PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf)** and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluating the associations between metabolic health, obesity and depressive symptoms: A prospective analysis of data from The English Longitudinal Study of Ageing (ELSA) with a two-year follow-up
AUTHORS	Slater, Natasha; Rowley, Charlotte; Venables, Rebecca; White, Simon; Frisher, Martin

VERSION 1 – REVIEW

REVIEWER	Gerardo Zavala Vrije Universiteit Amsterdam, Netherlands
REVIEW RETURNED	31-Jul-2018

GENERAL COMMENTS	The paper properly address the relationship between depressive symptoms with metabolic health and obesity. The manuscript is well written and it presents the results of large longitudinal cohort. Introduction This section needs to be revised: The concepts are not properly introduced and the research gaps are unclear. What do you mean by metabolic syndrome, who was it defined in the studies the authors are citing? Lines 25-26 the authors state that metabolic syndrome is attributed to diabetes, please revise In the second paragraph the authors mention some studies evaluating the relationship between components of metabolic syndrome and depression but did not state the research gaps. In the third paragraph, the authors should cite the last published systematic reviews on this subject to clearly show the research gaps on this area. Methods The methods are well written and consistent Results The results are clearly presented. In the tables I would not use : Odds ratios for the association Discussion In the discussion section the authors pay more attention to the co-variates (age, gender, etc) that had been explained and reviewed in other papers. I would recommend to focus more in the main research question (i.e. the relationship between depression and metabolic health and obesity) In page 8 line 46 the authors compare their findings with those of Hamer, however the results of this findings are not presented. My suggestion is to compare the magnitude so the readers have a better idea of what is being discussed.

REVIEWER	Paola Zaninotto

	UCL, UK
REVIEW RETURNED	07-Aug-2018

| **GENERAL COMMENTS** | This is an interesting paper exploring the relationship between metabolic health, obesity and depressive symptoms in a nationally representative sample of older people in England. I have several suggestions to improve the paper.

Introduction
This could be improved. In the second paragraph lines 28-37, the authors discuss previous studies on metabolic health and depression, and conclude the paragraph stating that results on obesity and depression are inconclusive. I think here they should discuss better the rationale for a relationship between metabolic health and depression, as well as gender differences. Then move on to obesity.

In terms of the aim, it seems to me that it would be better to explore metabolic health, obesity and a combination of both and have gender differences in the aim too.
So the exposure would be one variable
1 No metabolic health no obesity
2 Only metabolic health
3 Only obesity
4 Both metabolic health and obesity
And stratify by gender

Methods
Nurse visit: this should come after face-to-face interview section. Please note that demographic information is collected in the face-to-face interview of ELSA.

Which variable that measures wealth did the author use? Is it non-pension household wealth? Please specify and give the definition.

Why only these variables were chosen as confounders? Is there a rationale?
I don't really agree with the missing data approach adopted for the analyses. The authors should report the number of missing data and present the analyses on the complete case sample, and make comparisons between those who have complete information and those who don't, in terms of baseline characteristics and decide if multiple imputation (if they are confident enough to carry it out) might be a better approach.

I also wonder if starting with a sample of people free from depressive symptoms at baseline would be most appropriate rather than adjusting for baseline depression. So the author could have the exposure on people free from depression at baseline and the outcome which is new cases of depression. Given that now there is a new wave of ELSA, the authors could consider using a longer follow-up.

Results
Results reported in tables 2 and 3 are from the same model, only one exposure at the time is presented, which seems a bit odd.
The tables 2 and 3 do not have the number of observations.

