Author's response to reviews

Title: Age of onset in chronic diseases: New methods and application to dementia in Germany

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Author's response to reviews: see over
Reviewer 1’s report:

Overall Comments:
This paper develops a method to derive the mean age of onset of chronic disease and the mean duration of chronic disease. The authors focus on dementia and consider Germany as a case study. Overall, this paper has promise and may appeal to a wide audience of readers. I'm left wanting more details on the methods and the assumptions that the authors invoked. All papers have assumptions—I just want to know more about them.

First, I am not sure how equation 2 yields an average. I do not understand how the denominator indicates life-years.
Please confer to our reply to Methods point 6.
Second, I am not convinced that the relative mortality value (a constant value across age and population) is appropriate.
Please see reply to Application point 2.

This authors can improve this paper by outlining each sections and editing the paper to make it more concise. The methods section could be expanded to provide more details to the readers.

Specific Comments:

Abstract
1. I'm not sure 'figures' conveys the meaning the authors intend. How about "outcomes of interest" or simply "outcomes?"
We chose “outcomes of interest”.

2. The background doesn't flow. How about this? "Age of onset and mean duration of chronic diseases are important outcomes of interest. Dementia is an especially burdensome chronic disease." The authors analytic framework isn't part of the background, it's part of the methods. Thank you, we changed this.

3. "Age pyramid" is demographic jargon and may not be widely understood. Perhaps "age distribution"?
We replaced age pyramid by age distribution in the whole text.

4. The list of complicated in the results section and there seems to be a comma missing. How about a more specific list, since this is an important result. "Mean age of onset and mean duration depend on [1] the age-specific incidence of chronic disease, [2] age-specific prevalence of the chronic disease, and [3] on the age-profile of the population." Is the prevalence age-specific? I assume so, but could not tell from the sentence. Also, does sex matter? Finally, are these values for any chronic disease? Just dementia? Just major chronic diseases? I think just dementia, but I cannot tell from the sentence.
We changed this according to your suggestion, thank you.

5. The conclusion seems to be about those with dementia--their age at onset and mean length of duration. How is the prevalence of dementia incorporated?
We added this point.

Background
1. The first paragraph is not part of the background. I'm not sure it it necessary.
We agree and deleted this part.
2. I'd prefer a formal introduction section, rather than a background section. The introduction section could have three parts: [1] what is the overall problem?, [2] what is the specific problem?, and [3] how does this paper solve this specific problem?

Although dementia serves as an example for any chronic disease, we think it is quite common to say something about the disease.

3. These facts and figures don't fully reflect the problem of dementia. How does dementia rank (in terms of prevalence) with other chronic conditions? Is it the leading chronic disease? In the top five? In other words, give the reader context. Otherwise, I don't know if 36 million is small or large.

By mentioning social, cognitive, psychological, physical, economic and quality of life aspects, we think that we say a lot about the problem of dementia.

4. The authors do not know the prevalence will double and triple. So maybe soften the sentence by writing that the prevalence will likely double and triple.

We included “likely”.

5. Again, I don't know if 11 million DALYs lost is a little or a lot. DALYs are already an abstract concept. Maybe the right metric is a per-person measure. 11 million DALYs into how many people?

We deleted the aspect of DALYs, also with respect to your point 7.

6. I think USD is a more common way to write US dollars rather than US$. We changed this to “US dollars”.

7. It is hard to distinguish paragraphs. Either separate paragraphs with a separate line or indent. This isn't an issue for the final publication, it's just hard to review as a single block of text. And now that I read more, it looks like the second paragraph ("Worldwide,...") is just too long.

We shortened it.

8. There is an extra comma that makes the sentence difficult to understand. "In common diseases with a high background risk, rate ratios (i.e. ratios of person-time incidence rates) between groups, cannot be interpreted as risk ratios." No comma necessary in front of "cannot".

Pls see reply to Background point 11.

9. I think "in which" is more appropriate rather than "where" in the sentence beginning with "Boshuizen...".

Pls see reply to Background-11.

10. Should be "...of a highly prevalent disease (e.g., back disorder)...". Same with "lifting heavy loads".

We changed this.

