PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Contribution of Stress to the Comorbidity of Migraine and Major Depression: Results from a Prospective Cohort Study
AUTHORS	Colman, Ian; Swanson, Sonja; Zeng, Yiye; Weeks, Murray

VERSION 1 - REVIEW

REVIEWER	Dr. Z. Samaan, MBChB, DMMD, MSc, PhD, MRCPsych Assistant Professor, Dept of Psychiatry and Behavioural Neurosciences Associate Faculty, Population Genomics Program Associate Member, Dept of Clinical Epidemiology and Biostatistics, McMaster University Staff Psychiatrist, St. Joseph's Healthcare Hamilton and Hamilton Health Sciences Mood Disorders Program I have no competing interests.
REVIEW RETURNED	24-Sep-2012

THE STUDY	important study details are missing such as sample size included in the analysis at base line and follow up. no power estimation is provided. the study participants are not described adequately, including the inclusion and exclusion criteria. other comments are in the attached file.
RESULTS & CONCLUSIONS	missing elements of sample size and power may make the current conclusions difficult to interpret.
REPORTING & ETHICS	STROBE statement guidelines should be used to report this study. elements from STROBE are missing. ethics and consent are not applicable as authors used census data. I am unaware of any undeclared conflicts. the authors do need however to distinguish this study from previously reported similar study from the same dataset.
GENERAL COMMENTS	**Major general concerns** 1. The literature review is too narrow and many studies cited are restricted to studies reported migraine and depression findings from the same Canadian census dataset. 2. The authors need to introduce and discuss the impact of stressors and socioeconomic factors on both conditions. How might these factors explain a common aetiology or confounding effects? 3. A flow diagram following STROBE checklist should be provided 4. Number of study participants with the conditions of interests at baseline and each follow up point should be provided. 5. Follow the STROBE checklist, for example, items 13 and 14, b, provide the number of participants with missing data for

	each variable of interest. This is especially important in the presence of nine models to be tested and each model includes further variables. What is the number of subjects with migraine, depression included in model 9 for example? 6. Power estimation for the given sample size should be provided. For example the number of individuals with migraine and depression at baseline was 120, what is the power of a sample size of 120 to reject the null hypothesis? How many subjects out of 120 were present at each cycle of follow up? What is the final number? 7. Details of the questionnaires used in the census data should be provided 8. Most importantly, the authors need to explain the rationale for conducting a study on the same dataset asking similar questions to an earlier study cited in the introduction "Modgill et al" however reaching different conclusions? (A Population-Based Longitudinal Community Study of Major Depression and Migraine. Geeta Modgill, MSc; Nathalie Jette, MD, MSc; Jian Li Wang, PhD; Werner J. Becker, MD; Scott B. Patten, MD, PhD. Headache 2012;52:422-432). **Specific concerns** 1. On page 5, lines 25-35, the authors state that Modgill et all study "looked at a limited number of stressors ….". in fact this study, using the same dataset and longer duration of follow up (12 years), looked at the following factors: age, sex, marital status, income, education, smoking, self esteem, social support, chronic stress, childhood trauma, chronic conditions and family history of depression. 2. Methods of ascertaining "incident depression". CIDI-SFMD investigates depressive symptoms within the past 12 months only. Given the episodic and recurrent nature of depression, the absence of positive score to this question does not eliminate the possibility of prior depressive episodes and therefore the use of "incident" cases of depression should be considered very carefully and perhaps replaced with point prevalence. 3. Methods: Migraine assessment by a single question is very likely to overestimate the true prevalence. The authors mention this in the discussion [page 13, lines 15-25] and justifying these rates by citing similar rates in other Canadian studies (references 14 and 22). Both these references referring to data from the same census, and therefore not helpful in supporting the authors' argument. Studies from independent data sources should be cited to support these figures. 4. Methods: Stressors. Page 7, Line 33, "change in social support" how was this measured and what does "yes" mean in the results, change to the better? 5. Page 8, line 15, provide list of questions used in Cycle 4 and what are the new 7 added questions compared to earlier cycles. This will help to assess the differences between current study and previous reports of the same dataset. 6. Statistical methods, page 8. Provide power calculation for a given sample size.

	7. Results page 10, provide number of subjects for each given per cent at each cycle of follow up. Flow diagram will help here. Also provide inclusion and exclusion criteria for the study participants. 8. Show differences in socio-demographics and depression, migraine prevalence for completers versus non-completers of the survey. 9. Table 1. Provide mean age and SD; provide sample size for each variable. 10. Table 2, provide sample size for each variable at follow up, for example, I suspect model 9 has the least number of subjects based on the number of variables included. Same for Table 3. 11. Discussion. Several limitations should be included such as power, other confounders that may explain this association (socioeconomic status may be associated with stressors and with each condition independently; chronic stress may predict the onset of each disorder…). 12. Page 11, lines 38-43, these conclusion may not be justified based on the current findings as other confounders may be as important as stress 13. Page 12, lines 3-10. This argues for shared risk factors and does not disprove the bidirectional relationship despite stress. 14. Page 13, line 8 “rich assortment of well-validated stress measures” what are the validity data for such measures? 15. Same page line 9 “nationally-representative nature of the study”, the authors provide no data regarding the recruitment of study subjects from Canada, the study sample of over 9,000 participants were drawn from which parts of the country? 16. Page 13, line 13, “sample size and length of follow up are exceptional”. In fact we have no idea about the actual sample size with the conditions of interests and previous studies follow up duration was up to 12 years. 17. Page 14, lines 20-22. The sentence starting with “severity appears” is not clear, please rewrite. Same page line 25, please replace “mental health disorder” with psychiatric disorder. 18. References. Few references missing page numbers, volume, year, for example references 16 and 23

