Author’s response to reviews

Title: Anxiety and depression in children and adolescents with obesity: a nationwide study in Sweden

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“Anxiety and depression in children and adolescents with obesity: a nationwide study in Sweden”

Dear Dr. Diana Samuel, Associate Editor,

Thank you very much for the invitation to respond to the comments made by the reviewers. We very much appreciate the constructive and careful work of the reviewers and we have revised the manuscript according to their suggestions. A revised version of the manuscript is now submitted.

Regarding specific editorial comments pointed out by you we have (1) deleted the list of abbreviations and (2) uploaded each additional file separately.

For specific comments to editorial points and referees:

1. We have addressed all comments in this response letter and made appropriate changes in the revised manuscript.
2. A marked-up copy of the changes (using the "track changes" command) made from previous article file is provided.

Sincerely,

Louise Lindberg

Editorial comments:

E1.) Please define all abbreviations inline the first time they are used, and delete the list of abbreviations (so that the manuscript is in keeping with a recent change in our guidelines).

RESPONSE: Thank you for pointing out the recent changes in the guidelines. We have deleted the list of abbreviations on lines 313-315, page 12. All abbreviations are now defined inline the first time they are used.

E2.) As the sections are cited individually, please ensure you separate your 'Additional file' into 4 individual files and upload them separately.

RESPONSE: Thank you for the comment. This has now been corrected, and each additional file is uploaded separately.
Robert Berkowitz - Reviewer 1 (R1)

This manuscript examines the association between anxiety and depression (as defined by either physician diagnosis and/or prescription of medications) in treatment seeking children for obesity compared with a sample (matched on key variables but not on BMI) from the general population in Sweden. The authors report that even when adjusting for other risk factors, obesity remains associated with anxiety and depression to a greater degree in the former group compared to the latter group. The study of the association of obesity with anxiety and depression is an important area of inquiry but there are concerns regarding this manuscript as described below.

RESPONSE: The authors thank the reviewer for the valuable evaluation of our paper. We have carefully revised the manuscript to present our work more clearly.

R1.1: Lines 80 - 83. It is commendable that a very large sample of youth enrolled in the Swedish Childhood Obesity Treatment Register to assess and monitor progress in behavioral treatment of obesity and was included in this report. The number of youth and their characteristics who declined treatment was not however reported and it would be useful to understand if such data could be provided by the authors.

RESPONSE: Thank you for the important comment. The answer to this question can be divided into two parts. Firstly, data on individuals who decline treatment is not available in the register. Secondly, an opt-out approval is the current law and regulation in Sweden. This has been clarified in the methods section, line 87, page 4 as well as under ‘Ethics approval and consent to participate’ in the Declaration section, line 319, page 13. This means that for health care professionals to record an individual in the register who undergo treatment, they have to inform the patient/guardian orally or in writing. If the patient/guardian decline to participate in the quality register, no data can be collected or saved according to the law.

R1.2: Of note, these children and adolescents are to be considered 'treatment seeking’ as they sought participation in a behavioral program. It is possible, as the authors suggest in the discussion section, that treatment seeking youth are more distressed and, thus, may be more likely to have psychiatric diagnoses - and may be more likely to obtain more professional attention (and perhaps more likelihood of obtaining a psychiatric diagnosis). The authors would strengthen the manuscript by describing the literature on treatment seeking vs representative samples of youth with obesity and whether there are differences in prevalence of psychiatric diagnosis.
RESPONSE: Thank you for your reflections on this topic. As of today, there is no data on a representative sample of youth with obesity in Sweden. Hence, we are unfortunately not able to make the suggested comparison. And to the best of our knowledge, such comparison has not been made in any other country with similar health-care system. Of note, in Sweden, school health care services are also responsible for referring children with obesity to the health care regardless if other diagnoses are present or not.

