Author’s response to reviews

Title: Determining the joint effect of obesity and diabetes on functional disability at 3-months and on all-cause mortality at 1-year following an ischemic stroke

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Point-by-Point Response

Manuscript: Determining the joint effect of obesity and diabetes on functional disability at 3-months and on all-cause mortality at 1-year following an ischemic stroke.

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We thank the reviewers for their thoughtful and helpful review of BMC Endocrine Disorders Manuscript Number BEND-D-18-00041. The reviewers made several insightful comments and suggestions. Our responses to each are listed below.

Comments from Reviewer #1:

Issue #1: Abstract. Please clarify better the purpose of this study.

Response: We have modified the text describing the purpose of the study to include the following statement (Abstract, lines 28-31, page 2):
The purpose of the current study was to explore whether the effect of obesity on post-ischemic stroke outcomes differed by diabetes status in a cohort of acute ischemic stroke subjects with at least a moderate stroke severity.

Issue #2: Line 43-49. Explain better what Associations recommend.

Response: We have modified the text describing what the associations recommend to include the following statements (Abstract, lines 47-50, page 3):

Additionally, there was not sufficient evidence to determine that either factor was independently associated with all-cause mortality. Future studies could differentiate between metabolically healthy and metabolically unhealthy patients within BMI categories to determine if the effect of obesity on post-stroke outcomes differs by diabetes status.

Issue #3: Line 53: insert T2DM after type 2 diabetes. Please check in the text the position of this acronym.

Response: In general, the majority of published trend data related to diabetes in addition to the literature for the effect of diabetes on post-stroke outcomes do not differentiate between type 1 and type 2 diabetes. However, because 95% of all diagnosed cases are type 2 diabetes, it may be assumed that reported trends are primarily indicative of type 2 diabetes. Due to the inconsistency of the term used in the literature, we decided to use the term ‘diabetes.’

Issue #4: Aim: please explain better the aim of this post-hoc analysis.

Response: We have modified the text describing the purpose of the study to include the following statement (Background, lines 88-90, page 5):

The primary objective of this post-hoc analysis was to explore whether the effect of obesity on functional disability and all-cause mortality following an ischemic stroke differed by diabetes status.
Issue #5: Methods: even if this procedure has been specified in IMS III please insert more data about analysis.

Response: This is an interesting point. Because the objective of the current study differed from the objective of the IMS III clinical trial, additional information in terms of the primary analysis was not included in this paper. Instead, we referenced the objective, reason for the trial being stopped, and the primary papers that have been previously published [Materials and Methods, Study population, lines 93-107, pages 5-6]

Issue #6: Baseline data: have you data about duration of disease (T2DM)? It need to be evaluated with your other results and determine its implications on your data.

Response: This is a great point. Unfortunately, the IMS III data do not include information regarding the duration of diabetes. To note this limitation, we have included the following text (Discussion, Limitations and Strengths, lines 264-275, page 15):

Although these measures are based on high-quality data, the degree of obesity or diabetes could not be determined at baseline. Thus, the potential for measurement bias cannot be excluded. Future studies could capture multiple measures of obesity, specifically BMI, waist circumference, and/or waist-to-hip ratio, rather than a summary indicator for obesity and/or utilize the World Health Organization’s public health action points[57] to further define subject’s degree of obesity. These alternative measures would allow for greater interpretability. Additionally, the exposures of interest are only snapshots of subjects’ history of obesity and/or diabetes. As a result, it was not possible to determine the cumulative effect, or allostatic load, of either exposure of interest. Future studies could collect information on subjects’ weight histories in addition to the duration of diabetes to accurately determine whether the effect of obesity on post-ischemic stroke outcomes differs by diabetes status.

Comments from Reviewer #2:
Issue #1: In my opinion, the study has two main limitations that should be more highlighted in the text because they could reduce the generalizability of the conclusions:

1) The study chosen to perform the post hoc analysis (IMS III clinical trial) included only patients with NIHSS score > 8. This kind of selection could result in a selection bias, as the population could not be representative of real life post-stroke patients.

Response: This is an excellent point. We have added text to the limitations section regarding the potential for selection bias with the following text (Discussion, Limitations and Strengths, lines 254-257, page 15):

Thus, the potential for selection bias cannot be excluded. Future research could be performed to determine if the results demonstrated among a cohort of acute ischemic stroke subjects with at least a moderate stroke severity would be similar to the results among a cohort of acute ischemic stroke subjects.

Issue #2: The inclusion criteria for the condition “Obesity” was based exclusively on a retrospective analysis of a “yes or no” questionnaire. This kind of selection run the risk of being poor objective and to create dishomogeneity in the model, as it could include patients only mildly overweight. A more objective and clear selection criterion (BMI) would have lessened this kind of problem.

Response: This is an excellent point regarding the limitations of the data specifically pertaining to the exposures of interest. The exposures of interest (i.e., obesity and diabetes) were obtained at the time of randomization. It is also true that we were not able to determine the degree of obesity, as measured using BMI, for example. As a result, we have modified text to the limitations section regarding how the exposures of interest were captured following text (Discussion, Limitations and Strengths, lines 264-275, page 15):
Although these measures are based on high-quality data, the degree of obesity or diabetes could not be determined at baseline. Thus, the potential for measurement bias cannot be excluded. Future studies could capture multiple measures of obesity, specifically BMI, waist circumference, and/or waist-to-hip ratio, rather than a summary indicator for obesity and/or utilize the World Health Organization’s public health action points[57] to further define subject’s degree of obesity. These alternative measures would allow for greater interpretability. Additionally, the exposures of interest are only snapshots of subjects’ history of obesity and/or diabetes. As a result, it was not possible to determine the cumulative effect, or allostatic load, of either exposure of interest. Future studies could collect information on subjects’ weight histories in addition to the duration of diabetes to accurately determine whether the effect of obesity on post-ischemic stroke outcomes differs by diabetes status.