PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Anxiety and depressive disorders are associated with delusional-like experiences: a replication study based on a national mental health survey
AUTHORS	Sukanta Saha, James Scott, Daniel Varghese and John McGrath

VERSION 1 - REVIEW

REVIEWER	Vaughan Bell Institute of Psychiatry King's College London United Kingdom I have no interests to declare.
REVIEW RETURNED	18/03/2012

THE STUDY	I wasn't clear on the operational difference between the probe and screen items. I would need to know how they differed to interpret the results (e.g. Table 2) - perhaps an example might help? Please note: I do not have sufficient experience of the Jack-knife procedure of replication to know if it is being used appropriately.
GENERAL COMMENTS	The study is conceptually straightforward, aiming to replicate earlier findings with data from a national survey, and the methods are appropriate and well-applied. The review and integration of the literature is brief but appropriate and any changes I might like to see would be to better serve my own tastes rather than to improve the quality of the paper. As mentioned in an earlier section, I feel the difference between probe and screen items needs to be better explained, but generally the approach is clear and described in sufficient detail.

REVIEWER	Dana March, PhD, MPH Associate Research Scientist Department of Epidemiology Columbia University New York, NY USA
REVIEW RETURNED	21/03/2012

THE STUDY	There are issues with using cross sectional data to inform our understanding of pathways. These are addressed in the comments below.
RESULTS & CONCLUSIONS	The conclusions drawn should reflect the cross sectional study design. This is addressed in the comments below.
GENERAL COMMENTS	This paper proposes to investigate the cross-sectional association

	between severity of lifetime Major Depressive Disorder, specific subtypes of anxiety disorder and delusional-like experiences (DLE) using the 1997 population-based National Survey of Mental Health and Wellbeing in Australia. The authors find a significant association between lifetime diagnoses of any anxiety disorder and DLE, as well as a linear relation between MDD severity and DLE. The authors conclude that this and other examinations could shed light upon the common pathways leading to both psychotic and common mental disorders. Overall, the manuscript is analytically sound, with the appropriate use of statistics for the problem of interest. And while this investigation has a compelling foundation, the manuscript under review has several limitations that constrain the science presented, including issues with the study design and the frame in which the data are analyzed, the diagnoses examined, and the conclusions drawn in light of the study design. First, the authors overstate the value of using cross-sectional data to inform understanding of the mechanisms linking MDD, DLE, and anxiety disorders. In the introduction, the authors frame the problem concerning the relations among DLE, anxiety subtypes, and severity of lifetime MDD using longitudinal data. However, the authors employ cross sectional data to examine these relations. The authors rightfully highlight the primary limitation of cross-sectional data in their analyses, yet go on to state in the discussion that these examinations could inform understanding of the pathways linking DLE, MDD severity, and anxiety disorder subtypes. In fact, cross-sectional data does little to inform pathways—the progression of cause A to B to C and so on—because temporality cannot be established. Perhaps one way of addressing this issue is for the authors to frame their analyses in the context of a treatment and services issue—that is, is there a greater burden of DLE in more severe cases of MDD, and if so, what clinical and public health implications does that have? In this instance, the cross-sectional analysis arguably becomes of more value. Certainly, crisply specifying next steps required to investigate etiologic issues would be welcome in the discussion section, but to frame the entire paper in terms of pathways with only cross sectional data to inform the question elides what is perhaps the greater value of doing this kind of work. Another issue with the discussion section is the implication that the authors are testing specific hypotheses about the associations of interest (“As predicted…” lines 39-40, page 10). In fact, the authors specify no explicit hypotheses, nor do they indicate why they would make such predictions. Second, the authors examine lifetime diagnoses of MDD and a suite of anxiety disorders, assessed with DSM-IV criteria derived from the CIDI. The CIDI is indeed the gold standard for these types of assessments, although the use of lifetime, not 12-month diagnoses is an issue that is not addressed in the manuscript. A body of literature addresses the questionable reliability of lifetime diagnoses, which the authors should incorporate and cite. This paper would be strengthened by an analysis of 12-month diagnoses and their association with DLE. Furthermore, the authors do not indicate what constitutes their three categories of MDD—mild, moderate, and severe. Was this classification constructed using indicators of functional impairment in various domains (e.g., work, home, school),

	burden and type of symptoms, number and duration of episodes, or some other criteria? Given that severity of MDD is a primary outcome, more detail regarding this classification is necessary. Finally, the authors should ensure that complete sentences and typos are addressed.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.
Vaughan Bell
Institute of Psychiatry
King's College London

United Kingdom

I have no interests to declare.

Comment: I wasn't clear on the operational difference between the probe and screen items. I would need to know how they differed to interpret the results (e.g. Table 2) - perhaps an example might help?

Please note: I do not have sufficient experience of the Jack-knife procedure of replication to know if it is being used appropriately.

