

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)	SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up study
AUTHORS	Shi, Zumin; Atlantis, Evan; Taylor, Anne; Gill, Tiffany; Price, Kay; Appleton, Sarah L.; Wong, Ma-Li; Licinio, Julio

VERSION 1 - REVIEW

REVIEWER	Ellie Paige University of Cambridge, UK
REVIEW RETURNED	08-Feb-2017

GENERAL COMMENTS	<p>This paper outlines an original investigation of the association between antidepressant medication use and weight gain, and the interaction of this relationship with lifestyle factors. This paper addresses a question likely to be of clinical interest, particularly in relation to prescribing of SSRIs to people concerned about weight gain. Some points need further work/clarification:</p> <ol style="list-style-type: none">1. In Table 1, there are quite a few differences between men and women. Stratifying the analysis by sex (if numbers permit) might be useful.2. How was 5% weight change over five years calculated for those with <5 years of follow-up? Why not look at annual percentage weight change?3. Why was Poisson regression (used for modelling count data) used to analyse 5% weight change (pg. 8)?4. How were prescriptions across multiple classes of antidepressants handled?5. Some sub-group analyses outlined in the results (pg. 10) for people aged <50 and smokers are not described in the methods.6. The description of the variables used in the multivariable mixed regression analysis in the results (pg. 10) does not match the description in the methods (pg. 8).7. A limitation of the PBS dataset is that it provides information on dispensing, not actual use of an antidepressant. This should be mentioned in the discussion.8. Confounding by indication could be playing a role if doctors are more likely to prescribe SSRIs to people who are worried about weight gain. This could also explain why TCA use (which has been linked to weight gain in RCTs) was not associated with weight gain in this study. This should be discussed.9. The clinical importance of the level of absolute weight gain in context of the obesity epidemic is not clear. This needs to be more clearly demonstrated to justify the sentence (pg. 13) "As a matter of public health relevance, SSRI use ought to be clinically recognized as a risk factor for obesity."
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	10. Please provide page numbers against each point in the STROBE checklist.
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REVIEWER	Faruk Uguz Necmettin Erbakan University; Turkey
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	<p>Actually, this study has examined one of current interesting topics. According to previous studies, antidepressant treatments have some negative effects on body weights; however, prospective studies about this issue are very limited. Although, this study has longitudinal design, it is not a prospective observational study including patients taking antidepressants. In addition, as shown the limitations section, the study sample is very smaller than other register-based studies. Antidepressant prescriptions do not reflect clearly whether the patients regularly continue the antidepressants. Finally, the study does not exclude switches among the antidepressants. In conclusion, I think results of the presents study are based on important methodological limitations</p>
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REVIEWER	Deborah Gibson-Smith Vu medical center, Amsterdam, The Netherlands.
REVIEW RETURNED	20-Mar-2017

