

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The Influence Of Optimal Medical Treatment On The 'Obesity Paradox'; Body Mass Index and Long-Term Mortality in Patients Treated With Percutaneous Coronary Intervention; A Prospective Cohort Study
<b>AUTHORS</b>	Lisanne Schenkeveld, Michael Magro, Rohit M. Oemrawsingh, Mattie J. Lenzen, Peter P. T. de Jaegere, Robert J. van Geuns, Patrick W. Serruys and Ron T. van Domburg

### VERSION 1 - REVIEW

<b>REVIEWER</b>	David J. Maron, MD Professor of Medicine and Emergency Medicine Vanderbilt University School of Medicine United States
<b>REVIEW RETURNED</b>	20/11/2011

<b>RESULTS &amp; CONCLUSIONS</b>	The last sentence of the manuscript is confusing: "However a more optimal medical treatment in the obese group does not explain the improved outcome in these patients." This appears to contradict the message of the manuscript that OMT in patients with higher BMI may explain the obesity paradox. I don't understand why the authors conclude with this paradoxical statement.
<b>REPORTING &amp; ETHICS</b>	I cannot find mention of any ethics review, although data are presented in aggregate and no personal health information is disclosed.
<b>GENERAL COMMENTS</b>	<p>Page 2, line 6. Correct grammar: Does the obesity paradox persists in the long term</p> <p>Page 2, line 20. Strengths and limitations could be improved. Strengths: 1) Longer period of observation than previous studies; 2) Introduction of a novel explanation for the obesity paradox. Limitations: 1) Cannot prove mechanism with an observational study; 2) Important details about OMT are lacking, such as duration of therapy, medication adherence, and attainment of risk factor control; 3) BMI is based on self-report</p> <p>Page 2, line 21. Correct grammar: An limitation is that no differentiation was made between peripheral adiposity and central compartment adiposity.</p> <p>Page 3, line 29/31. "OMT was more common in obese patients as compared with normal weight patients (76% vs 85%; p&lt;0.001)." The percentages should be reversed if they are the respective numbers.</p> <p>Page 6, line 48. How often were questionnaires sent to living patients? Once? Annually?</p> <p>Page 15, line 32. You state that obese have more multivessel</p>

	<p>disease. Table 1 indicates no difference between BMI groups in % of patients with MVD. Please clarify.</p> <p>Page 16, line 50. The last sentence of the manuscript you state "However a more optimal medical treatment in the obese group does not explain the improved outcome in these patients." Isn't the entire message of the manuscript that OMT in patients with higher BMI may explain the obesity paradox? I don't understand why you conclude with this paradoxical statement.</p> <p>Limitations: the following should be addressed:</p> <ul style="list-style-type: none"> <li>- we do not know how long OMT has been prescribed</li> <li>- we do not know about medication adherence</li> <li>- we do not know about risk factor control during the period of follow-up</li> <li>- height and weight are self-reported (if this introduces bias, however, it will tend to underestimate, not overestimate, the strength of the association between obesity and prognosis because obese individuals tend to under-report their weight)</li> </ul>
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<b>REVIEWER</b>	<p>Professor Göran Nilsson Centre of Clinical Research Central Hospital Västerås, Uppsala University.</p> <p>No competing interest.</p>
<b>REVIEW RETURNED</b>	09/12/2011

<b>GENERAL COMMENTS</b>	<p>The Influence of Optimal Medical Treatment on The 'Obesity Paradox' ; Body Mass Index and Long- Term Mortality in Patients Treated With Percutaneous Coronary Intervention; A Prospective Cohort Study.</p> <p>This is a nice piece of work extending our knowledge of obesity in two important respects: Long-term follow-up: Figure 1 is illustrative. The gap between the survival curves widens even after two years. It would be of some interest to perform a Cox regression analysis after exclusion of the first two years of follow-up. Are the risk factors of short-term mortality and long-term mortality identical? The importance of differences in drug treatment as an explanation of the obesity paradox: Which drug is most important? Would it be meaningful to adjust for each drug separately in the Cox regression analyses?</p> <p>Page 5. I prefer expressing cholesterol levels both in mg/dl and mmol/L. It facilitates understanding among different groups of readers.</p> <p>Page 6. Line 5. The definition of normal weight is wrongly written as "18.5 to &lt;2524.9 kg/m<sup>2</sup>"</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer Comments:  
Reviewer: 1

## Comments to the Author

R: The last sentence of the manuscript is confusing: "However a more optimal medical treatment in the obese group does not explain the improved outcome in these patients." This appears to contradict the message of the manuscript that OMT in patients with higher BMI may explain the obesity paradox. I don't understand why the authors conclude with this paradoxical statement.

A: The reviewer is correct. This was a typing error. We changed the sentence into:  
However a more optimal medical treatment in the obese group may explain the improved outcome in these patients.

R: I cannot find mention of any ethics review, although data are presented in aggregate and no personal health information is disclosed.

A: We added the following sentence to the section 'Study population':  
The study was performed in line with ethical guidelines in accordance with the Declaration of Helsinki.

R: Page 2, line 6. Correct grammar: Does the obesity paradox persists in the long term

A: Thank you for pointing this out. We corrected the grammar.

R: Page 2, line 20. Strengths and limitations could be improved. Strengths: 1) Longer period of observation than previous studies; 2) Introduction of a novel explanation for the obesity paradox. Limitations: 1) Cannot prove mechanism with an observational study; 2) Important details about OMT are lacking, such as duration of therapy, medication adherence, and attainment of risk factor control; 3) BMI is based on self-report.