The study is conceptually straightforward, aiming to replicate earlier findings with data from a national survey, and the methods are appropriate and well-applied. The review and integration of the literature is brief but appropriate and any changes I might like to see would be to better serve my own tastes rather than to improve the quality of the paper. As mentioned in an earlier section, I feel the difference between probe and screen items needs to be better explained, but generally the approach is clear and described in sufficient detail.

Answer to the Reviewer's comment

We have added additional text in the Methods section to explain the nature of the screen and probe items.

"Briefly, within the CIDI there were three items related to identifying individuals who may be psychotic (G Items: "screen items"). For those who endorsed the screen item, a follow-up item was used to further explore the delusional-like nature or th experience.("probe items"). Full details of the screen and probe items are provided in Appendix 1. "

Reviewer 2
Dana March, PhD, MPH
Associate Research Scientist
Department of Epidemiology
Columbia University
New York, NY USA

This paper proposes to investigate the cross-sectional association between severity of lifetime Major Depressive Disorder, specific subtypes of anxiety disorder and delusional-like experiences (DLE) using the 1997 population-based National Survey of Mental Health and Wellbeing in Australia. The

authors find a significant association between lifetime diagnoses of any anxiety disorder and DLE, as well as a linear relation between MDD severity and DLE. The authors conclude that this and other examinations could shed light upon the common pathways leading to both psychotic and common mental disorders.

Overall, the manuscript is analytically sound, with the appropriate use of statistics for the problem of interest. And while this investigation has a compelling foundation, the manuscript under review has several limitations that constrain the science presented, including issues with the study design and the frame in which the data are analyzed, the diagnoses examined, and the conclusions drawn in light of the study design.

Comment 1.
First, the authors overstate the value of using cross-sectional data to inform understanding of the mechanisms linking MDD, DLE, and anxiety disorders. In the introduction, the authors frame the problem concerning the relations among DLE, anxiety subtypes, and severity of lifetime MDD using longitudinal data. However, the authors employ cross sectional data to examine these relations. The authors rightfully highlight the primary limitation of cross-sectional data in their analyses, yet go on to state in the discussion that these examinations could inform understanding of the pathways linking DLE, MDD severity, and anxiety disorder subtypes. In fact, cross-sectional data does little to inform pathways—the progression of cause A to B to C and so on—because temporality cannot be established. Perhaps one way of addressing this issue is for the authors to frame their analyses in the context of a treatment and services issue—that is, is there a greater burden of DLE in more severe cases of MDD, and if so, what clinical and public health implications does that have? In this instance, the cross-sectional analysis arguably becomes of more value. Certainly, crisply specifying next steps required to investigate etiologic issues would be welcome in the discussion section, but to frame the entire paper in terms of pathways with only cross sectional data to inform the question elides what is perhaps the greater value of doing this kind of work.

Answer Comment 1.
Good point – we certainly did not mean to mislead the reader that we had access to longitudinal data on these research questions. We have rewritten the introduction to clarify the modest nature of the research questions examined in this small replication study.

“While longitudinal studies are required to explore the temporal sequence between depression, anxiety and DLE, we had the opportunity to replicate our previous findings with respect to the cross-sectional association between DLE and (a) broadly defined anxiety disorders, and (b) MDD.9 Based on our previous studies, we predicted that those with anxiety disorder or major depression disorder would be more likely to endorse DLE. In addition, we were able to explore the association between DLE and a range of specific anxiety disorders. Furthermore, we were able to examine if severity of major depressive disorder influenced the risk of endorsement of DLE – we predicted that those with more severe MDD would be more likely to endorse DLE compared to those with milder forms of MDD”.

With respect to the clinical and public health implications of the findings, we have added extra text to the discussion to highlight the need to assess these symptoms in those with a primary diagnosis of anxiety disorder or depression.

“There is now robust and consistent evidence indicating that those with anxiety disorders and MDD have an increased risk of DLE. For example, clinicians involved in the care of those with primary

diagnoses of anxiety disorder or depression may not routinely enquire about DLE. In light of the association between DLE and suicidal ideation/behaviour3, the presence of these experiences may suggest that clinical care plans place greater emphasis on the detection and management of suicidal ideation. It is too early to be making such recommendations with confidence. However understanding the relationship and time course between DLE, anxiety and depression may provide insights into shared pathways that underpin both psychotic disorders and common mental disorders. Once we understand these causal pathways, potential clinical implications warrant closer scrutiny"

Comment 2.
Another issue with the discussion section is the implication that the authors are testing specific hypotheses about the associations of interest ("As predicted…" lines 39-40, page 10). In fact, the authors specify no explicit hypotheses, nor do they indicate why they would make such predictions.

Answer Comment 2.
We have rewritten the final paragraph of the Introduction to make our hypotheses explicit.

