

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cardiovascular mortality in bipolar disorder: A population based cohort study in Sweden
AUTHORS	Westman, Jeanette; Hällgren, Jonas; Wahlbeck, Kristian; Erlinge, David; Alfredsson, Lars; Ösby, Urban

VERSION 1 - REVIEW

REVIEWER	Jess Fiedorowicz, M.D., Ph.D. Assistant Professor Departments of Psychiatry, Epidemiology, and Internal Medicine The University of Iowa I have no competing interests to disclose.
REVIEW RETURNED	13-Dec-2012

GENERAL COMMENTS	<p>This is a very well-written manuscript presenting data from a nationally representative sample that extends prior findings on the strong association between bipolar disorder and cardiovascular mortality. The statistical methods are rigorous and appropriate. The data is well-presented and including reporting of excess deaths, which is useful for assessing public health impact.</p> <p>1) Introduction, the sentence referring to "different CVD subgroups" is not clear. I think the authors are referencing different types of vascular mortality.</p> <p>2) Please use the phrase "bipolar" to describe the disorder and not people. Please replace the phrase "bipolar patients" with the less problematic although more lengthy "patients with bipolar disorder." For clarification, the authors are encouraged to see Flanagan and Davidson "'Schizophrenics,' 'Borderlines,' and the Lingering Legacy of Misplaced Concreteness: An Examination of the Persistent Misconception That the DSM Classifies People Instead of Disorders."</p> <p>3) Discussion, Strengths and Limitations, paragraph 1. Please drop phrase beginning "which would have been of interest since antidepressant use have been linked to increased risk of fatal coronary heart disease" and reference 10. This short phrase misinterprets a very complex literature and the study cited uses antidepressant exposure as a marker for depression itself.</p> <p>4) Do the authors have any data from Sweden or countries with similar health care systems related to the proportion of individuals with bipolar disorder are at some point hospitalized? If so, that might add to the discussion of strengths limitations.</p> <p>Discretionary Revisions (encourage the authors to consider at their discretion):</p> <p>1) Although the point is clear, the use of the phrase "somatic illness" for cause of death invokes some unnecessary dualism. Given use of</p>
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	<p>unnatural for suicides and accidents, I encourage the authors to consider use of other natural causes.</p> <p>2) Discussion, CVD undertreated in bipolar disorder, the possibility that those with bipolar disorder have greater burden of sudden cardiac death could be considered as another explanation for the only slightly increased hospital admission rates.</p> <p>3) I think the authors should briefly include mention of the universal free access to medical care in Sweden as a strength of the study as well (this is mentioned in discussion trying to explain only slightly increased hospital admissions).</p> <p>4) Discussion, findings from other studies. The discussion is well-focused but if interested in expanding, authors may want to consider: Studies have shown greater mortality in type 1 (with mania) than type 2 bipolar disorder (Fiedorowicz et al. Psychosom Med 2009, Angst et al. Eur Arch Psychiatry Clin Neurosci 2012). Sodhi et al. (2012) also showed older patients with bipolar disorder deviating more from age-based norms on arterial stiffness measures.</p>
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REVIEWER	<p>Benjamin Goldstein Director, Centre for Youth Bipolar Disorder Sunnybrook Health Sciences Centre University of Toronto</p> <p>Competing interests: research funding from Pfizer, travel support from BMS, speaker's honoraria from Purdue Pharma, multiple peer-reviewed research grants focusing on the link between bipolar disorder and CVD</p>
REVIEW RETURNED	20-Dec-2012

