Author's response to reviews

Title: Identifying the determinants of premature mortality in Russia: overcoming a methodological challenge.

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Author's response to reviews: see over
Dear Sir/Madam,

We would like to thank you for your comments, the reviews, and the opportunity to revise this manuscript. The feedback is both thoughtful and useful and we have now incorporated several changes into the manuscript. Please see our responses point by point below.

**Major Compulsory Revisions**

**Reviewer 1**

1. This article would be even more useful to other researchers if the authors described in greater detail the data collected and the ways of reconciling information from several sources. So, what questions were used to ask the proxies about the proband’s alcohol consumption? Was the emphasis on acute effects of alcohol consumption or cumulative effects? How were the data from proxies and administrative records combined, particularly if these two sources were inconsistent (such as the data presented in Table 3)? What other measures were collected from the proxies?

   - This is an important point. We have already provided an overview of the ‘indicator questions’ incorporated into the study. The key issue here is that the questions were structured to address the use of proxy respondents. However, in the section ‘Obtaining information on subjects’, we have now added an overview of the alcohol questions employed in general in order to better illustrate the approach used. The overall questionnaire is of course available on request, and many questions are detailed in the key outcome paper already published from this study(1).

   - The reviewer’s query about the time period of interest with respect to alcohol behaviour is an important one, but we feel that the issue of specific data collection is not the focus of this paper. There is extensive discussion of the information we collected in a recent paper published by our group(1) where we describe that the emphasis was on both usual and recent behaviours, in order to inform us about events just before death (proximate exposures) as well as cumulative effects of alcohol.

   - With respect to combining external and questionnaire data, we would like to emphasise that external data were primarily used to validate the questionnaire data obtained from proxies. This is described at the beginning of the section ‘External validation’, and this section has now been modified in order to clarify this point. The data obtained from external sources was linked to questionnaire data using subject numbers.

   - In addition to obtaining information about the index from each proxy, we also included information about the proxy themselves (age, gender, occupation, education etc). This information was used to explore the extent of bias in the validity and reliability of proxy responses obtained, according to proxy characteristics. This has now been included in the manuscript.

2. Similarly, regarding the outcome, how were data from official records and autopsies combined and how were discrepancies reconciled?

   - Autopsies, where carried out, informed the cause of death entered on the death certificate. Any discrepancies between these two sources were therefore due to data entry errors. We found these and checked original records. The manuscript has now been amended to clarify this.
3. As shown in Table 2, for cases the proxy was less likely to be the spouse and more likely to be the mother - is this a problem?

- This difference in the best available proxy among cases and controls reflects the inherent difference in marital status and household composition between these two groups. Whilst it is possible that this introduced some bias into the sample, we have demonstrated elsewhere that provided the proxy fulfils certain criteria related to their ability to reliably report on the index, this bias will be minimal\(^2\). Additionally, analyses restricted to only spouses as proxies obtained the same results as unrestricted analyses\(^1\). These points have been clarified in the manuscript.

4. In the introduction, the authors describe the advantages of the case-control study design over a cohort study design. They should also discuss the relevance of a case-crossover design, which applies to the study of sudden and rare events.

- This is an interesting suggestion for an alternative type of study design that could be applied to this type of research question. It is true that a case-crossover design may be used in investigation of recent and rare events, by comparing recent and ‘usual’ (for example) time periods in the same individuals. We did in fact collect this range of information on our cases, asking questions about both recent and usual behaviours. However, we suggest that this paper is not intended as an exhaustive discussion of different study designs, but rather, we thought it important to acknowledge the weaknesses of the study design most conventionally applied to this type of problem (a cohort design) in this manuscript.

5. By design, the study only excluded individuals who were isolated. Does the risk of premature mortality or excessive alcohol consumption differ according to whether individuals live with someone or not? If yes, what is the extent of bias in the selection of the study population?

- It is almost certainly true that those individuals excluded due to living alone were more likely to die prematurely, or have more extreme alcohol consumption patterns, or both. Since proxies were used, this was an unavoidable type of exclusion, since no questionnaire data could be obtained on these cases. However, since controls that lived alone were also excluded, this would not have affected internal validity and would have introduced only a conservative bias, although it would have affected the generalisability of findings. This has now been commented upon in the manuscript.