REVIEWER	Francoise Radat, CHU Pellegrin, Bordeaux, France no competing interest
REVIEW RETURNED	01-Oct-2012

GENERAL COMMENTS	This paper aims at studying comorbidity between migraine and major depression, considering specifically the reason for the comorbidity. From this perspective two questions are asked: - what is the temporal relationship between each disorder?- does stress account for a part of the association? In order to respond to these questions, the authors proposed a prospective epidemiological study set up in the Canadian general population. These points are the strength of the study.

	Nevertheless some points need to be clarified: 1)The representativeness of the sample: the study design selected a sample of 17,276 subjects. But only 9,054 were included in the present analysis (start of the study 2000/2001). What is the representativeness of this sub-sample? 2)How many subjects were lost between 2000/2001 and 2008/2009, the end of the study? This data is only given for 2006/2007. 3)In the present study there is not a follow-up from 1994/1995 to 2008/2009 as it is specified in the abstract but between 2000/2001 and 2008/2009. This should be clarified. 4)The diagnosis of migraine relies only on the subject's self-report assessed by one question. This is the major weakness of the study. It should be specified in the abstract. Do we have Canadian data of the concordance between self-report migraine and other assessment methods? I think that there is European and US data for this. It should be added in the discussion. 5)In the introduction the reference 16 (Antonaci) is presented as a meta-analysis. It is in fact a review of literature. 6)Among childhood traumas it seems that sexual abuse has not been assessed. This is a weakness of the study and should be pointed out in the discussion. 7)In my opinion we cannot consider marital problems, unemployment, financial problems and work stress as acute stress in opposition to chronic stress as it is proposed by the authors. The acute and chronic characteristics of stress depend on its duration. Here the question raised is mostly a question of the nature of the stress. So I would have proposed to identify « chronic stress » which in fact is « problems in relationships and family strife » as interpersonal stress. 8)In the discussion, the authors state that their study allows considering stress as a confounder in the evaluation of comorbidity between migraine and depression. This is a statistical point of view, but I would prefer a clinical point of view, considering stress as a common environmental risk factor between the two disorders.

REVIEWER	Geeta Modgill, MSc Research Associate / Epidemiologist Mental Health Commission of Canada Canada
REVIEW RETURNED	06-Oct-2012

GENERAL COMMENTS	1. General comments: The study is well done. The major area I feel needs addressing is that the authors may want more clearly acknowledge that the present study replicates as well as extends and solidifies the results of a previous study. It closely resembles the findings reported in Modgill's study. Both studies use the same data source and primary outcome variables (migraine and depression), chronic stress and childhood trauma. However, the present study does include an additional year of follow-up data and slightly different methodology therefore it is an addition to the body of research on the topic. 2. Methods: A more though description of the study sample inclusion/exclusion and loss to follow-up is recommended.

	This could be done in a flowchart detailing how non-depressed and non-migraine cohorts were constructed. 3. Methods: What proportion of respondents answered questions about stress and childhood trauma? 4. Methods: It was noted that Cycle 4 was considered "baseline" so that the assessment of migraine and depression reflected current rather than diagnostic histories. Please clarify how the first three assessments (1994/1995, 1996/1997, 1998/1999) used to construct a several-year history of each disorder prior to baseline. Were the migraine history and depression history variables included as covariates in any of the models presented? 5. Methods: Research has shown that family history of depression is a significant risk factor for MDE, was this included in any models? 6. Statistical Analysis: As data was collected for migraine and depression at baseline and every 2 years thereafter, why were time-varying exposure variables not used? Could the analysis be repeated using time-varying variables and included in the results? 7. Results: In paragraph one, the description of results from Table 1 is not very clear. It would be helpful to indicate that 4.13% is a measure of the prevalence of depression in 2000/2001. 8. Results: In paragraph two, please clarify how the incidence of migraine value of 5.52% was calculated. Is this an incident proportion/ cumulative incidence proportion? If the former, how was the denominator calculated? 9. Discussion: The authors need to include add a paragraph on how confounding and bias could be impacting the results. Please explain how the disappearance of the association after adjustment for stress may be caused by the introduction of bias. Could a weakening of effect be caused by the occurrence of a causal chain of events, or caused by confounding? In which case, is adjustment for the variable as a confounder justified? If depression contributes to the experience of stress, would adjustment be inappropriate and could it underestimate the impact of depression? Could the exposure to stress lead to both an increased risk of depression and migraine, in other words this variable may be a shared risk factor?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

important study details are missing such as sample size included in the analysis at base line and follow up. no power estimation is provided. the study participants are not described adequately, including the inclusion and exclusion criteria.

missing elements of sample size and power may make the current conclusions difficult to interpret.

RESPONSE: We have tried to clarify the sample sizes used in these analyses, including adding a figure to illuminate inclusion/exclusion criteria for our two analytic samples.

STROBE statement guidelines should be used to report this study. elements from STROBE are missing.