"While longitudinal studies are required to explore the temporal sequence between depression, anxiety and DLE, we had the opportunity to replicate our previous findings with respect to the cross-sectional association between DLE and (a) broadly defined anxiety disorders, and (b) MDD.9 Based on our previous studies, we predicted that those with anxiety disorder or major depression disorder would be more likely to endorse DLE. In addition, we were able to explore the association between DLE and a range of specific anxiety disorders. Furthermore, we were able to examine if severity of major depressive disorder influenced the risk of endorsement of DLE – we predicted that those with more severe MDD would be more likely to endorse DLE compared to those with milder forms of MDD".

Comment 3.
Comment 3.1.
Second, the authors examine lifetime diagnoses of MDD and a suite of anxiety disorders, assessed with DSM-IV criteria derived from the CIDI. The CIDI is indeed the gold standard for these types of assessments, although the use of lifetime, not 12-month diagnoses is an issue that is not addressed in the manuscript. A body of literature addresses the questionable reliability of lifetime diagnoses, which the authors should incorporate and cite. This paper would be strengthened by an analysis of 12-month diagnoses and their association with DLE.

Answer Comment 3.1.
Good point – we have explored these issues. Broadly speaking, the pattern of association remains unchanged, however the estimates become imprecise due to lack of power. However, we choose not to present these data because we do not have comparable data about the time course of the DLE (i.e. while we can confirm that depression and anxiety disorders were present in the previous twelve months, we cannot determine this for the DLE). Because the outcome variable was lifetime ever, we feel it is better to present the predictor variable based on the same time period. As the reviewer notes, cross-sectional data are not able to explore the time sequence, even when one of the variables can be reduced to past year. We note this point in the Limitations section of the paper and noted that this issue warrants closer scrutiny in the future.

"While the CIDI has some information about the age of onset and the presence of the disorder in the past year, we do not have this information for the DLE. Prospective studies would be best suited to explore the temporal sequence of the variables of interest ".

Comment 3.2.

Furthermore, the authors do not indicate what constitutes their three categories of MDD—mild, moderate, and severe. Was this classification constructed using indicators of functional impairment in various domains (e.g., work, home, school), burden and type of symptoms, number and duration of episodes, or some other criteria? Given that severity of MDD is a primary outcome, more detail regarding this classification is necessary.

Answer Comment 3.2.
Sorry about that – we have now include text to explain these subtypes.

"For those with MDD, allocation to subtypes was based on the total number of particular 'depressive' symptoms with the duration of at least two weeks. Full details of the symptom list and related rules to deal with multiple episodes can be found in the full report 21. In brief, mild MDD was characterised by the presence of at least four symptoms, moderate MDD with at least six symptoms, and severe MDD with at least eight symptoms. These subtypes of MDD were mutually exclusive."

Comment 4.
Finally, the authors should ensure that complete sentences and typos are addressed.

Answer Comment 4. We have now checked the manuscript thoroughly again for any typos/mistakes

VERSION 2 – REVIEW

REVIEWER	Dana March, PhD, MPH Associate Research Scientist Department of Epidemiology Columbia University USA I have no competing interests.
REVIEW RETURNED	13/04/2012

RESULTS & CONCLUSIONS	In this resubmission, the authors addressed two of the areas flagged in the original review: the classification of MDD severity is now clear. In addition, lines 22-24 in the introduction reflect the acknowledgement that longitudinal data are necessary for informing pathways. The strengths of this article and the data they use would be better highlighted if the authors addressed two of the key suggestions in the initial review. First, there remains an overemphasis on the implications of this cross-sectional for the study of shared pathways for anxiety, MDD, and DLE. Page 12, lines 25-48 could be retained. However, page 13 in its entirety implies that DLE occur after MDD and anxiety, and yet the authors do not actually make use of age of onset data (Page 13, lines 24-45). Critically, more relative weight should be given to the clinical implications of the burden of comorbid DLE, anxiety, and MDD, per the initial review of this submission. Eliminating page 13, which potentially compromises the reach of the data used in these analyses, would achieve this end. Second, the authors have not addressed the limitations of lifetime psychiatric diagnoses, of which there is a fair amount of literature, again, per the initial review of this submission. Presumably, lifetime as opposed to 12-month diagnoses were used because of the relatively low prevalence of MDD and anxiety disorders in this sample. A couple of

	sentences addressing these issues would be helpful.

VERSION 2 – AUTHOR RESPONSE

Thank you for the opportunity to revise and resubmit this manuscript. In response to further reviewer's comment, we have now deleted much of the discussion and add more text alerting the reader to the issues of lack of information on the temporal course of the symptoms. We have included text (and a reference) about this well known issues related to lifetime diagnoses. We have added additional material about the clinical implications of the findings (including a recently published paper in the British Journal of Psychiatry).