GENERAL COMMENTS	<p>SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up</p> <p>This paper attempts to address an interesting research question (the relationship between antidepressant use and weight gain) in a novel manner (by looking at the number of prescriptions issued. It is well written and clearly a lot of analysis has been carried out. However, much of these analysis lack detail, there are missing explanations for some variables. Additionally there are many inconsistencies in the paper between the use of categorical variable, between the tables and texts and the statistical analysis and results. Furthermore, some of the conclusions made are too extreme especially given that this is not a clinical trial and that the antidepressant use is not known, only how much is prescribed.</p> <p>Below are some specific points to address:-</p> <p>1: Title</p> <ul style="list-style-type: none"> • This title suggests that you examine SSRI use only <p>2: Abstract, Results, line 36 "High association was caused by SSRI use"</p> <ul style="list-style-type: none"> • The use of the word caused is usually reserved for RCT's <p>3: Abstract, Limitations: A major limitation of this study is that you did not actually measure antidepressant use but the number of prescriptions given. There is no guarantee that the prescription are taken or completed. This point applies to applies to the use of the term "antidepressant use" which is used throughout the paper. Ideally another term would be better as this is a little misleading. You should at least make it clear early on in the paper (maybe under methods 2.3) that actual use is unknown.</p> <p>3: Methods 2.2 outcome variable</p> <ul style="list-style-type: none"> • Not sure where in your analysis overweight and obesity are used-> remove.
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	<ul style="list-style-type: none"> • No description of how weight gain is calculated or annual weight gain. 4: Methods 2.3 Exposure variable <ul style="list-style-type: none"> • No general information by what a prescription for antidepressants is: i.e. how long a period would a prescription cover. Also are the number of pills known. Also what was done about prescriptions issued immediately before the study period which covered the study period (so in an extreme case a prescription maybe issued 1 day before the study period began) • No mention of the assumption that prescription=use (see point above). • What happens if persons are receiving prescription for more than one sort of antidepressant? (adding up the N's in table 2 it looks like this happens) 5: Methods 2.4.1 Baseline covariates <ul style="list-style-type: none"> • Inconsistencies between text and tables for smoking categories, sometime ex-smoker and current smoker combined (S1), sometimes ex-smoker omitted from analysis (table3) and text suggests 3 categories used. 6: Methods 2.4.2 Follow-up covariates <ul style="list-style-type: none"> • No explanation of how diet scores are made or how used to make interaction terms 7: Methods 2.5 Statistical analysis <ul style="list-style-type: none"> • Line 15: "between groups"-which groups? • Line 29 "interaction between antidepressant use" but table 3 states SSRI use. • Line 43 "adjusted for depression and smoking status". According to results it was also adjusted for age and income as well? 8. Results <ul style="list-style-type: none"> • Line 21: First sentence is about table S1 so belongs to paragraph above • Line 38: "and this association was related to SSRI use" this is conclusive! Report only that SSRI use was related to weight gain. • Page 10 line 41 "No interaction between antidepressant use and gender was found" What does this relate to? Not mentioned in any tables? • Page 10 line 46-56 Results for this section not shown : mention that results are not shown. • No mention of the prudent diet 9. Discussion <ul style="list-style-type: none"> • Line 26: reference number 20 lifestyle factors were also only treated as confounding factors. • Line 49: "In the present study we also found a significant difference in energy intake between high antidepressant users and non-users." Using energy intake from a food frequency questionnaire is unreliable as it is often greatly over or under estimated. Additionally energy intake is dependent upon body size, physical activity and metabolic efficiency making it difficult to interpret as a stand alone variable. • Line 37: Do you know why TCA is positively associated with age? • Might be interesting to add to your discussion why those with unhealthier lifestyle gain more weight when using antidepressant. • Page 13: Limitations:-need to include that fact that the number of prescriptions is NOT the same as AD use • Page 13: Limitations:-Energy intake is not a reliable measurement • Page 13: Limitations:-The number of SSRI users far exceeds the number of TCA and Other antidepressant users. Could be that findings are due to lack of power. • Line 30 "SSRI use ought to be clinically recognized as a risk factor for obesity" I feel as this is not a clinical trial and only uses a proxy
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	<p>for SSRI use, such hard conclusions cannot be given</p> <p>10. Table 1</p> <ul style="list-style-type: none"> • Why stratify for gender when gender does not play a role in any of your analysis? Better to use table S1 as table 1. • Numbers do not always add up i.e Total TCA, SSRI and other antidepressant (0.1,0.3,0.2) does not add up to 0.7 Any antidepressant <p>11. Table 2</p> <ul style="list-style-type: none"> • To make the table easier to read I suggest that you indicate subheadings (Any antidepressants, SSRI's, TCA and other antidepressants) by either making them in bold text, indenting them or by underlining. <p>12. Table 3</p> <ul style="list-style-type: none"> • Title suggests these are interaction terms. It is not clear that these are stratified results. This point should also be made clear in statistical analysis (that you stratified analysis for the 4 lifestyle variables as well as explaining the categories and how they are made) • Western and Prudent What is low and high intake? Need to describe here or in text. • Where did the ex-smokers go to? <p>13 Supplementary table 1</p> <ul style="list-style-type: none"> • Check alignment of row headings and numbers • Why don't all the categories add up to the total n's for high users, low users and non-users? (e.g. Depression baseline High user= none=71, mild=26, moderate-severe=12 71+26+12=109 but total number of high users =111.) What have you done with missing variables? <p>14: supplementary table 2</p> <ul style="list-style-type: none"> • Title incorrect because table includes lifestyle variables • Why are the lifestyle variable included here as well as S1? Also the %'s differ from those given in S1. • Why report the macronutrients when they are not used in this analysis? <p>15: Table s3</p> <p>Title doesn't indicate how this differs from table 2</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Ellie Paige

University of Cambridge, UK

Please state any competing interests or state 'None declared': None declared.

We thank the reviewers for their comments, our responses are provided below.

1. In Table 1, there are quite a few differences between men and women. Stratifying the analysis by sex (if numbers permit) might be useful.

Response: As we found no significant interaction with gender and antidepressant use, stratification of the results is unnecessary. From a population perspective, we feel that this is more appropriate.

2. How was 5% weight change over five years calculated for those with <5 years of follow-up? Why not look at annual percentage weight change?