RESPONSE: We have gone through a STROBE checklist and incorporated all elements into our manuscript. This checklist is included at the end of this letter.

ethics and consent are not applicable as authors used census data. I am unaware of any undeclared conflicts. the authors do need however to distinguish this study from previously reported similar study from the same dataset.

RESPONSE: We have revised our introduction to more clearly describe how our study has specific goals that extend beyond the work from Modgill et al.

This study investigates the contribution of environmental factors, more specifically stress, to depression-migraine comorbidity. The authors used Canadian census data, the National Population Health Survey (NPHS) to address the study question.

The authors conclude that although a bidirectional association between migraine and depression exits, this association can be explained by the presence of chronic stress.

Major general concerns
1. The literature review is too narrow and many studies cited are restricted to studies reported migraine and depression findings from the same Canadian census dataset.

RESPONSE: We have revised our literature review in the introduction to focus further on studies justifying stress conceptually as a confounder, and highlight the recent meta-analysis of 12 studies, with detailed descriptions of the few prospective studies on the migraine-depression association. One of these studies, by Modgill et al, is indeed from the same population-based dataset, and we comment more specifically on how our results extend from theirs.

2. The authors need to introduce and discuss the impact of stressors and socioeconomic factors on both conditions. How might these factors explain a common aetiology or confounding effects?

RESPONSE: We have added more discussion of this to the introduction:

p. 4-5: “Few studies, however, have focused on stress, a known risk factor for both migraine and depression. In Modgill and colleagues’ analyses of the National Population Health Survey (NPHS), a representative longitudinal study of the Canadian population, childhood trauma attenuated the association between the two disorders, particularly for the direction of depression predicting migraine onset. However, their analyses only looked at a limited number of stressors and did not attempt to

address specifically how much different types of stressors may contribute to this association. A variety of stressors may confound the migraine-depression association, as many types have been found to be risk factors for both disorders: e.g., childhood trauma, unemployment, chronic/repeated stress, etc."

3. A flow diagram following STROBE checklist should be provided

RESPONSE: We have added this as Figure 1 to our report.

4. Number of study participants with the conditions of interests at baseline and each follow up point should be provided.

RESPONSE: This information is now better described in Figure 1 and in the text (p. 6).

5. Follow the STROBE checklist, for example, items 13 and 14, b, provide the number of participants with missing data for each variable of interest. This is especially important in the presence of nine models to be tested and each model includes further variables. What is the number of subjects with migraine, depression included in model 9 for example?

RESPONSE: Sample size for each model has been added to the tables.

6. Power estimation for the given sample size should be provided. For example the number of individuals with migraine and depression at baseline was 120, what is the power of a sample size of 120 to reject the null hypothesis? How many subjects out of 120 were present at each cycle of follow up? What is the final number?

RESPONSE: Given our focus on the role that stress may play in the assessed associations, we feel a power estimation is inappropriate: we are primarily interested in the change in effect estimate when adjusting for stress in the models and not the specific size of the estimate. If the editor views a power analysis for the crude association between migraine and depression (and vice versa) as being beneficial, we can add this. Notably, we see in the results that we had more than sufficient power to detect the crude associations (Model 1 in Table 2, Model 1 in Table 3). We also know a priori that finding a positive and "significant" crude association was likely given the previous work by Mogdill et al in the same study population.

7. Details of the questionnaires used in the census data should be provided

RESPONSE: We have updated our methods section to provide details on each of the measures we used. Reference #24 provides more information on the breadth and selection of questions in the NPHS.

8. Most importantly, the authors need to explain the rationale for conducting a study on the same dataset asking similar questions to an earlier study cited in the introduction "Modgill et al" however reaching different conclusions?
(A Population-Based Longitudinal Community Study of Major Depression and Migraine. Geeta Modgill, MSc; Nathalie Jette, MD, MSc; Jian Li Wang, PhD; Werner J. Becker, MD; Scott B. Patten, MD, PhD. Headache 2012;52:422-432).

RESPONSE: We hope we have clarified our intent of extending their findings and answering a new question, specifically, how much does stress explain the association between migraine and depression seen in their and others' studies. We have reframed our introduction to clarify this.

Specific concerns

1. On page 5, lines 25-35, the authors state that Modgill et all study “looked at a limited number of stressors ….”. in fact this study, using the same dataset and longer duration of follow up (12 years), looked at the following factors: age, sex, marital status, income, education, smoking, self esteem, social support, chronic stress, childhood trauma, chronic conditions and family history of depression.

RESPONSE: We note that we used the shorter follow-up in order to introduce more types of stressors that were not measured consistently throughout the 12 years in their study (and 14 years we had access to). Our report was specifically interested in stressors as confounders, while Modgill et al looked at these and others in their analyses. Specifically, we note that while both manuscripts looked at chronic stress and childhood trauma, we looked at changes in social support, marital status, and employment (as opposed to just absolute amounts studied by Modgill et al), and work stress.

2. Methods of ascertaining “incident depression”. CIDI-SFMD investigates depressive symptoms within the past 12 months only. Given the episodic and recurrent nature of depression, the absence of positive score to this question does not eliminate the possibility of prior depressive episodes and therefore the use of “incident” cases of depression should be considered very carefully and perhaps replaced with point prevalence.

