

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)	Effect of sex and age on the association between suicidal behavior and obesity in Korean adults: A cross-sectional nationwide study
AUTHORS	Kim, Dae-Kwon; Song, Hyun Jin; Lee, Eui-Kyung; Kwon, Jin-Won

VERSION 1 - REVIEW

REVIEWER	Alexandre González-Rodríguez Barcelona Clinic Schizophrenia Unit (BCSU). Institute Clinic of Neurosciences. Hospital Clinic of Barcelona. Barcelona, Spain
REVIEW RETURNED	29-Oct-2015

GENERAL COMMENTS	<p>I consider that this manuscript has an acceptable quality for publication on this journal. However, several clarifications should be made before publishing it. I would provide my comments according to the structure of the body of the manuscript.</p> <p>METHODS. Covariate variables. Concomitant diseases. In the methods section it is unclear whether the authors took into account psychiatric disorders when analyzing the effect of gender and age on suicidal ideation and behaviour. I consider that this should be clarified in this section.</p> <p>Analytical approach and statistics. What's the meaning of "psychological problems"? I consider it should be clarified in terms of adverse events, only suicidal ideation or behaviour or suicidality and depressive symptoms. Further, did the questionnaires include smoking status or number of cigarettes?</p> <p>RESULTS I would divide the results section into two subsections. (1) Characteristics of the whole sample and bivariate analyses, and (2) Multivariate regression models, to better report which findings are descriptive, and which are the most robust results from the study.</p> <p>DISCUSSION I would remove out the terms "As indicated in Figure 1", as the discussion section is not only a presentation of results, figures and tables, but a report of findings discussed with recent literature. I would discuss more in depth the relationship of serum levels of free fatty acid and central serotonin, by explaining it through a metabolic hypothesis or through an inflammatory hypothesis. Findings should be discussed in terms of biological underlying factors, instead of only psychosocial and physical factors.</p>
-------------------------	---

	Future directions in research investigating the relationship between suicide and obesity should be mentioned in a short subsection in the Discussion section.
--	---

REVIEWER	Arve Strandheim NTNU Norwegian University of Science and Technology, Norway
REVIEW RETURNED	02-Dec-2015

GENERAL COMMENTS	A very interesting and clarifying study with a great number of informants. The discussion is interesting, but too long. In the first part of the discussion the phrase "RISK" is often used despite the fact that this is a cross-sectional study with little causal impact. The etical discussion should be collected and specified in the method chapter
-------------------------	--

REVIEWER	Zainab Samaan McMaster University, Canada
REVIEW RETURNED	23-Jan-2016

GENERAL COMMENTS	<p>The authors used the Korean National Health and Nutrition Examination Survey to examine the effects of age and sex on the association between BMI and suicidal behaviour. The study question is important and has potential impact on assessment of risk factors of suicidal behaviors. This study may also clarify the controversial association between obesity and suicide.</p> <p>Specific comments</p> <ol style="list-style-type: none"> 1. Title and through out the paper, the use of "gender" is inappropriate as the authors used sex, a biological construct in the study and not gender, a social construct. There were no measurements of gender and therefore the term should be changed accordingly. 2. Introduction: the introduction is well written and justification for the study is presented clearly. The authors do need however to define "suicidal behaviour" as this may include different descriptors forming the primary study outcomes. 3. Methods: the definition of suicidal ideation needs clarification, please provide the exact question asked. 4. The nature of cross sectional design contains a measurement bias where BMI was measured at the time of recruitment while suicidal behaviour was a retrospective recollection of thoughts and acts within the previous year. The authors should discuss the implication of this bias. 5. The definition of "suicide attempt" is inadequate, the authors need to specify what an attempt is, does it require an intent to die? Not all self harm behaviours are considered suicidal behaviour, for example in certain psychiatric disorders such as borderline personality disorder, self harm is used as a maladaptive coping strategy to relief tension. It is also known that such disorder is also associated with impulsivity features such as binge eating (DSM-5) and therefore likely to have a higher BMI. An association between BMI and "suicidal behaviour" in this case is likely to be an association between self harm and borderline personality disorder.
-------------------------	--

	<p>6. “Concomitant diseases” a description of psychiatric disorders is needed and adjustment for these disorders in the analysis is important as these are known to have confounding effects.</p> <p>7. Over 40% of normal weight people in this ample had comorbidities, please explain why the rate of comorbidity of “normal” population is high.</p> <p>8. Statistical analysis: the authors conducted several subgroup analyses without correcting for multiple testing. The total sample size is large however the actual numbers in the individual subgroups are not so large for an observational study with poor phenotypic characterization.</p> <p>9. Discussion: the limitations of this study are not “few” there are several major limitations including the lack of clear definition of suicidal behaviour, a single question does not conclude a suicidal behaviour, the retrospective collection of suicidal behaviour data, the lack of description of comorbid psychiatric disorders and the lack of adjustment for multiple testing, that the authors must address.</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Alexandre González-Rodríguez

Barcelona Clinic Schizophrenia Unit (BCSU). Institute Clinic of Neurosciences. Hospital Clinic of Barcelona. Barcelona, Spain

I consider that this manuscript has an acceptable quality for publication on this journal. However, several clarifications should be made before publishing it. I would provide my comments according to the structure of the body of the manuscript.

