PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The incidence of admissions for schizophrenia and related psychoses in two cohorts: 1875-1924 and 1994-2010
AUTHORS	David Healy, Joanna Le Noury, Stefanie Caroline Linden, Margaret Harris, Chris Whitaker, David Linden, Darren Baker and Anthony P Roberts

VERSION 1 - REVIEW

REVIEWER	Edward Shorter, PhD, FRSC Hannah Professor of the History of Medicine/Professor of Psychiatry Faculty of Medicine, University of Toronto 150 College Street, #83G Toronto ON M5S 3E2 Canada
REVIEW RETURNED	14/10/2011

THE STUDY	As noted in comments, the inclusion/exclusion criteria could be a little more clearly presented.

This is another jewel from that vast cornucopia of epidemiological data at Denbigh in North Wales that has already brought forth important findings about the decline in puerperal psychoses and in psychotic depression. Here we're cracking the tougher nut of "schizophrenia," tougher because the diagnosis itself is so poorly characterized.

Schizophrenia is a heterogeneous diagnostic basin containing several different disorders, and the use of the term – as a supposed disease that has no single pathognomonic symptom, or unitary response to treatment, or distinctive genetics, or common prognosis – should probably be regarded as outmoded.

In any event, the Healy group are prisoners of the literature and clearly follow convention in their diagnostic classification. In the Denbigh records, the diagnosis "schizophrenia" appears only in 1924. So previous schizophrenia in that facility is a construct. What is unclear in their use of the term is how they classify psychotic illness having a strong affective flavor. They have already removed frank psychotic depression, which would mean psychotic melancholia, from the basin. But it's not clear from the presentation whether "schizoaffective disorder" is part of what they call schizophrenia or not. In the "discussion""section, schizophrenia and schizoaffective disorder seem to have been collapsed into one group. If so, then the authors' "schizophrenia" is not really "non-affective psychosis."

This point is important because of the recent decline in "schizophrenia." If schizoaffective disorders are included, maybe the decline is owing to some kind of abatement of affective illness? Diagnoses of mood disorders continue to rage about us like the whirlwind, but it is possible that their actual epidemiological occurrence is less. (See E Jane Costello et al., "Is there an epidemic of child or adolescent depression?" Journal of Child Psychology and Psychiatry, 47 (2006), 1263–-71, 1268.)

What else could account for the increase of chronic psychotic illness late in the 19th century, its decline in our own time? The authors reasonably propose better obstetrical care and a lessening of environmental lead. This would be the real challenge for historical epidemiology: nailing down the role of lead-based paint or the perinatal consequences of fewer traumatic deliveries.

But there are other entire realms of investigation in talking about changes in schizophrenia: There is, for example, Edward Hare's viral argument, which had led to speculation that better communications in the 19th century might have abetted the spread of a neurotropic virus. (Edward Hare, “Schizophrenia as a Recent Disease,” British Journal of Psychiatry, 153 (1988), 521–531). The 19th century witnessed enormous increases in the consumption of alcohol. Could this have proved teratogenic? It's early days in this very exciting field, and the Healy group is leading the train.

REVIEWER	Dr Maneesh Gupta Consultant Psychiatrist ESI Hospital Okhla, Delhi, India I declare that I have no competing interests.
REVIEW RETURNED	01/11/2011

THE STUDY	The research question was incidence rates, but the conclusion in the abstract mentions "The timing of these changes may help pinpoint aetiological contributions to this disorder." which has not been adequately addressed in the research presented in the paper. Similarly, in the section What this paper adds: it mentions "The timing of these changes in incidence are consistent with changes in ambient lead and in obstetrical practices" which again is not adequately addressed in the research.
RESULTS & CONCLUSIONS	Credible: I feel the results are partly credible. The diagnostic practices in the 19th century were very different and despite this diagnosis have been coded retrospectively as ICD-10, which reduces the applicability and acceptance. Apart from this the need for admission into an asylum/hospital has undergone a huge change over the last 100 years. This too may impact on the incidence of hospital admission. Well presented: I am not an academician but a clinician, and I felt lost in the maze of methods and results presented. Data conculsions: The question of whether the 'change' in admission was due to obstetric practices and/or changes in lead concentration was NOT the original research question. Hence any such conclusion in not derived from the research presented in this paper.