RESPONSE: We agree that this is a limitation and have stated it as such in our discussion. However, point prevalence would not be an appropriate term either as we are looking at whether they reported a new depressive episode at any of the subsequent time points (2, 4, 6, or 8 years later). We prefer to keep the terminology as “incident” and highlight in our limitations paragraph how measurement error is a concern. The following has been added:

p. 13-14: “While the measure of major depression (CIDI-SFMD) has demonstrated psychometric properties, the 12-month diagnosis (which thus does not cover the 2 years between each study assessment) hinders inference about history of major depression, possible episodes unmeasured in the gap years of the study, and actual timing of onset of the disorder; subjects who have less frequent depressive episodes or episodes that are shorter in duration would be less likely to be measured accurately. However, by using an interim cycle as “baseline”, we were able to construct over a half-decade profile of subjects’ “history” of major depression to diminish the issue regarding assessing history.”

3. Methods: Migraine assessment by a single question is very likely to overestimate the true prevalence. The authors mention this in the discussion [page 13, lines 15-25] and justifying these rates by citing similar rates in other Canadian studies (references 14 and 22). Both these references referring to data from the same census, and therefore not helpful in supporting the authors’ argument. Studies from independent data sources should be cited to support these figures.

RESPONSE: We have now included further information on measurement error for our single-question migraine assessment, citing studies regarding its validity (using other samples) and noting it as a limitation: “Self-reported symptom-based assessments do generally report a higher prevalence than doctor diagnoses; the assessment in the NPHS inquires about diagnosis by a health professional which may offset some of this over-reporting, but certainly misclassification may still be an issue. Specifically, self-report may be further inflated in depressed individuals, which may actually contribute to some overestimation in our associations.”

4. Methods: Stressors. Page 7, Line 33, “change in social support” how was this measured and what does “yes” mean in the results, change to the better?

RESPONSE: We thank the reviewer for noting this omission, and have clarified in the text: “Social support was measured by a 4-question scale in Cycles 3 and 4 (1998/99; 2000/01); this score was dichotomized at the median, and change in social support was conceptualized as a change from high to low social support.”

5. Page 8, line 15, provide list of questions used in Cycle 4 and what are the new 7 added questions compared to earlier cycles. This will help to assess the differences between current study and previous reports of the same dataset.

RESPONSE: We have clarified the timing of questions in the text and with the figure. Notably, work stress and chronic stress were not asked until Cycle 4; childhood trauma was updated in Cycle 4 for those who were not yet aged 18 in Cycle 1; and changes in employment, marital status, and social support all require at least two cycles to be defined and thus could not have been defined until at least Cycle 2.

6. Statistical methods, page 8. Provide power calculation for a given sample size.

RESPONSE: Please see our comment above regarding power calculations.

7. Results page 10, provide number of subjects for each given per cent at each cycle of follow up. Flow diagram will help here. Also provide inclusion and exclusion criteria for the study participants.

RESPONSE: Please see our new Figure 1 for this information.

8. Show differences in socio-demographics and depression, migraine prevalence for completers versus non-completers of the survey.

RESPONSE: We have added information regarding loss to follow-up in our study, both in Figure 1 and our limitations section: “Finally, we did not have complete follow-up for all subjects. Weighting was used to correct for attrition between Cycles 1 and 4. From Cycle 4 through 8 the majority of subjects were assessed eight years later (see Figure 1), and follow-up duration was not associated with migraine or depression status at baseline. Follow-up duration, however, was associated with age and a few stressors (greater chronic stress, recent unemployment, and recent divorce were associated with shorter follow-up; p’s<0.05); however, as stress likely predicts higher levels of the outcome disorders, its likely this implies that some subjects were censored prior to onset of the outcome, meaning that stress would explain even more of the association measured had complete follow-up occurred.

9. Table 1. Provide mean age and SD; provide sample size for each variable.

RESPONSE: We have incorporated this information in the table.

10. Table 2, provide sample size for each variable at follow up, for example, I suspect model 9 has the least number of subjects based on the number of variables included. Same for Table 3.

RESPONSE: We have updated the tables with this information as well.

11. Discussion. Several limitations should be included such as power, other confounders that may explain this association (socioeconomic status may be associated with stressors and with each condition independently; chronic stress may predict the onset of each disorder…).

RESPONSE: Certainly other confounders may be part of the pathway that connects stress to each of

these disorders; however, even if stress is part of a more complex pathway of confounding it itself would still be a confounder in the epidemiologic sense of the word. We have added some discussion on how this complexity might temper our conclusions regarding stress-reducing interventions: “Utilizing a stress-reducing strategy to address this comorbidity assumes that stress is (directly or indirectly) causative of both disorders, while it is possible that stress is a risk factor through associations with a common cause.”

12. Page 11, lines 38-43, these conclusion may not be justified based on the current findings as other confounders may be as important as stress

RESPONSE: We have altered the wording here to allow consideration of other important confounders.

13. Page 12, lines 3-10. This argues for shared risk factors and does not disprove the bidirectional relationship despite stress.

RESPONSE: We note that when accounting for all stressors in the model, migraine no longer is significantly predictive of depression and vice versa; thus, while there may be a bidirectional relationship despite stress, it cannot explain the full effect measured in this study.

14. Page 13, line 8 “rich assortment of well-validated stress measures” what are the validity data for such measures?

RESPONSE: We have taken out this wording regarding validity, stating instead that the stress measures considered are widely used in the literature. These measures have been used in numerous Statistics Canada reports and independent studies, including papers published in the American Journal of Epidemiology, the Canadian Medical Association Journal, and Social Psychiatry and Psychiatric Epidemiology. Our methods section incorporates information regarding the validity of these stress measures as available.