A: We agree with the reviewer. We changed this section into:  
Strengths of this study are that we examine the long term effects of BMI on outcome and we try to explore the mechanisms of the obesity paradox. Limitations of the study are that we cannot prove the mechanism with an observational study and that details about OMT, such as duration of therapy and medication adherence, are lacking.

R: Page 2, line 21. Correct grammar: An limitation is that no differentiation was made between peripheral adiposity and central compartment adiposity.

A: Thank you for pointing this out. The sentence was removed and replaced by the sentences from the previous comment.

R: Page 3, line 29/31. "OMT was more common in obese patients as compared with normal weight patients (76% vs 85%;  $p < 0.001$ )." The percentages should be reversed if they are the respective numbers.

A: The reviewer is correct. This is a typing error. We reversed the numbers.

R: Page 6, line 48. How often were questionnaires sent to living patients? Once? Annually?

A: The questionnaires were sent annually. We adjusted the sentence as follows:  
Questionnaires with information about anginal status, repeated hospital admissions, revascularization procedures and medication use were sent to all living patients on a yearly basis.

R: Page 15, line 32. You state that obese have more multivessel disease. Table 1 indicates no difference between BMI groups in % of patients with MVD. Please clarify.

A: The reviewer is correct. This is a typing error. We removed this sentence.

R: Page 16, line 50. The last sentence of the manuscript you state "However a more optimal medical treatment in the obese group does not explain the improved outcome in these patients." Isn't the entire message of the manuscript that OMT in patients with higher BMI may explain the obesity

paradox? I don't understand why you conclude with this paradoxical statement.

A: The reviewer is correct. This was a typing error. We changed the sentence into:

However a more optimal medical treatment in the obese group may explain the improved outcome in these patients.

R: Limitations: the following should be addressed:

- we do not know how long OMT has been prescribed
- we do not know about medication adherence
- we do not know about risk factor control during the period of follow-up
- height and weight are self-reported (if this introduces bias, however, it will tend to underestimate, not overestimate, the strength of the association between obesity and prognosis because obese individuals tend to under-report their weight)

A: We agree with the reviewer and added the following sentences to the discussion section:

Clinical measurement, rather than self reported height and weight would have provided a more accurate BMI data, eliminating any possible bias. OMT was defined according to patient medication at first time of contact but no information of duration or compliance of such treatment was available.

Objective parameters of lifestyle modifications and risk factor control would shed light on the importance of such a intervention on clinical outcome.

#### Reviewer 2

R: It would be of some interest to perform a Cox regression analysis after exclusion of the first two years of follow-up. Are the risk factors of short-term mortality and long-term mortality identical?

A: We thank the reviewer for this suggestion and performed a landmark analysis.

We added the following sentences to the statistical analysis section:

Landmark cox regression analysis at 2 years follow-up was performed to assess for changes in predictors of the endpoint mortality and to determine the effect of OMT on late outcome.

We added the following sentences to the results section:

In a landmark analysis at 2 years, multivariate predictors of late outcome included gender, BMI, age, hypercholesterolaemia, diabetes mellitus, family history of coronary artery disease, previous CABG and LVEF.

The introduction of OMT in the 2 year landmark cox-regression model also altered the significance of BMI from :overweight vs. normal HR 0.806 (0.678-0.960)  $p=0.015$ ; and obese vs. normal HR 0.840 (0.661-1.067)  $p=0.152$ . in the model without OMT to : overweight vs. normal HR 0.911 (0.722-1.149)  $p=0.429$  and obese vs. normal HR 1.122 (0.819-1.537 )  $p=0.472$  in the model with OMT.

R: The importance of differences in drug treatment as an explanation of the obesity paradox: Which drug is most important? Would it be meaningful to adjust for each drug separately in the Cox regression analyses?

A: The aim of our study was to assess the effect of a combination of drugs known to effect outcome in patients with coronary artery disease. The effect of individual drug on outcome and interaction with BMI status would be interesting but we feel it is not the purpose of the present study. However we add in the results section a multivariate analysis with the separate medication as opposed to the combination (OMT) as follows:

The individual medications, were analysed in a separate cox-regression model and statin use showed the strongest independent protective effect on long term mortality. Statins HR 0.60 (0.46-0.78)  $p<0.0001$ . All the other 3 medications also showed independent protective effect as follows: Aspirin HR 0.75 (0.60-0.95)  $p=0.014$ , B-blocker HR 0.83 (0.66-1.04)  $p=0.109$  and ACE inhibitors HR 0.84 (0.69-1.03)  $p=0.093$ .

R: Page 5. I prefer expressing cholesterol levels both in mg/dl and mmol/L. It facilitates understanding among different groups of readers.

A: We thank the reviewer for this suggestion. We adjusted the sentence as follows:  
Dyslipidaemia was defined as total cholesterol levels  $\geq 240$  mg/dl (6.21 mmol/L) or if the patient was on lipid-lowering medication.

R: Page 6. Line 5. The definition of normal weight is wrongly written as "18.5 to <2524.9 kg/m<sup>2</sup>"

A: The reviewer is correct. This is a typing error. We changed the sentence as follows:

Categorization of BMI was adopted from the World Health Organization and the National Institutes of Health(19) and defined as underweight (BMI <18.5 kg/m<sup>2</sup>), normal weight (18.5 to 24.9 kg/m<sup>2</sup>), overweight (25 to 29.9 kg/m<sup>2</sup>), and obese ( $\geq 30$  kg/m<sup>2</sup>).