Response: The calculation of 5-year weight gain was based on annual weight gain computed as change in weight between baseline and follow-up divided by years. The conclusion will be the same if we use annual percentage weight change.

3. Why was Poisson regression (used for modelling count data) used to analyse 5% weight change (pg. 8)?

Response: Because the prevalence of weight gain > 5% was above 10%, odds ratio from logistic regression will overestimate the association between antidepressant use and weight gain.

4. How were prescriptions across multiple classes of antidepressants handled?

Response: The coding of antidepressant prescription was based on ATC code. In the analysis of individual class of antidepressant use, we did not mutually adjust for other classes of antidepressant.

5. Some sub-group analyses outlined in the results (pg. 10) for people aged <50 and smokers are not described in the methods.

Response: Thank you for this comment. We revised the manuscript to make it clear that age was treated as a continuous or categorical (below/above 50 years) variable.

6. The description of the variables used in the multivariable mixed regression analysis in the results (pg. 10) does not match the description in the methods (pg. 8).

Response: Changes have been made in the method section to better describe the variables in our statistical analyses.

7. A limitation of the PBS dataset is that it provides information on dispensing, not actual use of an antidepressant. This should be mentioned in the discussion.

Response: We have now acknowledged this limitation in our discussion section; on page 14 " PBS dataset only provides information on dispensing but the actual use of antidepressant".

8. Confounding by indication could be playing a role if doctors are more likely to prescribe SSRIs to people who are worried about weight gain. This could also explain why TCA use (which has been linked to weight gain in RCTs) was not associated with weight gain in this study. This should be discussed.

Response: We agree and has included this point in the discussion; please see page 13. "Another explanation could be that doctors may be more likely to prescribe SSRIs to people who are worried about weight gain as TCA use has been linked to weight gain in clinical trials

9. The clinical importance of the level of absolute weight gain in context of the obesity epidemic is not clear. This needs to be more clearly demonstrated to justify the sentence (pg. 13) "As a matter of public health relevance, SSRI use ought to be clinically recognized as a risk factor for obesity."

Response: We believe that an extra annual weight gain of 0.5 kg due to high use of SSRIs is of great public health significance. We have revised the discussion on this topic. See page 14 ". As a matter of public health relevance, SSRI use should be accompanied by pro-active efforts to avoid weight gain."

10. Please provide page numbers against each point in the STROBE checklist.

Response: We have added page numbers.

Reviewer: 2

Faruk Uguz

Necmettin Erbakan University; Turkey

Please state any competing interests or state 'None declared': None declared

Although, this study has longitudinal design, it is not a prospective observational study including patients taking antidepressants.

In addition, as shown the limitations section, the study sample is very smaller than other register-based studies. Antidepressant prescriptions do not reflect clearly whether the patients regularly continue the antidepressants.

Finally, the study does not exclude switches among the antidepressants.

In conclusion, I think results of the presents study are based on important methodological limitations
Response: We have now acknowledged that there is only a record of antidepressant prescription but not the actual use as a limitation of the study (page 14). In addition to assess the association between individual type of antidepressant use and weight gain, we have also assessed the association between total antidepressant use and weight gain.

Reviewer: 3

Deborah Gibson-Smith

Vu medical center, Amsterdam, The Netherlands.

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below SSRI antidepressant use potentiates weight gain in the context of unhealthy lifestyles: Results from a four-year Australian follow-up This paper attempts to address an interesting research question (the relationship between antidepressant use and weight gain) in a novel manner (by looking at the number of prescriptions issued. It is well written and clearly a lot of analysis has been carried out.

However, much of these analysis lack detail, there are missing explanations for some variables.

Additionally there are many inconsistencies in the paper between the use of categorical variable, between the tables and texts and the statistical analysis and results. Furthermore, some of the conclusions made are too extreme especially given that this is not a clinical trial and that the antidepressant use is not known, only how much is prescribed.

-Response: We have revised the manuscript based on your comments point by point.

Below are some specific points to address:-

1: Title

- This title suggests that you examine SSRI use only

Response: Although we examined all antidepressant use, the main positive finding is for SSRI use.

2: Abstract, Results, line 36 "High association was caused by SSRI use"

- The use of the word caused is usually reserved for RCT's

Response: We have now replaced the term "caused" with "mainly due to"

3: Abstract, Limitations: A major limitation of this study is that you did not actually measure antidepressant use but the number of prescriptions given. There is no guarantee that the prescription are taken or completed. This point applies to applies to the use of the term "antidepressant use" which is used throughout the paper. Ideally another term would be better as this is a little misleading. You should at least make it clear early on in the paper (maybe under methods 2.3) that actual use is unknown.