REVIEWER	Joel Braslow, MD, PhD Professor UCLA United States. I have no competing conflicts.
REVIEW RETURNED	02/11/2011

THE STUDY	The primary research question the authors seek to address is whether the incidence of psychotic disorders and, specifically schizophrenia, has increased or decreased since 1875. This is a difficult question to answer given since one would want a population-based measure of new cases rather than one based on service utilization. The authors argue that since North Wales has a relatively stable population and that a single hospital has been responsible for the care of those with psychotic disorders, looking at admission

	rates between 1875 and 1925 and comparing those to admission rates between 1994 and 2010 is a legitimate proxy for incidence. This requires one to assume that the same phenomena that we deem as schizophrenia today would lead to identical rates of hospitalization. The authors need to demonstrate that the circumstances that led to hospitalization for psychosis in the late nineteenth and early twentieth centuries are comparable for those in the late twentieth and early twenty-first centuries. The authors do not explicitly state what their diagnostic criteria were in assessing the historical records. Given how different record keeping was in the historical period, it would be especially important to give examples of the records and how a particular diagnosis was arrived at based on those examples. Distinguishing between an affective psychosis and a non-affective psychosis sometimes is not easy in a clinical context. Making such a distinction from 19th century and early 20th century records is even more daunting. Since their calculations of incidence do require that these diagnostic differences are accurate, a clear description of how these distinctions were made is especially important. Similarly, the authors do not describe the method by which diagnoses were arrived at with the contemporary cohort and whether they used the identical criteria as they did for the historical cohort.
RESULTS & CONCLUSIONS	The authors seem to make too much of the drop in admission rates after 2006. Looking at the figures, it looks like the changes in admission rates might be simple random fluctuations. I am not a statistician but I found myself wondering whether there might be other statistical methods better to take into account changes over time. Another confounding feature of the drop after 2006 is that the authors exclude the acute and transient psychoses from their analysis. The authors don't provide criteria by which individuals were given these diagnoses but I wondered whether it was defined by whether or not they had subsequent hospitalizations. If this were the case, then wouldn't one be underestimating the number of individuals with schizophrenia since, as the data approaches the present, there are fewer opportunities for readmission and, hence, reclassification?
GENERAL COMMENTS	Even though the authors make an argument about incidence, I would encourage more detail about why there are no differences in first admission rates in the 19th and early 20th centuries compared to the present period. Such a discussion would need to address the kinds of behaviors that lead someone to be taken from the community to the attention of the medical system in both periods. If the authors' argument relies upon an assumption that the factors that led one to the attention of the medical authorities has changed little over the last 100 years, they also need to make a convincing case that the probability of admission for someone with psychosis hasn't changed either over the same period of time. Details of the admission process then and now would be helpful, especially if the authors believe the chances of admission have changed little over the period of time in question.

VERSION 1 – AUTHOR RESPONSE

Dr Shorter
We agree fully with Dr Shorter regarding the likely nature of schizophrenia and that it will turn out to

comprise a number of different disorders that at present have in common a chronic course. Some of our data support his argument. We point out that hebephrenic and catatonic presentations have almost completely disappeared.
In line with Dr Shorter's suggestions and those of the other referees we have given further details of the diagnostic process for both historical and contemporary records.
As regards complications from affective disorders, there were in fact very few schizoaffective cases (N=26). We make this clear in the revision. There has also been a drop in depressive psychoses, rather than the increase there might have been if cases of severe affective disorders had migrated from the schizophrenia to the affective group.
In addition to our suggestions regarding obstetrical care and lead poisonings, we have also noted in the introduction the suggestions from Torrey and Hare regarding infective processes.

Dr Gupta
In line with Dr Gupta's suggestions we have removed references to obstetrics and lead from the abstract and removed the lessons learnt box. He is correct in that our data do not investigate these specific hypotheses. Having provided data on changing incidences however we have thought it reasonable to offer possible explanations that might account for changes in incidence and might lay the basis for further research.
We have tackled the issue raised by both Drs Gupta and Braslow regarding the probability of admission during the contemporary and historical periods. This is primarily an issue for anyone attempting to make a direct comparison between the two periods which we do not do. The probability of admission likely remains roughly constant during the historical period in that there was no change to the legal framework or other procedural aspects to admission during this period. Similarly we are not aware of any factor that might lead to a change in the likelihood of admission during the contemporary period.

Dr Braslow
Dr Braslow raises an intriguing but unanswerable question – namely whether the probability of people being admitted in the historical period is the same as now. If we were directly comparing admission incidences in the historical and contemporary periods this would be a critical point. We aren't. For our purposes we assume constancy of probability of admission during the historical period – and there is no good reason not to assume this – and constancy of admission during the contemporary period. We make this clearer in the revised manuscript.

