International Journal of Cardiology 167 (2013) 1154–1158

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Obesity, health status, and 7-year mortality in percutaneous coronary intervention: In search of an explanation for the obesity paradox

John O. Younge [a], Nikki L. Damen [b], Ron T. van Domburg [a], Susanne S. Pedersen [a,b,*]

[a] Department of Cardiology, Erasmus MC, Rotterdam, The Netherlands
[b] Center of Research on Psychology in Somatic diseases (CoRPS), Department of Medical Psychology, Tilburg University, Tilburg, The Netherlands

ARTICLE INFO

*Article history:*
Received 19 January 2012
Received in revised form 7 March 2012
Accepted 8 March 2012
Available online 3 April 2012

*Keywords:*
Obesity
Obesity paradox
Health status
PCI
Mortality

ABSTRACT

*Background:* Obesity is a growing health problem and is associated with adverse outcomes in coronary artery disease (CAD). However, recent studies have shown better survival in cardiovascular patients with overweight or obesity, which has been referred to as the "obesity paradox". As there is no clear understanding of the phenomenon, we examined the association between body mass index (BMI) and all-cause mortality in patients treated with percutaneous coronary intervention (PCI) at 7-year follow-up, and the potential role of health status in explaining the obesity paradox.

*Methods:* Consecutive PCI patients (72.5% men; mean age 62.0 ± 11.2 years, range [27–90] years) from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry completed the 36-item short-form health survey (SF-36) to assess health status at baseline. Patients were classified into a normal weight, overweight or obesity group.

*Results:* The prevalence of normal weight was 34.7% (354/1019), overweight was seen in 45.9% (468/1019) of patients, and 19.3% (197/1019) was obese. After a median follow-up of 7.0 ± 1.7 years, 163 deaths (16.0%) from any cause were recorded. Cumulative hazard functions differed significantly for the obese and overweight group when compared to the normal weight group (log-rank $X^2 = 6.59$, $p < 0.05$). In multivariable analysis, overweight, but not obesity, remained associated with a lower risk for all-cause mortality (HR = 0.60, 95%CI [0.42–0.86], $p = 0.005$). Additionally, after adding the 8 health status SF-36 domains to the multivariate model, the association between overweight and mortality remained unchanged.

*Conclusion:* In our study population overweight, but not obesity, was associated with a lower risk for 7-year mortality in PCI patients. Health status as measured with the SF-36 did not seem to play a role in explaining the obesity paradox.



## 1. Introduction

Obesity is a growing epidemic, with prevalence rates in the general population ranging from 32% in men to 36% in women [1]. In coronary artery disease (CAD), obesity is prevalent in 29% of patients [2] and is associated with potential risk for cardiovascular morbidity and mortality [3,4]. However, evidence for a link between obesity and cardiovascular prognosis is based on a small number of studies, with results being mixed, as some [5] but not all studies support such a relationship [6]. Moreover, recent studies have demonstrated that there may not be a linear and straightforward relationship between overweight and obesity and mortality, as some studies show better survival in cardiovascular patients with overweight or obesity. This phenomenon is referred to as the "obesity paradox" [6–9].

In an attempt to explain the obesity paradox, studies have primarily focused on potential differences in the prescription of guideline-based medications [2,7]. A higher prevalence of invasive treatment has also been observed in obese patients with CAD [2]. Nevertheless, we still do not have a clear understanding of the obesity paradox.

Patient-reported health status might be another avenue to pursue in order to elucidate factors that may impinge on or help explain the obesity paradox. A recent systematic review demonstrated that poor health status in CAD and congestive heart failure increase the risk of mortality and hospital readmissions independent of indicators of disease severity and demographic and clinical characteristics [10]. Also a recent paper from our research group found an association between poor health status and higher mortality [11]. A paucity of studies focused on the association between obesity and health status [12–15], but the role of health status in the context of obesity and mortality in CAD has not yet been examined.