Response: We have added in the material and methods, and in the result sections, respectively in pages 6 and 10 that information on medication use is based on prescription. We have also now acknowledged this as a limitation in the discussion. See page 14 " PBS dataset only provides information on dispensing but the actual use of antidepressant".

3: Methods 2.2 outcome variable

- Not sure where in your analysis overweight and obesity are used-> remove.
- No description of how weight gain is calculated or annual weight gain.

Response: The prevalence of overweight/obesity was provided in Table 1 as populations characteristic, however we have only used those classified as obese as our population of interest. We have provided the calculation. See page 6 “Annual weight gain was calculated by the difference of body weight (kg) between follow-up and baseline divided by the duration of follow-up (in years)”.

4: Methods 2.3 Exposure variable

- No general information by what a prescription for antidepressants is: i.e. how long a period would a prescription cover. Also are the number of pills known. Also what was done about prescriptions issued immediately before the study period which covered the study period (so in an extreme case a prescription maybe issued 1 day before the study period began)

- No mention of the assumption that prescription=use (see point above).

- What happens if persons are receiving prescription for more than one sort of antidepressant? (adding up the N's in table 2 it looks like this happens)

Response: We have clarified that our predictor variable is based on prescription information derived from data linkage (please see page14) rather than actual use of antidepressant. Information on the number of pills is not available.

Exposure of specific antidepressants was assessed independent of one or more antidepressant.

5: Methods 2.4.1 Baseline covariates

- Inconsistencies between text and tables for smoking categories, sometimes ex-smoker and current smoker combined (S1), sometimes ex-smoker omitted from analysis (table3) and text suggests 3 categories used.

Response: We have made it clear that in the analysis (tables) smoking was categorised as non-smoker, and current or ex-smoker.

6: Methods 2.4.2 Follow-up covariates

- No explanation of how diet scores are made or how used to make interaction terms

Response: We have added the following detailed explanation in the methods section. See page 8 “Scores of each dietary pattern were calculated as the sum of the products of factor loading coefficients and standardized daily intake of the food intake. Dietary pattern scores were dichotomised as low and high”.

7: Methods 2.5 Statistical analysis

- Line 15: “between groups”-which groups?

Response: Changes have been made to clarify groups refer to gender and categories of antidepressant use. Changes have been made in the text to clarify this.

- Line 29 “interaction between antidepressant use” but table 3 states SSRI use.

Response: We have corrected ‘antidepressant use’ to ‘SSRI use’ (see page8)

- Line 43 “adjusted for depression and smoking status”. According to results it was also adjusted for age and income as well?

Response: We have added age and income as covariates. See page 8.

8. Results

- Line 21:First sentence is about table S1 so belongs to paragraph above

Response: The text was revised.

- Line 38: “and this association was related to SSRI use” this is conclusive! Report only that SSRI use was related to weight gain.

Response: This has been revised in the text; please see page 10.

- Page 10 line 41 “No interaction between antidepressant use and gender was found” What does this

relate to? Not mentioned in any tables?

Response: We have further clarified: "data not shown". See page 11.

• Page 10 line 46-56 Results for this section not shown: mention that results are not shown.

Response: The text was changed accordingly.

• No mention of the prudent diet

Response: We commented that no significant interaction between SSRI use and prudent dietary pattern was found on page 11.

9. Discussion

• Line 26: reference number 20 lifestyle factors were also only treated as confounding factors.

Response: The text was revised to reflect this.

• Line 49: "In the present study we also found a significant difference in energy intake between high antidepressant users and non-users." Using energy intake from a food frequency questionnaire is unreliable as it is often greatly over or under estimated. Additionally energy intake is dependent upon body size, physical activity and metabolic efficiency making it difficult to interpret as a stand alone variable.

Response: We agree with the reviewer. Although over or under estimation may be a problem in the use of FFQ, the FFQ has been validated in an Australian population. The difference in energy intake between may help to interpret the association between antidepressant use and weight gain.

• Line 37: Do you know why TCA is positively associated with age?

Response: The SSRI fluoxetine entered medical use in 1986; TCAs were the gold standard for depression treatment before SSRIs became popular. It is likely that older patients started their treatment with TCA and those that were treated with and responded to TCAs for many years before SSRIs became available may have been reluctant to be switched to SSRIs.

• Might be interesting to add to your discussion why those with unhealthier lifestyle gain more weight when using antidepressant.