Presumably the only possibility re probabilities of admission is that these were lower in the historical period – there was a greater stigma about admission and no possibility for informal admission. If in fact this translated into practice, it would make the contemporary finding even more salient.
It is possible that the drop after 2006 is a random fluctuation but this is the reason we have presented the data with confidence intervals. The only way to find out if it is a random fluctuation or local phenomenon is to publish and stimulate others to review and attempt replication. These data are however historically unprecedented.

We have tried to describe the data using several different statistical models, but settled on this one for publication after giving the matter extensive thought. We have provided the raw data because we agree with Dr Braslow that the model we have used may not be the only one that could be applied and we would welcome input from others on this point.
We have not excluded the acute and transient psychoses from our analysis after 2006.
We have neither stated that the incidence rates are the same in the early and later periods, nor does our argument hinge on this and hence the discussion about behaviors that lead to admission is redundant. Dr Braslow is making inferences regarding the data that we do not make. In fact we explicitly state that male admissions are initially higher in the contemporary than the historical period, with female admissions correspondingly lower.

VERSION 2 – REVIEW

REVIEWER	Dr Maneesh Gupta Psychiatry-Specialist ESI Hospital, Okhla Delhi, India
REVIEW RETURNED	25/11/2011

The reviewer completed the checklist but made no further comments.

REVIEWER	Joel Braslow, MD, PhD Departments of Psychiatry and History UCLA USA
REVIEW RETURNED	06/12/2011

THE STUDY	This revised manuscript still has problems that make it difficult for me to give a positive assessment. Granted, the authors' abstract is less ambitious than the first version, stating that they are simply comparing rates of first admissions in the late 19th and early 20th centuries to the contemporary period. But, they do not provide convincing evidence that the two cohorts are actually comparable. For the first cohort, they use a medical record review and for the second cohort they were less explicit about how the diagnoses were made. I would like to see the same methods used for both cohorts. It is not clear that this is the case. Further, there is still too little information on how the early case diagnoses were arrived at. Since determining the difference between an affective vs non-affective psychoses is difficult in a clinical context, making such distinctions from medical records from the 19th and early twentieth centuries seems nearly impossible. But, even if we are describing similar patients from the two eras, the only conclusions that can be drawn is about admission rates, whether they are similar or different between the eras. The data presented does not say anything about why rates may be similar or different.
RESULTS & CONCLUSIONS	I remain perplexed by the discussion in the article, which focuses on a possible decline in schizophrenia since 2005. First, the data only is on admission rates so, any conclusions about disease incidence seems unwarranted. Granted, the authors state: "the most salient finding is a decline in admission incidence for schizophrenia from 2005. This cannot be explained either in terms of administrative coding procedures or in terms of service changes." They then provide some details as to why this may be the case. Nevertheless, this is an assertion and not a proven fact. To make a claim that schizophrenia is declining one needs a community sample. Data from a single hospital admissions is not sufficient to make such a claim, even if speculative.
GENERAL COMMENTS	The authors seemed trapped in trying to make larger claims than their data will allow. In the end, they have only data on a single hospital's admission rates. While the catchment area is uniquely stable over time, the massive historical changes over the last century in clinical meaning of illness and clinical care, make

	comparisons difficult, especially if one is trying to compare diagnostic categories of the late 20th and early 21st century to medical records a century earlier. A more qualitative approach may be more useful. As it stands, the authors have imposed a contemporary diagnostic system on patient records that do not necessarily conform to our present-day diagnostic standards. Instead, I would like to see rich descriptions of the kinds of patients admitted in the first cohort, what mattered to the physicians when they wrote about their patients, and then compare these descriptions of contemporary patients. In this way, we might have a clearer picture on what mattered as psychotic illness then and now--at least to the admitting physicians. Discussion of disease incidence seems misleading and, though the authors state clearly they are only looking at admission rates, the discussion of incidence confuses the aim of the article and suggests much more than the data shows.

VERSION 2 – AUTHOR RESPONSE

We have made the changes in the manuscript you have asked for. The former manuscript had over two pages of speculation on lead and obstetrics (pages 18-20). This has been reduced to one paragraph - five lines at the end of page 17. We have also removed the seven lead and obstetric references.

There are two other minor changes. We have corrected information about the 1921 census - the data were lost in a fire rather than not collected. We have also added a reference on page 13 on recovery rates in non schizophrenic disorders.