

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality in Schizophrenia and Related Psychoses: Data from Two Cohorts, 1875-1924 & 1994-2010.
AUTHORS	Healy, David ; Le Noury, Joanna; Harris, Margaret; Butt, Mohammed; Linden, Stefanie; Whitaker, Chris; Zou, Lu; Roberts, Anthony

VERSION 1 - REVIEW

REVIEWER	Edward Shorter, PhD, FRSC Jason A Hannah Professor of the History of Medicine Professor of Psychiatry Faculty of Medicine, University of Toronto Toronto, Canada Competing interests: none to report
REVIEW RETURNED	02-Aug-2012

THE STUDY	no supplemental documents; the tables supplied are appropriate
RESULTS & CONCLUSIONS	paper is a little too focused on the evidence and technique.
GENERAL COMMENTS	<p>This represents yet another contribution from the flow of papers of Dr David Healy's highly productive group in Bangor comparing patterns of psychiatric illness late in the nineteenth century and today. Some of these comparisons have proven extraordinarily interesting, such as the finding that schizophrenia increased late in the 19th century and has evidently declined in frequency today. This occasions much fruitful speculation.</p> <p>The current paper is no exception. The authors find that, despite a cornucopia of modern treatments, mortality in general from schizophreniform illnesses is just as high today as then, and that suicides among schizophrenics are considerably more common now. The paper contains the pregnant sentence, "The historical data suggest there is something about the modern delivery of care that contributes to suicide as an outcome." (15) This is really extraordinarily interesting and well worth the price of admission. Further, the authors conclude that earlier treatment of schizophrenic illness could produce much more favorable outcomes. This, of course, is not new, but the historic documentation of it is impressive. It goes without saying that I recommend the paper be published. It is one of the most important to have crossed my desk in the last while.</p> <p>I do however have one editorial suggestion. The paper is written too closely to the evidence, and takes on at times the character of a discourse on the technique of conducting historical and contemporary epidemiology rather than a presentation of findings. Indeed, I had to labor at several points to figure out what the important trend was (as for example in the section on the discussion of SMRs and life expectancy). This emphasis on technique gives the</p>

	<p>prose a certain clunkiness, as though it were written for techno-geeks rather than inquiring minds. The writing needs to be simplified and the main findings clearly signaled at each juncture.</p> <p>I hope these comments are of use.</p>
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REVIEWER	<p>Dr Sukanta Saha Senior scientist Queensland Centre for Mental Health Research The Park Centre for Mental Health Wacol QLD 4076 Australia</p> <p>Conflict of interest: None</p>
REVIEW RETURNED	03-Aug-2012

RESULTS & CONCLUSIONS	The results are not well presented.
GENERAL COMMENTS	<p>General comments:</p> <p>The paper assessed mortality rates in schizophrenia and related psychoses using a historical and a contemporary cohort. As expected the results show that there was an increased mortality in schizophrenia/psychoses in both historical and contemporary cohorts. The authors report that the SMRs (Standardised mortality rate) were similar in both the cohorts. The years of life lost in schizophrenia was 4.3 years in the contemporary cohort while for historical cohorts it was between 8 and 11 years.</p> <p>The paper is of interest to the research community, and the results have implications for service planning.</p> <p>Other comments:</p> <ol style="list-style-type: none"> 1. The paper is too detail in many places. There are unnecessary discussions inside the result section (p. 11 para4), main results not reported in the abstract, results not properly analysed but discussed etc. Overall, it needs tidy up: <ol style="list-style-type: none"> a. Causes of death (Table 1 & 2): It is good to present causes of death in detail. However readers may like to see the SMRs for all these causes of death. The authors opted to present SMRs only for