As the reviewer point out, we have raised the issues with risk of selection bias as well as surveillance bias. Please see the discussion section, lines 288-289 page 11-12. In addition to this, we have further clarified surveillance bias as following: “It is possible that children in obesity treatment are diagnosed with anxiety or depression to a greater extent than individuals with obesity who are not in treatment, or compared to peers from a population-based comparison group”. Please see the discussion section, lines 295-297, page 12.

Of note, those who are registered in the national obesity register are not participating in a specific national behavioral program. The delivery of the treatment looks different throughout the country – some get advice on diet and physical activity, some participate in local projects, some participate in camps and so on.

R1.3: Lines 88 - 90. The control group was from the general population via a national database and youth were matched on year of birth, sex and living area. However, an important issue is that anthropometric data regrettably were not available on this group; thus, it is not possible to assess BMI within this control condition. The authors would strengthen the discussion about this limitation as they may be comparing a clinical sample with a representative sample; it is possible that greater levels of anxiety and depression are evident in clinical samples compared to epidemiological samples.

RESPONSE: Yes, the lack of anthropometric data on individuals in the control group (i.e. from the general population) is indeed unfortunate. Everyone who get a diagnosis of anxiety or depression are registered in national registers. That is, diagnoses found in the comparison group are registered the same way as diagnoses found in the obesity cohort, regardless if it is a primary, or secondary diagnosis.

In addition, as mentioned in the previous response, we have clarified the risk of surveillance bias in the discussion section, lines 295-297, page 12.
R1.4: In the discussion, the authors mention that one limitation is the lack of BMI data in the general population sample. They report very low rates of diagnosed obesity - this rate seems to be too low and the authors would strengthen the manuscript by describing whether there is under-diagnosing by clinicians of obesity in the database.

RESPONSE: We thank the reviewer for the comment, and yes, we agree that the rate of obesity in the comparison group is very low (1.3%). The goal in Sweden is that all children under 18 years of age in obesity treatment should be registered in the National childhood obesity treatment register. Hence, the rate of individuals with obesity, but who are not registered in BORIS, should be low. Naturally, there is a proportion of individuals with obesity who never come in contact with health care and thus remain undiagnosed. Unfortunately, we will never know how many, nor who, these people are.

We estimate that approximately 80% of the Swedish pediatric clinics report cases of obesity to the obesity-register. The clinics themselves, report back to us that they register almost 100% of their patients with obesity to the register. Whether a clinician who meet a child with, say asthma, who also has obesity, diagnose this patient in the National Patient Register with only asthma, or with both asthma and obesity, remains unknown. This is a delicate issue when using registers for research. Nevertheless, we want to acknowledge that children with obesity are present in the comparison group.

R1.5: If the authors had access to BMI data in the general population group, they might have assessed youth with and without obesity and not in treatment, as well as compared these two groups with the youth with obesity who were treated. It is presumed that the authors are not able to obtain BMI data; do the authors have suggestions for future studies in which BMI data are collected along with data regarding anxiety and depressive disorders?

RESPONSE: It is correct that we are not able to obtain BMI data in the general population group. Comparing three groups with each other as the reviewer suggested above would indeed be interesting and add to the knowledge gap of several raised questions. However, it is well-known from previous studies that it is hard to get reliable population-based data on prevalence of overweight and obesity in children and adolescents as well as in adults. However, we hope that conducting this kind of study will be made possible in the future. After many years of investigation, foremost due to ethical issues, a school register is starting in Sweden. Unfortunately, it will take many years before a linkage to this register will be possible.
R1.6: Lines 113 - 122. Anxiety and depression were defined on health care provider diagnosis and/or prescribed medications. There are several issues here: 1) The authors would strengthen the manuscript by describing the heterogeneity and (low) reliability of clinician diagnoses regarding anxiety and depression; 2) There are a number of types of anxiety and mood disorder diagnoses - these are not described; how were diagnoses chosen to be combined? 3) Was there a standard method that clinicians used to make diagnoses? 4) Were the clinicians making diagnoses trained psychiatrists or primary care physicians and were there differences in rates of diagnosis by training?