Hence, in the current study we examined 1) the association between BMI and all-cause mortality in patients treated with percutaneous coronary intervention (PCI) at 7-year follow-up, and 2) the potential role of health status in explaining the obesity paradox.

* Corresponding author at: Center of Research on Psychology in Somatic diseases (CoRPS), Tilburg University, P.O. Box 90153, 5000 LE, Tilburg, The Netherlands. Tel.: +31 13 466 2503; fax: +31 13 466 2067.
*E-mail address:* s.s.pedersen@uvt.nl (S.S. Pedersen).

0167-5273/$ – see front matter 
doi:10.1016/j.ijcard.2012.03.105

## 2. Methods

### 2.1. Study population

The study sample comprised consecutive CAD patients treated with PCI with either sirolimus-eluting stenting (SES) or bare metal stenting (BMS), between October 16, 2001 and October 15, 2002 at the Erasmus Medical Center, Rotterdam, The Netherlands, as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. The design of the RESEARCH registry has been published elsewhere [16]. In brief, the registry was designed to evaluate the efficacy and safety of SES implantation in the "real world" of interventional cardiology. Hence, no exclusion criteria were applied for patients entering the registry, and all PCI patients were eligible for enrolment regardless of anatomical or clinical presentation [17].

At 6 months post PCI (referred to as baseline in the remainder of the paper), all living patients were asked to complete a standardized and validated health status measure. In accordance with previous studies, assessment at 6 months was chosen so as to represent patients in a stable condition, as the risk for restenosis is increased in the 0–6 month period post PCI [18]. All patients were prospectively followed-up for adverse clinical events.

### 2.2. Socio-demographic and clinical characteristics

Socio-demographic variables included gender and age. Clinical variables were obtained from patients' medical records at the time of the index PCI and included BMI body mass index; (i.e., weight in kilograms divided by the square of the height in meters), type of stent (SES vs. BMS implantation), multi-vessel disease (multi-vessel disease vs. single-vessel disease/no vessel disease), indication for PCI (stable angina/silent ischemia, unstable angina, or MI), cardiac history (i.e., previous myocardial infarction (MI), coronary artery bypass graft surgery (CABG), or PCI), CAD risk factors (i.e., hypertension, hypercholesterolemia, diabetes mellitus, family history of CAD, or self-reported current smoking) and prescribed cardiac discharge medications (i.e., ACE-inhibitors, beta-blockers, calcium antagonists diuretics, oral nitrates or statins). Information on clinical variables was prospectively collected at the time of the index-PCI and recorded in our institutional database.

### 2.3. Health status

Health status was assessed at baseline post PCI, using the short form health survey (SF-36) [19]. The SF-36 consists of 36 items that contribute to 8 health status domains (i.e., physical functioning, role physical functioning, role emotional functioning, mental health, vitality, social functioning, bodily pain, and general health). Scale scores are obtained by summing the items together within a domain, dividing this outcome by the range of scores, and then transforming the raw scores to a scale from 0 to 100 [19]. A higher score on the SF-36 sub domains represents better functioning. A high score on the bodily pain scale indicates freedom from pain. The scale has good reliability with Cronbach's alpha ranging from 0.65 to 0.96 for all subscales [20].

### 2.4. Endpoint

The primary endpoint was defined as all-cause mortality. Deaths ($n=54$) occurring between PCI and psychological assessment were excluded as an endpoint from analyses. Information on survival status was obtained from the Municipal Civil Registries in May 2009. The median follow-up period for all-cause mortality was $7.0\pm1.7$ years (range [0.8–9.4 years]). Information on survival status at follow-up was complete for 1007 patients (98.8%).

### 2.5. Informed consent

The study protocol was approved by the medical ethics committee of the Erasmus Medical Center, Rotterdam, and conducted according to the Helsinki Declaration [21]. Every patient provided informed consent.

