PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland
AUTHORS	Räisänen, Sari; Lehto, Soili; Nielsen, Henriette; Gissler, M; Kramer, Michael; Heinonen, Seppo

VERSION 1 - REVIEW

REVIEWER	Kirkinen, Pertti University of Tampere, Finland
REVIEW RETURNED	05-Mar-2014

GENERAL COMMENTS	In this large population-based and register-based study some associated factors for depression during pregnancy were analyzed. This topic has not been previously largely examined in this kind of scale. The same group has previously published similar analysis for postpartum depression, and some overlapping between these studies exists. This does not disturb the present analysis, because interest is now concentrated into the antepartal period. However, because postpartal depression is often more severe and – obviously , looking at the risk of suicide, more important than the antepartal depression, the authors could discuss more of associating features between ante- and postpartal diseases. Also the main interest of obstetrical complications is now in late pregnancy and delivery, and the harmful events at early pregnancy (bleeding, imminent abortion, findings in fetal diagnosis and trisomy screening et cet) are not correspondingly presented. A large part in discussion covers the strengths and limitations of the study. Is it really needed? I am not very convinced that the diagnostic accuracy of depression in this study is completely representative for the whole problem. Similarly, speaking of “social deprivation” is now based on the SES-scale used in Finland, and in my opinion the present SES-scale does not very well describe the social well-being of any individual person. Thus “social deprivation” would be replaced by some more cautious term. Maybe the next study by this group will be directed to the risk of suicide during pregnancy and at postpartal period?

REVIEWER	Dawn Kingston University of Alberta
REVIEW RETURNED	06-May-2014

GENERAL COMMENTS	Abstract: -should indicate years of data included in study Background: -It is important to note for ref 2 in the introduction…in which country these data were collected and for what period of time -The background requires greater focus in highlighting the main gaps in the current literature leading to the study purpose. The background 'bounces' between the determinants and consequences of perinatal depression and could benefit from improved organization and highlighting of key gaps (the 'why' this study is important should be highlighted more) -unclear why the purpose states (line 23) 'especially in women with no previous depression episodes' when pre-pregnancy depression was a factor of interest in the study -given the intent of the study to examine a variety of risk factors, the title might need a bit of readjustment Purpose -my initial impression is that too much is being covered in this paper. I would recommend splitting into 2 papers: i) determinants of prenatal depression; and ii) consequences of prenatal depression and mediators of association between prenatal depression and neonatal outcomes Methods: - -please describe what the specialized health care units are. This is important because it provides context for the diagnostic coding/prevalence rates -rationale for dates studied (2002-2010) should be provided -depression and anxiety are comorbid in as many as 50% of pregnant women….rationale for limiting to depression alone? -rationale for limiting depression to 'major depression' should be stated e.g., depression not identified as 'major depression' has also been linked to poor child outcomes -should briefly describe who provides the majority of prenatal care to Finnish women, and what depression screening approaches are utilized -please clarify → outpatient visits – who was likely to be the provider? (line 26 p6) -please clarify – for the variables listed on page 6-7 the registers that these variables were derived from -how was fear of childbirth diagnosed? Is this routinely screened for in pregnant women? Analysis: -the approach for the analysis does not make complete sense. It is unclear why the reference categories did not include ' no prenatal depression + has a history' -for first research aim, please describe how models built -in looking at the results…it is unclear what the reference categories are in the analysis – further elaboration is required. By the time the categories are described in the results it is quite confusing (p9). For example, 'no antepartum depression (categories 1 and 2) as a reference population' requires too much effort to think this through in current format (line 13 p9) -why was fetal sex included in models?

