European Heart Journal (2013) **34**, 345–353
doi:10.1093/eurheartj/ehs217



# Evidence for obesity paradox in patients with acute coronary syndromes: a report from the Swedish Coronary Angiography and Angioplasty Registry

**Oskar Angerås[1]*, Per Albertsson[1], Kristjan Karason[1], Truls Råmunddal[1], Göran Matejka[1], Stefan James[2], Bo Lagerqvist[2], Annika Rosengren[1], and Elmir Omerovic[1]**

[1]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; and [2]Uppsala Clinical Research Center, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

*Received 22 February 2012; revised 11 June 2012; accepted 27 June 2012; online publish-ahead-of-print 4 September 2012*

**See page 330 for the editorial comment on this article (doi:10.1093/eurheartj/ehs237)**

**Aims** The obesity paradox refers to the epidemiological evidence that obesity compared with normal weight is associated with counter-intuitive improved health in a variety of disease conditions. The aim of this study was to investigate the relationship between body mass index (BMI) and mortality in patients with acute coronary syndromes (ACSs).

**Methods and results** We extracted data from the Swedish Coronary Angiography and Angioplasty Registry and identified 64 436 patients who underwent coronary angiography due to ACSs. In 54 419 (84.4%) patients, a significant coronary stenosis was identified, whereas 10 017 (15.6%) patients had no significant stenosis. Patients were divided into nine different BMI categories. The patients with significant stenosis were further subdivided according to treatment received such as medical therapy, percutaneous coronary intervention (PCI), or coronary artery by-pass grafting. Mortality for the different subgroups during a maximum of 3 years was compared using Cox proportional hazards regression with the lean BMI category (21.0 to $<$23.5 kg/m$^2$) as the reference group. Regardless of angiographic findings [significant or no significant coronary artery disease (CAD)] and treatment decision, the underweight group (BMI $<$18.5 kg/m$^2$) had the greatest risk for mortality. Medical therapy and PCI-treated patients with modest overweight (BMI category 26.5–$<$28 kg/m$^2$) had the lowest risk of mortality [hazard ratio (HR) 0.52; 95% CI 0.34–0.80 and HR 0.64; 95% CI 0.50–0.81, respectively]. When studying BMI as a continuous variable in patients with significant CAD, the adjusted risk for mortality decreased with increasing BMI up to ~35 kg/m$^2$ and then increased. In patients with significant CAD undergoing coronary artery by-pass grafting and in patients with no significant CAD, there was no difference in mortality risk in the overweight groups compared with the normal weight group.

**Conclusion** In this large and unselected group of patients with ACSs, the relation between BMI and mortality was U-shaped, with the nadir among overweight or obese patients and underweight and normal-weight patients having the highest risk. These data strengthen the concept of the obesity paradox substantially.

**Keywords** Obesity paradox • Acute coronary syndrome • Body mass index • SCAAR

## Introduction

In the general population, obesity is associated with increased mortality.[1] Obese individuals have a higher frequency of cardiovascular risk factors such as hypertension, hyperlipidaemia, and diabetes. Therefore, these individuals have higher cardiovascular disease-related morbidity and mortality rate. As weight reduction is associated with improved risk factor profile, the guidelines for

* Corresponding author. Tel: +46 31 3421000, Fax: +46 31 823762, Email: oskar.angeras@vgregion.se

primary prevention of cardiovascular diseases recommend weight loss in overweight and obese individuals.[2] Despite limited scientific evidence, this recommendation has also been extended to the guidelines for secondary prevention of coronary artery disease (CAD)[3–5] and heart failure (HF).[6] In fact, a number of epidemiological studies suggest that obesity may confer protection in some common disease settings. This was first shown in patients with end-stage renal failure, in whom obesity constituted a favourable prognostic factor.[7] This led to the proposal of the obesity paradox.[8–10] Subsequently, obesity paradox has been reported in cardiac conditions including HF,[11] atrial fibrillation,[12] sudden cardiac death,[13] and CAD.[14] It has also been confirmed by several meta-analyses,[9,15] which support the view that obesity, in certain clinical conditions, could lead to a favourable prognosis.[9,15]

Acute coronary syndromes (ACSs) are among the most important causes of mortality and reduced quality of life in modern Western societies. Some studies indicate that obesity paradox is also present in patients with ACSs. However, this evidence is relatively weak as it is based on retrospective studies.[16] Therefore, the aim of this study was to evaluate the relationship between body mass index (BMI) and mortality in one of the largest-to-date ACS population based on the prospectively collected data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[17]

# Methods

## Study design

In this prospective registry study, we established a cohort of all consecutive patients admitted to Swedish hospitals, during the period May 2005–December 2008, with ACSs such as unstable angina, ST-elevation myocardial infarction (STEMI), and non-STEMI and who underwent coronary angiography. Non-STEMI, STEMI, and unstable angina were defined according to the criteria established by the European Society of Cardiology.[18,19]

## Patient population

The data were collected from SCAAR, which was established in 1992. This registry currently contains information about all coronary angiographies and percutaneous coronary interventions (PCIs) performed in Sweden.[17] Each catheterization procedure is described with ~50 angiographies and 200 PCI variables that includes both demographic and procedure-related data. The registry is sponsored by the Swedish Health Authorities and does not receive any funding from commercial interests. Details about patients' weight and height (measured or self-reported) were entered into the SCAAR starting from May 2005. All patients in Sweden who were admitted with ACSs and underwent angiography during the period May 2005–December 2008 were included in the analysis. The information about patients' characteristics and co-morbidities were based on the data extracted from the patients' medical records.

## Statistics

### Primary analysis

The primary outcome was all-cause mortality in the patients who had significant stenosis (>50% diameter narrowing) in one or more coronary arteries. The patients with significant CAD were divided into the subgroups according to the physician's initial decision for treatment strategy such as coronary artery bypass grafting (CABG), PCI, or medical therapy. The treatment strategy was defined based on intention-to-treat decision following the index catheterization.

BMI is defined as the weight divided by length in meters squared. The patients were divided into nine different BMI categories according to the National Institute of Health–AARP cohort[16]: <18.5 kg/m$^2$ (underweight), 18.5 to <21.0 kg/m$^2$ (normal weight); 21.0 to <23.5 kg/m$^2$ (normal weight); 23.5 to <25.0 kg/m$^2$ (normal weight); 25.0 to <26.5 kg/m$^2$ (overweight); 26.5 to <28.0 kg/m$^2$ (overweight); 28.0 to <30.0 kg/m$^2$ (overweight); 30.0 to <35.0 kg/m$^2$ (obese) and ≥35.0 kg/m$^2$ (obese). Baseline characteristics of patients across the categories were examined by $\chi^2$ tests for linear trend for nominal variables and by the Jonckheere–Terpstra test for trend for continuous variables to account for the ordinal nature of the BMI categories.