METHODS.

Covariate variables. Concomitant diseases. In the methods section it is unclear whether the authors took into account psychiatric disorders when analyzing the effect of gender and age on suicidal ideation and behaviour. I consider that this should be clarified in this section.

Answer: Thank you for your thoughtful comment. We analyzed to add the depression as covariate variable. This item was recorded in the “covariate variables” of “Methods” (page 7, line 6-9) as below. Also, the re-analyses results were corrected in the “Results” (page 12, line 9-13; page 15 line 3-8) as below and the “table 1” (page 9-11), “table 2” (page 13-14), and “table 3” (page 15).

If patients indicated on the questionnaires that they had been diagnosed with coronary heart disease (e.g., angina pectoris and myocardial infarction), stroke, **depression**, and osteoarthritis through physicals, they were defined as having those diseases.

After controlling for other socio-demographic factors and concomitant diseases, obese men had a low odds ratio (OR) for suicide ideation (OR=0.87, 95% CI=0.76–1.00). Among women, the ORs of severely obese or underweight women were 1.27 (95% CI=1.06–1.52) and 1.24 (95% CI=1.06–1.45), respectively. However, the severity of obesity did not have a significant effect on suicide attempts among men and women (Table 2).

For women aged 18–<30 years old, the ORs for suicide ideation and attempts among severely obese women were 2.30 (95% CI=1.36-3.89) and 1.22 (95% CI=0.43-3.48), respectively. The ORs were 1.62 (95% CI=1.21–2.16) and 3.07 (95% CI=1.50-6.31), respectively, among women aged 30–<50 years. Overweight and obese women aged more than 50 years exhibited significantly lower ORs of suicide ideation, at 0.87 (95% CI=0.76–0.99) and 0.85 (95% CI=0.75–0.96).

Analytical approach and statistics. What's the meaning of "psychological problems"? I consider it should be clarified in terms of adverse events, only suicidal ideation or behaviour or suicidality and depressive symptoms.

Answer: Thank you for the kind comment. We found that wording of “psychological problem” may confuse the authors. So, we adopted “suicidal behavior (i.e., suicide ideation and suicide attempts)” instead of “psychological problems” in the “study samples and data collection” (page 5, line 18-22) and “analytical approach and statistics” (page 7, line 22-page 8, line 2) of “methods” as below.

The KNHANES consisted of personal interviews comprising a nutritional survey and various health-related questions, including individual health examinations, concomitant diseases, and suicidal behavior (i.e., suicide ideation and suicide attempts). Suicide behavior in this manuscript is the comprehensive word including both suicide ideation and attempts.

The number of patients with suicidal behavior (i.e., suicide ideation and suicide attempts) was summarized by obesity level. The relationship between obesity level and suicidal behavior according to sex were determined through multiple logistic regressions, after controlling for socio-economic variables and concomitant diseases.

Further, did the questionnaires include smoking status or number of cigarettes?

Answer: Thank you for your thoughtful comment. We analyzed to add the smoking status as covariate variable. This item was recorded in “Socio-demographic variables” of “Methods” (page 7, line 17) as below. Also, the re-analyses results were corrected in the “Results” and the “table 1” (page 9-11), “table 2” (page 13-14), and “table 3” (page 15).

Smoking status was included “none”, “current smoker”, and “ex-smoker”.

The discussion for smoking status was added in “discussion” (page 19, line 23-page 20, line 3) as below.

Regarding smoking status, current smokers in women showed statistically significant associations for increasing of suicide behaviors like other study. But smoking in men shows the tendency in prohibiting the suicide ideation even though the statistical association was not existed for suicide attempts. Further research on the sex difference in relationship between smoking and suicide behavior would be required.

RESULTS

I would divide the results section into two subsections. (1) Characteristics of the whole sample and bivariate analyses, and (2) Multivariate regression models, to better report which findings are descriptive, and which are the most robust results from the study.

Answer: Thank you for the kind comment. We described the results in two subsections in the “results” (page 8, line 9; page 12, line 8) as below.