**Reviewer 2**

The text rightly claims that proxy interviews could be compared to interviews with the controls, but provides no example of such comparisons. Moreover, what should be done, if both sources disagree.

- This is a good comment. Such comparisons have been carried out extensively and reported elsewhere, as referenced. However, we agree that it is important to include an example here, and have now added this to the manuscript.

- Since for a study such as this, only proxy (as opposed to index) interview data is available for the cases, it is most appropriate to use proxy data for the controls too in analyses. However, the collection of index data for the controls provided an opportunity to validate the proxy data obtained in order to inform about which questions are appropriate for inclusion in analyses, and previously, to guide the development of the questionnaire. We acknowledge the difficulty that arises when these two sources disagree: it is not possible in the absence of a gold standard to determine which is right.
However, where a gold standard is available, this should be used in preference to either. This is a very interesting debate, and has been discussed extensively elsewhere\(^{(2)}\)

**Reviewer 3**

None

**Minor Essential Revisions**

**Reviewer 1**

6. In the abstract, a description of the method used to address the shortcomings of previous research would be useful (ie indicate the design that was used).
   - This is a good idea, and has now been inserted. We have also now included a more comprehensive description of the shortcomings of previous research elsewhere in the manuscript.

7. In the discussion, could the authors indicate how the method they describe could be used in other settings? Could it be used to collect information on exposures other than alcohol consumption?
   - This is also a helpful suggestion. The discussion has been amended to provide further examples of where this method could be applied.

8. In the introduction, the authors mention an earlier study conducted in Izhevsk. What were the findings of that study?
   - The findings of the previous study are now outlined, along with its main weaknesses on page 5.

9. If the aim is to collect data on alcohol use, it is not clear what table 4 on smoking status adds to the paper. This information could perhaps be replaced by alcohol use.
   - The aim of the study is to explore the determinants of premature mortality. Whilst alcohol use is the primary exposure, data on a wide range of other exposures and confounders were also collected and were an essential part of the analyses. Table 4 (now 5) was intended to illustrate the extent of proxy-proxy agreement for one of these additional exposures, tobacco use.

**Reviewer 2**

The referencing is not very specific. To give but one example: For the statement "Specifically, it has been suggested that alcohol is a key proximate driver of the very sharp fluctuations in mortality seen in this group since the mid-1980s including a seven year period when, on average, male life expectancy at birth fell by more than one year for each calendar year." ten references are given, some of which to cross-sectional surveys or to specific disease relations with alcohol.

- We agree that the referencing was not specific in this instance. Have removed references which do not directly support this point. We have not found other instances in the manuscript where referencing is too broad.

Abbreviations such as "Surr" for surrogate alcohol on Table 3 should be avoided.

- This has been corrected
Re: the use of external information, the following is claimed: "It also provided an opportunity to fill an important gap in the literature on proxy informants by asking not just whether indexes or proxies agreed but also which were more accurate and, exceptionally, doing so in relation to issues that are often considered stigmatising and therefore subject to biased informant response."
The authors should give one example of a comparison, which demonstrates such comparisons with respect to accuracy. Table 3 provided here is not clearly interpreted in this way, and it is not clear, what the Chi square statistic in Table 3 refers to substantially.

- With respect to the latter part of this comment, Table 3 is intended to illustrate the use of external data in identifying the extent of recall bias. The reference to this table has been moved and adjusted in order to better achieve this. The chi squared statistic has now been labeled.

- The overall point we were attempting to make is that both indexes and proxies can be separately compared to the same external source. Formal statistical comparisons regarding their relative validity with respect to this ‘gold standard’ can then be made using a variety of methods, most appropriately loglinear models. We believe that this is the forum to describe that such comparisons are possible, but not to explain how to do this in detail, nor to present results (which are available elsewhere\(^2\). The manuscript has now been modified to clarify this point.

There are at various times superfluous "." in the text.

- These have been found and removed

**Reviewer 3**

The paper needs only minor revisions in terms of the flow of English. An “on” is missing at the end of the 8th line of the Abstract. An “on” is missing in the 4th line of the 2nd page of text. On page 4, “obligate” about 2/3 of the way down needs to be something like “obligatory”. In the next paragraph, an “and is needed between “challenges” and “issues”. Reference (28) needs completion.

- Thank you. These minor errors have all been corrected

**Discretionary Revisions**

None

**References**


Yours faithfully,

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