	Results: -% of women successfully linked between health registers should be reported -the prevalence of 0.8% with major depression during pregnancy seems very low compared to studies of self-report measures, particularly when 46.9% had a history of depression. This was aptly noted in first paragraph of main findings. Some studies have shown a history of depression to be predictive of depression in pregnancy….so the low prevalence rate requires greater explanation of a thoughtful nature. -if possible please provide estimate of the % of women who would be diagnosed and treated in primary healthcare…and please describe primary health care (versus specialty health care units….for those outside of the Finnish healthcare system this is difficult to understand) -it is a key finding that determinants of depression were similar, regardless of history of depression; however, I would like to see this analysis repeated with a ref category of no depression + history to verify this conclusion -please provide a footnote….were all variables in Table 2 entered simultaneously into the model and adjusted for each other? Please report the n, %, and unadjusted ORs for Table 2 and 3 Limitations -not having measured antidepressant use is a key limitation when neonatal outcomes were considered -also – need to identify that treatment outside of inpatient/outpatient system was not included as a covariate Interpretation -true that 'the first episode of depression is not uncommon during pregnancy'…but equally true and important is that pre-conception depression was almost as common -the interpretation section requires greater depth to provide context around the findings and to discuss why these associations may be present. In its present form, it is the weakest section of the paper. The only way that I can think to adequately do this is to split the paper as previously recommended -for example, there is a need to provide possible explanation as to why these findings show positive significant associations between prenatal depression and adverse neonatal outcomes, when other studies do not Article summary – recognizing that word limit is an issue, would highly recommend defining the outcomes of pregnancy that were worse among with depression than without

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

In this large population-based and register-based study some associated factors for depression during pregnancy were analyzed. This topic has not been previously largely examined in this kind of scale. The same group has previously published similar analysis for postpartum depression, and some overlapping between these studies exists. This does not disturb the present analysis, because interest is now concentrated into the antepartal period. However, because postpartal depression is often more severe and – obviously, looking at the risk of suicide, more important than the antepartal depression, the authors could discuss more of associating features between ante- and postpartal diseases. Also the main interest of obstetrical complications is now in late pregnancy and delivery, and the harmful events at early pregnancy (bleeding, imminent abortion, findings in fetal diagnosis and trisomy screening et cet) are not correspondingly presented.

A large part in discussion covers the strengths and limitations of the study. Is it really needed? I am not very convinced that the diagnostic accuracy of depression in this study is completely representative for the whole problem.

We have now discussed more maternal consequences and rewrote the interpretation.

Similarly, speaking of “social deprivation” is now based on the SES-scale used in Finland, and in my opinion the present SES-scale does not very well describe the social well-being of any individual person. Thus “social deprivation” would be replaced by some more cautious term.

We replaced social deprivation by low socioeconomic status.

Maybe the next study by this group will be directed to the risk of suicide during pregnancy and at postpartal period?

Thank you for this novel idea.

Reviewer 2.

Thank you for the opportunity to review this manuscript. It addresses an important, understudied topic related to determinants of prenatal depression, and does so using population-based data.

Abstract:
-should indicate years of data included in study

Done.

Background:
-It is important to note for ref 2 in the introduction…in which country these data were collected and for what period of time

Revised as suggested.

-The background requires greater focus in highlighting the main gaps in the current literature

leading to the study purpose. The background ‘bounces’ between the determinants and consequences of perinatal depression and could benefit from improved organization and highlighting of key gaps (the ‘why’ this study is important should be highlighted more)

We rewrote the introduction and highlighted more the gap between the literature and our study.

-unclear why the purpose states (line 23) ‘especially in women with no previous depression episodes’ when pre-pregnancy depression was a factor of interest in the study
-given the intent of the study to examine a variety of risk factors, the title might need a bit of readjustment

We revised aim of the study; our aim was to study an association between a history of depression prior to pregnancy, and major depression during pregnancy.

Purpose
-my initial impression is that too much is being covered in this paper. I would recommend splitting into 2 papers: i) determinants of prenatal depression; and ii) consequences of prenatal depression and mediators of association between prenatal depression and neonatal outcomes

The referee is correct, but we decided to revise the paper based on other comments and not to split it into two different papers, because the journal also publishes the first submitted manuscript drafts as supplementary material. This type of publication means that we actually cannot submit the possible second paper elsewhere, at last not in the same format (the same types of analyses).

Methods:
-
-please describe what the specialized health care units are. This is important because it provides context for the diagnostic coding/prevalence rates

Describes in methods.

-rationale for dates studied (2002-2010) should be provided

The present time period was chosen because first aim was to study a prior history of major depression and that information was available since 1996 for inpatient care and since 1998 for outpatient visits.

-depression and anxiety are comorbid in as many as 50% of pregnant women….rationale for limiting to depression alone?