11. The Background section really is an introduction, and should probably be labeled as such. That said, the background could benefit from some simple reorganization and editing. I find the example of back pain and lifting long and detracting from the main argument. What is the general problem? It seems that the general problem is that dementia is a leading chronic disease and knowing when dementia first occurs and for how long are extremely useful facts for planning. What is the specific problem? It seems the specific problem is that we want to
develop measures of the burden of dementia that have certain properties. Has dementia been described in incorrect ways? What is the research gap? What is the hole in the literature? How does this paper address the specific problem? It seems the paper uses an IBM model (incidentally, this should be written in full and then use the acronym, not the other way around). Why is this method an advantage or better than what has been done before? We agree that the example of back pain is distracting and deleted this part. The acronym used after the full expression.

Methods
1. I find this phrase a bit awkward. "...In the general IPM model, the intensities depend on calendar time \( t \), age \( a \) and sometimes also on the duration \( d \) of the disease." Does the authors’ version of the IPM model depend on the duration of the disease? Why not just write that the intensities depend on calendar time \( t \), age \( a \), and disease duration \( d \)? We did as you suggested. Thank you.

2. I think the assumption invoked by the authors make the stochastic process a first-order Markov process, rather than a semi-Markov process in which duration affects the transition probability. It would be nice to include such a statement (if true), to provide the implications for this assumption. Although there are general relations between Markov processes and state-models, introducing their nomenclature does not give insights here and may be distracting. Note that we are modelling absolute numbers \( C \) and \( S \), not transition probabilities between states.

3. "The benefits of such ODEs are obvious." seems a bit off to me. I agree, there are benefits to a closed-form ODE. Just tell the readers what they are. How about, "The advantages of such closed-form ODEs include: ...". Thank you, we reformulated the paragraph.

4. I'm not sure what the authors mean by "dissolved". Is this mathematical jargon? Maybe "mathematically decomposed into X and Y"? Or even "mathematically separated" to avoid the verbs dissolved and decomposed, neither of which are probably well understood by readers. We have chosen the word “obtained”.

5. Same concern with the word "susceptibles". I know what the authors mean, but there's an opportunity to make this sentence more readable. How about "number of people at risk to developing the disease"? Or something similar? The word “susceptible” is common and lasts back for decades, we added your suggestion in brackets.

6. Equation 2. Do the authors mean to use the symbol "omega" instead of "w" to denote the oldest age? Also, I'm not clear how equation 2 denotes the mean duration of disease at age \( a \). The mean duration of disease at age \( a \) should equal the ratio of: [1] the number of diseased at age \( a \) and [b] the number of person-years lived by this group. Is this not correct? How does the denominator express person-years lived by the diseased? Right now, the denominator \( i(a) S(a) \) gives the product of the incidence at age \( a \) times the number susceptible to becoming developing the disease at age \( a \). So the product of \( i(a) \) and \( S(a) \) gives the number of incident disease cases. What I am expecting is the equivalent to \( a_x \) in the life table. There are 4 groups that contribute to person-years: [1] the prevalent disease cases that live the entire year of age, [2] the prevalent disease cases that die within the year of age \( a \), [3] the incident cases that live the entire year of age \( a \) and contribute whole or partial life years, and [4] the incident cases that die within the year of age \( a \) and contribute partial life years. Where are these
groups? I am missing something in the denominator in equation 2. I suspect other readers may have similar confusion.

Thank you for asking. The argument of the former equation 2 was that we divide the total of all years spent with disease in the population by the number of person who contract the disease. If the population is stationary, the total is the integral of C(a). Although the concept of a stationary population is common in demography, real populations merely are stationary and the equation is nearly useless. With a view to the aim of the article (chronic disease in a real population), we decided to completely remove the aspect “mean duration” from the article. We deeply regret the mistake and once again thank you.

7. I'm not sure what "=" means. Equivalent to?
This was deleted.
8. Equation 3. The "2" power is difficult to read. The right ] is on top of the superscript 2.
We retyped the equations.
9. It seems that the derivation of equations 2, 3, and 4 are novel. Is this true? If so, I encourage the authors to spend more time developing these ideas and walking the reader through the math.
It is difficult to judge, if the derivations are novel. So far we have not seen anything similar, neither in journal articles nor in encyclopaedias. We extended the explanation of the equations.
10. N represents the age distribution of the population. I think that might be preferable (and less jargon) than the age pyramid.
We changed this in the whole document.