Response: We have added a discussion on the issue. See page 13 "Clustering of unhealthy behaviours and chronic diseases including depression may partly explain the interaction between unhealthy lifestyle and weight gain among those using antidepressant".

• Page 13: Limitations:-need to include that fact that the number of prescriptions is NOT the same as AD use

Response: We have acknowledged this as a limitation.

• Page 13: Limitations:-Energy intake is not a reliable measurement

Response: We have acknowledged this as a limitation.

• Page 13: Limitations:-The number of SSRI users far exceeds the number of TCA and Other antidepressant users. Could be that findings are due to lack of power.

Response: We have acknowledged this as a limitation.

• Line 30 "SSRI use ought to be clinically recognized as a risk factor for obesity" I feel as this is not a clinical trial and only uses a proxy for SSRI use, such hard conclusions cannot be given

Response: We have deleted this statement.

10. Table 1

• Why stratify for gender when gender does not play a role in any of your analysis? Better to use table

S1 as table 1.

Response: Table 1 gives an overall distribution of the sample while Table S1 only describes the sample by SSRI use. Thus, we find it more relevant to keep Table 1 as it is.

- Numbers do not always add up i.e Total TCA, SSRI and other antidepressant (0.1,0.3,0.2) does not add up to 0.7 Any antidepressant

Response: This is due to rounding, which can introduce rounding errors.

11. Table 2

- To make the table easier to read I suggest that you indicate subheadings (Any antidepressants, SSRI's, TCA and other antidepressants) by either making them in bold text, indenting them or by underlining.

Response: Changes have been made to address this issue.

12. Table 3

- Title suggests these are interaction terms. It is not clear that these are stratified results. This point should also be made clear in statistical analysis (that you stratified analysis for the 4 lifestyle variables as well as explaining the categories and how they are made)

Response: We have changed the title of the table to Subgroup analyses of the association between SSRI use and annual weight gain.

- Western and Prudent What is low and high intake? Need to describe here or in text.

Response: We have added a footnote that describes those terms.

- Where did the ex-smokers go to?

Response: Current and ex-smokers are categorised as one group.

13 Supplementary table 1

- Check alignment of row headings and numbers

Response: Row headings have been changed.

- Why don't all the categories add up to the total n's for high users, low users and non-users? (e.g. Depression baseline High user= none=71, mild=26, moderate-severe=12 71+26+12=109 but total number of high users =111.) What have you done with missing variables?

Response: There are missing values of depression at baseline. In the regression analyses, missing values were excluded. See age 8 "Participants with missing information of depression were excluded in the corresponding analyses".

14: supplementary table 2

- Title incorrect because table includes lifestyle variables

Response: Thank you for pointing this out; the title has been changed.

- Why are the lifestyle variable included here as well as S1? Also the %'s differ from those given in S1.

Response: Supplementary table 2 describes the sample characteristics of any antidepressant users. Table S1 described the characteristic of SSRI users.

- Why report the macronutrients when they are not used in this analysis?

Response: This helps to interpret the findings.

15: Table s3

Title doesn't indicate how this differs from table 2

Response: We have changed Table S3 title and stated that these results are from mixed linear models.

VERSION 2 – REVIEW

REVIEWER	Ellie Paige The Australian National University, Australia
REVIEW RETURNED	15-May-2017

GENERAL COMMENTS	Thank you for these revisions. I have no further comments to add.
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REVIEWER	Deborah Gibson-Smith VU medical center, Amsterdam, Netherlands
REVIEW RETURNED	25-May-2017