	<p>schizophrenia and all psychoses (divisions of psychoses are not necessary then). It will make more sense to discuss about them only or present SMRs for all causes of death and discuss. In p. 16, there is a discussion about acute and transient psychosis, without knowing SMRS, we do not know what the results hold.</p> <ul style="list-style-type: none">b. Tables 3a & 3b are too detail for no good reason, why presenting age groups data while it was not discussed at all. Ideally these four tables should go to the Appendicesc. Discussions on suicide and tuberculosis take an important part of this paper (P. 9, 10, 11, 13, 14, 15). However, readers may like to see the SMRs for them. One of the most important analyses about suicide has been presented in the discussions (p. 15, para 3) without presenting in the results. Without knowing how the results unfold it was difficult to understand what has been saying.d. The authors report that the SMRs for schizophrenia were similar in both the cohorts. In Table 4, in the contemporary cohort we see that the SMR for persons is 11.8 while in table 5 for historical cohorts it was 4.0. How it is similar? In the discussion it was also claimed that the all cause SMR for schizophrenia are similar with other recent studies. In fact, we see from several systematic reviews that the SMRs are between 1.5 and 3 (eg., Brown et al 1.51, Harris et al. 1.57, Saha et al. 2.58).e. It is advisable to present both observed and expected deaths when presenting SMRs.f. The result about the survival analysis has not been mentioned in the abstract while it was one of the aims in the paper. The graphs are too difficult to extract, may be because they are too busy or the resolution has been compromised.g. Male female differences are not highlighted while tables 4, 5 & 6 are dedicated for this. However, in places M:F differences were mentioned for suicide (p. 14, para4) while we do not see the results as
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	<p>such.</p> <p>h. Readers may prefer to see main results in a succinct manner, may be at the end or the start of the discussion chapter?</p> <p>2. I do not understand the diagnostic patterns. How reliable and complete are diagnoses in the electronic records the historical cohort given the well known comorbidity patterns (e.g. common combination substance use disorder or depression and schizophrenia), makes me worry about the reliability of the diagnostic data.</p> <p>3. In several places (eg., p.11, para 3; p.14, para 3) results for affective disorders were mentioned. I think it is out of context here.</p> <p>4. The reference list has some inconsistency in it and also not exactly follow the system BMJ Open follows:</p> <ol style="list-style-type: none"> a. If the ref contains more than 3 authors, after 3 names it needs to write 'et al'. b. No bold for the volume number c. Some places the journal name has been abbreviated, sometimes full names were given d. Journal names to be in <i>italics</i> (eg., 21 not italics) <p>5. Other minor points:</p> <ol style="list-style-type: none"> a. There are spell mistakes, large sentences in places, needs thorough editing b. Table 6 should go the appendix.
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REVIEWER	<p>Professor Eric Chen Department of Psychiatry University of Hong Kong</p> <p>No competing interest to be declared.</p>
REVIEW RETURNED	06-Aug-2012

THE STUDY	<p>The study is highly interesting and informative from a historical perspective. It therefore does not fit very well the standard review structure.</p> <p>The rationale for making the comparison made in this study is can be expressed in a more focused and convincing manner.</p>
RESULTS & CONCLUSIONS	<p>There is some problems with interpretation of data given that these two samples are treated very differently (see below). It would be desirable to formulate several explicit research questions that the data could address</p>
GENERAL COMMENTS	<p>This study set out to compare the mortality in schizophrenia and</p>