GENERAL COMMENTS	<p>This study examined causes of death among adults with bipolar disorder, and replicated previous findings regarding increased risk of CVD death and unchanged rates of CVD treatment nonetheless. The sample is unique, the findings are strong, the paper is well written, and topic is exceedingly timely and of tremendous public health importance. Limitations are appropriately acknowledged. The manuscript would benefit from covering the previous literature in greater detail and going into greater depth regarding putative pathophysiologic links and treatment implications. Suggestion follow below:</p> <ol style="list-style-type: none"> 1. A stylistic comment: The comparison of medical causes of death vs. suicide is somewhat overemphasized. It would be preferable to demonstrate the burden of CVD rather than highlighting a perceived over-emphasis on suicide. 2. Most of the studies cited re CVD prevalence are Scandinavian; it is worth point out that similar findings have been observed in a representative study of the United States population (Goldstein et al, Bipolar Disorders 2009). The same study also converges with present findings regarding the earlier age of CVD among people with bipolar disorder. Likewise, previous findings from Kilbourne and colleagues regarding younger age of CVD and lower rates of nutritional counseling among adults with bipolar disorder should be acknowledged. Both studies confirm that current findings extend beyond hospitalized samples. 3. The Introduction should more explicitly highlight the specific aspects of this study that extend previous findings. This clarifies the overall rationale for the current study. 4. Previous findings suggested that bipolar disorder confers greater
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	<p>SMR for CVD among females vs. males, whereas the current study did not. Please comment.</p> <p>5. The number of figures is excessive.</p> <p>6. Because the study focuses on CVD, it would be helpful to highlight, in the first paragraph of the Discussion and in the abstract, the number of excessive deaths due to CVD. As written, CVD is combined with other somatic illnesses that are not the focus of the current manuscript.</p> <p>7. In the Discussion, potentially shared biological causes are relatively understated compared to medications and lifestyle. These include inflammation and endothelial dysfunction.</p> <p>8. The findings regarding undertreatment of CVD should be better contextualized with previous findings on this topic.</p> <p>9. The Discussion regarding under-treatment could benefit from greater elaboration. For example, a potential explanation suggested by current findings is that under-treatment may be explained by the young age of patients with bipolar disorder who have CVD. Could it be that clinicians are trained and guided to screen for CVD and CVD risk factors at ages that are already too late for patients with bipolar disorder? It would be helpful to summarize the Swedish guidelines for management of medical conditions in bipolar disorder. In particular, is early age of CVD incorporated in those guidelines, in addition to the increased prevalence?</p>
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REVIEWER	<p>Maria Paz Garcia-Portilla Gonzalez Associate Professor Dept. of Psychiatry, University of Oviedo, Spain</p> <p>I declare that I do not have any conflict of interest that could influence my review of the submitted paper</p>
REVIEW RETURNED	02-Jan-2013

GENERAL COMMENTS	In the Results section there is not any reference to Figs. 2a, 2c, 3a-3c. Please provide them.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: Jess Fiedorowicz, M.D., Ph.D.
Assistant Professor
Departments of Psychiatry, Epidemiology, and Internal Medicine
The University of Iowa

I have no competing interests to disclose

This is a very well-written manuscript presenting data from a nationally representative sample that extends prior findings on the strong association between bipolar disorder and cardiovascular mortality. The statistical methods are rigorous and appropriate. The data is well-presented and including reporting of excess deaths, which is useful for assessing public health impact. We thank the reviewer for these comments to our manuscript.

1) Introduction, the sentence referring to "different CVD subgroups" is not clear. I think the authors are referencing different types of vascular mortality.
The text has been changed to "different types of vascular mortality". (p 4)

2) Please use the phrase "bipolar" to describe the disorder and not people. Please replace the phrase "bipolar patients" with the less problematic although more lengthy "patients with bipolar disorder." For clarification, the authors are encouraged to see Flanagan and Davidson "'Schizophrenics," "Borderlines," and the Lingering Legacy of Misplaced Concreteness: An Examination of the Persistent Misconception That the DSM Classifies People Instead of Disorders."

We agree with the reviewer and have changed "bipolar patients" to "persons with bipolar disorder".

3) Discussion, Strengths and Limitations, paragraph 1. Please drop phrase beginning "which would have been of interest since antidepressant use have been linked to increased risk of fatal coronary heart disease" and reference 10. This short phrase misinterprets a very complex literature and the study cited uses antidepressant exposure as a marker for depression itself.

The sentence has been deleted. (p 9)

4) Do the authors have any data from Sweden or countries with similar health care systems related to the proportion of individuals with bipolar disorder are at some point hospitalized? If so, that might add to the discussion of strengths limitations.

Information about hospitalizations in bipolar disorder has been added, but there is no information about patients only in out-patient treatment. Bipolar I disorder cannot be separated from bipolar II in the register data, but will be much less likely to be hospitalized. (p 9)

Discretionary Revisions (encourage the authors to consider at their discretion):

1) Although the point is clear, the use of the phrase "somatic illness" for cause of death invokes some unnecessary dualism. Given use of unnatural for suicides and accidents, I encourage the authors to consider use of other natural causes.

