Author's response to reviews

Title: The descriptive epidemiology of delirium in a large population-based cohort study: results from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)

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Author's response to reviews: see over
Dear Editor,

The descriptive epidemiology of delirium in a large population-based cohort study: results from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)

Many thanks for the opportunity to revise this manuscript. The reviewers’ comments have been of great help in clarifying important points in the text. We hope you consider this version to be a stronger submission. Specific responses to the reviewer comments are given below.

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Editor:
Editorial Comments:
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Major comments:
Page 2, Abstract - The authors base their study design and conclusions primarily on the premise that prediction of mortality and dementia demonstrate criterion validity. But, they also acknowledge in the first sentence of the Abstract that these associations have not been well established in the general population. A major limitation of the study is that the associations with mortality and dementia are not specific to delirium; numerous other factors may account for the associations, including the possibility that what was diagnosed as delirium was actually symptoms of early dementia. Though the authors acknowledge this limitation in the Discussion, much of the paper is not written in a manner influenced by how critical this limitation is. The diagnosis made is referred to as delirium in the title and throughout the manuscript, when a better description would be "delirium symptoms" since the current design did not allow for the diagnosis of delirium to be validated as specific.

We greatly appreciate the reviewer’s thoughts on this and share his view on the difficulties here. Delirium and dementia are difficult to disentangle, be they differential diagnoses or superimposed (especially at the extremes, i.e. delirium on
mild dementia or delirium on severe dementia). This is true at the bedside, so of course yet harder epidemiologically. Part of the difficulty lies in defining the boundaries of psychiatric classifications and attempting binary constructs of delirium and dementia.

For delirium research, the issue of accounting for prior cognitive impairments is absolutely central, but the vast majority of delirium studies have *not* been able to fully adjust for prior (especially undiagnosed) dementia. Use of IQCODE or informant CDR is the best there is for establishing prior dementia and that may not be sufficient.

We have flipped this approach to ask the question: “In the context of a cohort study where there were serial, prospective measures of cognition leading to diagnoses of incident dementia, can we now see whether there was evidence that delirium symptoms were temporally prior to the diagnosis of dementia?” For all the difficulties in interpreting the data, we believe that these analyses add something new to the epidemiology of delirium in the general population, especially as the literature is so sparse.

Page 6, Statistical Analyses - The associated examined are very likely confounded by unmeasured variables. Only age, sex, and a subjective measure of severity of illness (which, as far as I can tell, has never been validated to accurately reflect severity of illness) are accounted for. The authors should discuss the possibility of confounding in the Discussion. This is an important issue. As with any observational study, both over-adjustment and residual confounding remain considerations. It is recognised that the effect of age on total dementia risk is so large that it overshadows many of other associations under investigation (particularly modifiable risk factors).(1, 2). This has been specifically observed in previous CFAS analyses (3, 4).

For delirium, the major dimensions to account for are predisposing and precipitating factors. Here, we have used age, sex and prior dementia (predisposing) and the interviewer’s impression of illness severity (precipitating). As mentioned above, the literature in this area is very small, but the analyses here are consistent with other studies (reviewed in (5)). Mention of this has now been made in the discussion.

Page 7, Results - Nearly one-fourth of the sample had dementia at baseline. Please describe the sensitivity and specificity of this approach taken to diagnose dementia. How likely was it that mild cognitive impairment (which may lead to some of the symptoms characterized as delirium symptoms) or even frank dementia went undiagnosed at baseline? Is it possible that the symptoms of delirium are actually indicators of early dementia? Associations with mortality and dementia could be taken as criterion validity indicators of MCI or early dementia just as well as of delirium. Couldn't the increasing prevalence of delirium with age be the result of symptoms of dementia being misdiagnosed as delirium?
The ascertainment of dementia at baseline and follow-up used the AGECAT algorithm. This is a standardised approach in psychiatric epidemiology and has been extensively validated and used in a range of studies and settings ((6-8)). As mentioned above, many of the points raised by the reviewer relate to the difficulties in defining categories in psychiatric epidemiology, though the AGECAT approach at least benefits from a standardised operationalisation the reference criteria.

4. Table 1 - To identify "acute change," the respondent is asked about confusion (which would indicate a change in cognition), but a change in consciousness is also required to diagnose delirium. As mentioned earlier, couldn't these symptoms all occur in the context of worsening cognition (without any disorder of consciousness) attributable to MCI?

The assessment of altered consciousness is captured in two domains (Table 1):
- Inattention, whereby the participant was asked to perform ‘serial 7s’
- Drowsiness, where the informant was asked:
  - ‘is there a disturbance of consciousness, that is either being sleepy, or awake but unaware of their surroundings’ AND/OR
  - ‘is the subject drowsy now?’

We agree that these domains are critical, and are therefore part of the algorithmic diagnosis. As to the more general point about disentangling different cognitive states such as delirium, MCI and early dementia, this has been addressed above.