Unadjusted survival was examined using a Kaplan–Meier survival curve and the log-rank test. To evaluate the association between BMI and mortality, multivariable-adjusted hazard ratios (HR) were calculated using Cox proportional-hazards regression models for each treatment strategy. All potential confounders listed in *Table 1* were entered into the model. The BMI category 21–<23.5 kg/m$^2$ was considered the reference category and statistical significance was set at $P < 0.05$. All tests were two sided. Interactions between BMI category with age, and BMI category and sex were tested using the likelihood ratio test. The assumption of proportional hazards for each covariate was reviewed separately by the means of log-minus-log survival plots.

The database was scrutinized for missing data. Logistic regression showed that a number of variables were associated ($P < 0.05$) with missing data including diabetes, previous myocardial infarction (MI), previous HF, previous stroke, chronic obstructive pulmonary disease, hyperlipidaemia, hypertension, smoking habits, and dementia. This relationship indicates that the presence of missing data was not completely random. Thus, in addition to the complete case analysis, we applied multiple imputation method to estimate the missing data[20,21] and performed Cox proportional hazards regression with the imputed data set under the assumption that missing data are missing at random. Multiple imputation was implemented using the same covariates as in the main model with addition of cumulative hazard and event indicator.[22] Cumulative hazard was estimated with the Nelson–Allens test using STATA software (version 12, StataCorp, College Station, TX, USA). IBM SPSS missing data module software (version 20, IBM Corporation, New York, NY, USA) was used for the imputation procedure with 10 imputed data sets. The imputation procedure and subsequent Cox proportional hazards regression estimation was performed according to the Rubin's protocol.[23]

The continuous risk relationship between BMI and all-cause mortality was analysed by entering BMI as a continuous variable into fractional polynomial Cox proportional-hazards regression[24] adjusted for the covariates used in the main analysis with the addition of treatment strategy. This analysis was performed using STATA software.

### Secondary analysis

Three types of secondary analyses were performed. First, we examined the relationship between BMI and mortality in patients who received a cardiac catheterization but were not diagnosed with CAD (<50% diameter narrowing or normal coronaries). Second, we explored the mortality data as all-cause mortality, in-hospital mortality, 30-day mortality, and 3-year mortality. Third, we examined the relationship between BMI category and hospitalization for MI, HF, and stroke after the index procedure.

**Table 1** Baseline characteristics of 38 667 acute coronary syndrome patients with significant coronary artery disease

| BMI group (kg/m$^2$) | <18.5 (*n* = 344) | 18.5 to <21 (*n* = 1578) | 21 to <23.5 (*n* = 5146) | 23.5 to <25 (*n* = 6113) | 25 to <26.5 (*n* = 6286) | 26.5 to <28 (*n* = 5456) | 28 to <30 (*n* = 5604) | 30 to <35 (*n* = 6383) | ≥ 35 (*n* = 1757) | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Age mean; ±D (years) | 71.2 ± 11 | 71.4 ± 11 | 69.7 ± 11 | 68.9 ± 11 | 67.3 ± 11 | 66.5 ± 10 | 65.7 ± 11 | 64.4 ± 11 | 62.0 ± 11 | <0.001 |
| Female; *n* (%) | 218 (63) | 736 (47) | 1804 (35) | 1565 (26) | 1345 (21) | 1255 (23) | 1253 (22) | 1882 (30) | 688 (39) | <0.001 |
| Prior PCI; *n* (%) | 33 (9.6) | 133 (8.4) | 482 (9.4) | 687 (11.2) | 750 (11.9) | 670 (12.3) | 741 (13.2) | 930 (14.6) | 274 (15.6) | <0.001 |
| Prior CABG; *n* (%) | 18 (5.2) | 134 (8.5) | 429 (8.3) | 527 (8.6) | 633 (10.1) | 516 (9.5) | 579 (10.3) | 641 (10.0) | 171 (9.7) | <0.001 |
| Diabetes; *n* (%) | 31 (9.0) | 166 (10.5) | 635 (13.8) | 844 (13.8) | 982 (15.6) | 1047 (19.2) | 1261 (22.5) | 1876 (29.4) | 726 (41.3) | <0.001 |
| Current smoker; *n* (%) | 141 (41.0) | 473 (30.0) | 1342 (26.1) | 1395 (22.8) | 1319 (21.0) | 1182 (21.7) | 1193 (21.3) | 1395 (21.9) | 437 (24.9) | <0.001 |
| Former smoker; *n* (%) | 76 (22.1) | 403 (25.5) | 1496 (29.1) | 1963 (32.1) | 2269 (36.1) | 1947 (35.7) | 2207 (39.4) | 2569 (40.2) | 655 (37.3) | <0.001 |
| Treated hypertension; *n* (%) | 148 (43.0) | 651 (41.3) | 2228 (43.3) | 2790 (45.6) | 2970 (47.2) | 2802 (51.4) | 2988 (53.3) | 3865 (60.6) | 1203 (68.5) | <0.001 |
| Treated hyperlipidaemia; *n* (%) | 122 (35.5) | 641 (40.6) | 2175 (42.3) | 2657 (43.5) | 2882 (45.8) | 2595 (47.6) | 2871 (51.2) | 3420 (53.6) | 1035 (58.9) | <0.001 |
| Previous myocardial infarction; *n* (%) | 109 (31.7) | 417 (26.4) | 1244 (24.2) | 1479 (24.2) | 1567 (24.9) | 1370 (25.1) | 1487 (26.5) | 1706 (26.7) | 534 (30.4) | <0.001 |
| Stroke; *n* (%) | 48 (14.0) | 144 (9.1) | 403 (7.8) | 413 (6.8) | 452 (7.2) | 378 (6.9) | 355 (6.3) | 425 (6.7) | 119 (6.8) | <0.001 |
| Kidney failure; *n* (%) | 10 (2.9) | 43 (2.7) | 94 (1.8) | 103 (1.7) | 77 (1.2) | 94 (1.7) | 96 (1.7) | 104 (1.6) | 40 (2.3) | 0.32 |
| Heart failure; *n* (%) | 29 (8.4) | 138 (8.7) | 361 (7.0) | 363 (5.9) | 370 (5.9) | 315 (5.8) | 376 (6.7) | 498 (7.8) | 189 (10.8) | 0.001 |
| Cancer; *n* (%) | 30 (8.7) | 57 (3.6) | 169 (3.3) | 174 (2.8) | 203 (3.2) | 146 (2.7) | 151 (2.7) | 148 (2.3) | 34 (1.9) | <0.001 |
| Peripheral vascular disease; *n* (%) | 33 (9.6) | 129 (8.2) | 252 (4.9) | 285 (4.7) | 260 (4.1) | 168 (3.1) | 232 (4.1) | 242 (3.8) | 56 (3.2) | <0.001 |
| Dementia; *n* (%) | 0 (0) | 6 (0.4) | 7 (0.1) | 10 (0.2) | 10 (0.2) | 5 (0.1) | 7 (0.1) | 6 (0.1) | 1 (0.1) | 0.05 |
| Chronic obstructive pulmonary disease; *n* (%) | 78 (22.7) | 180 (11.4) | 407 (7.9) | 394 (6.4) | 374 (5.9) | 317 (5.8) | 358 (6.4) | 476 (7.5) | 213 (12.1) | 0.03 |
| *Indication* | | | | | | | | | | |
| Unstable angina/ non-STEMI; *n* (%) | 223 (64.8) | 1120 (71.0) | 3686 (71.6) | 4406 (72.1) | 4610 (73.3) | 4075 (74.7) | 4338 (77.4) | 4969 (77.8) | 1442 (82.1) | <0.001 |
| STEMI; *n* (%) | 120 (34.9) | 456 (28.9) | 1440 (28.0) | 1699 (27.8) | 1665 (26.5) | 1371 (25.1) | 1260 (22.5) | 1404 (22.0) | 309 (17.6) | <0.001 |
| Other; *n* (%) | 1 (0.3) | 2 (0.1) | 20 (0.4) | 8 (0.1) | 11 (0.2) | 10 (0.2) | 6 (0.1) | 10 (0.2) | 6 (0.3) | 0.22 |
| *Angiographic findings* | | | | | | | | | | |
| One vessel disease; *n* (%) | 133 (38.7) | 615 (39.0) | 2068 (40.2) | 2397 (39.2) | 2495 (39.7) | 2158 (39.6) | 2245 (40.1) | 2650 (41.5) | 750 (42.7) | 0.005 |
| Multi-vessel disease; *n* (%) | 211 (61.3) | 963 (61.0) | 3078 (59.8) | 3716 (60.8) | 3791 (60.3) | 3298 (60.4) | 3359 (59.9) | 3733 (58.5) | 1007 (57.3) | 0.005 |
| *Primary decision* | | | | | | | | | | |
| PCI; *n* (%) | 258 (75.0) | 1156 (73.3) | 3817 (74.2) | 4606 (75.3) | 4741 (75.4) | 4068 (74.6) | 4200 (74.9) | 4843 (75.9) | 1267 (72.1) | 0.54 |
| CABG; *n* (%) | 39 (11.3) | 206 (13.1) | 691 (13.4) | 846 (13.8) | 877 (14.0) | 786 (14.4) | 830 (14.8) | 899 (14.1) | 246 (14.0) | 0.04 |
| Medical therapy; *n* (%) | 47 (13.7) | 216 (13.7) | 638 (12.4) | 661 (10.8) | 668 (10.8) | 602 (11.0) | 574 (10.2) | 641 (10.0) | 224 (13.9) | 0.002 |