Characteristics and bivariate analyses

Multivariate regression analyses

DISCUSSION

I would remove out the terms “As indicated in Figure 1”, as the discussion section is not only a presentation of results, figures and tables, but a report of findings discussed with recent literature.

Answer: Thank you for the kind comment. We removed out the terms “As indicated in Figure 1” in the sentence of “discussion” (page 16, line 6-7) as below.

In our study, the prevalence of suicide ideation and attempts by BMI differed substantially between men and women.

DISCUSSION

I would discussed more in depth the relationship of serum levels of free fatty acid and central serotonin, by explaining it through a metabolic hypothesis or through an inflammatory hypothesis. Findings should be discussed in terms of biological underlying factors, instead of

only psychosocial and physical factors.

Answer: Thank you for the kind comment. We added metabolic hypothesis of obese people in terms of biological underlying factors in the “discussion” (page 19, line 8-15) as below.

In biological psychiatry, the most replicated finding is a low and experimentally lowered central serotonin and its linkage with increased suicide, aggression, and reduced harm avoidance. In obese people, the insulin resistance syndrome is associated with increased blood level of free fatty acids, which compete with tryptophan for binding to serum albumin. As a result, increased unbound tryptophan in the blood could easily penetrate blood brain barrier, which is the rate-limiting step of serotonin synthesis, and result in increased central synthesis of serotonin. Increased central serotonin synthesis might be related with the protective effects on the risk of suicidal behavior.

DISCUSSION

Future directions in research investigating the relationship between suicide and obesity should be mentioned in a short subsection in the Discussion section.

Answer: Thank you for the kind comment. We added future directions of research in the “discussion” (page 23, line 13-17) as below.

Despite numerous studies, whether the obesity and suicide are independently associated or not is still unclear. At the same time, the prevalence of obesity and suicide already became a concerning public health problem throughout the world. For the practical point of view, it seems that further researches on a discovery of specific conditions, which could amplify the risk of suicide in obese people, are necessary in different cultures.

Reviewer 2:

Arve Strandheim

Institution and Country

NTNU -Norwegian University of Science and Technology,

A very interesting and clarifying study with a great number of informants. The discussion is interesting, but too long. In the first part of the discussion the phrase “RISK” is often used despite the fact that this is a cross-sectional study with little causal impact.

Answer: Thank you for the correct comment. We changed the phrase “risk” into “OR (odds ratio)” or “a tendency” throughout the “discussion”. The yellow mark was highlighted in the revised manuscript to reflect your comments.

As your kind comments, we tried to shorten the discussion. But, to response the comments by other reviewers, we could not reduce the discussion. If the length of the discussion does not bother you too much, we'd like to keep the length of the discussion. We hope reviewer understands of this situation.

Arve Strandheim

The ethical discussion should be collected and specified in the method chapter

Answer: Thank you for the kind comment. We specified the ethical discussion in the “study samples and data collection” of “methods” (page 5, line 22-page 6, line 1) as below.

The individual data for the research were available to the public through the KNHANES homepage (<https://knhanes.cdc.go.kr>). The study protocol including study design, interview questionnaire, and informed consent got approved by the ethics committee in KCDC.

Reviewer 3:

Zainab Samaan

McMaster University, Canada

The authors used the Korean National Health and Nutrition Examination Survey to examine the effects of age and sex on the association between BMI and suicidal behaviour.

The study question is important and has potential impact on assessment of risk factors of suicidal behaviors. This study may also clarify the controversial association between obesity and suicide.

Specific comments

1. Title and throughout the paper, the use of “gender” is inappropriate as the authors used sex, a biological construct in the study and not gender, a social construct. There were no measurements of gender and therefore the term should be changed accordingly.

Answer: Thank you for the correct comment. We changed the phrase “gender” into “sex” in the “title” and throughout “manuscript”. The yellow mark was highlighted in the revised manuscript to reflect your comments.

2. Introduction: the introduction is well written and justification for the study is presented clearly. The authors do need however to define “suicidal behaviour” as this may include

different descriptors forming the primary study outcomes.

Answer: Thank you for the kind advice. We revised the sentence in the “study sample and data collection” of “methods” section (page 5, line 21-22) as below.

Suicide behavior in this manuscript is the comprehensive word including both suicide ideation and attempts.

3. **Methods: the definition of suicidal ideation needs clarification, please provide the exact question asked.**

Answer: Thank you for the kind advice. We added the exact question for suicidal ideation in the “dependent variables” of “methods” (page 6, line 13-14) as below.

The specific question is “Have you ever thought about committing suicide within the previous year?”