I suggest restructuring the tables as follows: |
|---|---|

	Model 0
	unadjusted Model 1
	Adjusted for age Model 2
	Adjusted for age and depression Model 3
	Adjusted for age, wealth Model 4
	Adjusted for age, depression wealth
	Men
	No metabolic health no obesity
	Only metabolic health
	Only obesity
	Both metabolic health and obesity Metabolic
	Percentage decrease in OR after adjustment
	Women
	No metabolic health no obesity
	Only metabolic health
	Only obesity
	Both metabolic health and obesity Metabolic
	Percentage decrease in OR after adjustment
	By reporting percentage decrease in OR after adjustment, the authors could discuss which of the predictors contributed to explain the association between the exposure and outcome.
	Table 4 does not fit well with the paper, I would drop it and report the results as suggested above and was never set as an aim in the introduction.
	Lines 52-54: the authors explain the finding of wealth by saying that individuals living in affluent areas… wealth does not measure area-poverty.
	Discussion
	The authors seem to go into great details about associations between confounders and depression, which was not really the aim of the paper.
	Line 40: that is not true, in ELSA there is a variable that states whether the respondents reports a doctor-diagnosis of depression, the author might want to consider repeating their analysis on this outcome to check for consistency (sensitivity analysis)
	Conclusions: the authors mention social factors as confounders, but they have not explored them.
	Strobe checklist
	Items not addressed in the study
	10: this has not been reported
	13: this should be improved and reported in supplementary materials, b and c not addressed

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

We would like to take this opportunity to thank you for reviewing our manuscript. Our responses to your specific comments are detailed below.

The paper properly address the relationship between depressive symptoms with metabolic health and obesity. The manuscript is well written and it presents the results of large longitudinal cohort.

Introduction

This section needs to be revised: The concepts are not properly introduced, and the research gaps are unclear.

The introduction has been rewritten to clearly identify the following gaps in the existing literature:

- There is inconsistent evidence regarding the association between obesity and depression
- There is also inconsistent evidence regarding the role of metabolic health in the aforementioned association.
- Data on this subject is predominantly derived from cross-sectional studies, rather than prospective studies
- There is a need to conduct this research as obesity and depression are significant public health concerns in the UK

What do you mean by metabolic syndrome, who was it defined in the studies the authors are citing? Various definitions of metabolic syndrome exist, and these definitions have been discussed in previous papers. This paper examines the association between metabolic health, obesity and depression from a public health perspective; therefore, the information presented about metabolic syndrome has been revised to reflect this decision.

Lines 25-26 the authors state that metabolic syndrome is attributed to diabetes, please revise
This has been removed from the new introduction.

In the second paragraph the authors mention some studies evaluating the relationship between components of metabolic syndrome and depression but did not state the research gaps.

Research gaps have been now been clarified, please refer to our comments above.

In the third paragraph, the authors should cite the last published systematic reviews on this subject to clearly show the research gaps on this area.

Details about the latest systematic reviews on this subject have now been included in the introduction, and the review findings have been discussed.

Methods
The methods are well written and consistent

Results
The results are clearly presented. In the tables I would not use: Odds ratios for the association

The titles of Tables 2-4 have been amended. The new titles are presented below:

Table 2: The association between poor metabolic health and the risk of depressive symptoms at two-year follow-up (Wave 7) (n= 6,084)

Table 3: The association between obesity and the risk of depressive symptoms at two-year follow-up (Wave 7) (n=6,084)

Table 4: The association between the independent variables and the risk of depressive symptoms at two-year follow-up (Wave 7) (n=6,084)

Discussion

In the discussion section the authors pay more attention to the co-variates (age, gender, etc) that had been explained and reviewed in other papers. I would recommend focusing more in the main research question (i.e. the relationship between depression and metabolic health and obesity)

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We have added an additional aim our manuscript. Our revised aims are below:

"The primary aim of this study is to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up, using the latest data from the English Longitudinal Study of Ageing. In addition, we will determine whether the covariates used in our analyses are independently associated with depressive symptoms at follow-up."

To meet our revised aims, we have decided to retain the information about the covariate associations in the discussion section. However, we have also broadened our discussion to discuss some of the underlying biological mechanisms in the association between metabolic health, obesity and depression.