	<p>related psychosis in two cohorts one century apart in a defined catchment area in North Wales. Follow up was between one to ten years.</p> <p>This is an interesting historical study. The rationale of comparison, save having access to such a cohort, is yet stated in a focused and convincing manner.</p> <p>The authors suggested that comparison could highlight the difference between having and not having antipsychotic medications. It does not need to be stressed that apart from medication, there is a host of difference between the experiences of psychosis a century apart. In particular, the social and physical treatment context (e.g. that earlier patients virtually become long-stay patients from their first episode illness) would make the social and psychological experience of psychosis fundamentally different and simple comparison difficult.</p> <p>For example the authors reviewed the lack of suicide in the early sample compared with the modern sample and concluded that the dysphoric effect of antipsychotic medication may play a role. This is however likely to be a gross over-simplification. From early description of the illness, we know that clinical remission is in fact unusual, many patients continued to experience and be preoccupied with psychotic symptoms (this can be tested with data in this sample). Most suicides occur in psychosis at the time when psychotic symptom resolves and insight emerges. Patients a century ago have less chance to experience this emergence of insight into their illness, and consequently were less exposed to the demoralization and difficulties associated with coming to terms with having had a psychotic illness, which may be associated with suicide. It would be important to discuss this possible interpretation to the increase in suicide in contemporary patients compared with those in the past.</p> <p>To clarify the above, it would be desirable to give psychopathology information for these two cohorts.</p> <p>In understanding the other causes of death it would be important to have information about the ages of the patients at the start of the study.</p>
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REVIEWER	Nordentoft, Merete Psychiatric Centre Bispebjerg, Psychiatric Department
REVIEW RETURNED	27-Aug-2012 No conflicts of interest

GENERAL COMMENTS	<p>The topic is important and the authors have done a heroic work in trying to identify old and new cases.</p> <p>However, it is very difficult to compare to very different periods of time. Many things have changed. The threshold for psychiatric treatment has changed, and just to determine incidence of schizophrenia in the two periods will be difficult. As length of admissions also have changed the likelihood of dying during inpatient stay has changed, and therefore it is important to look into not only post discharge mortality. Diagnostic traditions have</p>
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	<p>changed, and medication and the society as such underwent an enormous change for last 100 years. It is therefore unclear how the authors can reach the conclusion that it is likely that antipsychotic treatment is the only factor left to play an important role in increasing excess mortality by suicide?</p> <p>The authors have overlooked that a more recent analysis than Mortensen and Juul reached the opposite conclusion, namely that suicide rates among patients with schizophrenia in Denmark declined with the same fast speed as in the general population (1) It is almost impossible to compare two such different dataset and two very different time periods. Therefore it is very risky to put the data in the same survival figure. It is not mentioned whether age (at first admission, or at least age at discharge) was included as a covariate in the analyses. How was inpatient deaths handled? A statistician should evaluate the calculation of mortality rates and the survival analyses.</p> <p>When the insecurity of data is taken into account, the very long discussion about possible explanations for the findings is not warranted.</p> <p>Reference List</p> <p>(1) Nordentoft M, Laursen TM, Agerbo E, Qin P, Hoyer EH, Mortensen PB. Change in suicide rates for patients with schizophrenia in Denmark, 1981-97: nested case-control study. <i>BMJ</i> 2004 Jun 22;329:261-6.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (E Shorter)

There are no substantial criticisms here. We have taken on board the points about not having an unduly lengthy exposition of our methods and have focused on giving the details of new methods employed in the course of this study.

Reviewer 2 (SukantaSaha)

1 This reviewer's trenchant comments have been most helpful. We agree that we were somewhat jumbled and out of order with our presentation and that things could have been a lot more clear. We have now removed discussion from Results, put the findings in a more logical sequence and trimmed the discussion section considerably.

A It is not possible to give SMRs for all causes of death. One reason is that it is unlikely that many deaths outside the asylum historically were classified as exhaustion and certainly of those that were few if any will have had lethal catatonia.

In the contemporary sample, suicide accounted for 50% of all deaths. There are not enough deaths under other headings to make SMRs for all disorders realistic. The SMR for the non-suicide group, as mentioned in the text is directly comparable to other cited figures.

B We have opted to leave these tables in as while the discussion about age is not extensive we believe it is critical to the interpretation of the paper.

C We have improved the presentation of the data with more suicide specific SMR data in the results section.

D This is an excellent point but we believe we have covered this by stressing that after year 1 the data approximate. The reviewer is correct but we do not want to be too provocative.