4. **The nature of cross sectional design contains a measurement bias where BMI was measured at the time of recruitment while suicidal behaviour was a retrospective recollection of thoughts and acts within the previous year. The authors should discuss the implication of this bias.**

Answer: Thank you for the thorough advice. We added our limitation of study in the “discussion” (page 20, line 14-18) as below.

First, the nature of cross-sectional design used in our study entails a measurement bias because BMI was measured at the time of recruitment while suicide behavior was a retrospective recollection of thought and acts within the previous year. Therefore, we could not test for causal inferences regarding the development of suicidal behaviors and obesity over time.

5. **The definition of “suicide attempt” is inadequate, the authors need to specify what an attempt is, does it require an intent to die? Not all self harm behaviours are considered suicidal behaviour, for example in certain psychiatric disorders such as borderline personality disorder, self harm is used as a maladaptive coping strategy to relief tension. It is also known that such disorder is also associated with impulsivity features such as binge eating (DSM-5)**

and therefore likely to have a higher BMI. An association between BMI and “suicidal behaviour” in this case is likely to be an association between self harm and borderline personality disorder.

Answer: Thank you for the thoughtful advice. We added our limitation of study in the “discussion” (page 20, line 18-23) as below.

Second, we used suicidal behaviors (i.e., suicide ideation and suicide attempts) only in the analysis. Therefore, the association between obesity and completed suicide could not be elucidated. Especially, the limitation of general population-based survey, the definition of suicide attempts was presented with a general terms to the respondents, therefore suicide attempts in our study inevitably include the cases of self-injury related with certain psychiatric disorders such as borderline personality disorder.

6. “Concomitant diseases” a description of psychiatric disorders is needed and adjustment for these disorders in the analysis is important as these are known to have confounding effects.

Answer: Thank you for the kind advice. We analyzed to add the depression as covariate variable. This item was recorded in “Methods” (page 7, line 6-9) as below. Also, the re-analyses results were corrected in the “Results” (page 12, line 9-13; page 15 line 3-8) as below and the “table 1” (page 9-11), “table 2” (page 13-14), and “table 3” (page 15).

If patients indicated on the questionnaires that they had been diagnosed with coronary heart disease (e.g., angina pectoris and myocardial infarction), stroke, depression, and osteoarthritis through physicals, they were defined as having those diseases.

After controlling for other socio-demographic factors and concomitant diseases, obese men had a low odds ratio (OR) for suicide ideation (OR=0.87, 95% CI=0.76–1.00). Among women, the ORs of severely obese or underweight women were 1.27 (95% CI=1.06–1.52) and 1.24 (95% CI=1.06–1.45), respectively. However, the severity of obesity did not have a significant effect on suicide attempts among men and women (Table 2).

For women aged 18–<30 years old, the ORs for suicide ideation and attempts among severely obese women were 2.30 (95% CI=1.36-3.89) and 1.22 (95% CI=0.43-3.48), respectively. The ORs were 1.62 (95% CI=1.21–2.16) and 3.07 (95% CI=1.50-6.31), respectively, among women aged 30–<50 years. Overweight and obese women aged more than 50 years exhibited significantly lower ORs of suicide ideation, at 0.87 (95% CI=0.76–0.99) and 0.85 (95% CI=0.75–0.96).

7. Over 40% of normal weight people in this ample had comorbidities, please explain why the rate of comorbidity of “normal” population is high.

Answer: Thank you for the kind comment. We revised as the correct percentage of comorbidity for normal weight in the “characteristics and bivariate analyses” of “results” (page 8, line 14-15) as below.

The presence of concomitant diseases was **26.0%** for people of normal weight and **76.8%** for people with severe obesity.

8. Statistical analysis: the authors conducted several subgroup analyses without correcting for multiple testing. The total sample size is large however the actual numbers in the individual subgroups are not so large for an observational study with poor phenotypic characterization.

Answer: Thank you for the kind advice. We conducted the subgroup analysis by sex and age level. It makes weaken the statistical significance due to small sample size as you indicated. It was added the limitation section of “discussion” (page 21, line 1-3) as below.

Fourth, we conducted the subgroup analysis by sex and age level. It might weaken the statistical significance due to small sample size.

9. Discussion: the limitations of this study are not “few” there are several major limitations including the lack of clear definition of suicidal behaviour, a single question does not conclude a suicidal behaviour, the retrospective collection of suicidal behaviour data, the lack of description of comorbid psychiatric disorders and the lack of adjustment for multiple testing, that the authors must address.

Answer: Thank you for the kind advice. With the previous revisions (number 4 and 5), we reinforced our limitation of study in the “discussion” (page 20, line 23-page 21, line 1) as below.