## 3. Statistical analyses

Prior to statistical analyses, we dichotomized all 8 health status domains, as suggested by others, in order to enhance clinical interpretability [22,23]. The lowest tertile was used to indicate poor health status and the 2 highest tertiles to indicate good health status. Categorization of BMI was adopted from the World Health Organization and defined as normal weight: 18.5 to 24.99 kg/m$^2$, overweight: 25 to 29.99 kg/m$^2$, and obese: $\geq$30 kg/m$^2$ [24,25]. For all analyses, normal weight was used as the reference group.

Group differences were examined using the Chi-square test (Fisher's exact test if appropriate) for nominal variables, while one-way ANOVA was used for continuous variables. Cumulative survival curves for BMI classes were constructed using the Kaplan–Meier method. The log-rank test was used to compare cumulative survival curves between groups. Univariable and multivariable Cox regression models were used to examine the effect of BMI on all-cause mortality. Covariates were forced into the model, thereby reducing the risk of overfitting [26]. In multivariable analyses, we adjusted for socio-demographic and clinical characteristics (i.e., gender, age, type of stent, multi-vessel disease, indication for PCI, cardiac history, CAD risk factors, and prescribed cardiac medications). Covariates were selected a priori based on the literature [10,27–30]. Health status was added to the final model to examine the role of health status in explaining the obesity paradox. Hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs) are reported for Cox regression analyses. All results were based on two-tailed tests and a $p$-value$<0.05$ was used to indicate statistical significance. All statistical analyses were performed using SPSS for Windows 17.0 (SPSS Inc., Chicago, Illinois, USA).

## 4. Results

### 4.1. Patient characteristics

Of 1675 eligible patients treated with PCI in the study period, 54 patients died within 6 months. Of the remaining 1621 patients asked to participate in the study, 602 did not return the questionnaire at baseline (62.9% response rate). Final analyses were based on data from 1019 patients (72.5% men; mean age $62.0\pm11.2$ years, range [27–90] years). No systematic differences between participants and non participants were found on baseline characteristics, except for non participants more often having diabetes mellitus compared to the participants (21.0% vs. 14.8%, $p<.05$).

In the current sample, the prevalence of normal weight was 34.7% (354/1019), overweight was seen in 45.9% (468/1019) of patients, whereas 19.3% (197/1019) was obese. At follow-up, 163 deaths (16.0%) from any cause were recorded. Patient baseline characteristics stratified by the 3 BMI categories are presented in Table 1. Overweight and obese patients were more likely to be younger, compared to the reference BMI group. Furthermore, obese patients were more likely to be female, smoke, have diabetes mellitus, and be prescribed diuretics.

### 4.2. BMI and all-cause mortality

The incidence of all-cause mortality at follow-up was 7.1% (72/1019) in the normal weight group versus 6.3% (64/1019) in the overweight group and 3.0% (31/1019) in the obesity group. Cumulative hazard functions differed significantly for the obese and overweight groups when compared to the normal weight group (log-rank $X^2=6.59$, $p<0.05$). In univariable Cox regression analysis, overweight was significantly associated with a cumulative decreased risk for all-cause mortality (HR = 0.71, 95%CI [0.51–0.97], $p=0.030$) whereas obesity was not (HR = 0.96, 95%CI [0.64–1.42], $p=0.82$) (Fig. 1). After adjusting for socio-demographic and clinical characteristics, overweight remained associated with a lower risk for all-cause mortality (HR = 0.60, 95%CI [0.42–0.86], $p=0.005$), whereas no association was found between obesity and mortality (HR = 0.87, 95%CI [0.55–1.37], $p=0.55$) (Table 2).

### 4.3. BMI, all-cause mortality and health status

In a final model, each of the 8 health status subdomains was added to the separate multivariable Cox regression analyses. After adjusting for socio-demographic, clinical characteristics, and the health status sub domains, the association between overweight and mortality remained unchanged (Table 2).