E We agree and will lodge these data with the paper in an excel file. Presented in the table it would be overwhelming

F We have remedied the omission in the abstract and improved the graphs to make them more readily understandable.

G This is reasonable but the gender breakdown in the tables does help make sense of the impact of tuberculosis in the historical cohort and suicide in the contemporary cohort and this is mentioned in the text.

H We have tried to clarify this

2 The reliability of the diagnostic data is dealt with in an earlier BMJ Open paper. This will be an issue stressed by those who do not like the findings. We now have over 10 papers published using these methods so a great number of reviewers have accepted the argument that these are reliable diagnoses.

3 We agree and have removed these.

4 The references have been corrected as suggested.

5 We have checked all spellings and tried to shorten sentences throughout.

Reviewer 3 (E Chen)

We have taken on board Professor Chen's recommendation to state the rationale for the study in a clear fashion.

We agree that the original draft was too focused on antipsychotic medication and have changed the emphasis to suggest that this may have been a contributory factor. The importance of this factor however lies in the possible route to improvement that it opens up.

Professor Chen suggests that most suicides in psychosis arise when psychosis remits and insight returns. This is a hypothesis that has been around for some time but is not supported by the data. We attempt to point out why we believe this view to be incorrect – we think it would be more likely to be correct if the suicides happened in later years of the illness rather than primarily in the first year for instance.

Reviewer 4 (M Nordentoft)

The original paper takes DrNordentoft's main point into consideration primarily by having both historical and contemporary diagnoses made by the same set of contemporary diagnosticians.

We have not reached the conclusion that antipsychotic medication is the only contributory factor – our view is that this is the contributory factor for which the greatest amount of evidence is available. There may well be other factors. The redraft of the paper hopefully makes this clear.

DrNordentoft's paper is one that fits well with our data and we have included it in discussion section.

The mortality rates and survival analysis were calculated by a statistician. The statistical files will be submitted with the paper if accepted. The long discussion has lost close to a 1000 words. There is nothing speculative in this discussion. Some of the length stems from responses to the questions and speculations that have been raised when we present the data and will arise for many readers of the paper.

Reviewer: Edward Shorter, PhD, FRSC

no supplemental documents; the tables supplied are appropriate

paper is a little too focused on the evidence and technique; see comments below

This represents yet another contribution from the flow of papers of Dr David Healy's highly productive group in Bangor comparing patterns of psychiatric illness late in the nineteenth century and today. Some of these comparisons have proven extraordinarily interesting, such as the finding that schizophrenia increased late in the 19th century and has evidently declined in frequency today. This occasions much fruitful speculation.

The current paper is no exception. The authors find that, despite a cornucopia of modern treatments, mortality in general from schizophreniform illnesses is just as high today as then, and that suicides among schizophrenics are considerably more common now. The paper contains the pregnant sentence, "The historical data suggest there is something about the modern delivery of care that contributes to suicide as an outcome." (15) This is really extraordinarily interesting and well worth the price of admission. Further, the authors conclude that earlier treatment of schizophrenic illness could produce much more favorable outcomes. This, of course, is not new, but the historic documentation of it is impressive. It goes without saying that I recommend the paper be published. It is one of the most important to have crossed my desk in the last while.

I do however have one editorial suggestion. The paper is written too closely to the evidence, and takes on at times the character of a discourse on the technique of conducting historical and contemporary epidemiology rather than a presentation of findings. Indeed, I had to labor at several points to figure out what the important trend was (as for example in the section on the discussion of SMRs and life expectancy). This emphasis on technique gives the prose a certain clunkiness, as though it were written for techno-geeks rather than inquiring minds. The writing needs to be simplified and the main findings clearly signaled at each juncture.

I hope these comments are of use.