RESPONSE: Thank you, these are all very imperative comments/questions. Please see responses below to each of the four parts.

1) Determining a diagnosis of anxiety- or depressive disorder may in some cases be difficult. However, in Sweden diagnoses of depression or anxiety in pediatric patients are most often given by a pediatric psychiatrist. In case a diagnosis of anxiety or depression in youths would be detected in other medical contexts, for example during a visit to a dermatologist, the patient should be referred for evaluation by a child psychiatrics or a pediatric doctor with expertise in the area. To strengthen the manuscript further, we have added the following in the discussion section, lines 298-300, page 12: “Determining a diagnosis of anxiety- or depressive disorder can be difficult. In Sweden, a licensed specialist in psychiatry treatment most often provides the diagnosis.”

2) We decided to examine anxiety and depression without connection, or as a consequence of, other morbidities such as organic anxiety disorder and post-schizophrenic depression. Further, the diagnoses were grouped into anxiety and depression respectively based on the definition of the ICD-code. In accordance to your important query, we have specified the types of anxiety- and depressive disorders diagnoses into more detail in Additional file 1.
3) There is no gold standard that physicians in Sweden are obligated to use to make a diagnosis. However, the diagnosis of anxiety and depression is most often based on several personal interviews with the patient and often also the guardian. Most clinicians also use validated questionnaires to be completed by the patient as additional support for the medical and psychiatric assessment.

4) As stated in the methods section, lines 127-128, page 5, a diagnosis of anxiety or depression is given by a physician during in- or outpatient visits. Hence, the clinician does not have to be a trained psychiatrist, and, we do not have data from the primary care. Our data does not allow investigation of rates of diagnoses stratified by type of physicians, but it would certainly be interesting to study.

R1.7: Although other studies have used 'self-report' methods, there has been great effort in developing validated and reliable methods using standardized questionnaires completed by youth, parents, and clinicians to diagnose anxiety and depression; a more thorough review of the benefits of these standardized methods compared with clinician diagnosis would strengthen the manuscript.

RESPONSE: We agree with the reviewer that there has been an extensive effort in developing validated questionnaires in the field. The children’s Depression Inventory, the Center for Epidemiological Studies Depression Scale, Kiddie Sads Present and Lifetime version and the Diagnostic Interview Schedule for Children are some questionnaires frequently used to measure symptoms of anxiety or depression in youth. Different questionnaires are used as praxis at the clinic but always as a complement to a clinical evaluation. It has been suggested that there is insufficient evidence that these types of screening tools accurately assess anxiety- and depressive disorder (Roseman et al. Canadian journal of psychiatry, 2016). Some of the questionnaires includes questions concerning appetite and sleep, which both primarily can be affected by other factors than anxiety or depression. In an effort to keep the introduction short and concise we decided not to reflect upon this.

R1.8: Line 119. Of note, anxiety and depression may be treated by psychotherapy, to which there are no references in the draft. The authors should comment on this.
RESPONSE: Thank you for pointing this out. Children and adolescents in Sweden with a diagnosis of anxiety/depression may be offered treatment with psychotherapy alone, or in combination with psychotropic mediation. The majority has most likely been treated with therapy session in form of supportive talks or cognitive therapy session. We have followed the reviewer’s recommendation and added a sentence and references on this in the discussion, lines 269-270, page 11. “Psychotherapy is an alternative treatment for anxiety and depression (39) and is always considered as part of the treatment of patients with these diagnoses.”

R1.9: Lines 172-. Greater levels of anxiety and depression were found in the group of youth with obesity compared with that of the general population. Greater levels were found in girls vs boys and there was an association with parental anxiety and depression. When controlling for parental diagnoses as well as neuropsychiatric diagnoses in youth, the association between obesity in youth anxiety and depression was found as well. These are important results - especially if the authors can respond sufficiently to the earlier concern regarding the potential bias of comparing a clinical sample with a representative sample.

