Author's response to reviews

Title: Health States for Schizophrenia and Bipolar Disorder within the Global Burden of Disease 2010 Revision.

Authors:

Alize J Ferrari (alize_ferrari@qcmhr.uq.edu.au)
Sukanta Saha (sukanta_saha@qcmhr.uq.edu.au)
John J McGrath (john_mcgrath@qcmhr.uq.edu.au)
Rosana Norman (r.norman@sph.uq.edu.au)
Amanda J Baxter (amanda_baxter@qcmhr.uq.edu.au)
Theo Vos (t.vos@sph.uq.edu.au)
Harvey A Whiteford (h.whiteford@uq.edu.au)

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Author's response to reviews:

To the Editor,

We thank you for considering our paper for publication. Please find below our response to the 2 reviewers who commented on our paper. Also attached is a new draft of our paper where we have incorporated the relevant amendments as track changes. We have also made some minor amendments to the text, also as track changes.

Looking forward to your response,

Sincerely

Alize J Ferrari (on behalf of all other co-authors)

15/06/2012

Reviewer 1: Somnath Chatterji

Comment 1

The authors need to provide in the results not just the proportion of cases in the defined states for schizophrenia and bipolar disorder, but also need to provide what the final health state descriptions were for these different health states to make the results more valuable and of utility to the mental health community. This would help mental health researchers to also understand the inputs for
deriving the disability weights for these conditions since those would be used to
derive the health state specific disability estimates - the ultimate aim of this
exercise.

Response

We agree with the reviewer that it would be useful to present the final health
state descriptions for bipolar disorder and schizophrenia. However, the
development of these descriptions was a separate GBD 2010 deliverable which
will be reported on separately.

In this separate piece of work, ‘lay descriptions’ of the bipolar disorder and
schizophrenia health states were included in the population- and internet-based
surveys (mentioned in paragraph 4 of the introduction) to derive disability
weights. These lay definitions were created by members of the GBD mental
disorders expert group, under the directive of the GBD core group. Although lay
descriptions captured the disability attributed to an acute and residual state of
schizophrenia, and similarly a manic, depressive and residual state of bipolar
disorder; this was a separate exercise to what we have presented in this paper. A
separate GBD 2010 publication by the GBD 2010 Disability Weights
Collaborating Group is focussed on discussing this methodology.

Although related, the aim of this paper was to present ‘clinical definitions’ of the
schizophrenia and bipolar disorder health states (based on a review of the
literature), which would be used to investigate the overall proportion of cases in
each health state. These proportions will be used in aggregating health
state-specific disability weights (which will also be discussed in the upcoming
GBD 2010 publication).

In response to the reviewer’s comments we have clarified this distinction in the
introduction. The first half of paragraph 5 of the introduction now states;

“The purpose of this paper is to describe GBD health states for schizophrenia
and bipolar disorder. This involves (1) presenting clinical definitions for each
health state and (2) using these definitions to quantify the overall distribution of
cases in each health state. Although related, this is a separate exercise to the
formulation of lay descriptions of each health state included in the population-
and internet-based disability weight survey mentioned earlier. Rather, the
derivables of this paper will inform the differences within the course of the
disorder for which health state specific disability weights are being developed.”

Comment 2

In the analysis section the authors mention the quality effects model and state
that is preferred over the random effects model but the references provided
(40-42) have nothing to do with the quality effects model and need to be changed
to the original references to the QEM.
Response

In response to comment 2 we have amended the error in the references used for the quality effects model. The publications cited in paragraph 9 of the methods sections have been changed to;


Comment 3

In the background the authors say that the GBD exercise is to be completed by 2011 and cite a reference that indeed did say that but I wonder if this should somehow be modified to suggest that it will be completed in 2012 so that readers are not confused.

Response

In response to comment 3 we have changed the completion year to the GBD study to 2012. The first sentence of the paragraph 2 of the background section now states:

“While the World Health Organization (WHO) has provided interim updates of GBD estimates since 2000 for the world and 14 regions, a new GBD study (GBD 2010 study) is expected to be completed by 2012 [8].”