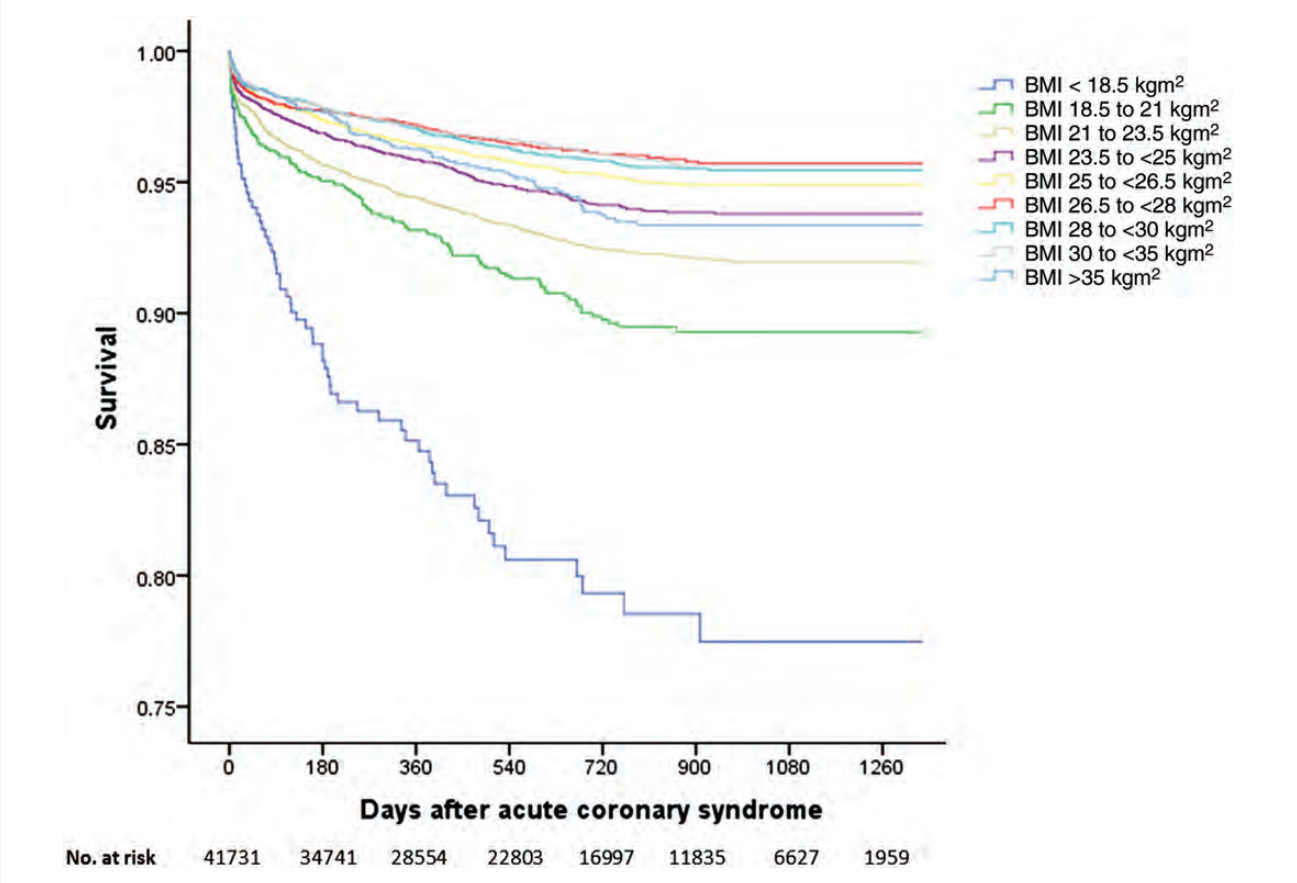


**Figure 1** Kaplan–Meier survival curve for patients with acute coronary syndrome and significant coronary artery disease according to the different BMI categories.