The classification of causes of death varies. We have chosen to keep "somatic illness" and change "unnatural" to "suicides and other external", according to the ICD classification.

2) Discussion, CVD undertreated in bipolar disorder, the possibility that those with bipolar disorder have greater burden of sudden cardiac death could be considered as another explanation for the only slightly increased hospital admission rates.

We have added sudden cardiac death, defined as cardiac arrest/ventricular fibrillation, to the causes of death in Table 1. Although it is increased, the extent does not explain the difference in hospital admissions. (p 10)

3) I think the authors should briefly include mention of the universal free access to medical care in Sweden as a strength of the study as well (this is mentioned in discussion trying to explain only slightly increased hospital admissions.

The universal free access to medical care in Sweden has been stressed as a strength of the study. (p 8)

4) Discussion, findings from other studies. The discussion is well-focused but if interested in expanding, authors may want to consider: Studies have shown greater mortality in type 1 (with mania) than type 2 bipolar disorder (Fiedorowicz et al. Psychosom Med 2009, Angst et al. Eur Arch Psychiatry Clin Neurosci 2012). Sodhi et al. (2012) also showed older patients with bipolar disorder deviating more from age-based norms on arterial stiffness measures.

The findings and studies proposed by the reviewer have been included in the Discussion. (p 9-10)

Reviewer: Benjamin Goldstein
Director, Centre for Youth Bipolar Disorder
Sunnybrook Health Sciences Centre
University of Toronto

Competing interests: research funding from Pfizer, travel support from BMS, speaker's honoraria from Purdue Pharma, multiple peer-reviewed research grants focusing on the link between bipolar disorder and CVD

This study examined causes of death among adults with bipolar disorder, and replicated previous findings regarding increased risk of CVD death and unchanged rates of CVD treatment nonetheless. The sample is unique, the findings are strong, the paper is well written, and topic is exceedingly timely and of tremendous public health importance. Limitations are appropriately acknowledged. The manuscript would benefit from covering the previous literature in greater detail and going into greater depth regarding putative pathophysiologic links and treatment implications.

We thank the reviewer for these comments, and have extended the coverage of previous literature, putative pathophysiologic links, and treatment implications.

Suggestion follow below:

1. A stylistic comment: The comparison of medical causes of death vs. suicide is somewhat overemphasized. It would be preferable to demonstrate the burden of CVD rather than highlighting a perceived over-emphasis on suicide.

The burden of CVD deaths has been emphasized both in the Introduction (p 4), the Discussion (p 8), and in the Abstract.

2. Most of the studies cited re CVD prevalence are Scandinavian; it is worth point out that similar findings have been observed in a representative study of the United States population (Goldstein et al, Bipolar Disorders 2009). The same study also converges with present findings regarding the earlier age of CVD among people with bipolar disorder. Likewise, previous findings from Kilbourne and colleagues regarding younger age of CVD and lower rates of nutritional counseling among adults with bipolar disorder should be acknowledged. Both studies confirm that current findings extend beyond hospitalized samples.

The points made by the reviewer have been included in the discussion. (p 9)

3. The Introduction should more explicitly highlight the specific aspects of this study that extend previous findings. This clarifies the overall rationale for the current study.

A sentence specifying what this study adds to previous findings has been included. (p 4)

4. Previous findings suggested that bipolar disorder confers greater SMR for CVD among females vs. males, whereas the current study did not. Please comment.

We have included a sentence analyzing the difference between absolute mortality and MRR for men and women. (p 9)

5. The number of figures is excessive.

Although the number of figures is high, we believe that they add specific information that is of interest for the readers. This has been further explained in the Results (p 7). Thus, we have not reduced the number of figures.

6. Because the study focuses on CVD, it would be helpful to highlight, in the first paragraph of the Discussion and in the abstract, the number of excessive deaths due to CVD. As written, CVD is combined with other somatic illnesses that are not the focus of the current manuscript.

Excessive deaths due to CVD has been emphasized both in the Discussion (p 8) and in the Abstract.

7. In the Discussion, potentially shared biological causes are relatively understated compared to medications and lifestyle. These include inflammation and endothelial dysfunction.