GENERAL COMMENTS	<p>The authors have addressed the majority of my comments, however the some points still need improvement. I have also found a few additional points and given that this paper is likely to be finally accepted by BMJ open, I think the paper could benefit some other changes to give it more structure. Finally, this paper could be of great clinical importance as it indicates the SSRI's mostly potentiate weight gain in the presence of unhealthy behaviours. As such I think that this point could be better highlighted. Given how useful these finding could be I think it is well worth the effort to spend time on further improvements. Details of changes are given below:-</p> <ol style="list-style-type: none"> 1. Abstract-Results (line 43): suggest the authors say association between SSRI use and weight gain was STRONGER among those with a high intake of Western diet, GREATER sedentary activity and WHO SMOKED. 2. Abstract-Conclusion: Suggest emphasise that SSRI's potentiates weight gain in the presence of unhealthy behaviours (followed by naming the unhealthy behaviour). 3. Abstract limitations: The authors still need to add that antidepressant use was not measured (point 3 in original review). 4. Introduction, Line 16: The authors cite that rising trends in global obesity prevalence has increased the risk of developing depression. However this statement only serves to confuse the reader as the topic of this paper is looking at the association in the other direction. Suggest. removal . 5. Introduction, line 21: " Indeed data from the Global Burden ...in 2010" Remove as this statement is about depression disorder which is not the problem being resolved in this paper. (This paper revolves around the problem of weight gain). 6. Introduction, line 33-39: The high use of antidepressants is a problem. This paper would benefit from further explanation of this problem and the alternative therapies that could be used (such as Cognitive behaviour therapy). 7. Introduction line 50: "In our animal paradigm... obesegenic diet". Please elaborate the hypothesis behind this statement. 8. Introduction, line 54: " Based on those findingswe have hypothesised that the increased antidepressant exposure might be a contributory factor". This sentence would be better as a statement of fact (i.e exclude the hypothesis part) as this paper does not primarily relate the increase of antidepressant use to increase weight gain but more look at the strength of the association between antidepressant use and weight gain and the influence of unhealthy behaviours. 9. Introduction, line 58 " Data from a recent....with increased energy
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	<p>intake". Please insert a sentence before introducing the topic of side effects of antidepressant use.</p> <p>10. Introduction, line 12: " understand interactions. " The interactions between SSRI use and lifestyle factors is of great clinical importance. Therefore the authors should continue this topic elaborate this point. Interactions with what, what is their hypothesis, what would the clinical implications be if such interactions exist. Maybe even make it clear what an interaction is (How antidepressants may have a different effect on weight changes for exhibiting different behaviours/age) The latter may make the paper more accessible for non-epidemiologists.</p> <p>11. Introduction, Line 18: Also name the lifestyle factors in brackets.</p> <p>12. Methods, 2.3 exposure variable: I understand that the authors have no details on the prescriptions but it possible to add information about general prescription practice in Australia such as the average prescription length?</p> <p>13. Methods, 2.3 exposure variable. With regard to my previous comment about what happens if participants are in receipt of more than one prescription, can the authors please add their reaction (exposure of specific antidepressants was assessed independent of one or more antidepressants) to the methods.</p> <p>14. Methods, Baseline and follow up covariates. How were physical activity categories made? Did the participants report low, moderate or high activity or was there a mets/day score that was categorised?</p> <p>15. Methods 2.4.1 Follow-up covariates: The authors have added that diet scores were dichotomised but more detail is required (i.e. what cut-offs were used, and possibly mention the range)</p> <p>16. Methods: Statistical analysis, Line 36: It is still unclear what interaction terms were made. In the first sentence it appears that the product of age and SSRI was used, however in the following sentence antidepressant use is mentioned.</p> <p>17. Methods: Statistical analysis The paragraph about interaction terms would benefit from expressly repeating (or mentioning in the case of age) how each of the lifestyle variables were treated. This could be resolved by adding the categories in brackets after each lifestyle factor.</p> <p>18. Methods, statistical analysis , Line 43: what is " weight status"? How is this variable made? When is it measures, baseline or follow-up?</p> <p>19. Methods, statistical analysis: No mention after the paragraph about interaction terms that the analysis was subsequently stratified for the lifestyle factors (producing table 3).</p> <p>20. Methods, Statistical analysis: A general comment. This section lacks structure and would benefit from linking the research question to the analysis. In other words adding why each analysis was done. This has been done already in the case of the linear regression analysis but could be added to the paragraph about interaction terms and that about the sensitivity analysis. Additionally, it would be good to emphasise why the authors choose to only check for interactions with SSRI's and not antidepressant use as a whole.</p> <p>21. Results, third paragraph: The structure of this paragraph could be improved. It would be better to start with the fact that interactions were found for the unhealthy lifestyle factors and then go through them one by one keeping the points about the diet scores together . The interaction between age and antidepressants should separate say at the end (and not in the middle of the paragraph) as this is not a lifestyle factor. Additionally, I presume that this interaction is between antidepressant use and not SSRI use (this was not clear in the methods section- see earlier comment).</p>
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	<p>22. Discussion, line 37: with regard to my previous comment about why TCA was positively associated with age. If the word limit allows it maybe good to add the authors reaction to the discussion.</p> <p>23. Discussion: The concluding section would greatly benefit from more discussion about the interactions and what this means for society and GP's. The authors could also speculate in promoting combined care for the treatment of depression.</p> <p>24. Supplementary table 3 : What is "body weight" mentioned in the title? BMI or kg? In the methods this is called " weight status". The authors need to be consistent with their terms .</p> <p>25. Supplementary table 3, footnote: add " time variant" to the relevant variables.</p> <p>26. Supplementary figure 2: Is this antidepressant use or SSRI use?</p>
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VERSION 2 – AUTHOR RESPONSE