# Results

## Patient characteristics

Between May 2005 and December 2008, a total of 64 436 patients underwent catheterization for suspected ACSs in Sweden. Missing data for one or more variables occurred in 18 743 (29.1%). The variable most often missing was BMI (15 159) followed by smoking status (4588), hyperlipidaemia (2040), hypertension (1663), diabetes (642), prior PCIs (46), and prior CABG (28). Implausible BMI values (defined as BMI $>70$ or $<11$ kg/m$^2$) were present in 27 patients and were treated as missing data. In the total 45 693 patients who had complete data, 38 667 had significant stenosis at angiography whereas 7026 did not. Patients excluded from the complete case analysis due to missing data were older, had more co-morbidities, more STEMI, and a higher mortality rate (HR 1.65, 95% CI 1.53–1.77) than patients who were included. The mean time of follow-up for the study cohort was 21 months (SD $\pm$ 13 months). Patient characteristics according to the different BMI categories at the time of cardiac catheterization are shown in *Table 1*. It was observed that obese patients were more likely to be younger, have hyperlipidaemia, hypertension, and diabetes mellitus, but were less likely to smoke and to have high-risk coronary anatomy. The underweight patients were more likely to be females and the indication for angiography was more often STEMI.

## Survival

### Primary analysis

During follow-up, 3018 (4.7%) deaths were registered in patients with significant CAD. Unadjusted survival is presented as a Kaplan–Meier curve in *Figure 1*. This demonstrates substantial difference in mortality between the different BMI categories ($P <$ 0.001; log-rank test for trend). Patients who were underweight with BMI $<18.5$ kg/m$^2$ had the highest risk followed by patients with normal weight, whereas overweight patients had the lowest risk. The unadjusted HR ranged from 2.94 (2.25–3.83) to 0.52 (0.44–0.61) compared with the reference group. The same pattern was present in ACS patients with significant coronary artery stenosis treated with PCIs. In this group, the highest mortality rate was also in the underweight patients (12.4%) followed by the patients with normal BMI whereas the lowest mortality was in the overweight and obese patients (3.9%). The adjusted HR ranged from 2.31 (1.67–3.21) to 0.66 (0.53–0.82) compared with the reference group (*Figure 2A*). In patients who were treated with CABG or medical therapy alone the differences in HR were smaller (*Figure 2B* and *C*). Examination of BMI as a

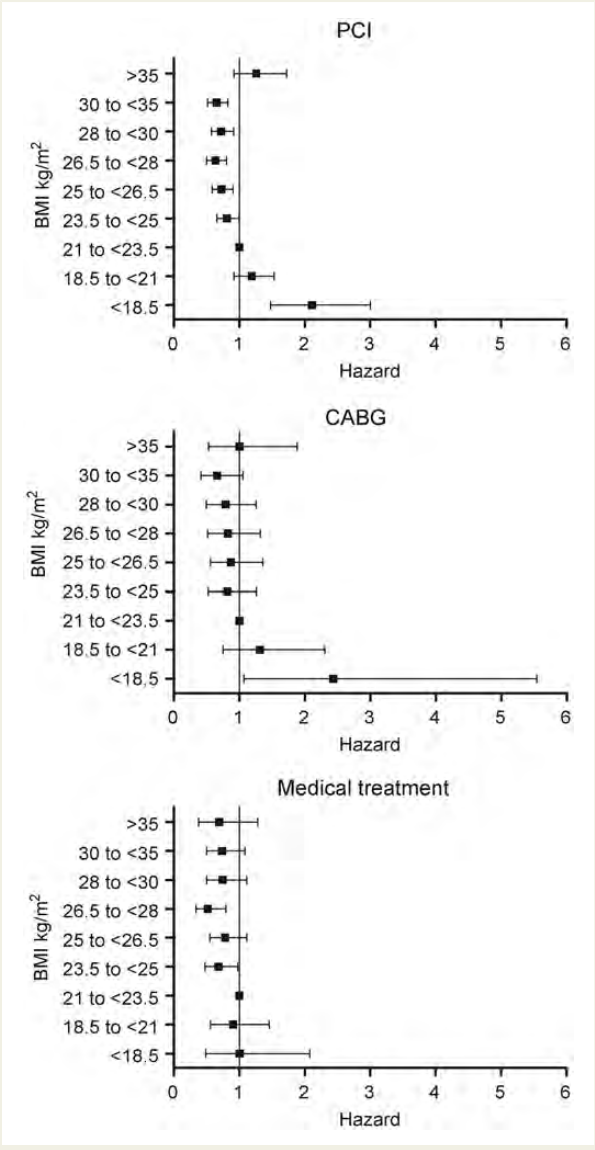


**Figure 2** Adjusted risk for mortality (95% CI) in patients with acute coronary syndrome and significant coronary artery disease in whom the treatment decision was (*A*) PCI ($n = 28\,956$), (*B*) CABG ($n = 5420$) and (*C*) Medical therapy ($n = 4291$) according to the different BMI categories. Patients with missing variables are not included.

continuous variable (*Figure 3*) using fractional polynomial Cox regression demonstrated a U-shaped association between BMI and adjusted all-cause mortality, where mortality decreased with increasing BMI between 30 and 40 kg/m$^2$, and then began to increase again at a BMI of >40 kg/m$^2$. The results of Cox-regression based on the estimation after the multiple imputation procedure have shown congruent data when compared with the unadjusted and adjusted complete case-analysis models in patients with significant stenosis (*Table 2*). There was no interaction between BMI category and age, and BMI category and sex. There was no difference in mortality between the BMI categories regarding in-hospital mortality and 30-day mortality (*Figure 4*).

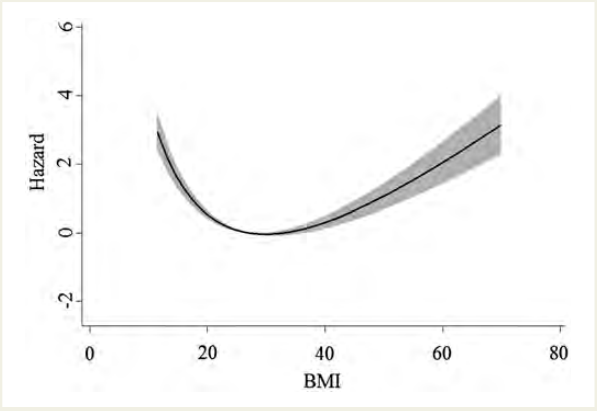


**Figure 3** Adjusted fractional polynomial Cox proportional-hazards regression (95% CI, shaded area) with continuous risk relationship between BMI and all-cause mortality in patients with acute coronary syndrome and significant coronary artery disease.