15. Same page line 9 “nationally-representative nature of the study”, the authors provide no data regarding the recruitment of study subjects from Canada, the study sample of over 9,000 participants were drawn from which parts of the country?

RESPONSE: We have added further description in the methods section regarding how the data were collected and weighted to be representative of the Canadian population.

16. Page 13, line 13, “sample size and length of follow up are exceptional”. In fact we have no idea about the actual sample size with the conditions of interests and previous studies follow up duration was up to 12 years.

RESPONSE: We hope our edits explaining sample size have clarified why we feel our sample size and length of follow-up are indeed noteworthy.

17. Page 14, lines 20-22. The sentence starting with “severity appears” is not clear, please rewrite. Same page line 25, please replace “mental health disorder” with psychiatric disorder.

RESPONSE: This sentence has been clarified, and the terminology has been changed.

18. References. Few references missing page numbers, volume, year, for example references 16 and 23

RESPONSE: We have updated our references to incorporate complete available information.

Reviewer #2

This paper aims at studying comorbidity between migraine and major depression, considering specifically the reason for the comorbidity. From this perspective two questions are asked:
- what is the temporal relationship between each disorder?- does stress account for a part of the association?
In order to respond to these questions, the authors proposed a prospective epidemiological study set up in the Canadian general population. These points are the strength of the study.

Nevertheless some points need to be clarified:
1)The representativeness of the sample: the study design selected a sample of 17,276 subjects. But only 9,054 were included in the present analysis (start of the study 2000/2001). What is the representativeness of this sub-sample?

RESPONSE: We hope the addition of Figure 1 provides clarity to this question. Specifically, the reduced sample size comes primarily from an age restriction (those ages 18-64 in 2000/01), with minimal loss to follow-up between study inception and 2000/01. For each analysis (migraine predicting incident depression, and vice versa), we further restrict to subjects who have not yet had the outcome disorder. We also note that in the original submission the manuscript quoted the sample size as n=9,054. This is indeed the appropriately weighted sample size. However, data in Figure 1 reflects unweighted sample sizes, which results in marginally different n's. We have tried to clarify when we are discussing weighted vs. unweighted analyses as clearly as possible.

2)How many subjects were lost between 2000/2001 and 2008/2009, the end of the study? This data is only given for 2006/2007.

RESPONSE: We have updated our study description to include loss to follow-up information.

3)In the present study there is not a follow-up from 1994/1995 to 2008/2009 as it is specified in the abstract but between 2000/2001 and 2008/2009. This should be clarified.

RESPONSE: We have clarified this in the abstract by stating that we used eight years of follow-up time in the present analyses.

4)The diagnosis of migraine relies only on the subject's self-report assessed by one question. This is the major weakness of the study. It should be specified in the abstract. Do we have Canadian data of the concordance between self-report migraine and other assessment methods? I think that there is European and US data for this. It should be added in the discussion.

RESPONSE: As stated above, we have updated our discussion of the validity of this measure, along with appropriate mention to its limitations.

5)In the introduction the reference 16 (Antonaci) is presented as a meta-analysis. It is in fact a review of literature.

RESPONSE: While the reference we intended to cite is also a systematic review, the authors report a meta-analysis of 12 studies within their manuscript. We have tried to clarify this in our discussion of their results: "In a recent review of such comorbidities, Antonaci et al reported a meta-analysis of 12 studies, concluding that the odds ratio may be near 2.2 for major depression and migraine."

6)Among childhood traumas it seems that sexual abuse has not been assessed. This is a weakness of the study and should be pointed out in the discussion.

RESPONSE: We have noted this as a limitation: "…these analyses represent a rich assortment of stressors, but several other stressors may also merit examination, e.g., childhood sexual abuse, acute recent traumas such as injury or illness, etc."

7)In my opinion we cannot consider marital problems, unemployment, financial problems and work stress as acute stress in opposition to chronic stress as it is proposed by the authors. The acute and chronic characteristics of stress depend on its duration. Here the question raised is mostly a question of the nature of the stress. So I would have proposed to identify « chronic stress » which in fact is « problems in relationships and family strife » as interpersonal stress.

RESPONSE: We have taken out terminology regarding acute and chronic versions of stress, and highlighted differences in type of stress, as per this suggestion.

8)In the discussion, the authors state that their study allows considering stress as a confounder in the evaluation of comorbidity between migraine and depression. This is a statistical point of view, but I would prefer a clinical point of view, considering stress as a common environmental risk factor between the two disorders.

RESPONSE: We have tried to address this in our introduction. Namely, we had viewed stress as already meeting the criteria for being a confounder (i.e., shared risk factor) clinically, because it is already known to be a risk factor for each disorder; we have expanded upon this point in our introduction. Thus, we try to show statistically how much of the crude association between these disorders can be explained by this common cause.

Reviewer #3

1. General comments: The study is well done. The major area I feel needs addressing is that the authors may want more clearly acknowledge that the present study replicates as well as extends and solidifies the results of a previous study. It closely resembles the findings reported in Modgill's study. Both studies use the same data source and primary outcome variables (migraine and depression), chronic stress and childhood trauma. However, the present study does include an additional year of follow-up data and slightly different methodology therefore it is an addition to the body of research on the topic.