Application
1. This is an awkward use of a citation, "The age-specific incidence is taken from [8]...".
What is the data source? Write it in words and the cite with [8]. In other words, use the same format as, "The mortality m of the general population is taken from the life tables of the Federal Statistical Office of Germany [9].".
We changed this according to your suggestion. Thank you.
2. What do the authors mean by relative mortality? 2.4 what? What are the units of this measure and what does it mean? Where is relative mortality in the derivation of equations 2, 3, and 4? Why is this necessary? The authors only have general population mortality and they need dementia-specific mortality and non-dementia-specific mortality? Is it reasonable to believe that dementia mortality at age a is *always* 2.4 times greater than non-dementia mortality for *all* ages a in [0, w]? This seems like a tenuous claim. It seems more appropriate for R to be age-dependent, R(a), rather than a fixed constant.
Reply: We added to the text that the relative mortality R is the ratio between the mortality rates m1 and m0. R(a) = m1(a) / m0(a). Thus, it is a dimensionless number, which we keep fixed for all ages R(a) = R = 2.4. In this sense, the ratio is sometimes referred to as a “proportional hazard”. Please note, that this does not affect any of the equations (1) – (4). R does not play a role in these equations. We just use it to calculate the age-specific prevalence p(a). If you have p(a) from somewhere else, maybe from another survey, you may use this.
The discussion if the model in equations (5) and (6) as well as keeping R constant is beyond the scope of this paper. The reason is two-fold: First, in our Statistics in Medicine (SIM) paper (cited in the text) we compared the appropriateness of the model with simulated and real world data, which led to a rather technical discussion. The interested reader may refer to our SIM paper (including the appendix where much of the stuff is). Second, the ODE model
in equations (5) and (6) is an approximation. It neglects the fact that the mortality \( m_1 \) does depend on the duration of dementia. We know that from the Rait 2010 reference. What happens in general when you apply the model in equations (5) and (6) to a duration dependent mortality cannot be said right now, because this is subject to intense research we are currently doing. The only justification for applying the ODE model, comes from the fact that in this case (dementia in Germany) it yields a good approximation to the age-specific prevalence. We clarified this in the text and gave an additional reference (Schulz & Doblhammer 2011) for illustration of the appropriateness.

Results
1. I don't think "prevelances" is a word. The prevalence of what? Dementia?
   We included “of dementia”.
2. I don't think the word "obviously" is necessary. It's not obvious at all. That's the point of this paper.
   We deleted “obviously”.
3. There could be a better verb than "get it" in "whereas females get it three years later at 81.9 years of age." Someone doesn't "get dementia". Develop dementia, maybe?
   We changed to “develop”. Thanks.
4. I have no context to compare the standard deviations of the disease durations. Is 4.6 years high? 11 years is larger. I would encourage the authors to just report the results and not add their interpretation. That's better left for the discussion section, or perhaps for the readers. It's distracting in the results section.
   We deleted the interpretation.

Discussion
1. Again, I prefer age distribution rather than age pyramid.
   Yes.
2. This sentence should be reworded. "It is striking how big the difference of males and females in the numbers of patients with dementia is." I keep reading the word "striking" and every time, I find it distracting. Is it striking to the authors?
   Maybe “striking” is the wrong word for the article, we replaced it by “it becomes obvious, how big...”.
3. I don't think higher female incidence and a larger number of females are contrasting facts when describing the number of dementia cases. They do not contrast. In fact, they complement each other to create the twofold difference.
   Sorry - of course you are right. We replaced the “on the one hand ... on the other” construction by “first” and “second”.
4. What do the authors mean when they write that dementia will peak among males in their 90s? I do not know how to interpret this. The prevalence is simply the proportion of people in the population with a disease (in this case, dementia). Are the authors saying that of all ages, the proportion of males with dementia will be greatest for males in their 90s?
   Yes, exactly. We are discussing the age-specific prevalence \( p(a) \) in 2002 (i.e. the proportion of people with dementia aged \( a \) in 2002) as a function of \( a \). As shown in Figure 2, \( p(a) \) is peaking at about 96 years of age in males and females. Unfortunately, the now quoted survey by Schulz & Doblhammer is from another data source and another year. Moreover, it separates two regions of Germany. Thus, our findings and the Schulz data cannot be compared in a rigorous way.