Comment 4

In defining health states, the authors state that the DSM IV criteria ‘place less emphasis on severity and functional impairment...’ . However, a diagnosis of schizophrenia or bipolar disorder in the DSM IV cannot be made in the absence of ‘functional impairment’ or ‘distress. The text needs to be modified accordingly.

Response

In response to comment 4, the last sentence of paragraph 2 of the methods section stating “These diagnostic criteria place less emphasis on severity and functional impairment and more on symptomatology of schizophrenia [19], which is consistent with the GBD conceptualization of “within the skin” disability” has been removed. Instead, the discussion on symptomatology and functional impairment has been moved to the discussion section (See response to
Comment 1 from reviewer 2).

Comment 5

In the discussion section the authors should acknowledge that the Cruz et al paper for bipolar disorder that was selected was a study on rapid cycling which is a sub-set of bipolar disorder and may have influenced the results.

Response

In response to comment 5, the 3 last sentences of paragraph 5 of the discussion section now state:

“The study from Ethiopia [41] and the one conducted across multiple European countries [37] assessed bipolar I cases only. The latter of which also included cases of bipolar I disorder with rapid cycling. Although this was less representative of the spectrum of bipolar disorder, these studies were included to maximize the global distribution of the data.”

Comment 6

The authors use the word 'acute' to refer to the health state of schizophrenia associated with predominant positive symptoms; this may be confusing given that 'acute' psychotic disorder is understood as a different disorder in the ICD 10; hence, may be better to call this 'active 'schizophrenia as opposed to 'residual'.

Response

While we agree with the suggestion made by the reviewer, it would be undesirable to use different terminology to describe the health states for schizophrenia to what’s already been used to derive disability weights for schizophrenia in GBD 2010.

As all of the health state descriptions required for the GBD 2010 study have been finalised we are unable to make any changes to the allocated names at this late stage of the study. Changing the name acute to active schizophrenia in this paper may create some confusion as it would mean that our methodology is inconsistent to what’s been used to calculate the burden of schizophrenia in GBD 2010.

Comment 7

In the Conclusions the authors state that 'Schizophrenia...(is) an episodic disorder with a chronic course'. Much of the mental health community would disagree with this. In fact the reference cited here (45), states '...predominant course of illness includes chronically poor functioning with little evidence of long-term improvement'; hence, it would be useful for the authors to explain this
statement if indeed this is how the GBD study has modelled schizophrenia.

Response

By the word ‘episodic’ we were referring to the fluctuations in the symptomatology and disability of schizophrenia and bipolar disorder (i.e. the different health states that make up both disorders). In response to comment 7 we have clarified this in the discussion. The two last sentences of the discussion state:

“Schizophrenia and bipolar disorder both have a chronic course, with fluctuations in symptomatology and disability [47, 53, 54]. Rather than deriving burden estimates that fail to capture the changes in disability within these disorders, we will use the data available to us to make more representative estimates of disease burden in the GBD 2010 study.”

Reviewer 2: Helen Herrman

Comment 1

The definition of health states is clear (p6). However the description of how health states for schizophrenia are defined seems to have circular elements and is potentially misleading. The authors state (p6) that the emphasis is placed on symptoms, also equated with ‘within the skin’ disability. They describe the second health state as residual and ascribed to schizophrenia with predominantly negative symptoms. Finally they note that both positive and negative symptoms are associated with impaired functioning.

These last two points lead to some confusion. The description of the second health state as residual does not accord with evidence and experience about the level of disability associated with negative symptoms. Nor does the use of these health states accord with the lack of differentiation in the literature between the levels of disability (whether ‘within the skin’ – functional impairment – or that associated with participation restrictions) associated with positive and negative symptom states in schizophrenia.