Third, we could not describe and adjust the comorbid psychiatric disorders such as anxiety, eating disorders, and borderline personality disorder due to lack of data.

The authors really appreciated the reviewer's kind and accurate comments. Revision based on these comments has improved the accuracy and the quality of the manuscript. We appreciate your efforts.

VERSION 2 – REVIEW

REVIEWER	Alexandre González-Rodríguez Barcelona Clinic Schizophrenia Unit (BCSU). Neuroscience Institute. Hospital Clínic of Barcelona. Barcelona, Spain I have been paid for talks, or registration/travels for congresses from Janssen, Lundbeck-Otsuka, Ferrer and Pfizer; however this conflicts of interest are not related to the content of the manuscript.
REVIEW RETURNED	25-Mar-2016

GENERAL COMMENTS	I consider that the content of the manuscript is without doubt of interest in this clinical field. The authors have improved the introduction section, the definition of the methodology used, and have better defined the statistical procedures, which are more complex. I would congratulate them, and suggest only to introduce the statistical analysis in the abstract section.
-------------------------	---

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:

Alexandre González-Rodríguez

Institution and Country

Barcelona Clinic Schizophrenia Unit (BCSU). Neuroscience Institute. Hospital Clínic of Barcelona.
Barcelona, Spain

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

I have been paid for talks, or registration/travels for congresses from Janssen, Lundbeck-Otsuka, Ferrer and Pfizer; however this conflicts of interest are not related to the content of the manuscript.

Please leave your comments for the authors below

I consider that the content of the manuscript is without doubt of interest in this clinical field.
The authors have improved the introduction section, the definition of the methodology used, and have better defined the statistical procedures, which are more complex.
I would congratulate them, and suggest only to introduce the statistical analysis in the abstract section.

Answer: Thank you for your kind comment. We added the statistical method in abstract (page 2, line 10-12) as follow.

Design and analysis: Cross sectional study was performed. Multiple logistic regressions after controlling for socio-economic variables and concomitant diseases were applied to see the relationship between obesity level and suicidal ideation or attempt.

Editorial Requirements:

Please complete and include a STROBE check-list, ensuring that all points are included and state the

page numbers where each item can be found: the check-list can be downloaded from here: <http://www.strobe-statement.org/?id=available-checklists>

Answer: Thank you for the correct comment. We filled in the STROBE check-list (attached file), and revised the text according to the format in methods (page 8, line 2-4, 6-8) and results (page 8, line 14-15) as follow.

Multiple logistic regressions were performed in 34,482 (suicidal ideation) and 34,448 adults (suicidal attempt) excluding people who had missing data for each variable.

This study complied with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cross-sectional studies.

A total of 36,211 individuals with BMI data were selected among 38,497 and the mean age was 49.6 years.

Please adjust the manuscript title. As per BMJ Open guidelines, the title should frame the research question and include the study design and setting

Answer: Thank you for the kind advice. We revised the title including study design and setting in title (page 1, 3-4) as follow.

Effect of sex and age on the association between suicidal behavior and obesity in Korean adults: A cross-sectional nationwide study

Please add an 'Article summary' section consisting of the heading: 'Strengths and limitations of this study', and containing up to five short bullet points, no longer than one sentence each, that relate specifically to the methods of the study reported. They should not include the results of the study and should be placed after the abstract.

Answer: Thank you for your correct comment. We revised the Article summary as rule (page 3, line 9-17) as follow.

Strengths and limitations of this study

- This study used nationwide population representative 5-year combined survey data of Korean adults, and the large population sample size could represent the general population of adults in South Korea.
- In-depth analysis by age and sex provide a clear understanding for the dynamic pattern between obesity level and suicidal behavior including ideation and attempt
- Reports of the respondents were a subjective recollection of thought and act of the previous year, potentially influenced by perception and recall bias.
- Due to the lack of data, our study could not adjust the comorbid psychiatric disorders.

The authors really appreciated the reviewer's kind and accurate comments. Revision based on these comments has improved the accuracy and the quality of the manuscript. We appreciate your efforts.

VERSION 3 - REVIEW

REVIEWER	Alexandre González-Rodríguez Barcelona Clinic Schizophrenia Unit (BCSU). Neuroscience Institute. Hospital Clinic of Barcelona, Barcelona (Spain).
REVIEW RETURNED	28-Apr-2016

GENERAL COMMENTS	The authors have implemented all changes and recommendations suggested in previous reviews of the manuscript. The paper is well-written, the introduction has been reformulated more in depth, the methods section is clear, and the presentation of the results are well
-------------------------	---

	done. I consider that this manuscript should be accepted.
--	--