5. Can this hypothesis be tested now? The authors have age-specific prevalence data.
   Not directly (see point 4). Thus, we weakened the formulation by “there are indications ...”.
6. I strongly disagree with this statement. "The analytical representations of the mean age of onset and mean durations have several advantages. First, assume that incidence of and mortality from a chronic disease are similar in two populations, but the age-pyramids are different." How are these advantages? Assuming the age-specific incidence is similar between two populations is very tenuous. Similarly tenuous is the assumption of equality in age-specific mortality from dementia between two populations. Are these two populations males and females? Why would I believe that? That's not true with other chronic diseases. That's not true with any disease I know. I thought the authors consider age-specific incidence, prevalence, and mortality separately for males and females in their derivation.

Although we do not think that the observation of similar incidence rates of dementia in South Asia and Canada is too tenuous, we agree that the assumptions about the mortality are merely fulfilled. Thus, we deleted this point.

7. Can the authors elevate the point about incidence reduction and its impact on Abar and Dbar? I find this very interesting. It could be a separate subsection in the results. The impact of reducing the incidence has been described in our SIM publication. It is straightforward to apply it to the age at onset. We added some information about this.

8. I don't understand this sentence. "With respect to the age of onset, Chen et al were aware of the problem of choosing a representative age distribution and gave a corresponding advice [14]." How does this method differ from the approach of Chen et al? Chen gives practical advice for performing surveys. We stressed the point that in empirical studies for surveying the age of onset (e.g. by patient questionnaires about the age at time of diagnosis) the study sample has to be representative.

9. The reference to the method is vague. "First, the method described...". How about "First, our method requires...".

We clarified this point. The possibly weak point is the ODE model for calculating the age-specific prevalences in men and women. We gave a reference that our ODE model is reasonable (Schulz & Doblhammer).

10. The discussion section could benefit from an outline and editing. What are the main contributions of this paper? How does this paper contribute to the current demographic literature? Dementia-related literature? Right now, the discussion section does not seem to flow well.

So far, there is no study in Germany that allows a valid estimate of the age of onset. We added this point to the discussion.

Conclusion

1. There is no need to refer to the model as "simple". Also, no need to be vague when discussing the chronic disease. Just write dementia.

We deleted “simple”.

2. I'm still *very* concerned about the relative mortality constant. This really should be age and sex dependent, R(a,s). Not just R=2.4.

We hope that we could give justification for our ODE model deriving the prevalence.

3. Is a separate conclusion section necessary? I'm not sure that it is.

We have the feeling that it is quite common.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests

General comment to Reviewer 1: Thank you very much for your very detailed revision and helpful comments.
Reviewer 2’s report

This paper uses an IPM framework to develop formulas for the mean age of onset and duration of chronic conditions from age-specific incidence, age-specific prevalence, and the age distribution. The paper provides a cogent description of the method and compelling justifications for using the two measures. The method appears sound and the application to dementia in Germany is illustrative. I have a few minor questions/comments for the authors.

(1) Is the finding that the peak prevalence for men and women are identical an artifact of the age heaping at 100+ or do the authors have another hypothesis?

We think this is just a coincidence. While the paper was reviewed, we found evidence for the peaks from a different data source and added it to the paper (see our reply to Methods point 6 above).

(2) The authors make several simplifying assumptions to implement the analysis. They recognize the limitation and state that their estimates are “just approximations.” Approximations are perfectly fine when the benefits outweigh the costs, which I believe they do in this case. My only (minor) concern is about the assumption of duration-independence. Perhaps the authors could give some rough guidelines as to when (or for what diseases) this is, or is not, a reasonable assumption.

This is a very good point, but it is difficult to give an answer that is generally applicable. We are working hard on this. Please refer to our reply to point 2 in the Application section above.

(3) To help researchers implement this method, are the authors willing to share their R-code?

The main points in this work are equations 2, 3 and 4. Everyone familiar with R, can write it down quickly. I guess what you are interested in, is the R-code of the ODE model in equations 5 and 6. Although we are planning to release it to a broader audience later, currently it is available upon request from the authors only.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: No competing interests to declare.

General comment to Reviewer 2: Thank you for complaisant review.