Response

In response to comment 1, the last sentence of paragraph 2 of the methods section stating “These diagnostic criteria place less emphasis on severity and functional impairment and more on symptomatology of schizophrenia [19], which is consistent with the GBD conceptualization of “within the skin” disability” has been removed. Instead, the discussion on symptomatology and functional impairment has been moved to the discussion section where we have also discussed the limitations to the health state definitions proposed. The second paragraph of the discussion now states;
“Our definition of health states for both disorders conformed as much as possible to ‘within the skin’ elements of functioning required by GBD. However the DSM diagnostic criteria and literature (particularly for schizophrenia) includes both symptom severity and functional impairment, part of which is dependent on the environmental context. Consequently, trying to fit the multidimensional features of schizophrenia into 2 domains remains controversial. The fragility of the empirical data is a concern, particularly the lack of consensus on a health state definition and how the corresponding proportion of cases in each state is measured. For the purposes of this exercise, we have adopted a pragmatic approach in using the best available data to come up with a sensible set of health states (and health state proportions) which can be used in the GBD 2010 study.”

Comment 2

The very small number of papers from the extensive literature on the epidemiology of schizophrenia that bear on this definition of health states adds to concern that the data analysed may mislead rather than assist in understanding the disease burden associated with schizophrenia. The discussion does not consider the implications of these analyses for understanding the disease burden of schizophrenia and its ranking relative to other conditions, nor possible alternative approaches to its estimation. Nor does the paper refer to debates about the diagnosis of schizophrenia and related psychotic conditions.

Response

We agree with the reviewer that we could only base our findings on a very small number of papers. We re-iterated this limitation in the last paragraph of the discussion which states;

“Gaps in the literature meant that only a small selection of studies could be used to derive pooled proportions. Consequently, there may not have been enough data to yield a representative indication of proportions. Also, the data sources identified reported a range of methodological differences. This has led to considerable heterogeneity in the data. We expect that the inclusion criteria used and the quality-effects model has controlled for some of this heterogeneity in the final pooled proportions but the wide uncertainty intervals reflect the poor state of knowledge. Schizophrenia and bipolar disorder both have a chronic course, with fluctuations in symptomatology and disability [47, 53, 54]. Rather than deriving burden estimates that fail to capture the changes in disability within these disorders, we will use the data available to us to make more representative estimates of disease burden in the GBD 2010 study. “

An alternative approach to estimating health state proportions was briefly discussed in the last 3 sentences of the introduction which state;

“The distribution of schizophrenia and bipolar disorder cases across multiple health states can be summarized differently depending on the approach used.
For instance the number of cases within the population in each state or the mean or median time spent in each state may be reported. Since burden of disease estimates are cross-sectional measurements of health loss in a population, in a particular year, the former approach of measuring the number of cases in each health state fits best and will be used here.”

It was outside the scope of this paper to go into more details about this as well as into debates about the diagnosis of schizophrenia and related psychotic conditions. As burden estimates for the GBD 2010 study are not yet finalised we were unable to discuss the effect of our findings on the burden ranking of schizophrenia and bipolar disorder, relative to other conditions. That said, we do recognise the value of considering the issues raised by the reviewer. Consequently, the last sentence of paragraph 4 in the discussion now states:

“Further investigation into the alternative approaches to measuring the distribution of schizophrenia and bipolar disorder health states in the population, and how these affect overall results (and ultimately burden estimates) is required for a better understanding of the above findings.”

Comment 3
The health states described for bipolar disorders are easier to understand. However as the authors acknowledge, the conclusion drawn from these analyses that equal time is spent in manic and depressive states does not accord with other evidence and experience. Similar points to those above can be added to the need for discussion on the implications of these analyses for the estimation of disease burden for these conditions.

Response
We have addressed comments 2 and 3 simultaneously (See response to comment 2).

Comment 4
The link is not clear between this work and the population-based survey across several countries mentioned on page 5.

Response
Health-state specific disability weights as captured by the population- and internet-based surveys, together with data on the overall proportion of cases in each health state presented in this paper were used to calculate an average disability weight for schizophrenia and bipolar disorder respectively. In response to comment 4, we have re-iterated this is the paper. The first half of paragraph 5 of the introduction now states:
“The purpose of this paper is to describe GBD health states for schizophrenia and bipolar disorder. This involves (1) presenting clinical definitions for each health state and (2) using these definitions to quantify the overall distribution of cases in each health state. Although related, this is a separate exercise to the formulation of lay descriptions of each health state included in the population-and internet-based disability weight survey mentioned earlier. Rather, the deliverables of this paper will inform the differences within the course of the disorder for which health state specific disability weights are being developed.”