The authors have addressed the majority of my comments, however the some points still need improvement. I have also found a few additional points and given that this paper is likely to be finally accepted by BMJ open, I think the paper could benefit some other changes to give it more structure. Finally, this paper could be of great clinical importance as it indicates the SSRI's mostly potentiate weight gain in the presence of unhealthy behaviours. As such I think that this point could be better highlighted. Given how useful these finding could be I think it is well worth the effort to spend time on further improvements. Details of changes are given below:-

1. Abstract-Results (line 43): suggest the authors say association between SSRI use and weight gain was **STRONGER** among those with a high intake of Western diet, **GREATER** sedentary activity and **WHO SMOKED**.

-Response: Changes have been made accordingly.

2. Abstract-Conclusion: Suggest emphasise that SSRI's potentiates weight gain in the presence of unhealthy behaviours (followed by naming the unhealthy behaviour).

-Response: Change has been made accordingly.

3. Abstract limitations: The authors still need to add that antidepressant use was not measured (point 3 in original review).

-Response: Perhaps missed by the reviewer, we have already stated the following on page 6: 'Information on medication use (based on prescription) according)..'

4. Introduction, Line 16: The authors cite that rising trends in global obesity prevalence has increased the risk of developing depression. However this statement only serves to confuse the reader as the topic of this paper is looking at the association in the other direction. Suggest. removal .

-Response: We respectfully disagree. This statement highlights that depression is a major health problem worldwide, which is relevant to our topic because the main medical treatment for depression is antidepressant medication.

5. Introduction, line 21: " Indeed data from the Global Burden ...in 2010" Remove as this statement is about depression disorder which is not the problem being resolved in this paper. (This paper revolves around the problem of weight gain).

-Response: We respectfully disagree. This statement highlights that depression is a major health problem worldwide, which is relevant to our topic because the main medical treatment for depression is antidepressant medication.

6. Introduction, line 33-39: The high use of antidepressants is a problem. This paper would benefit from further explanation of this problem and the alternative therapies that could be used (such as Cognitive behaviour therapy).

-Response: We respectfully disagree with this simplistic dichotomy of alternative therapies for depression, which suggests a bias against antidepressant medication; this is not our aim. For example, the guidelines released by the NICE recommendation (Depression in adults: recognition and management, Clinical guideline [CG90] Published date: October 2009 Last updated: April 2016) a range of effective treatments for depression which should be offered to patients in a stepped model of care based on depressive subtypes and personal characteristics; e.g. there are scenarios where antidepressants should be offered to patients who refuse or do not respond to psychological treatments.

7. Introduction line 50: "In our animal paradigm... obesogenic diet". Please elaborate the hypothesis behind this statement.

-Response: We have replaced this term with 'obesity promoting diet'.

8. Introduction, line 54: " Based on those findingswe have hypothesised that the increased antidepressant exposure might be a contributory factor". This sentence would be better as a statement of fact (i.e exclude the hypothesis part) as this paper does not primarily relate the increase of antidepressant use to increase weight gain but more look at the strength of the association between antidepressant use and weight gain and the influence of unhealthy behaviour.

-Response: We agree, the following change has been made: "Thus, increased antidepressant exposure might be a contributory factor to the obesity pandemic"

9. Introduction, line 58 " Data from a recent....with increased energy intake". Please insert a sentence before introducing the topic of side effects of antidepressant use.

-Response: We have added a sentence. See page 5. "It is supported by the change of energy intake related to antidepressant use"

10. Introduction, line 12: " understand interactions. " The interactions between SSRI use and lifestyle factors is of great clinical importance. Therefore the authors should continue this topic elaborate this point. Interactions with what, what is their hypothesis, what would the clinical implications be if such interactions exist. Maybe even make it clear what an interaction is (How antidepressants may have a different effect on weight changes for exhibiting different behaviours/age) The latter may make the paper more accessible for non-epidemiologists.

-Response: We have added a statement. See page 5

"Therefore, whether specific antidepressant medications interaction with lifestyle risk factors (poor diet, inadequate physical activity, and smoking) partially explain the development of human obesity long term is still unclear. Identifying the potential mechanism by which antidepressant medication increases the risk of obesity may could help develop targeted strategies for prevention".

11. Introduction, Line 18: Also name the lifestyle factors in brackets.

-Response: Change has been made accordingly.