### Secondary analysis

The baseline characteristics of patients without significant stenosis are shown in *Table 3*. The distribution of co-morbidity between the BMI categories is quite similar to the cohort with stenosis. However, this subgroup had younger patients, a higher proportion of women, and fewer co-morbidities. Adjusted HR are shown in *Figure 5*. In this analysis, only underweight patients had a significantly higher HR compared with the reference group in both the adjusted and the unadjusted models.

Among the patients with significant CAD there was no difference between the BMI categories with regard to hospitalization for MI, HF, and stroke after the index procedure (data not shown).

## Discussion

The most important result from our study is that overweight and obese patients with ACSs had lower mortality rate compared with patients with normal BMI. This was independent of the treatment strategy until up to 3 years after hospitalization. This large observational study with prospectively collected data strengthens the existing evidence and increases the awareness of obesity paradox.

An inverse relationship between obesity and all-cause and cardiovascular mortality has previously been described in patients with CAD.[8–14] In fact, in two recent large observational studies obesity paradox has also been associated in patients with ACSs.[14,25] Our study verifies and emphasizes this phenomenon, but it does not offer any evident explanation for the paradox. Two arguments have been put forth to account for the existence of obesity paradox. First is that the obesity paradox is a mere consequence of one or several confounding factors present in the obese population. The second argues that the explanation has to be found in the biology of the obese phenotype itself, which means we need to define known or to detect yet unknown protective biological pathways that protect obese patients with cardiovascular diseases from premature death.

In accordance with the previous studies, our data show that obese patients are younger and have less severe CAD at the

**Table 2** Adjusted and unadjusted hazard ratios (95% CI) of cumulative mortality according to the BMI group from different Cox proportional hazards regression models in patients with acute coronary syndrome and significant stenosis on angiography

| | | BMI group (kg/m$^2$) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | <18.5 | 18.5 to 21 | 21 to <23.5 | 23.5 to <25 | 25 to <26.5 | 26.5 to <28 | 28 to <30 | 30 to <35 | >35 |
| Unadjusted analysis | 41 731 | 2.94 (2.27–3.83) | 1.31 (1.08–1.59) | 1.0 | 0.76 (0.65–0.88) | 0.62 (0.53–0.73) | 0.52 (0.44–0.62) | 0.55 (0.46–0.65) | 0.52 (0.44–0.61) | 0.75 (0.60–0.94) |
| Adjusted[a] complete case analysis | 38 667 | 1.90 (1.41–2.55) | 1.13 (0.92–1.40) | 1.0 | 0.79 (0.67–0.93) | 0.75 (0.63–0.89) | 0.63 (0.52–0.76) | 0.71 (0.60–0.86) | 0.66 (0.55–0.79) | 1.04 (0.81–1.34) |
| Unadjusted multiple imputation | 54 419 | 2.77 (2.13–3.61) | 1.26 (1.05–1.52) | 1.0 | 0.81 (0.69–0.94) | 0.72 (0.63–0.84) | 0.66 (0.57–0.77) | 0.67 (0.57–0.78) | 0.62 (0.53–0.73) | 0.73 (0.58–0.92) |
| Adjusted[a] multiple imputation | 54 419 | 2.04 (1.57–2.04) | 1.13 (0.93–1.34) | 1.0 | 0.85 (0.73–0.99) | 0.82 (0.71–0.95) | 0.76 (0.65–0.88) | 0.78 (0.66–0.92) | 0.75 (0.64–0.89) | 0.98 (0.78–1.24) |

[a]Adjustments are made for age, gender, prior PCI, prior CABG, diabetes mellitus, smoking status, treated hypertension, treated hyperlipidaemia, previous MI, prior stroke, prior kidney failure, prior heart failure, prior cancer, prior peripheral vascular disease, prior dementia, prior chronic obstructive pulmonary disease, indication for coronary angiography, angiographical finding, and primary treatment decision.

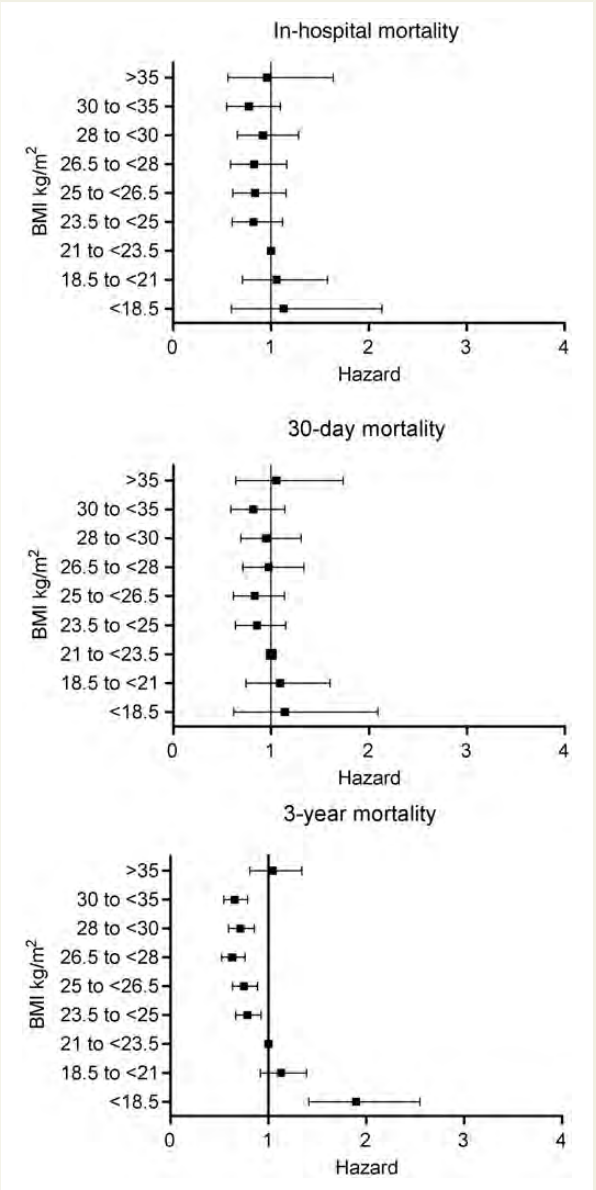


**Figure 4** Adjusted risk for (*A*) in-hospital, (*B*) 30-day, and (*C*) 3-year mortality (95% CI) in patients with acute coronary syndrome and significant coronary artery disease according to the different BMI categories.