The reviewer is correct, depression and anxiety are highly comorbid. However, the impact of anxiety in the context of depression is best examined by taking into account the level of symptoms of anxiety, which we unfortunately are unable to do, due to the nature of a register based study (i.e., there are no registers related to the levels of anxiety symptoms available). Of course, we could also use the diagnoses of anxiety disorders, as well. Although this is a very intriguing idea, currently our manuscript already contains very large amounts of data (as also observed by the reviewer), and thus we would prefer to concentrate only on depression.

Fear of childbirth was also physician-diagnosed in the present data and we have published another manuscript concerning an association between perinatal outcomes and fear of childbirth.

-rationale for limiting depression to ‘major depression’ should be stated e.g., depression not identified as ‘major depression’ has also been linked to poor child outcomes

Our Hospital Discharge Register includes information on diagnoses and procedures for inpatient and outpatient care only. Thus, due to the register based setting, we had no information on individuals with depressive symptoms not fulfilling the diagnostic criteria (i.e., questionnaire based data on the study participants).

-should briefly describe who provides the majority of prenatal care to Finnish women, and what depression screening approaches are utilized

Described in the methods section; primary health care is provided in health care centers mainly by general practitioners, nurses and midwives. All health care professionals are instructed to evaluate the mother's mental wellbeing as part of all appointments.

-please clarify → outpatient visits – who was likely to be the provider? (line 26 p6)

Defined as suggested.

-please clarify – for the variables listed on page 6-7 the registers that these variables were derived from

Clarified as suggested.

-how was fear of childbirth diagnosed? Is this routinely screened for in pregnant women?

We have previously published a paper on that topic. This paper describes screening and treatment of fear of childbirth in Finland. The paper was published in February 2014, and is cited in the present manuscript.

Analysis:
-the approach for the analysis does not make complete sense. It is unclear why the reference categories did not include ' no prenatal depression + has a history'

In the first model (Table 2) the reference group was women with no major depression during pregnancy without or with a history of depression prior to pregnancy.

In the second model (Table 3) risk factors for major depression during pregnancy were determined separately for the women without and with a history of major depression prior to pregnancy. For the women with major depression without a history of depression prior to pregnancy the reference group was women without major depression and a history of major depression prior to pregnancy. For the women with major depression with a history of depression prior to pregnancy the reference group was women without major depression during pregnancy without and with a history of depression prior to pregnancy (this reference group was changed based on the reviewer's comment).

-for first research aim, please describe how models built

Covariates were chosen based on bivariable analyses and literature. All selected covariates were entered simultaneously. (Tables 2 and 3)

-in looking at the results…it is unclear what the reference categories are in the analysis – further elaboration is required. By the time the categories are described in the results it is quite confusing (p9). For example, 'no antepartum depression (categories 1 and 2) as a reference population' requires too much effort to think this through in current format (line 13 p9)

We have revised that point throughout the paper.

-why was fetal sex included in models?

Fetal sex was significantly associated with major depression during pregnancy.

Results:
-% of women successfully linked between health registers should be reported

Our information was gathered from national health registers and using unique identification number of each woman we are able to link 100% of the information.

-the prevalence of 0.8% with major depression during pregnancy seems very low compared to studies of self-report measures, particularly when 46.9% had a history of depression. This was aptly noted in first paragraph of main findings. Some studies have shown a history of depression to be predictive of depression in pregnancy….so the low prevalence rate requires greater explanation of a thoughtful nature.

As described earlier, due to the register based study setting, we had no information based depressive symptoms (i.e., self-reported, questionnaire based data). The self-reported questionnaires typically provide data on “elevated depressive symptoms”, a concept referring to a state of different severity compared with a diagnosis of depression. Thus, the prevalence figures provided based on questionnaire data are not comparable to the data based on diagnoses of depression, the latter being lower. At the beginning of our discussion, we refer to another diagnosis-based study that observed prevalence figures of the level similar to those in our study.

-if possible please provide estimate of the % of women who would be diagnosed and treated in primary healthcare…and please describe primary health care (versus specialty health care units….for those outside of the Finnish healthcare system this is difficult to understand)

Unfortunately, we have no access to the type of data the reviewer refers to. Nevertheless, within the Finnish system, high-risk pregnancies such as women with a diagnosis of depression are treated by specialized maternity care, and thus it is likely that we had information on most women with major depression.