RESPONSE: Thank you for the reflection. We hope we have managed to respond sufficiently to the reviewer’s concerns regarding bias in previous questions (R1:2, R1:3), as well as with the clarifications made in the manuscript. Please see discussion section, lines 296-300, page 12.

R1.10: What is the level of association of anxiety and depression with obesity as well as with the other risk factors such as parental disorders and with presence of neuropsychiatric disorders? What is the level of prediction of each of the risk factors including obesity?

RESPONSE: We thank the reviewer for the questions. The worldwide prevalence of anxiety and depression in children, regardless of weight status, is estimated to stand at 6.5% and 2.6%, respectively (Polanczyk et al, 2015), please see “Background”, line 58, page 3. We have not found any worldwide prevalence numbers of anxiety or depression in children with obesity. The prevalence reported in the present study for the comparison group was approx. 3.9% and 2.7% for anxiety and depression respectively. In the obesity cohort, the corresponding numbers were 7.5% and 5.9% respectively. Hence, the percentage of anxiety as well as depression is higher in the obesity cohort, while the comparison group is closer to the prevalence reported in the worldwide report from 2015.
Further on, the association between anxiety and depression with intellectual disability was for example reported in a study by Emerson (2003) to be 8.7% and 1.5% in children with ID, compared to 4.1% and 0.9% in children without ID.

With regards to parental disorders, the level of association between parental depression and depression in the child, is similar to what has been reported previously, which we touch upon in the discussion, lines 243-245, page 10. We hope that the above responses sufficiently answer the reviewer’s questions.

R1.11: Line 268. In the general population sample, only 1.3% of individuals were diagnosed as having obesity. This seems to be an unusually low rate and it would help for the authors to comment on whether obesity in youth is not often diagnosed and/or is under-diagnosed (and what the literature says about obesity diagnosis in youth in the general medical records).

RESPONSE: We appreciate the reviewer’s reflection. We agree with the reviewer that it is a low rate and refer to our previous response in question R1.4. “The goal in Sweden is that all children under 18 years of age in obesity treatment should be registered in the National childhood obesity treatment register. Hence, the rate of individuals with obesity, but who are not registered in BORIS, should be low.”

Aviva Must - Reviewer 2 (R2)

This is a solid study that takes advantage of the stellar health data systems in Sweden that make large epidemiological studies possible. There are some important study design and generalizability issues that need to be more clearly communicated, as articulated along with some other minor comments below.

RESPONSE: The authors thank the reviewer for acknowledging the study and providing important reflections and comments that contributes to improving the paper.
Major issues:

R2:1. The inability to remove youth with obesity from the population comparison group is a major limitation of the approach. Even though the rate of obesity is low, their inclusion muddies the comparison. The lack of the information should be presented in the methods section (in the paragraph that includes lines 88-94 to make clear that the population based data lack information on weight status. The figure might be revised to make this clearer by labeling the "obese" group as Obesity treatment and adding a footnote to the comparison group that indicates "obesity status unknown"

RESPONSE: Thank you for the comment. In line with the reviewer’s recommendation, we have added a sentence about the lack of BMI information in the method section, lines 93-94 page 4: “Information on anthropometry was not available for individuals in the general population.” In addition, we have added the following in the discussion section, lines 282-285, page 11, “However, in the National Patient Register we found a diagnosis of obesity in only 1.3% of individuals in the comparison group, enlightening the fact that our comparison group consists of not just healthy individuals of normal weight.”

Of note, based on the current study design, we do not have the possibility, nor the intention, to compare obesity with normal weight.

R2:2. The issue regarding how youth who present for obesity treatment make differ from obese youth who do not deserves more primacy in the discussion of limitations. In the US, at least, we know there are strong selection factors at work. If present, these issues undermine the generalizability of the findings.

