Author’s response to reviews

Title: Simulation Studies of Age-Specific Lifetime Major Depression Prevalence

Authors:

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Author’s response to reviews: see over
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Dear BMC Psychiatry Editorial Staff:

Please find attached a revised version of our paper: “Simulation Studies of Age-Specific Lifetime Major Depression Prevalence.” A summary of changes in response to the reviewers’ comments may be found below. For ease of reference, the reviewers’ comments have been restated and the response appears subsequently, in italics.

Reviewer #1

1. “The authors need to cite the well-known Giuffra-Risch paper and explain what’s new in the current paper that was not done in that earlier paper.”

This citation has been added. The current paper (as well as the Kruijshaar, Barendregt et al. contribution) add to this by incorporating the issue of mortality, which is one of the important determinants of age-specific prevalence. The current study also made use of contemporary epidemiologic estimates, whereas the Guiffra-Risch paper needed to rely on outdated incidence data which were not actually included (only referenced as a guide to the reasonableness of numbers used in their simulations). The innovation of the Guiffra-Risch paper, when it was published was that they showed that false negative measurement errors could result in a pattern suggestive of a cohort effect in cross-sectional data – the current study goes much further in identifying the specific assumptions needed to attribute an observed pattern to a cohort effect, mortality effect or false negative measurement errors and by adding a greater degree of quantification.

Reviewer #2

1. “Validity of the model. The authors present some cursory test results, and conclude from them the model is valid. But I see odd 5 year patterns in the figures (eg 3 & 4) that are not explained, and from what I understand of the model specification, should not be there. Also, I find it odd that the model needs more than 100 years of burn in to get stable LTPs: surely with constant incidence and mortality selection, replacing the entire population should do.”

Point #5, below refers to the possibility that the n=100 replications from which the confidence intervals were calculated may have been too few so that the confidence intervals are too wide. A related issue is that the simulated age-specific prevalence, which is simulated in five year age categories, is subject to some degree of random variation. In the revised paper, we have recreated the figures using 1000 replications, leading to
narrower confidence intervals.

The models do become stable earlier than 100,000 days (273 years), in some of the later simulations we want the model to be in steady state prior to simulating the experience of birth cohorts eighty years prior to the end of the simulation. Using 100,000 days allows us to use the same simulation interval in all parts of the analysis. We have included a sentence to indicate to readers that the long period of time used in the simulation is not required for the model to achieve a steady state.

2. “The specification of the incidence function. The function used allows incidence to either increase, decline, or stay constant over the entire age range. A likely pattern is an increase at young ages, followed by a decline after ~ age 30. Some evidence suggests that this is followed by an increase at old age. The incidence function used seems far too simplistic.

The idea that incidence may increase in late life has been reported by some but not all prior studies. We have found no evidence of this in any of the Canadian studies upon which these analyses were based (nor have previous authors[1]). The pattern of LTP upon which the simulations were based did not show this pattern. However, the point raised by the reviewer cannot be easily discounted since: (1) we may have lacked power to detect an increase in elderly age groups, (2) institutionalized elderly were not presented in the CCHS sampling frame and (3) the CIDI may not be highly sensitive in elderly age groups. A sentence acknowledging this possibility has been added to the paper (section ‘c’ in Methods).

Some more minor concerns:

1. “Fig 1 needs CIs.”

Confidence intervals have been added to Figure 1.

2. “P8: age-specific mortality. Why not convert the age-specific mortality to a survival curve, and use a single draw from it to get age at death?”

Our goal was to subject each entity to an elevated mortality rate following the onset of their depression. The approach taken was to: (1) simulate an age of death, (2) simulate a date of onset of MDE and (3) subject the entities to an elevated mortality rate (defined by a relative risk) after the age of onset of their depression. Step (1) could certainly have been simplified by the approach described by the reviewer, but the advantages would not be great because the series of age specific mortality rates that we use in the existing model are imported from Excel spreadsheets from the national statistics agency – the model path basically represents a survival curve but we don’t need to fit it each time we update the model.

3. “P10: RR mortality. Was the mortality rate of the non-depressed population recalculated?”

The question here, as I understand it, is that since the RR associated with major depression accounts for a component of total mortality it may be better to view the mortality rate from the national data as representing a weighted average of the mortality rates in the depressed and non-depressed segments of the population. The model was not set up in this way. The relative risk was conceptualized as a ratio with the total population rate in the numerator, similar to an SMR. In the revised manuscript, the term mortality ratio (MR) has been used to replace the earlier term, relative risk.
4. “Fig 2: colourful, but quite unclear.”

Additional description of what the graphic portrays has been added to the revised manuscript.

5. “P13: only 100 runs! To get stable 95% CIs I would think that you need at least 1000 runs.”

See the first point above. Using a much larger number of replications does lead to more stable estimates.

6. “P13: the animation is not accessible.”

The dspace links have been double checked and they are working. Perhaps there was a connection or firewall problem when the reviewer attempted to connect. The “handle” used by dspace leads to a page from which a “view/open” link leads to an animation, which could also be missed by by people not familiar with Dspace, however, the “handle” URL is the one that is recommended for use.

7. “Fig 5: it would be helpful to have the real LTP in the graph as well.”

Real (in the paper the term “actual LTP” has been adopted) LTP has been added to the graphic.

8. “P14: an RR of 2 is extremely high for LTP. It might be appropriate when people are in an episode, but fortunately most people with a history of MD are not in an episode most of the time.”

We agree that it is very high. By demonstrating that the effect of such an extreme degree of mortality would only have a minor effect, the simulations are able to demonstrate more clearly that mortality is not a plausible explanation for the decline in LTP that begins in middle age.

9. “Figs 9 & 10 are not discussed at all (and they are certainly not self-explanatory).”

A description of these Figures has been added to the text. Please note that the numbering of the Figures is changed in the revised manuscript.

10. “P17: staring should be starting.”

Thank you, this typographical error has been corrected.

Sincerely,

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