12. Methods, 2.3 exposure variable: I understand that the authors have no details on the prescriptions but it possible to add information about general prescription practice in Australia such as the average prescription length?

-Response: To our knowledge, this information is not available. Please note that national and international use of antidepressants is expressed in defined daily doses (DDDs) per 1000 population per day.

13. Methods, 2.3 exposure variable. With regard to my previous comment about what happens if participants are in receipt of more than one prescription, can the authors please add their reaction (exposure of specific antidepressants was assessed independent of one or more antidepressants) to

the methods.

-Response: We have added this in the method section.

14. Methods, Baseline and follow up covariates. How were physical activity categories made? Did the participants report low, moderate or high activity or was there a mets/day score that was categorised?

-Response: We have added this in the method section. Respondents were asked about the amount of walking, moderate and vigorous activity they had undertaken in the past two weeks.

15. Methods 2.4.1 Follow-up covariates: The authors have added that diet scores were dichotomised but more detail is required (i.e. what cut-offs were used, and possibly mention the range)

-Response: As the mean score of dietary pattern was zero, the dichotomised cut-off is zero. Please see page 8 '(i.e. below or above zero)'.

16. Methods: Statistical analysis, Line 36: It is still unclear what interaction terms were made. In the first sentence it appears that the product of age and SSRI was used, however in the following sentence antidepressant use is mentioned.

-Response: For Figure S2, the interaction term of age (continuous) and any antidepressant use was used. For Table 3, the interaction term was for SSRI and lifestyle factors.

17. Methods: Statistical analysis The paragraph about interaction terms would benefit from expressly repeating (or mentioning in the case of age) how each of the lifestyle variables were treated. This could be resolved by adding the categories in brackets after each lifestyle factor.

-Response: Additional information has been provided on pages 8-9

18. Methods, statistical analysis , Line 43: what is " weight status"? How is this variable made? When is it measured, baseline or follow-up?

-Response: We have clarified this on page 9: 'both baseline and follow-up'.

19. Methods, statistical analysis: No mention after the paragraph about interaction terms that the analysis was subsequently stratified for the lifestyle factors (producing table 3).

-Response: We have added further clarification in the method section. Please see page 8.

20. Methods, Statistical analysis: A general comment. This section lacks structure and would benefit from linking the research question to the analysis. In other words adding why each analysis was done. This has been done already in the case of the linear regression analysis but could be added to the paragraph about interaction terms and that about the sensitivity analysis. Additionally, it would be good to emphasise why the authors choose to only check for interactions with SSRI's and not antidepressant use as a whole.

-Response: We have changed the section accordingly. See page 8.

21. Results, third paragraph: The structure of this paragraph could be improved. It would be better to start with the fact that interactions were found for the unhealthy lifestyle factors and then go through them one by one keeping the points about the diet scores together . The interaction between age and antidepressants should separate say at the end (and not in the middle of the paragraph) as this is not a lifestyle factor. Additionally, I presume that this interaction is between antidepressant use and not SSRI use (this was not clear in the methods section- see earlier comment).

-Response: We have changed the text accordingly.

22. Discussion, line 37: with regard to my previous comment about why TCA was positively associated with age. If the word limit allows it maybe good to add the authors reaction to the discussion.

-Response: We have added the comment in the discussion. "The SSRI fluoxetine entered medical use in 1986; TCAs were the gold standard for depression treatment before SSRIs became popular. It is likely that older patients started their treatment with TCA and those that were treated with and responded to TCAs for many years before SSRIs became available may have been reluctant to be switched to SSRIs".

23. Discussion: The concluding section would greatly benefit from more discussion about the interactions and what this means for society and GP's. The authors could also speculate in promoting combined care for the treatment of depression.

-Response: We have expanded the conclusion. Please see page 14. "General practitioners should encourage their patients adopt healthy lifestyle while treating depression with antidepressants or cognitive behaviour therapy."

24. Supplementary table 3 : What is "body weight" mentioned in the title? BMI or kg? In the methods this is called " weight status". The authors need to be consistent with their terms .

-Response: "body weight" is in kg. Changes have been made accordingly in the method section.

25. Supplementary table 3, footnote: add " time variant" to the relevant variables.

-Response: This change has been made accordingly. Please see supplement table 3: "In the model, age, income, depression and smoking were treated as time-variant variables".

26. Supplementary figure 2: Is this antidepressant use or SSRI use?

-Response: This is any antidepressant (shown in the figure)

VERSION 3 – REVIEW

REVIEWER	Deborah Gibson-Smith VUMC Amsterdam, The Netherlands
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	I am satisfied with the changes.
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