Reviewer's report

Title: Serum leptin and ghrelin are associated with depressive symptoms in Japanese women but not in men

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Reviewer: Seren Roberts

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PEER REVIEW

General comments

This is an interesting paper about the association of specific appetite hormones and depressive symptoms. It is generally well written though some work is need on the discussion section. The study does not offer any insights into the mechanism of effect or possible improvements to treatment or management of depression but provides further insight into the biological mechanisms that may underlie or mediate some depressive symptoms. The study has a number of limitations, some of which are discussed in the paper. The study does not take into account likely treatments for depression which may interfere with the hormones in question and the depression rating scores.

Introduction

The authors make a clear and concise case for the study and report compelling evidence to support their argument.

There is little evidence to support their methods or approach. I would also like to have seen a bit more detail about the proposed mechanism of effect. For example, how might these hormones have a possible effect on mood? Also some more discussion about how lifestyle factors in people with depression and antidepressants might influence possible levels for these hormones would be helpful.

The aim of the study is transparent.

Methods

This cross sectional study was undertaken as part of a large study with main methods reported elsewhere. Survey data were collected about demographics, lifestyle and depressive symptoms (using Centre for Epidemiologic Studies Depression Scale) together with a blood sample (after overnight fasting). There is a good description of the procedures for blood testing, data management and analyses. However, the authors need to justify why the hormone values were treated in tertiles (low, medium and high) and not as continuous variables. They also need to specify the value ranges for three tertiles in the text. The authors should also justify why they adjusted for all the additional variables in the second model.

Results
The results are well presented and clear. The authors report an association between higher leptin levels and reduced odds of depressive symptoms in women which is not statistically significant. For me, this should be reported as a trend rather than an associated because the lack of significant result. The authors report similar findings for CES-D #19 but do not provide the results. These should be included in table 3. I assume the results that follow this assertion relate to the depressive symptoms scores CES-D #19 but this needs to be clarified. The clause ‘whereas no clear association was found for men’ (results - end of second paragraph) indicates an association in the preceding clause but again, the association between leptin tertile and depressive symptom in women is not statistically significant (bar the mid tertile). I would suggest rephrasing as this is rather misleading.

Discussion

The first sentence of the discussion again claims leptin is inversely associated with depressive symptom in women with no apparent linear trend. However, this claim is not support by statistical evidence as noted above. The first 2 sentences of the discussion should be removed. First 2 sentences of the second paragraph under discussion also seem repetitive. I suggest starting with …our data are in line….

The discussion overall feels repetitive, covering themes raised in the introduction and results. I would like to seem much more discussion about the authors’ interpretation of the findings, to try to explain some of these findings, particularly exploring how the findings fit with possible models of mechanism of effect (inflammation-depression touched on but not fully explored). Even though this is not a longitudinal study with data to indicate a clear causal relationship, I think it would benefit the paper if the authors made clear their views about their findings and what they think it means. Some discussion about the likely cause and effect relationship might help explain some of the findings in the context of the evidence which conflicts with their findings. The paragraph about the underlying mechanism (pg 13 line 9 - pg 14 line 5) should be included in the introduction. In the discussion, the authors should discuss how their findings fit in with these models. There is no discussion about the differences between the CES-D #19 and the CES-D #16 depression cut off values. I think this warrants further discussion here because the authors suggest in the methods section that the threshold of CES-D #19 is more suitable to Japanese population yet they manly report the CES-D #16 cut off findings.

The brief discussion about the relationship between depression and diet should be included the main body of the discussion. For the limitations section, once they identify the limitation, I suggest the authors propose a study design that might address these issues. E.g. longitudinal studies with multiple times point assessments, data capture about dietary intake, treatment for depressions, or a study with a clinical sample and so forth. I also think the authors should mention limitations of the analyses e.g. using tertiles etc.

- Major Compulsory Revisions
1. Include discussion of possible mechanisms of effects in introduction along with a brief discussion about how lifestyle factors in people with depression and antidepressants might influence possible levels for these hormones.

2. Justify why the hormone values were treated in tertiles (low, medium and high) and not as continuous variables in results.

3. Specify value ranges for three tertiles in the text.

4. Justify why they adjusted for all the additional variables in the second model.

5. Rephrase wording of the association between leptin and depressive symptoms is a trend rather than a statistical association.


7. Develop the discussion further by discussing author’s interpretation of the findings and try to explain them, contextualise the findings and how they fit with existing evidence on the mechanism of effect of hormones and make some suggestions about how their findings add to the existing knowledge base.

8. Propose study designs that might take their research a step further in overcoming some of the limitations of this work.

- Minor Essential Revisions

  1. Pluralise 'human' at the start of second paragraph in introduction

- Discretionary Revisions

  None

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

NO COMPETING INTERESTS TO DECLARE