RESPONSE: Thank you for the comment. Factors that could impact the reason of whether one seek obesity treatment or not could for example be socioeconomic factors, demographic factors, cultural factors, family support, other morbidity etcetera. In accordance to your important query, we have expanded the discussion-section with this limitation, lines 288-289, page 11-12.

R2:3. The selection of tables for the main paper vs. the supplementary ones seemed quite odd. A classic table 1 is important here— to get a sense of how variable not matched on differed in the 2 groups.
RESPONSE: Thank you for the comment. We agree with the reviewer and have moved “Additional file 2” to be displayed as “Table 1” in the manuscript.

Minor issues:

R2:4. The paper is well organized and well-written by and large. However, there are some odd word choices and a few grammatical errors. Copy editing by a native speaker of English is encouraged if the journal doesn't provide this service. One specific term identified is "register"— I think the correct term would be registry. Figure 2 title — consider removing "belonging"

RESPONSE: We have seen both ‘register’ and ‘registry’ used in the research field. The reason why we chose to use Register throughout the manuscript was because the English translation for the Swedish Childhood Obesity Treatment Register, is called just that, Register. Further, Statistics Sweden and the National Board of health and welfare where we collect data from uses ‘Register’ as the English term for each of their specific registers.

Further, the word “belonging” has been removed from the title in Figure 2. Please see under the List of figures, line 466, page 18.

We appreciate that the reviewer is alerting us on the inaccuracies found in the manuscript when it comes to wording and grammar. Before submitting this revision, the paper was sent to a professional language editing service and so all errors should now have been corrected.

R2:5. Line 71 — "this group" is ambiguous, several groups are described in the paragraph— which group is referred to?

RESPONSE: Thank you for the comment. This has now been clarified to “in children with obesity” in the background section, line 72, page 3.

R2:6. Line 89 - how was living area defined or characterized?
RESPONSE: Thank you for this essential question. Living area (now rephrased to ‘area of residence’) was characterized as district. There are approximately 2000 districts in Sweden. The matching of the variables (gender, year of birth, and living area) were done by the year the child started obesity treatment. This has been clarified in the Methods section, lines 91-93, page 4: “Individuals from the general population were matched to individuals in the obesity cohort according to year of birth, sex, and area of residence, by the year in which obesity treatment commenced. Area of residence was defined by the approximately 2000 districts in Sweden.”

R2:7. Is it really heredity that one is controlling for, or family history—one doesn't know if it genetics or shared environment, or both that are at play here.

RESPONSE: We agree with the reviewer’s reflection and have replaced the term heredity, with family history, throughout the manuscript.

R2:8. Presumably only participants who provided data on "heredity" (if that term is to be retained) are those with information from a biological parent.

RESPONSE: Thank you for the comment. We have data on “heredity” for all parents, both adoptive and biological. When thinking about heredity from that perspective, we agree with what the reviewer stated in the previous question, that it could be either genetically or shared environment. After reflecting upon this we therefore decided family history to be a more proper word to describe anxiety and depression.

R2:9. Lines 281-2. That statement is highly debatable at least in the US.

RESPONSE: Thank you for the comment. Our reasoning behind the statement “…overall rates of anxiety and depression may be underestimated as a large proportion of individuals suffering from these conditions do not seek medical care. However, there is no reason to believe that this pattern would differ between the children and adolescents with and without obesity.” is as follows;
On the one hand, one could speculate that children with comorbidities are more likely to receive treatment for anxiety and depression if they already are in contact with the healthcare due to obesity. It is likely that health care givers detect, and take action, if suspicion of mental illness arises. On the other hand, it may be that children in contact with the healthcare due to their obesity, only are treated for that disease. The doctor might believe that if the patient lose weight, some of the sequelae, such as mental health issues, will be solved automatically.

R2:10. Reference 39 appears to be incomplete.

RESPONSE: Thank you for acknowledging this. This has now been corrected in the reference section, lines 456-458, page 18.