-it is a key finding that determinants of depression were similar, regardless of history of depression; however, I would like to see this analysis repeated with a ref category of no depression + history to verify this conclusion

In the present paper we have three different types of analyses of risk factors for major depression, and also analysis suggested by the reviewer is now performed.

1. Risk factors for major depression, the reference group women without major depression without or with a history of major depression prior to pregnancy
2. Risk factors for major depression without a history of major depression prior to pregnancy, the reference group women without major depression and without a history of major depression prior to pregnancy
3. Risk factors for major depression with a prior history of major depression, the reference group women without major depression without or with a history of major depression prior to pregnancy

-please provide a footnote….were all variables in Table 2 entered simultaneously into the model and adjusted for each other? Please report the n, %, and unadjusted ORs for Table 2 and 3

Done.

Limitations
-not having measured antidepressant use is a key limitation when neonatal outcomes were considered
-also – need to identify that treatment outside of inpatient/outpatient system was not included as a covariate

These facts were included in the limitations.

Interpretation
-true that 'the first episode of depression is not uncommon during pregnancy'…but equally true and important is that pre-conception depression was almost as common

We have now added discussion related to this issue to the interpretation section.

-the interpretation section requires greater depth to provide context around the findings and to discuss why these associations may be present. In its present form, it is the weakest section of the paper. The only way that I can think to adequately do this is to split the paper as previously recommended

Revised as suggested. Regarding the suggestion of splitting the paper to two manuscripts, we kindly refer to our earlier response to this issue.

-for example, there is a need to provide possible explanation as to why these findings show positive significant associations between prenatal depression and adverse neonatal outcomes, when other studies do not
Revised as suggested.

Article summary – recognizing that word limit is an issue, would highly recommend defining the outcomes of pregnancy that were worse among with depression than without.

The sentence has been added.

VERSION 2 – REVIEW

REVIEWER	Pertti Kirkinen Dept Obstet Gynecol, University of Tampere Finland
REVIEW RETURNED	08-Jun-2014

GENERAL COMMENTS	Many of the findings of this study are self-evident and do not give much clinical impact. The tables are very heavy for a reader. However, this large population-based study by proper statistical methods gives, in spite of the fact that its clinical importance is not very high, some relevant information for epidemiology and social sciences, for example. Thus I am suggesting acceptance.

REVIEWER	Dawn Kingston University of Alberta, Alberta, Canada
REVIEW RETURNED	02-Jul-2014

GENERAL COMMENTS	Abstract – results indicate 53.1% had a history of depression prior to

	pregnancy but Results section p9 line 36 indicates that 53.1% did NOT have a history of depression Manuscript – -the introduction is incomplete in that only studies without significant associations between prior history of depression and antenatal depression are described (Lancaster); however at least 2 additional studies (Austin; Milgrom) have found significant associations and this is not mentioned -the models (Table 2, 3) are virtually the same, suggesting that the specific risk factors and their magnitudes are similar whether women have a history of depression or not. While examining factors associated with major depression is an interesting approach, it was complex, difficult to interpret meaning, and its rationale is not clear. It is unclear what models in Table 3 add beyond that presented in Table 2 – and I would recommend deleting models in Table 2 from the paper. The model in Table 2 is clear – suggesting that previous history is a major risk factor with significant clinical implications. -An additional concern with the data as presented is that fear of childbirth (Models in table 3) is identified as the strongest predisposing factor for major depression. Firstly, the data for the independent and dependent variables were collected simultaneously, and thus it cannot be said that fear is a predisposing factor; rather, it is a correlate or factor associated with depression. Secondly and more importantly, I think this is misleading. Looking at Table 2, the strongest association is between history of depression and depression in pregnancy. This is a key message that is lost in the discussion and results. -again, be careful in the discussion about framing the findings as predisposing risk factors…they are risk factors or correlates -On page 11 line 49 the key results seem to be unrelated to the main questions of the paper (factors associated with major depression; outcomes of major depression). Main findings could be elucidated much more clearly in the first paragraph of the Discussion section -the paper needs to centre much more around the main questions. For example, the title and sections of the discussion focus on SES and health behaviours. Yet, the main questions are related to factors associated with major depression and outcomes of major depression. I would strongly urge the authors to keep the message consistent and clear and related to the key questions. The key questions are significant in this field, need to be addressed well, and would be important pieces of evidence given the population-based approach. Thus, major revisions to the discussion section are required. -p33 lines 19-24 – this statement is very important in terms of the rigor of the study. It should be substantiated with data – not simply supposition -I would highly recommend that the paper be framed around risk factors for major depression in pregnancy, versus low SES and unhealthy behaviours, as in the title etc. Few studies have been conducted regarding risk factors for mental health in pregnancy, and a population-based analysis of this nature would be a welcomed contribution to the evidence