Reviewer: DrSukantaSaha

The results are not well presented, please see my comments to authors

General comments:

The paper assessed mortality rates in schizophrenia and related psychoses using a historical and a contemporary cohort. As expected the results show that there was an increased mortality in schizophrenia/psychoses in both historical and contemporary cohorts. The authors report that the SMRs (Standardised mortality rate) were similar in both the cohorts. The years of life lost in schizophrenia was 4.3 years in the contemporary cohort while for historical cohorts it was between 8 and 11 years.

The paper is of interest to the research community, and the results have implications for service planning.

Other comments:

1. The paper is too detail in many places. There are unnecessary discussions inside the result section (p. 11 para4), main results not reported in the abstract, results not properly analysed but discussed etc. Overall, it needs tidy up:

a. Causes of death (Table 1 & 2): It is good to present causes of death in detail. However readers may like to see the SMRs for all these causes of death. The authors opted to present SMRs only for

schizophrenia and all psychoses (divisions of psychoses are not necessary then). It will make more sense to discuss about them only or present SMRs for all causes of death and discuss. In p. 16, there is a discussion about acute and transient psychosis, without knowing SMRS, we do not know what the results hold.

b. Tables 3a & 3b are too detail for no good reason, why presenting age groups data while it was not discussed at all. Ideally these four tables should go to the Appendices

c. Discussions on suicide and tuberculosis take an important part of this paper (P. 9, 10, 11, 13, 14, 15). However, readers may like to see the SMRs for them. One of the most important analyses about suicide has been presented in the discussions (p. 15, para 3) without presenting in the results.

Without knowing how the results unfold it was difficult to understand what has been saying.

d. The authors report that the SMRs for schizophrenia were similar in both the cohorts. In Table 4, in the contemporary cohort we see that the SMR for persons is 11.8 while in table 5 for historical cohorts it was 4.0. How it is similar? In the discussion it was also claimed that the all cause SMR for schizophrenia are similar with other recent studies. In fact, we see from several systematic reviews that the SMRs are between 1.5 and 3 (eg., Brown et al 1.51, Harris et al. 1.57, Saha et al. 2.58).

e. It is advisable to present both observed and expected deaths when presenting SMRs.

f. The result about the survival analysis has not been mentioned in the abstract while it was one of the aims in the paper. The graphs are too difficult to extract, may be because they are too busy or the resolution has been compromised.

g. Male female differences are not highlighted while tables 4, 5 & 6 are dedicated for this. However, in places M:F differences were mentioned for suicide (p. 14, para4) while we do not see the results as such.

h. Readers may prefer to see main results in a succinct manner, may be at the end or the start of the discussion chapter?

2. I do not understand the diagnostic patterns. How reliable and complete are diagnoses in the electronic records the historical cohort given the well known comorbidity patterns (e.g. common combination substance use disorder or depression and schizophrenia), makes me worry about the reliability of the diagnostic data.

3. In several places (eg., p.11, para 3; p.14, para 3) results for affective disorders were mentioned. I think it is out of context here.

4. The reference list has some inconsistency in it and also not exactly follow the system BMJ Open follows:

a. If the ref contains more than 3 authors, after 3 names it needs to write 'et al'.

b. No bold for the volume number

c. Some places the journal name has been abbreviated, sometimes full names were given

d. Journal names to be in italics (eg., 21 not italics)

5. Other minor points:

a. There are spell mistakes, large sentences in places, needs thorough editing

Table 6 should go the appendix.

Reviewer: Professor Eric Chen

Department of Psychiatry

University of Hong Kong

The study is highly interesting and informative from a historical perspective. It therefore does not fit very well the standard review structure.

The rationale for making the comparison made in this study is can be expressed in a more focused and convincing manner.

There is some problems with interpretation of data given that these two samples are treated very differently (see below). It would be desirable to formulate several explicit research questions that the data could address.

This study set out to compare the mortality in schizophrenia and related psychosis in two cohorts one century apart in a defined catchment area in North Wales. Follow up was between one to ten years.

This is an interesting historical study. The rationale of comparison, save having access to such a cohort, is yet stated in a focused and convincing manner.