time of cardiac catheterization. As obese patients with ACSs are younger,[26,27] they are more likely to be referred to experts in secondary prevention[28] and to receive treatment for co-morbidities. The obese patients also tend to have higher blood pressure, which may lead to more aggressive use of disease-modifying medications such as ACE-inhibitors and beta-blockers—the pharmacological treatment particularly beneficial for secondary prevention. However, Oreopoulos *et al.*[14] were not able to demonstrate that obese patients with CAD are being more aggressively treated with statins, beta-blockers, ACE-inhibitors, and nitrates. Unfortunately, we were not able to address this issue as our database does not contain information about adequacy of

**Table 3** Baseline characteristics of 7026 acute coronary syndrome patients without significant coronary artery disease

| BMI group (kg/m$^2$) | <18.5 (*n* = 122) | 18.5 to <21 (*n* = 443) | 21 to <23.5 (*n* = 1059) | 23.5 to <25 (*n* = 1044) | 25 to <26.5 (*n* = 992) | 26.5 to <28 (*n* = 913) | 28 to <30 (*n* = 916) | 30 to <35 (*n* = 1154) | ≥35 (*n* = 384) | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Age mean; ± SD (years) | 65.9 ± 12 | 64.9 ± 12 | 64.1 ± 12 | 63.7 ± 12 | 63.8 ± 12 | 63.7 ± 11 | 62.6 ± 12 | 61.7 ± 11 | 58.7 ± 12 | <0.001 |
| Female; *n* (%) | 96 (78.7) | 331 (74.7) | 656 (61.9) | 545 (52.2) | 501 (50.5) | 463 (50.7) | 434 (47.4) | 610 (52.9) | 220 (57.3) | <0.001 |
| Previous PCI; *n* (%) | 5 (4.1) | 30 (6.8) | 74 (7.0) | 92 (8.8) | 89 (9.0) | 110 (12.0) | 113 (12.3) | 137 (11.9) | 39 (10.2) | <0.001 |
| Previous CABG; *n* (%) | 0 (0) | 1 (0.2) | 11 (1.0) | 7 (0.7) | 5 (0.5) | 9 (1.0) | 9 (1.0) | 14 (1.2) | 4 (1.0) | 0.07 |
| Diabetes; *n* (%) | 4 (3.3) | 24 (5.4) | 80 (7.6) | 75 (7.2) | 91 (9.2) | 114 (12.5) | 128 (14.0) | 235 (20.4) | 134 (34.9) | <0.001 |
| Current smoker; *n* (%) | 43 (35.2) | 122 (27.5) | 215 (20.3) | 202 (19.3) | 158 (15.9) | 141 (15.4) | 133 (14.5) | 187 (16.2) | 76 (19.8) | <0.001 |
| Former smoker; *n* (%) | 34 (27.9) | 120 (27.1) | 294 (27.8) | 308 (29.5) | 332 (33.5) | 312 (34.2) | 321 (35.1) | 420 (36.4) | 132 (34.4) | <0.001 |
| Treated hypertension; *n* (%) | 41 (33.6) | 149 (33.6) | 396 (37.4) | 433 (41.5) | 446 (45.0) | 454 (49.7) | 466 (45.0) | 645 (55.9) | 227 (59.1) | <0.001 |
| Treated hyperlipidaemia; *n* (%) | 38 (31.1) | 161 (36.3) | 385 (36.4) | 426 (40.8) | 423 (42.6) | 386 (42.3) | 437 (47.8) | 544 (47.1) | 202 (52.6) | <0.001 |
| Previous myocardial infarction; *n* (%) | 9 (7.4) | 56 (12.6) | 144 (13.6) | 140 (13.4) | 160 (16.1) | 141 (15.4) | 150 (16.4) | 218 (18.9) | 64 (16.7) | <0.001 |
| Stroke; *n* (%) | 8 (6.6) | 28 (6.3) | 54 (5.1) | 40 (3.8) | 52 (5.2) | 33 (3.6) | 34 (3.7) | 47 (4.1) | 20 (5.2) | 0.07 |
| Kidney failure; *n* (%) | 2 (1.6) | 1 (0.2) | 14 (1.3) | 9 (0.9) | 4 (0.4) | 13 (1.4) | 6 (0.7) | 10 (0.9) | 5 (1.3) | 0.91 |
| Heart failure; *n* (%) | 10 (8.2) | 30 (6.8) | 57 (5.4) | 48 (4.6) | 48 (4.8) | 51 (5.6) | 46 (5.0) | 78 (6.8) | 48 (12.5) | 0.007 |
| Cancer; *n* (%) | 2 (1.6) | 26 (5.9) | 37 (3.5) | 30 (2.9) | 27 (2.7) | 23 (2.5) | 29 (3.2) | 30 (2.6) | 6 (1.6) | 0.01 |
| Peripheral vascular disease; *n* (%) | 3 (2.5) | 11 (2.5) | 20 (1.9) | 16 (1.5) | 16 (1.6) | 22 (2.4) | 16 (1.7) | 26 (2.3) | 7 (1.8) | 0.83 |
| Dementia; *n* (%) | 0 (0) | 2 (0.5) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1(0.1) | 1 (0.1) | 0 (0) | 0.54 |
| Chronic obstructive pulmonary disease; *n* (%) | 35 (28.7) | 71 (16.0) | 117 (11.0) | 101 (9.7) | 75 (7.6) | 76 (8.3) | 97 (10.6) | 125 (10.8) | 66 (17.2) | 0.15 |
| *Indication* | | | | | | | | | | |
| Unstable angina/non-STEMI; *n* (%) | 99 (81.1) | 388 (87.6) | 937 (88.5) | 891 (85.3) | 867 (87.4) | 800 (87.6) | 836 (91.4) | 1060 (91.9) | 356 (92.7) | <0.001 |
| STEMI; *n* (%) | 22 (18.0) | 49 (11.1) | 115 (10.9) | 148 (14.2) | 121 (12.2) | 107 (11.7) | 75 (8.2) | 90 (7.8) | 28 (7.3) | <0.001 |
| Other; *n* (%) | 1 (0.8) | 6 (1.4) | 7 (0.7) | 5 (0.5) | 4 (0.4) | 6 (0.7) | 4 (0.4) | 4 (0.3) | 0 (0) | 0.02 |

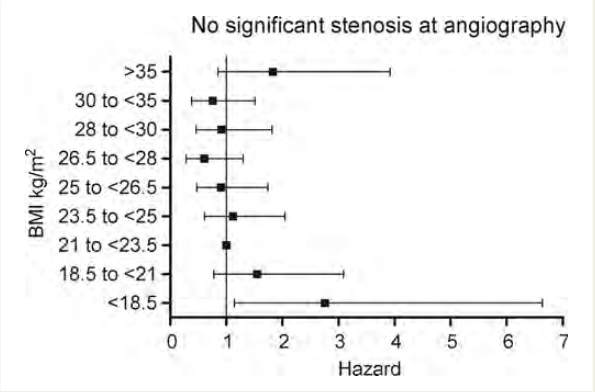


**Figure 5** Adjusted risk for mortality (95% CI) in patients with acute coronary syndrome with no significant coronary artery disease according to the different BMI categories ($n = 7026$).

pharmacological treatment before and after catheterization, which is an important limitation of the study. However, the positive association between guideline-recommended treatment and obesity has not yet been unequivocally established.