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Pertti Kirkinen
Institution and Country Dept Obstet Gynecol, University of Tampere Finland
Please state any competing interests or state 'None declared': None declared

Many of the findings of this study are self-evident and do not give much clinical impact. The tables are very heavy for a reader. However, this large population-based study by proper statistical methods gives, in spite of the fact that its clinical importance is not very high, some relevant information for epidemiology and social sciences, for example. Thus I am suggesting acceptance.

Table 3 has been deleted now.

Reviewer: 2
Reviewer Name Dawn Kingston
Institution and Country University of Alberta, Alberta, Canada
Please state any competing interests or state 'None declared': None declared

Thank you for the opportunity to review this important work.
Abstract – results indicate 53.1% had a history of depression prior to pregnancy but Results section p9 line 36 indicates that 53.1% did NOT have a history of depression

This has been corrected now.

Manuscript –
-the introduction is incomplete in that only studies without significant associations between prior history of depression and antenatal depression are described (Lancaster); however at least 2 additional studies (Austin; Milgrom) have found significant associations and this is not mentioned

We could not find any previous studies by Austin or Milgrom that reported an association between history of depression and antenatal depression. We found a study by Milgrom et al., which reported an association between antenatal depression/history of depression and postpartum depression (Antenatal risk factors for postnatal depression: a large prospective study).

In the present paper we cited a recent systematic review, which included large number of manuscripts considering risk factors for antenatal depression.

-the models (Table 2, 3) are virtually the same, suggesting that the specific risk factors and their magnitudes are similar whether women have a history of depression or not. While examining factors associated with major depression is an interesting approach, it was complex, difficult to interpret meaning, and its rationale is not clear. It is unclear what models in Table 3 add beyond that presented in Table 2 – and I would recommend deleting models in Table 2 from the paper. The model in Table 2 is clear – suggesting that previous history is a major risk factor with significant clinical implications.

We deleted Table 3 and added a sentence in the discussion that risk factors for antenatal depression were somewhat the same among woman with and without history of depression prior to pregnancy.

-An additional concern with the data as presented is that fear of childbirth (Models in table 3) is identified as the strongest predisposing factor for major depression. Firstly, the data for the independent and dependent variables were collected simultaneously, and thus it cannot be said that fear is a predisposing factor; rather, it is a correlate or factor associated with depression.
This has been revised throughout the paper.

Secondly and more importantly, I think this is misleading. Looking at Table 2, the strongest association is between history of depression and depression in pregnancy. This is a key message that is lost in the discussion and results.

We revised the discussion and conclusion of the paper.

-again, be careful in the discussion about framing the findings as predisposing risk factors…they are risk factors or correlates
-On page 11 line 49 the key results seem to be unrelated to the main questions of the paper (factors associated with major depression; outcomes of major depression). Main findings could be elucidated much more clearly in the first paragraph of the Discussion section
-the paper needs to centre much more around the main questions. For example, the title and sections of the discussion focus on SES and health behaviours. Yet, the main questions are related to factors associated with major depression and outcomes of major depression. I would strongly urge the authors to keep the message consistent and clear and related to the key questions. The key questions are significant in this field, need to be addressed well, and would be important pieces of evidence given the population-based approach. Thus, major revisions to the discussion section are required.
-p33 lines 19-24 – this statement is very important in terms of the rigor of the study. It should be substantiated with data – not simply supposition

The discussion and the conclusion have been revised based on the comment. In the discussion second and third paragraphs are now better connected to each other, but we did not delete the analyses concerning whether SES and smoking contributed adverse perinatal outcomes, since that is important information. Low SES and smoking are risk factors for depression and also important associated factors with adverse perinatal outcomes. That is now also presented in the introduction.

