Author's response to reviews

Title: Association between mortality from suicide in England and antidepressant prescribing: an ecological study

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Author's response to reviews: see over
Dear Editor

I would like to thank both reviewers for their helpful comments.

We have revised our manuscript with their comments in mind and outline below specifically what changes have been made. We feel confident that we have addressed the reviewers’ comments fully. We have also checked all the calculations in the paper and corrected a few minor errors.

Kind regards

Oliver Morgan

Reviewer 1: Andrea Mant

1. On page 7/16 the authors mention that they accessed data on hospitalisations for drug poisoning – however no such data are presented. Please clarify.
This has crept in from a previous version. The reference to hospitalizations has now been removed.

2. Presumably the suicide and drug poisoning data are mutually exclusive – ie a death is classified in one category only.
In the method section, suicide is defined as “deaths where the coroner has given a verdict of suicide or where an open verdict was reached in a death from injury or poisoning” (page 5). This definition includes drug poisoning deaths which had a verdict of suicide or an open verdict in the suicide rates, as well as deaths involving drugs which had accident, homicide or drug abuse/dependence verdicts. As the number of deaths involving antidepressants (n=4,417) is small compared to all suicides (n=46,747), excluding them has an minimal effect on suicide rates. We have therefore decided to include them, according to the definition above.

3. Could they have strengthened their analysis by estimating values for age and sex specific prescribing rates to address the issue of whether the correlations differ by age and sex? cf ref 6 methods
We certainly considered the possibility of conducting age-specific analyses. However, we do not readily have information about prescribing by age group for the whole of our study period. As anecdotal information suggests that the pattern of prescribing by age group has changed during the last 10 years, we decided not
to ‘guestimate’ this. Assessing prescription rates by age group could be done using other data sets such as the General Practice Research Database. However, this is a separate project in its own right.

4. **Table 2 legend: it is not clear in the legend that the correlations are for rates.**
The title has been modified to “Table 2. Spearman’s rank correlation coefficients and p-values for directly age-standardised suicide and antidepressant poisoning rates and prescription rates, England 1993 to 2002”

5. **Can they comment on the literature attesting to the direction for the England & Wales alcohol consumption and unemployment rates either as total or age-specific?**
Figures from the Office for National Statistics show that during our study period, unemployment fell from about 10% to below 5%. This may be an alternative explanation for some of the decline in suicide rates. In contrast, consumption of alcohol, mentioned in 28% of antidepressant poisoning deaths, remained relatively stable. These two points have been addressed in Interpretation section on the bottom of page 12.

**Reviewer 2: Corrado Barbui**

*I believe that ecological analyses describing trends in suicide mortality and trends in antidepressant drug prescribing are useful public health tools to assess the "real world" impact of specific policies (the introduction of SSRIs) on hard outcome indicators (suicide mortality). However, these studies cannot establish causal associations between variables. In the present study the authors state that "increased prescribing of antidepressants was associated with reduced suicide mortality rates". To me it is not possible to draw such a conclusion from ecological analyses, and the term "associated" should not be used. In addition, it is not correct, in my opinion, to carry out statistical analyses to show whether these two trends were correlated. It’s a misleading way of presenting data, since suicide mortality can be influenced by a number of factors, and in the time interval during which suicide mortality decreased many other factors could have played a role. In other words, the increasing prescribing of antidepressants might (or might not) be related with suicide mortality, and this study cannot address this issue. Consider that (1) a relevant proportion of antidepressants is not prescribed to depressed patients at risk of suicide; (2) suicide mortality in most countries was already declining before the dramatic increase in drug use; (3) only a minority of individuals committing suicide were taking antidepressants.*

We feel that our presentation of statistical analysis showing an association between antidepressant prescribing and suicide or poisoning deaths is not misleading. This if for the following reasons:

- It is common practice in ecological studies to carry out statistical analyses and to report associations between ecological variables. An extensive overview of statistical and design issues for ecological analysis is given in Chapter 23 of Modern Epidemiology by Rothman and Greenland (1998).
The reviewer was concerned that by reporting an association, we are claiming that this is causal. We are not. According to the Dictionary of Epidemiology by Last (2001), an association is a “statistical dependence between two or more events”. This can be further defined as symmetrical or causal and asymmetrical or noncausal.

Finally, ecological analysis has had a long history and has been useful in elucidating many important public health associations, such as the relationship between poverty and health.

Having said that, I suggest: (1) to avoid statistical analyses suggesting correlations that cannot be established with the present study design; (2) to avoid the term associated and associations in the text; (3) to discuss this study limitation, and the reason why no statistical analyses were performed, critically and frankly reviewing the limitations of ecological analyses.

On the basis of the points above, we feel that it is wholly appropriate to conduct statistical analyses and to present them as an association. In addition, in our original manuscript clearly states that “the ecological nature of our data means that we cannot say whether reduced suicide rates is a direct consequence of increased antidepressant prescribing rates.” (page 12).

Nevertheless, we have tried to introduce greater clarity. Where possible, we have avoided the word “association”. Where it is not possible, we have replaced “association” with “statistical association”. We have also included an additional sentence in the first paragraph of the discussion (page 10) outlining the inability for our study to show causal relationships: “Because our study uses population level data, we cannot conclude that these associations are necessarily causal”.

We feel that these changes should sufficiently address the reviewers concern that “association” may be confused with “causal association”.

A second point is the use of “prescriptions per 100 population”. Authors should consider to calculate the number of DDD/1000/day. The DDD is a theoretical unit of measurement defined as the assumed average maintenance daily dose for a drug, used for its main indication in adults. The DDD/1,000/day indicates how many people per 1,000 of the population have in theory received a standard dose (i.e. the DDD) of a particular medication or category of medication daily. Expression of drug use in terms of DDDs/1,000/day allows comparisons to be made independent of differences in price, preparation and quantity per prescription. It's a standard way of presenting data on drug use (see www.whocc.no/atcddd).

The reviewer is correct in that DDDs are a standard way of presenting drug usage statistics. However, the Prescription Cost Analysis system in England has only recently started to included DDD figures. For the time series back to 1993, DDD figures are not routinely available. Nevertheless, analysis by Henry et al (BMJ 1995;310:221-4) has shown that in England, analysis prescriptions and DDDs are highly correlated and it makes little difference which one you use. We have therefore continued to use prescription items, similar to previous papers in the UK.