RESPONSE: As stated above, we view our results as an extension of the Modgill et al study, where our focus is on how different types of stressors may explain the migraine-depression association seen in their study of this same sample. We hope that the edits to our introduction and discussion better highlight this distinction.

2. Methods: A more though description of the study sample inclusion/exclusion and loss to follow-up is recommended. This could be done in a flowchart detailing how non-depressed and non-migraine cohorts were constructed.

RESPONSE: Please see the newly added Figure 1.

3. Methods: What proportion of respondents answered questions about stress and childhood trauma?

RESPONSE: We have clarified the respondent sample sizes for each of our models presented in Tables 2 and 3. We hope this addresses this concern.

4. Methods: It was noted that Cycle 4 was considered “baseline” so that the assessment of migraine and depression reflected current rather than diagnostic histories. Please clarify how the first three assessments (1994/1995, 1996/1997, 1998/1999) used to construct a several-year history of each disorder prior to baseline. Were the migraine history and depression history variables included as covariates in any of the models presented?

RESPONSE: Disorder histories were used as exclusion criteria for assessing new onset of each disorder. We have clarified this in the methods section: “We performed two sets of analyses. First, among those with no history of major depression (unweighted n=7,818), we assessed the onset of incident major depression comparing those with and without migraine at baseline; second, among those with no history of migraine (unweighted n=7,765), we assessed the onset of incident migraine comparing those with and without major depression at baseline.”

5. Methods: Research has shown that family history of depression is a significant risk factor for MDE, was this included in any models?

RESPONSE: We did not include family history variables in our models. As we have tried to clarify (see comments above), our primary purpose is to assess whether and which kinds of stress play an explanatory role in the crude association between migraine and depression; other exposures (genetic or otherwise) were not part of our consideration. The reviewer raises an interesting point that there are other potential confounding effects that may warrant investigation (although we note that family history of depression would need to also be related to migraine for this to be a confounder); this is beyond the scope of our study, particularly as the family history variable in the NPHS is only self-report.

6. Statistical Analysis: As data was collected for migraine and depression at baseline and every 2 years thereafter, why were time-varying exposure variables not used? Could the analysis be repeated using time-varying variables and included in the results?

RESPONSE: A time-varying analysis would be an interesting approach for many important questions in this area of research, but it is beyond the scope of this manuscript. Notably, we are interested in whether stress, as shared risk factor of both migraine and stress, may explain much of the perceived association between the two disorders. We felt the cleanest approach to addressing this question was to assess stress only at baseline to see how adjusted results differ from those without adjustment for stress. Further, some of the stressors we considered were not assessed at multiple time points.

7. Results: In paragraph one, the description of results from Table 1 is not very clear. It would be helpful to indicate that 4.13% is a measure of the prevalence of depression in 2000/2001.

RESPONSE: We have reorganized Table 1 to address this and other concerns raised by the reviewers.

8. Results: In paragraph two, please clarify how the incidence of migraine value of 5.52% was calculated. Is this an incident proportion/ cumulative incidence proportion? If the former, how was the denominator calculated?

RESPONSE: This was indeed a report of cumulative incidence, the (weighted) number of new-onset migraine in the eight-year period divided by all subjects without history of migraine at Cycle 4 (2000/01). We note this does not incorporate censoring, unlike our survival models, but we present this percent to give context to the models.

9. Discussion: The authors need to include add a paragraph on how confounding and bias could be impacting the results. Please explain how the disappearance of the association after adjustment for stress may be caused by the introduction of bias. Could a weakening of effect be caused by the occurrence of a causal chain of events, or caused by confounding? In which case, is adjustment for the variable as a confounder justified? If depression contributes to the experience of stress, would adjustment be inappropriate and could it underestimate the impact of depression? Could the exposure to stress lead to both an increased risk of depression and migraine, in other words this variable may be a shared risk factor?

RESPONSE: We hope that our clarifications in the introduction and discussion alleviate some of these points. We feel we more clearly describe how we view the migraine-depression association may be confounded by stress, which is a known risk factor for both disorders, and that our goal was to quantify how much stress might attenuate the association. We agree that stress may be a consequence and not just a cause of one or both of these disorders (i.e., a time-varying confounder), but we alleviate introduction of such bias by focusing on subjects with no history of the outcome and measuring stress at baseline. We discuss the potential for future directions in on p. 14: “Given that we found recent and prior stress to be relevant in this comorbidity, future research may wish to more closely examine the time-varying relationship between stress and these two conditions individually and comorbidly. Specifically, while stress is a risk factor for both disorders, it may also be caused by each disorder, and thus assessing temporal relationships using models that account for time-varying confounding appropriately (e.g., marginal structural models), may highlight the relationship between these variables further.”