Other possible explanations for obesity paradox are that obesity may protect against malnutrition and energy wastage post-revascularization and that altered neuroendocrine status in obese patients may play a role in modulating progression of pathologic cardiac remodelling after MI. The size of the coronary vessels increases with increasing BMI and small vessels is a risk factor for worse outcome after PCI and CABG.[29] Despite the significant differences in baseline characteristics, our findings regarding the inverse association between BMI and outcomes persisted after multivariate adjustments in several models, suggesting an independent association between BMI and mortality risk. However, it is important to keep in mind that inverse association between BMI and outcomes is U-shaped with increasing risk in patients with morbid obesity. Indeed, this finding has been independently reported by others.[14,25]

In addition to the suggested explanations for obesity paradox, we tentatively propose that obesity may protect against malignant ventricular arrhythmias during and after MI and therefore decrease the risk for sudden death. This hypothesis is indirectly supported by clinical evidence from patients with HF secondary to AMI,[13] with cautious support from our data. During the follow-up period, overweight and obese patients did not differ in the frequency of hospitalization for HF, MI, and stroke—common causes of death in this population—suggesting that obesity is not associated with lower risk for these clinical events. By process of elimination, these observations strengthen the hypothesis that obesity may protect against malignant ventricular arrhythmias as it is another frequent cause of mortality in patients with CAD.

Thus far, the growing evidence for the existence of obesity paradox has had no impact on the current guidelines for secondary prevention in CAD. The European Society of Cardiology and the American College of Cardiology/American Heart Association recommend a BMI of $<25$ kg/m$^2$ in their guidelines of secondary prevention strategies.[4,5] We believe that no evidence exists that proves weight reduction in itself has a positive prognostic value after ACSs. Actually, some evidence suggests that weight loss after ACSs might in fact have a negative effect.[30] We believe that given the current state of our knowledge, obesity paradox requires much more attention and deserves to be recognized in the guidelines. However, our study should not be interpreted as a support for *status quo* in obese patients. Instead we think that multidisciplinary scientific approach to obesity paradox, both clinical and preclinical (including experiments investigating hypothetically protective pathways), may lead us to important discoveries that we can use to improve treatment of ACSs, HF, and arrhythmias. Indeed, experimental evidence is emerging suggesting that adipose tissue as the largest endocrine organ[31] produces hormones (e.g. leptin, adiponectin, resistin) that may have cardioprotective effects in MI.[32–35] There is considerable evidence demonstrating that leptin and adiponectin have direct cardioprotective effects. These hormones possess anti-inflammatory, anti-apoptotic, anti-hypertrophic effects and reduce infarct size.[36–38] All these effects may lower arrhythmogenicity in the infarcted myocardium and therefore potentially prevent sudden death.

There are six limitations that need to be addressed. First, this is an observational study and as such it provides only associative evidence, not causative. We cannot rule out the possibility of selection bias, residual confounding and survival bias as only surviving hospitalized patients are included in the registry. On the other hand, the observational nature of our study provides real-world data on the largest cohort studied to date. Second, SCAAR does not contain data on pharmacological treatment and we were not able to adjust for the possible differences known to have impact on clinical outcome. Third, although BMI is the most commonly used measure of obesity, it does not directly distinguish between adipose and lean tissue or central and peripheral adiposity. Fourth, we were unable to control for the role of unintentional weight loss. Our risk-adjusted analysis, however, did include age, smoking status, history of malignancy, dementia, renal failure, HF, and chronic obstructive pulmonary disease, which are all important factors that could lead to involuntary weight loss. Fifth, we did not have data on cause-specific mortality. Finally, 30% of the patients had missing data. These patients had higher mortality and therefore their exclusion from the analysis might have produced biased results. However, results from the multiple imputation model were congruent with the data from the complete case analysis.

In conclusion, we found that among ACS patients the relation between BMI and mortality is U-shaped, with the nadir among overweight or obese patients, and underweight and normal-weight patients having the highest risk. Therefore, these data strengthen the concept of obesity paradox substantially.

**Conflict of interest:** none declared.

## References

1. Fontaine KR, Redden DT, Wang C, Westfall AO, Allison DB. Years of life lost due to obesity. *JAMA* 2003;**289**:187–193.
2. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. *N Engl J Med* 1999;**341**:427–434.
3. Klein S, Burke LE, Bray GA, Blair S, Allison DB, Pi-Sunyer X, Hong Y, Eckel RH. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on nutrition, physical activity, and metabolism: Endorsed by the American College of Cardiology Foundation. *Circulation* 2004;**110**:2952–2967.

4. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-st-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1598–1660.
5. Wright RS, Anderson JL, Adams CD, Bridges CR, Casey DE Jr., Ettinger SM, Fesmire FM, Ganiats TG, Jneid H, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP, Antman EM, Califf RM, Chavey WE 2nd, Hochman JS, Levin TN. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;**57**:e215–e367.
6. Malcom J, Arnold O, Howlett JG, Ducharme A, Ezekowitz JA, Gardner MJ, Giannetti N, Haddad H, Heckman GA, Isaac D, Jong P, Liu P, Mann E, McKelvie RS, Moe GW, Svendsen AM, Tsuyuki RT, O'Halloran K, Ross HJ, Sequeira EJ, White M. Canadian Cardiovascular Society consensus conference guidelines on heart failure—2008 update: best practices for the transition of care of heart failure patients, and the recognition, investigation and treatment of cardiomyopathies. *Can J Cardiol* 2008;**24**:21–40.
7. Degoulet P, Legrain M, Reach I, Aime F, Devries C, Rojas P, Jacobs C. Mortality risk factors in patients treated by chronic hemodialysis. Report of the diaphane collaborative study. *Nephron* 1982;**31**:103–110.
8. Ellis SG, Elliott J, Horrigan M, Raymond RE, Howell G. Low-normal or excessive body mass index: newly identified and powerful risk factors for death and other complications with percutaneous coronary intervention. *Am J Cardiol* 1996;**78**: 642–646.
9. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: A systematic review of cohort studies. *Lancet* 2006;**368**:666–678.
10. Gruberg L, Weissman NJ, Waksman R, Fuchs S, Deible R, Pinnow EE, Ahmed LM, Kent KM, Pichard AD, Suddath WO, Satler LF, Lindsay J Jr. The impact of obesity on the short-term and long-term outcomes after percutaneous coronary intervention: the obesity paradox? *J Am Coll Cardiol* 2002;**39**:578–584.
11. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: A meta-analysis. *Am Heart J* 2008;**156**:13–22.
12. Badheka AO, Rathod A, Kizilbash MA, Garg N, Mohamad T, Afonso L, Jacob S. Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox. *Am J Med* 2010;**123**:646–651.
13. Choy B, Hansen E, Moss AJ, McNitt S, Zareba W, Goldenberg I. Relation of body mass index to sudden cardiac death and the benefit of implantable cardioverter-defibrillator in patients with left ventricular dysfunction after healing of myocardial infarction. *Am J Cardiol* 2010;**105**:581–586.
14. Oreopoulos A, McAlister FA, Kalantar-Zadeh K, Padwal R, Ezekowitz JA, Sharma AM, Kovesdy CP, Fonarow GC, Norris CM. The relationship between body mass index, treatment, and mortality in patients with established coronary artery disease: a report from approach. *Eur Heart J* 2009;**30**:2584–2592.
15. Oreopoulos A, Padwal R, Norris CM, Mullen JC, Pretorius V, Kalantar-Zadeh K. Effect of obesity on short- and long-term mortality postcoronary revascularization: a meta-analysis. *Obesity (Silver Spring)* 2008;**16**:442–450.
16. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT, Spencer E, Moons KG, Tjonneland A, Halkjaer J, Jensen MK, Stegger J, Clavel-Chapelon F, Boutron-Ruault MC, Chajes V, Linseisen J, Kaaks R, Trichopoulou A, Trichopoulos D, Bamia C, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, May AM, Bueno-de-Mesquita HB, van Duijnhoven FJ, Hallmans G, Weinehall L, Manjer J, Hedblad B, Lund E, Agudo A, Arriola L, Barricarte A, Navarro C, Martinez C, Quiros JR, Key T, Bingham S, Khaw KT, Boffetta P, Jenab M, Ferrari P, Riboli E. General and abdominal adiposity and risk of death in europe. *N Eng J Med* 2008;**359**:2105–2120.
17. www.ucr.uu.se/scaar (13 July 2012).
18. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the task force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. *Eur Heart J* 2008;**29**:2909–2945.
19. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D, Bax JJ, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S, Achenbach S, Badimon L, Bertrand M, Botker HE, Collet JP, Crea F, Danchin N, Falk E, Goudevenos J, Gulba D, Hambrecht R, Herrmann J, Kastrati A, Kjeldsen K, Kristensen SD, Lancellotti P, Mehilli J, Merkely B, Montalescot G, Neumann FJ, Neyses L, Perk J, Roffi M, Romeo F, Ruda M, Swahn E, Valgimigli M, Vrints CJ, Widimsky P. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**: 2999–3054.
20. Rubin DB. Inference and missing data. *Biometrika* 1976;**63**:581–592.
21. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ: Wiley-Interscience; 2004.
22. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009;**28**:1982–1998.
23. Rubin DB. Inference and missing data. *Biometrika* 1976;**63**:581–590.
24. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999;**28**:964–974.
25. Das SR, Alexander KP, Chen AY, Powell-Wiley TM, Diercks DB, Peterson ED, Roe MT, de Lemos JA. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50 149 patients with st-segment elevation myocardial infarction results from the ncdr (national cardiovascular data registry). *J Am Coll Cardiol.* 2011;**58**:2642–2650.
26. Madala MC, Franklin BA, Chen AY, Berman AD, Roe MT, Peterson ED, Ohman EM, Smith SC Jr., Gibler WB, McCullough PA. Obesity and age of first non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2008;**52**: 979–985.
27. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, Sarwar N, Kizer JR, Lawlor DA, Nordestgaard BG, Ridker P, Salomaa V, Stevens J, Woodward M, Sattar N, Collins R, Thompson SG, Whitlock G, Danesh J. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. *Lancet* 2011;**377**:1085–1095.
28. Williams MA, Fleg JL, Ades PA, Chaitman BR, Miller NH, Mohiuddin SM, Ockene IS, Taylor CB, Wenger NK. Secondary prevention of coronary heart disease in the elderly (with emphasis on patients > or =75 years of age): an American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on exercise, cardiac rehabilitation, and prevention. *Circulation* 2002;**105**:1735–1743.
29. O'Connor NJ, Morton JR, Birkmeyer JD, Olmstead EM, O'Connor GT. Effect of coronary artery diameter in patients undergoing coronary bypass surgery. Northern New England Cardiovascular Disease Study Group. *Circulation* 1996;**93**: 652–655.
30. Myers J, Lata K, Chowdhury S, McAuley P, Jain N, Froelicher V. The obesity paradox and weight loss. *The Am J Med* 2011;**124**:924–930.
31. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J Clin Endocrinol Metab* 2004;**89**:2548–2556.
32. Smith CC, Dixon RA, Wynne AM, Theodorou L, Ong SG, Subrayan S, Davidson SM, Hausenloy DJ, Yellon DM. Leptin-induced cardioprotection involves JAK/STAT signaling that may be linked to the mitochondrial permeability transition pore. *Am J Physiol. Heart Circul Physiol* 2010;**299**:H1265–H1270.
33. Kondo K, Shibata R, Unno K, Shimano M, Ishii M, Kito T, Shintani S, Walsh K, Ouchi N, Murohara T. Impact of a single intracoronary administration of adiponectin on myocardial ischemia/reperfusion injury in a pig model. *Circul. Cardiovasc Interv* 2010;**3**:166–173.
34. Tao L, Gao E, Jiao X, Yuan Y, Li S, Christopher TA, Lopez BL, Koch W, Chan L, Goldstein BJ, Ma XL. Adiponectin cardioprotection after myocardial ischemia/reperfusion involves the reduction of oxidative/nitrative stress. *Circulation* 2007; **115**:1408–1416.
35. Gao J, Chang Chua C, Chen Z, Wang H, Xu X, C Hamdy R, McMullen JR, Shioi T, Izumo S, Chua BH. Resistin, an adipocytokine, offers protection against acute myocardial infarction. *J Mol Cell Cardiol* 2007;**43**:601–609.
36. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat Med* 2005;**11**: 1096–1103.
37. Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, Kumada M, Sato K, Schiekofer S, Ohashi K, Funahashi T, Colucci WS, Walsh K. Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat Med* 2004;**10**:1384–1389.
38. Smith CC, Mocanu MM, Davidson SM, Wynne AM, Simpkin JC, Yellon DM. Leptin, the obesity-associated hormone, exhibits direct cardioprotective effects. *Br J Pharmacol* 2006;**149**:5–13.