This has been added to the Discussion. (p 10)

8. The findings regarding undertreatment of CVD should be better contextualized with previous findings on this topic.

The text on undertreatment of CVD has been revised. (10-11)

9. The Discussion regarding under-treatment could benefit from greater elaboration. For example, a potential explanation suggested by current findings is that under-treatment may be explained by the young age of patients with bipolar disorder who have CVD. Could it be that clinicians are trained and guided to screen for CVD and CVD risk factors at ages that are already too late for patients with bipolar disorder? It would be helpful to summarize the Swedish guidelines for management of medical conditions in bipolar disorder. In particular, is early age of CVD incorporated in those guidelines, in addition to the increased prevalence?

We have added further information to the Discussion regarding under-treatment, including specifying

the importance of the younger age at CVD disease, which also should be further emphasized in the Swedish guidelines for management of medical conditions in bipolar disorder. (p 10-11)

Reviewer: Maria Paz Garcia-Portilla Gonzalez
Associate Professor
Dept. of Psychiatry, University of Oviedo, Spain

I declare that I do not have any conflict of interest that could influence my review of the submitted paper

In the Results section there is not any reference to Figs. 2a, 2c, 3a-3c. Please provide them. References to Fig 2 and 3 have been added to the Results section. (p 7-8)

VERSION 2 – REVIEW

REVIEWER	Benjamin Goldstein, MD, PhD Director, Centre for Youth Bipolar Disorder Sunnybrook Health Sciences Centre University of Toronto Canada Please see previous COI.
REVIEW RETURNED	07-Feb-2013

GENERAL COMMENTS	The authors have been highly responsive to the previous reviews. Several minor comments remain: 1. I would encourage the authors to more carefully consider the sex-difference findings. Their previous data from the same population showed greater SMR for females, and the response to this point was that the total number of deaths is greater among females. The response does not address why the mortality ratio for females would be different in this sample compared to previous samples. 2. The added statements regarding inflammation and endothelial dysfunction follow a discussion of genetic factors. Instead these statements should follow the comment regarding arterial stiffness. 3. Can the authors provide a citation for their assertion that younger age of CVD among patients with bipolar disorder is unlikely to explain lower rates of invasive treatment? 4. It would be helpful for the reader if the manuscript included a brief summary regarding the main emphasis of Sweden's guidelines in relation to metabolic disturbance in SMI.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: Benjamin Goldstein, MD, PhD
Director, Centre for Youth Bipolar Disorder Sunnybrook Health Sciences Centre University of Toronto
Canada

The authors have been highly responsive to the previous reviews.
We thank the reviewer for constructive feedback which improves the study.

Several minor comments remain:

1. I would encourage the authors to more carefully consider the sex-difference findings. Their previous data from the same population showed greater SMR for females, and the response to this point was that the total number of deaths is greater among females. The response does not address why the mortality ratio for females would be different in this sample compared to previous samples. In our previous study, SMR for CVD but not for cerebrovascular mortality was higher for women compared to men. This difference was not found in our present study. SMR and MRR are relative measurements, affected both by population trends and trends among the cases. Thus, the different findings between our previous study and the present could be related both to changing mortality rates in the population and to changes among persons with bipolar disorder, or a combination of those factors. It is important to point out, that CVD contains several different causes of mortality, which may have different trends over time, which is shown in the population data presented below, where CVD is more decreased among women, while CHD is more decreased among men (figure 1 and 2).

Figure 1 and 2. The Swedish Board of Health and Welfare population data for CVD and CHD mortality per 100,000 for men and women during 1997-2011.

An advantage with the present study is more specific causes of death. This has been pointed out in the text. The specific causes of death related to the previous finding of a sex difference in CHD mortality cannot be answered in the present study. (p 9).

2. The added statements regarding inflammation and endothelial dysfunction follow a discussion of genetic factors. Instead these statements should follow the comment regarding arterial stiffness. The text has been changed according to the reviewer's statement (p 10).

3. Can the authors provide a citation for their assertion that younger age of CVD among patients with bipolar disorder is unlikely to explain lower rates of invasive treatment?

No, we have no citation to support this statement, which is based upon the general assumption that people at younger age generally would be expected to receive more intensive treatment. Further study is needed to explain the reduced cardiac treatment in bipolar disorder.

4. It would be helpful for the reader if the manuscript included a brief summary regarding the main emphasis of Sweden's guidelines in relation to metabolic disturbance in SMI.

The text on the Swedish guidelines in relation to metabolic disturbances have been expanded (p 10).