Minor comments:
Page 3, Introduction - The phrase "inverse relationship" suggests that as predisposing factors increase, precipitating factors decrease, which is not necessarily the case. I believe the authors mean to say that in the setting of multiple (or severe) predisposing factors, fewer (or less severe) precipitating factors are required. Please clarify.

Thank you, clarified as suggested.
Table 1 - How was "sudden" defined? This could be taken as anything from a period of minutes to a period of weeks or even months.

Sudden was specified as ‘recent weeks or months’. So while not as brief as seconds or minutes, this is still a broad timeframe, acknowledged in the discussion.

Table 2 - It appears that almost everyone who had delirium died prior to the 2-year follow-up. Is this true? If so, how was the association with dementia demonstrated?

The demonstration of an association with dementia was undertaken in the survivors. It is correct that most of the persons with delirium symptoms were dead by follow-up, a finding that highlights the clinical relevance of delirium for older persons.
Reviewer 2

Abstract: no comments

Introduction:
• In the 3rd line from the end of the section, the word “predicative” is found. Did you mean “predictive”?

  Thank you, corrected

Methods:
• Throughout the paper, the abbreviations SO, AO and C2 are mildly distracting and caused a good deal of page flipping to find out what they stand for. Please consider either getting rid of these shorthand abbreviations and using labels consistently to refer to the different stages of the survey.

  This is a useful suggestion and the stages: S0; A0; H0; C2 are described here as “Screen”; “Ascertainment”; “Informant”; “Follow-up” respectively. We have added a footnote so that other readers familiar with the CFAS design can compare with other publications.

• In the 4th line from the bottom of the 5th page, the word “organitiy” should be changed to “organicity”.

  Thank you, corrected

Results:
• My main complaint with the results is confusion over the changing denominators throughout the section. I realize that in this kind of study, the denominator changes are quite complicated but it would help to know why, for example, n’s in the “no delirium” group in table one at the top of the column indicated 2075, but the denominator for the dementia at baseline was 2065, and similarly the n for the delirium group was 122 but the denominator for the dementia at baseline was 119.

• In the same vein, why in Table 3 is the n for inattention 2637?
• And finally why in Table 4 are the n’s for symptom clusters so different?
• Two possible suggestions for making this more clear to the reader might be to consider adding the loss to follow-up, mortality, refusal etc to figure 1 with the resultant denominators in the flow diagram and to include numbers of missing data, etc in the footnote of each of the tables.

  Thanks for the opportunity to clarify this, the tables have been amended to in line with your recommendations.

Discussion: no comment. It’s well written and doesn’t over-reach.

Table 1:
• In the footnote of the table, consider changing the wording (as noted in my first comment of the methods section above) to make the direct respondent examination and the informant interviews more evident to the reader. Also putting “(informant)” following the interview question for acute change in the body of the table is confusing, since you haven’t done this for all of the informant interview-derived questions.

  This has been clarified in line with the previous suggestions.

Table 2: Comments as above in the methods section
Table 3 and 4:
• Footnotes for both of these tables include the phrase “The middle part”. Consider quoting the section that you are making reference to, such as “Delirium: final model”. Also note that in both tables you have made reference twice to “the middle part”.
  Clarified as suggested

Table 5:
• Age grouping for 75-80 should be 75-79.
  Table 5 removed

Figure 2:
• Redundant with table 5. I would present either Table 5 or Figure 2 but not both.
  Table 5 removed
Reviewer 3
This paper is interesting. I only have some minor or mild comments to share with the authors.

1. The authors have not systematically examined the validity of their proposed diagnostic algorithm. To check its validity, the algorithm should be applied to different populations and/or compared with other similar well-established ones in the same population. Also if possible, the test-retest validity of the proposed algorithm should be presented.

   These are useful suggestions, though are not possible with the current dataset. As the present paper is the first to derive such an algorithm, the analyses suggested could form part of a future program of work of validation studies of delirium in population samples.

2. Abstract: Methods: Proportional hazard might be better termed as proportional hazard ratios; odds of dementia might be better termed as odds ratios.

   Thank you, clarified as suggested

3. Page 3, last paragraph: The percentage 0.7% in the first half of the very first sentence is for the general population or for the elderly population? It should be more specific.

   Specified as aged ≥60 as suggested

4. Table 4: Why is the "severe" category of illness severity omitted as the "none" category is the reference group?

   The effect of severe illness was not estimated due to no participants being assigned to this category

5. Many other health conditions are associated with mortality. Will the relative hazards in Table 3 be altered if these covariates are controlled?

   Thank you for raising this, the issues surrounding confounding have been addressed in response to reviewer 1.

6. Page 6: related to above point, how is the current acute illness defined? What items are included? This should be clarified.

7. Figure 2 and Table 5 reflect the same story. Only one is needed. If Table 5 is needed, age 75-80 should be 75-79, and a table not is needed to indicate whether the odds ratios are adjusted or unadjusted.

   Table 5 removed

8. Page 9, Line 5 from bottom: for the phrase "That delirium": Does this mean there is another delirium?

   Phrasing adjusted for clarity

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