In page 8 line 46 the authors compare their findings with those of Hamer, however the results of this findings are not presented. My suggestion is to compare the magnitude, so the readers have a better idea of what is being discussed.

Thank you for your feedback, we have added the key findings from Hamer et al into our discussion section. Please see tracked changes in the manuscript.

Reviewer 2
We would like to take this opportunity to thank you for reviewing our manuscript. Our responses to your specific comments are detailed below.

This is an interesting paper exploring the relationship between metabolic health, obesity and depressive symptoms in a nationally representative sample of older people in England.

I have several suggestions to improve the paper.
Introduction

This could be improved. In the second paragraph lines 28-37, the authors discuss previous studies on metabolic health and depression, and conclude the paragraph stating that results on obesity and depression are inconclusive. I think here they should discuss better the rationale for a relationship between metabolic health and depression, as well as gender differences. Then move on to obesity.

The introduction has been rewritten to provide more information about the inconsistent evidence regarding the association between metabolic health, obesity and depression. Inconsistent findings in relation to gender have also been discussed. Please refer to the manuscript to see our new introduction.

In terms of the aim, it seems to me that it would be better to explore metabolic health, obesity and a combination of both and have gender differences in the aim too.
So the exposure would be one variable
1 No metabolic health no obesity
2 Only metabolic health
3 Only obesity
4 Both metabolic health and obesity
And stratify by gender

During the initial stages of our research, we created the four models you have suggested but we did not stratify the data by gender. Instead, we decided to keep gender as a confounder. The independent association between metabolic health and depression results are presented in Table 2 and the independent association between obesity and depression results are presented in Table 3. We decided to present our findings this way, rather than using the models, to clearly show the separate associations. This approach also enabled us to show our readers how we adjusted for confounders in a step-wise manner. Reviewer feedback regarding the presentation of our results has

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been considered, and we have decided not to amend the presentation of our results. We feel that our existing results tables adds new perspective and clarity regarding the association.

Methods

Nurse visit: this should come after face-to-face interview section. Please note that demographic information is collected in the face-to-face interview of ELSA.

The nurse interview section has been moved as suggested, and the face-to-face interview section has also been amended to reflect your comment about demographic information collection.

Which variable that measures wealth did the author use? Is it non-pension household wealth? Please specify and give the definition.
Non-pension household wealth was used in our analyses. The following information has been added to our manuscript

'Wealth quintiles refer to household wealth (financial assets, physical assets and housing wealth) but not pension wealth. Wealth was calculated less debts and included the value of owner-occupied housing (less mortgage); all assets held in bank accounts in England; the value of any business property or holiday home (less mortgage) and the value of physical assets such as antiques, artwork and jewellery.'

Why only these variables were chosen as confounders? Is there a rationale?

Age, gender, baseline depression, metabolic health and obesity have been identified as potential confounders in other studies examining this association. We also included wealth as a variable because our previous ELSA work has shown that wealth is a powerful predictor of health outcomes. This finding has been supported by several other ELSA studies too. Despite controlling for these variables, there is still the potential for residual confounding. This has been acknowledged as a limitation in our discussion section.

I don't really agree with the missing data approach adopted for the analyses. The authors should report the number of missing data and present the analyses on the complete case sample and make comparisons between those who have complete information and those who don't, in terms of baseline characteristics and decide if multiple imputation (if they are confident enough to carry it out) might be a better approach.

We acknowledge that there are varying opinions about the most appropriate methods for handling missing data. Multiple imputation was considered; however, we decided to present missing data as a separate category for two reasons. Firstly, complete data were available for the 98% (n= 6665/6804) of the study participants. Of the remaining 139 participants, 130 were only missing wealth data and 9 were only missing BMI data. Secondly, this approach meant that no cases were excluded from the analyses.

I also wonder if starting with a sample of people free from depressive symptoms at baseline would be most appropriate rather than adjusting for baseline depression. So the author could have the exposure on people free from depression at baseline and the outcome which is new cases of depression. Given that now there is a new wave of ELSA, the authors could consider using a longer follow-up.

