>31 (4)</td>
<td>16 (5)</td>
<td>10 (8)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Regular Use of Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>192 (32)</td>
<td>295 (35)</td>
<td>115 (35)</td>
<td>37 (29)</td>
<td>0.29</td>
</tr>
<tr>
<td>Lipid Lowering Drug (%)</td>
<td>38 (6)</td>
<td>68 (8)</td>
<td>22 (7)</td>
<td>11 (9)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Characteristics of Index Hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF (%)</td>
<td>96 (16)</td>
<td>103 (12)</td>
<td>54 (16)</td>
<td>18 (14)</td>
<td>0.18</td>
</tr>
<tr>
<td>VT (%)</td>
<td>86 (14)</td>
<td>99 (12)</td>
<td>31 (9)</td>
<td>14 (11)</td>
<td>0.18</td>
</tr>
<tr>
<td>Thrombolytic Therapy (%)</td>
<td>212 (35)</td>
<td>319 (38)</td>
<td>111 (34)</td>
<td>41 (32)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; CHF, congestive heart failure; VT, ventricular tachycardia *P values for binary and continuous variables derive from exact tests and ANOVA, respectively. † Mean values with SD are shown for continuous variables. ‡Noncardiac comorbidity included a previous history of stroke, cancer, gastrointestinal disease, renal disease, or respiratory disease. § <1 episode/week of Exertion ≥6 MET.

#Household income was derived from zip codes according to 1990 United States Census Bureau data. Of 1898 participants, missing values: race: 22; education: 14, previous MI: 14; current and former smoking: 22; tea consumption: 32 and income: 59.
Table 2. Hazard Ratios for All-Cause Mortality following acute MI according to BMI (kg/m²)

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Normal (18.5-24.9)</th>
<th>Overweight (25.0-29.9)</th>
<th>Obesity Class I (30.0-34.9)</th>
<th>Obesity Class II&amp;III (≥35.0)</th>
<th>P-value for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk (%)</td>
<td>607 (32)</td>
<td>832 (44)</td>
<td>331 (17)</td>
<td>128 (7)</td>
<td></td>
</tr>
<tr>
<td>Person-years of follow-up</td>
<td>2193</td>
<td>3104</td>
<td>1210</td>
<td>455</td>
<td></td>
</tr>
<tr>
<td>Total deaths (n=311)</td>
<td>113</td>
<td>117</td>
<td>58</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>90</td>
<td>87</td>
<td>41</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Incidence/1000 person years</td>
<td>51</td>
<td>38</td>
<td>48</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

I. All Cause Mortality

* The covariates included age, sex, race, current smoking, former smoking, use of thrombolytic therapy, exertion of episode/week of ≥ 6 MET (<1, 1-4, ≥ 5), usual alcohol consumption of servings/week (none, <7, in ≥ 7), usual tea consumption in cups/week (none, <14, ≥14), educational attainment (< high school, high school, some college), household income.

† Adjusting for the same covariates as model 1, and excluding participants with noncardiac comorbidity (included a previous history of stroke, cancer, gastrointestinal disease, renal disease, or respiratory disease)

I. All Cause Mortality

Age/sex/race Adjusted

Model 1 *

Model 2 †

Model 2 †

II. Cardiovascular mortality

Model 2 †

Of the 1898 eligible patients, 311 (16%) died during a median (and mean) follow-up of 3.8 years. Among these deaths, 110 patients had some non-cardiac co morbidity. Table 2 shows the relationship of BMI category to total mortality. In age-sex and race-adjusted analyses, we found a graded relationship between higher BMI and mortality (p-value= 0.01 for linear trend). Additional adjustment for known risk factors still showed a graded association that did not reach statistical significance (p-value, 0.13). Because weight loss among patients with non-cardiac illness may bias the association of BMI with mortality, we repeated our analyses excluding such patients. After excluding 457 patients with noncardiac co morbidity, a clear linear relationship of borderline statistical significance (p-trend= 0.08) between increasing BMI and all-cause mortality became apparent (Table 2, model 2). When we compared the all cause mortality rate among all obese patients (regardless of obesity class) to normal weight patients (Figure), obesity was associated with a hazard ratio for post-MI mortality of 1.46 (95% CI, 0.98-
Chapter 2

Relative risk of all-cause mortality following acute myocardial infarction among normal weight, overweight and obese patients

![Graph showing hazard ratios for normal weight, overweight, and obese categories.]

Relative risk of all-cause mortality following acute myocardial infarction among normal weight, overweight and obese patients free of non-cardiac comorbidity (stroke, cancer, gastro-intestinal disease, renal disease, or respiratory disease). Adjusted for age, sex, race, current smoking, former smoking, use of thrombolytic therapy, exertion of episode/week of ≥6 MET (<1, 1-4, ≥5), usual alcohol consumption of servings/week (none, <7, ≥7), usual tea consumption in cups/week (none, <14, ≥14), educational attainment (<high school, high school, some college), and household income.

When we assessed BMI as a continuous variable, we found a hazard ratio of 1.03 for each 1 kg/m² increment in BMI (95% CI for the hazard ratio, 0.99-1.06).