STROBE Statement—Checklist of items that should be included in reports of cohort studies
Check? Recommendation
Title and abstract x (a) Indicate the study’s design with a commonly used term in the title or the abstract
(b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction
Background/rationale x Explain the scientific background and rationale for the investigation being reported
Objectives x State specific objectives, including any prespecified hypotheses
Methods
Study design x Present key elements of study design early in the paper
Setting x Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants x (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
(b) For matched studies, give matching criteria and number of exposed and unexposed
Variables x Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement x For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias x Describe any efforts to address potential sources of bias
Study size x Explain how the study size was arrived at
Quantitative variables x Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

Statistical methods x (a) Describe all statistical methods, including those used to control for confounding
(b) Describe any methods used to examine subgroups and interactions
(c) Explain how missing data were addressed
(d) If applicable, explain how loss to follow-up was addressed
(e) Describe any sensitivity analyses
Results
Participants x (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
(b) Give reasons for non-participation at each stage
(c) Consider use of a flow diagram
Descriptive data x (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
(b) Indicate number of participants with missing data for each variable of interest
(c) Summarise follow-up time (eg, average and total amount)
Outcome data x Report numbers of outcome events or summary measures over time
Main results x (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
(b) Report category boundaries when continuous variables were categorized
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses x Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion
Key results x Summarise key results with reference to study objectives
Limitations x Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation x Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability x Discuss the generalisability (external validity) of the study results
Other information
Funding x Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

VERSION 2 – REVIEW

REVIEWER	Dr. Z. Samaan, MBChB, DMMD, MSc, PhD, MRCPsych Assistant Professor, Dept of Psychiatry and Behavioural Neurosciences Associate Faculty, Population Genomics Program Associate Member, Dept of Clinical Epidemiology and Biostatistics, McMaster University Staff Psychiatrist, St. Joseph's Healthcare Hamilton and Hamilton Health Sciences Mood Disorders Program I have no competing interests.
REVIEW RETURNED	01-Jan-2013

RESULTS & CONCLUSIONS	Tables are still missing the number of subjects per variable of interest. as the events are uncommon (for example childhood trauma) the actual numbers of positive events could be very small

	and therefore the conclusions drawn are difficult to validate.
GENERAL COMMENTS	the main limitation of this work is that it is based on loosely defined phenotypes and does not add any new knowledge to the field as previous work from the same data provided evidence for stress as an important factor in migraine-depression comorbidity.

REVIEWER	Francoise RADAT, MD, PhD Centre Douleur Chronique, CHU Pellegrin, Bordeaux, France No conflict of interest
REVIEW RETURNED	21-Jan-2013

THE STUDY	I am fully satisfied with the authors ' responses to my comments with the exception that I cannot find figure 1 in the revised manuscript
GENERAL COMMENTS	provide figure 1

REVIEWER	Geeta Modgill, MSc Research Associate (Epidemiologist), Opening Minds Mental Health Commission of Canada
REVIEW RETURNED	19-Jan-2013

THE STUDY	1. The authors have adequately revised the manuscript to clarify how their study is an extension of the Modgill et al study however, the abstract should be revised to reflect the same. As stated in the abstract, the objective is " To estimate the comorbidity of migraine and major depression, ...". The authors should consider a revised objective which aligns with the study purpose described at the end of the introduction, "to assess how much the association between migraine and depression may be explained by various measure of stress" . The abstract (results) could more clearly describe the findings of the contribution of stress and how much of the migraine –depression association is explained by stress, the primary outcome and goal of the paper, as reflected in the results section (19.75% depression – migraine and 23.23% migraine-depression).

RESULTS & CONCLUSIONS	The authors note that “we more clearly describe how we view the migraine-depression association may be confounded by stress, which is a known risk factor for both disorder, and that our goal was to quantify how much stress might attenuate the association” and they also note that “the literature review has been revised to include studies justifying stress conceptually as a confounder”. However, missing is an explanation of how the stress variables were assessed as potential confounders during the analysis and results. The authors could address this by describing how each of the stress variables was individually assessed to determine if they were indeed risk factors in the NPHS study population. A more detailed explanation of the figures presented in Tables 2 and 3 is suggested. For example, in Table 2, it appears some of the stressors, such as recent marital events (Model 4), recent unemployment (Model 5), work stress (Model 6), and change in social support (Model 8), were not associated with incident migraine. Similarly, in Table 3, it appears that recent marital stress, recent unemployment, work stress, and change in social support were not predictive of depression. 3. Results: “When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated by 19.75%.” How was this figure calculated? 4. Discussion, second paragraph, line 35: “The present study suggests that prior studies those theses stressors collectively explain...” Is not clear, please rewrite.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

1. Tables are still missing the number of subjects per variable of interest. as the events are uncommon (for example childhood trauma) the actual numbers of positive events could be very small and therefore the conclusions drawn are difficult to validate.

RESPONSE: In the prior revision, we added the unweighted number of subjects for each level of each variable in Table 1 (see column titled “Unweighted N”); in Tables 2 and 3 we added the total sample size used for each model (see column headers).
We are unsure what further numbers the reviewer is requesting, but would be happy to add further information if the request was clarified. Using the reviewer’s example, we can see (in Table 1) that 4,194 subjects reported no childhood trauma, 2,265 reported one event, and 2,274 reported two or more. In Table 2, we can see the hazard ratio for childhood trauma predicting migraine onset, adjusting for baseline depression, in a model utilizing 6,678 observations. In Table 3, we can see the hazard ratio for childhood trauma predicting depression onset, adjusting for baseline migraine, in a model utilizing 6,840 observations.

Reviewer 2

1. The authors have adequately revised the manuscript to clarify how their study is an extension of the Modgill et al study however, the abstract should be revised to reflect the same. As stated in the abstract, the objective is “ To estimate the comorbidity of migraine and major depression, ...”. The authors should consider a revised objective which aligns with the study purpose described at the end

of the introduction, “to assess how much the association between migraine and depression may be explained by various measure of stress” . The abstract (results) could more clearly describe the findings of the contribution of stress and how much of the migraine –depression association is explained by stress, the primary outcome and goal of the paper, as reflected in the results section (19.75% depression –migraine and 23.23% migraine-depression).