We re-ran our analyses based upon your suggestion and only included participants with no baseline depression. Results for the unadjusted and adjusted metabolic health models are below. A negligible change in OR is observed when people with depressive symptoms at baseline are excluded, and

consequently our key findings do not change. The latest ELSA wave was not available when we conducted our analyses; however, we intend to use the new wave in future research.

	Metabolic health OR (includes participants with baseline depression) (Table 2)	Metabolic health OR (excludes participants with baseline depression)
No adjustment	1.24 (1.07-1.44, p<0.01)	1.20 (0.98-1.47, p=0.05)
Fully adjusted	1.17 (0.99-1.38, p=0.06)	1.14(0.98-1.40, p=0.21)

Results
Results reported in tables 2 and 3 are from the same model, only one exposure at the time is presented, which seems a bit odd.

I suggest restructuring the tables as follows:

Model 0
unadjusted   Model 1
Adjusted for age   Model 2
Adjusted for age and depression Model 3
Adjusted for age, wealth   Model 4
Adjusted for age, depression wealth
Men
No metabolic health no obesity
Only metabolic health
Only obesity
Both metabolic health and obesity Metabolic
Percentage decrease in OR after adjustment
Women
No metabolic health no obesity
Only metabolic health
Only obesity
Both metabolic health and obesity Metabolic
Percentage decrease in OR after adjustment

By reporting percentage decrease in OR after adjustment, the authors could discuss which of the predictors contributed to explain the association between the exposure and outcome.

Please refer to the comments above regarding the four models and presentation of results.

The tables 2 and 3 do not have the number of observations.
We have added the number of observations to both tables

Table 4 does not fit well with the paper, I would drop it and report the results as suggested above and was never set as an aim in the introduction.

We acknowledge that Table 4 did not meet the original aims of this paper; however, the aims has been revised and we feel that this table should remain within the paper. Details about our revised aims are presented in our comments below.

Lines 52-54: the authors explain the finding of wealth by saying that individuals living in affluent areas… wealth does not measure area-poverty.

This sentence has been changed to 'This suggests that individuals in the higher wealth quintiles are less likely to experience depressive symptoms at two-year follow-up, compared to individuals in the lower wealth quintiles.'

Discussion
The authors seem to go into great details about associations between confounders and depression, which was not really the aim of the paper.

Thank you for bringing this to our attention, we have added an additional aim our manuscript to reflect your feedback. Our revised aims are below:

"The primary aim of this study is to determine whether metabolic health or obesity are independently associated with depressive symptoms at two-year follow-up, using the latest data from the English Longitudinal Study of Ageing. In addition, we will determine whether the covariates used in our analyses are independently associated with depressive symptoms at follow-up."

Line 40: that is not true, in ELSA there is a variable that states whether the respondents reports a doctor-diagnosis of depression, the author might want to consider repeating their analysis on this outcome to check for consistency (sensitivity analysis)

The strengths and limitation paragraph has been revised and the inaccurate statement has been removed. Please see tracked changes in the manuscript.

Conclusions: the authors mention social factors as confounders, but they have not explored them.

The sentence about social factors has been changed to 'Previous research has predominantly identified medical factors as confounders; however, this study highlights the importance of considering wealth, in addition to medical factors, as confounders in future research'.

Strobe checklist10: this has not been reported - The minimum sample size required for our multivariate models has been calculated and this has been added to the manuscript.

Strobe checklist13: this should be improved and reported in supplementary materials, b and c not addressed

A flow chart illustrating participation has been added as supplementary material. This flow chart has been referred to in the main text.

VERSION 2 – REVIEW

REVIEWER	Paola Zaninotto
	UCL, UK
REVIEW RETURNED	29-Oct-2018

GENERAL COMMENTS	Thank you for addressing my comments.