The authors suggested that comparison could highlight the difference between having and not having antipsychotic medications. It does not need to be stressed that apart from medication, there is a host of difference between the experiences of psychosis a century apart. In particular, the social and physical treatment context (e.g. that earlier patients virtually become long-stay patients from their first episode illness) would make the social and psychological experience of psychosis fundamentally different and simple comparison difficult.

For example the authors reviewed the lack of suicide in the early sample compared with the modern sample and concluded that the dysphoric effect of antipsychotic medication may play a role. This is however likely to be a gross over-simplification.

From early description of the illness, we know that clinical remission is in fact unusual, many patients continued to experience and be preoccupied with psychotic symptoms (this can be tested with data in this sample). Most suicides occur in psychosis at the time when psychotic symptom resolves and insight emerges. Patients a century ago have less chance to experience this emergence of insight into their illness, and consequently were less exposed to the demoralization and difficulties associated with coming to terms with having had a psychotic illness, which may be associated with suicide. It would be important to discuss this possible interpretation to the increase in suicide in contemporary patients compared with those in the past.

To clarify the above, it would be desirable to give psychopathology information for these two cohorts.

In understanding the other causes of death it would be important to have information about the ages of the patients at the start of the study.

Reviewer: Merete Nordentoft
Psychiatric Centre Bispebjerg, Psychiatric Department

The topic is important and the authors have done a heroic work in trying to identify old and new cases.

However, it is very difficult to compare to very different periods of time. Many things have changed. The threshold for psychiatric treatment has changed, and just to determine incidence of schizophrenia in the two periods will be difficult. As length of admissions also have changed the likelihood of dying during inpatient stay has changed, and therefore it is important to look into not only post discharge mortality. Diagnostic traditions have changed, and medication and the society as such underwent an enormous change for last 100 years. It is therefore unclear how the authors can reach the conclusion that it is likely that antipsychotic treatment is the only factor left to play an important role in increasing excess mortality by suicide?

The authors have overlooked that a more recent analysis than Mortensen and Juul reached the opposite conclusion, namely that suicide rates among patients with schizophrenia in Denmark declined with the same fast speed as in the general population (1)

It is almost impossible to compare two such different dataset and two very different time periods. Therefore it is very risky to put the data in the same survival figure. It is not mentioned whether age (at first admission, or at least age at discharge) was included as a covariate in the analyses. How was inpatient deaths handled?

A statistician should evaluate the calculation of mortality rates and the survival analyses. When the insecurity of data is taken into account, the very long discussion about possible explanations for the findings is not warranted.

Reference List

(1) Nordentoft M, Laursen TM, Agerbo E, Qin P, Hoyer EH, Mortensen PB. Change in suicide rates for patients with schizophrenia in Denmark, 1981-97: nested case-control study. *BMJ* 2004 Jun 22;329:261-6.

VERSION 2 – REVIEW

REVIEWER	Merete Nordentoft Professor in Psychiatry Copenhagen University Hospital Denmark
REVIEW RETURNED	06-Sep-2012

THE STUDY	It is interesting to investigate mortality in two different historical periods, but it is a very difficult task. The lower suicide rate in the historical cohort, and it is not possible to sort out whether the higher mortality from tuberculosis meant that some people did not survive sufficiently long to commit suicide. However, the data are interesting even though the methodological challenges are numerous and no firm conclusions can be based on such a soft basis
RESULTS & CONCLUSIONS	It is very likely that it is very difficult to compare to essentially uncomparable samples. The authors have improved the self critical elements in the manuscript. I assume the pages 29+ in the manuscript is not planned to be published? It is not suited for publication
GENERAL COMMENTS	The difficulties in comparing two very different cohorts should be underlined. Everything is different: Recruitment, psychiatric treatment, treatment for physical disorders, composition of background population, and health status and mortality pattern in background population. The figures with different survival plots are beautiful - but should be cautiously interpreted