RESPONSE: We have made the suggested revisions to the abstract. The pertinent sections of the abstract now read:

“Objectives: To assess how much the association between migraine and depression may be explained by various measures of stress.

…

Results: Adjusting for sex and age, depression was predictive of incident migraine (HR: 1.62; 95% CI: 1.03-2.53) and migraine was predictive of incident depression (HR: 1.55; 95% CI: 1.15-2.08). However, adjusting for each assessed stressor (childhood trauma, recent marital problems, recent unemployment, recent household financial problems, work stress, chronic stress, and change in social support) decreased this association, with chronic stress being a particularly strong predictor of outcomes. When adjusting for all stressors simultaneously, both associations were largely attenuated (depression-migraine HR: 1.30; 95% CI: 0.80-2.10; migraine-depression HR: 1.19; 95% CI: 0.86-1.66).

Conclusions: Much of the apparent association between migraine and depression may be explained by stress.”

2. The authors note that “we more clearly describe how we view the migraine-depression association may be confounded by stress, which is a known risk factor for both disorder, and that our goal was to quantify how much stress might attenuate the association” and they also note that “the literature review has been revised to include studies justifying stress conceptually as a confounder”. However, missing is an explanation of how the stress variables were assessed as potential confounders during the analysis and results. The authors could address this by describing how each of the stress variables was individually assessed to determine if they were indeed risk factors in the NPHS study population. A more detailed explanation of the figures presented in Tables 2 and 3 is suggested. For example, in Table 2, it appears some of the stressors, such as recent marital events (Model 4), recent unemployment (Model 5), work stress (Model 6), and change in social support (Model 8), were not associated with incident migraine. Similarly, in Table 3, it appears that recent marital stress, recent unemployment, work stress, and change in social support were not predictive of depression.

RESPONSE: We feel that these variables still likely fit a common definition of a confounder. Specifically, via subject-matter knowledge supported by the literature (and cited in our manuscript), these variables are risk factors for both the exposure and the outcome. Accounting for each of these variables, individually and collectively, changes our exposure-outcome association, further suggesting that a backdoor pathway between our exposure and outcome exists via each of these variables. We recognize that, in our data, not all of these covariates are strongly predictive of the outcome – e.g., some of the covariate-outcome associations are not ‘significant’ or are minor in magnitude. We agree with Reviewer 2 that this is an important point; however, in our view, these variables still are potential confounders, but perhaps just not strong confounders.

To address this, we have amended our conclusions with further discussion of the magnitude of confounding due to each variable. This includes discussion of how the strength of the relationship between the confounder and outcome, confounder and exposure, and the prevalence of the

confounder all impact the magnitude of confounding.

“The perceived migraine-depression associations presented in many prior studies may be largely explained by unmeasured confounding by such types of stressors. The magnitude of confounding due to each specific stressor is dependent on several factors, including the strength of the covariate-exposure association, the strength of the covariate-outcome association, and the prevalence of the covariate. Our measure of chronic stress was strongly predictive of both migraine and depression onset, as well as associated with these disorders at baseline, and thus was the strongest risk factor considered in the present analyses. On the other hand, recent changes in employment and marital status were relatively rare life events, and were not strongly predictive of these disorders, so the magnitude of attenuation when considering each of these variables was minor. Optimally, future studies of migraine and depression would assess all potential confounders; as this is not always feasible, investigators may consider prioritizing assessing chronic stress over some of these other stressors, and accompany results with sensitivity or bias analyses for any stressors that remained unmeasured.”

3. Results: “When adjusting for all forms of stressors simultaneously, the depression-migraine estimate was attenuated by 19.75%.” How was this figure calculated?

RESPONSE: We estimated these as relative to the age- and sex-adjusted HR, with this formula: (HR1- HR2)/HR1

For depression predicting migraine: (1.62-1.30)/1.62 = 19.75%

For migraine predicting depression: (1.55-1.19)/1.55 = 23.23%

We realize there are alternative ways to present the absolute and relative amounts of attenuation, and that these percentage decreases may not be intuitive to the readers. As such, we have removed this presentation of the results, an replaced it with discussions of the exact values we are comparing (1.62 vs. 1.30, and 1.55 vs. 1.19). We would be open to suggestions from the reviewers and editor.

4. Discussion, second paragraph, line 35: “The present study suggests that prior studies those theses stressors collectively explain...” Is not clear, please rewrite.

RESPONSE: We have rewritten this sentence as follows: “The perceived migraine-depression associations presented in many prior studies may be largely explained by unmeasured confounding by such types of stressors.”

Reviewer 3

1. I am fully satisfied with the authors ‘ responses to my comments with the exception that I cannot find figure 1 in the revised manuscript.

RESPONSE: We apologize for this oversight. Figure 1 is now included.

VERSION 3 - REVIEW

REVIEWER	Geeta Modgill, MSc Research Associate (Epidemiologist), Opening Minds Mental Health Commission of Canada
REVIEW RETURNED	04-Feb-2013

GENERAL COMMENTS	I am fully satisfied with the authors' responses to my comments.