-I would highly recommend that the paper be framed around risk factors for major depression in pregnancy, versus low SES and unhealthy behaviours, as in the title etc. Few studies have been conducted regarding risk factors for mental health in pregnancy, and a population-based analysis of this nature would be a welcomed contribution to the evidence

We have revised the paper as suggested, for example the title and the conclusion were revised.

VERSION 3 - REVIEW

REVIEWER	Dawn Kingston University of Alberta, Canada
REVIEW RETURNED	08-Aug-2014

GENERAL COMMENTS	Thank you for the opportunity to review this submission. Introduction: -line 30 – it is more accurate to indicate that few studies of predictors of antenatal depression have been conducted, because most of these have in fact included history of depression as a predictor --given the equal prevalence of antenatal depression and anxiety, and the paradigm shift in perinatal mental health to encompass more than just depression (Priest; Austin), clear justification needs to be made as to why only depression is focused on in this study (or, identified as a limitation if the data are not available) -given that SES was a main confounder (p8 line 47) but missing in 40% of cases, the discussion needs to include and place into context the significant AOR of 'missing SES' (e.g., it is unlikely that

	this is random……are there any other data from studies based on these databases that can provide insight into the characteristics of women who do not provide income data – for example, do they tend to be lower or higher income women?) -p11 line 57 should clarify….the sample was similar to general population based on WHAT socio-demographics, if not SES? -the discussion does not place the findings in context of other literature -while the low prevalence rate of MDD is mentioned, it is not discussed -p11 line 13-15 beginning 'outcomes of pregnancy' should be elaborated upon (e.g., associated with major depression during pregnancy phrase does not make sense within this sentence) -even though various models with /without smoking were run, it does not appear that formal meditational analyses were conducted. Thus, the statements regarding smoking as a mediator are suppositional and not demonstrated by the current analysis.

VERSION 3 – AUTHOR RESPONSE

Introduction:
-line 30 – it is more accurate to indicate that few studies of predictors of antenatal depression have been conducted, because most of these have in fact included history of depression as a predictor

Introduction revised as suggested.

--given the equal prevalence of antenatal depression and anxiety, and the paradigm shift in perinatal mental health to encompass more than just depression (Priest; Austin), clear justification needs to be made as to why only depression is focused on in this study (or, identified as a limitation if the data are not available)

Unfortunately, we did not have information on anxiety, which has been acknowledged as a limitation. Furthermore, we mentioned this aspect in thetext and cited the papers by Austin and Priest.

-given that SES was a main confounder (p8 line 47) but missing in 40% of cases, the discussion needs to include and place into context the significant AOR of 'missing SES' (e.g., it is unlikely that this is random……are there any other data from studies based on these databases that can provide insight into the characteristics of women who do not provide income data – for example, do they tend to be lower or higher income women?)
-p11 line 57 should clarify….the sample was similar to general population based on WHAT socio-demographics, if not SES?

For the present study information on SES was imputed based on other variables in the models such as smoking, maternal age, parity etc, which did not change the results suggesting that missing SES was quite random. Also our previous analyses are in line with this assumption. The sentence has been revised as suggested.

-the discussion does not place the findings in context of other literature

We have now discussed maternal perinatal mental health in the discussion as regards its complexity, confounding factors, and diagnostic problems.

-while the low prevalence rate of MDD is mentioned, it is not discussed

Revised as suggested; use of self-reported screening methods may overestimate the prevalence of depression, which in turn suggests that their sensitivity and specificity are not adequate.

-p11 line 13-15 beginning ‘outcomes of pregnancy’ should be elaborated upon (e.g., associated with major depression during pregnancy phrase does not make sense within this sentence)
Revised as suggested.

-even though various models with /without smoking were run, it does not appear that formal meditational analyses were conducted. Thus, the statements regarding smoking as a mediator are suppositional and not demonstrated by the current analysis.

We did not perform exact meditational analyses since the associations between SES, smoking and depression are very complex. Whether there is causation between smoking and depression and how these are linked with each other, i.e., whether depression leads to smoking or smoking alters the risk of depression, could not be fully evaluated in the present setting.