To evaluate the robustness of our findings, we performed several sensitivity analyses. Although the risk of mortality seemed to be higher in males and in subjects less than 65 years old, we did not find an interaction of significance. Among patients that were never or former smokers, the hazard ratios for mortality were non-graded with respect to their BMI category. However, the risk of mortality across BMI categories was higher among current smokers and increased with increasing BMI (p-value = 0.02 for trend). The hazard ratio for total mortality among current smokers was 4.51 (95% CI, 1.42-14.3) in obesity class ≥II, compared to 1.18 (95% CI, 0.42-2.58) for former smokers.

Compared to our multivariate model, further simultaneous adjustment for diabetes,
hypertension, history of previous MI or CHF, that may mediate the association between BMI and mortality attenuated the hazard ratios by 8, 12 and 20 percent for the three BMI categories, respectively (p-value for trend for the further adjusted model = 0.2)

Discussion

In this multicenter, prospective study of early survivors of acute MI followed for an average of 3.8 years, we found that BMI had a positive, graded relationship with post-MI mortality of borderline statistical significance. The association was most apparent among patients free of major non-cardiac comorbid conditions at baseline. This association remained essentially similar after adjustment for sociodemographic and clinical characteristics.

Recent data from the 1999-2000 National Health and Nutrition Examination Survey (NHANES), documented that the age-adjusted prevalence of obesity (BMI >30) among US adults is 30.5% (14). Although excess adiposity appears to increase the risk of mortality in the general population (1), its importance among patients with established CHD is less clearly defined. Recently Rea et al. showed that patients with established CHD had increased risk of recurrent coronary events, with increased BMI (15). Kaplan et al. (6) reported a U-shaped relationship between BMI and death among survivors of first MI. However their analysis lacked information on some important obesity and cardiovascular risk factors, such as physical exertion (16) and socioeconomic status (17). In another study Hoit et al. (7) did not find any significant association between BMI and post-MI mortality among patients less than 65 years of age. However they included patients with BMI of <18 Kg/m², who may have non-cardiac comorbidity, in their referent group (18).

Studies evaluating the relationship between BMI and mortality are often limited by uncontrolled or residual confounding by smoking (19), pre-existing disease at baseline (20), socioeconomic status or inappropriate control for mediating factors (17). In our multivariate model, we adjusted for commonly known risk factors such as smoking, exercise, race, income, and education. We also controlled for alcohol and tea consumption, which have recently been shown to have a protective effect on post-MI mortality (21,22). Because there is an increased risk of mortality in an underweight
Given the increased risk of mortality, and recurrent coronary events (15) among obese patients with CHD, more aggressive interventions are required for secondary prevention. Observational studies regarding weight loss in overweight and obese population have shown mixed results (23). A recent prospective, randomized, controlled study (24) examined the effect of a short-course cardiac rehabilitation and prevention program on short- and long-term exercise capacity, quality of life and body anthropometry in obese patients with CHD who had a recent acute MI or had undergone percutaneous coronary intervention. Although they showed improvement in exercise capacity and quality of life, there was no significant change in BMI and they did not assess the effect of the intervention on long term morbidity or mortality.

As with any observational study, the associations we observed could be accounted for, at least in part, by differences between normal weight and obese patients in characteristics other than BMI itself. For example, obese patients might have been instructed to be relatively more physically active and may have received more aggressive counseling on smoking cessation. We do not have information on how Onset study participants may have changed their lifestyle habits following hospitalization. Confounding by changes in exercise and in smoking habits may have led us to underestimate or overestimate the difference between normal weight and obese patients.

Another limitation of our study is that only 24% of our patients were in the obese and very obese categories. Thus, there were fewer total person-years of follow-up in these categories than in the normal and overweight categories, although the average duration of follow-up was similar for all four BMI categories examined. Obese patients accounted for only 81 deaths during follow-up. This tended to limit the precision of our relative risk estimates and limited the statistical power of our study. Despite our inclusion of frequency of physical exertion, educational attainment, race, and median household income by ZIP code of residence in the multivariate model, residual confounding by these factors (as well as by unmeasured factors) may exist. We had incomplete information regarding diagnosis of patients with hypercholestrolemia and the diagnosis was based on patient’s use of hypolipidemic agents in the early statin era, thus underestimating the degree to which hypercholestrolemia may have mediated the
effects of BMI in our population. This limitation would not change the validity of the underlying association between BMI and mortality, however. Another issue inherent in any study with an end point of all-cause mortality is that the independent variable is usually unlikely to influence all causes of death. In this case, relative risks associated with obesity are generally lower for all-cause mortality than for specific diseases (25,26). Importantly, mortality is only a part of the substantial burden of obesity conferred by obesity-related conditions such as diabetes, hypertension and nonfatal cardiovascular disease (20). Thus, the overall disease burden of obesity, which includes both morbidity and mortality, may be underestimated in our study.

In summary, we found that BMI had a positive, graded relationship with post-MI mortality. The association was stronger among patients free of major non-cardiac comorbid conditions at baseline. This association remained essentially similar after adjustment for sociodemographic and clinical characteristics. Whether specific weight reduction and secondary prevention strategies could reverse this effect in obese patients with myocardial infarction requires further evidence from well-conducted randomized trials.

Acknowledgements

This study was supported by Grant HL41016 (for the Determinants of Myocardial Infarction Onset Study) from the National Heart, Lung, and Blood Institute, Bethesda, Maryland; Grant T32-HL07374-22 from the National Institutes of Health, Bethesda, Maryland; and Grant 9630115N from the American Heart Association, Dallas, Texas. There is no conflict of interest in connection with the submitted article.

References