Dear Dr. Ahmadi Abhari

Manuscript ID BMJ.2016.034697 entitled "Recent trends and future projections for dementia in England and Wales to 2040: Estimates from the IMPACT-Better Ageing Model"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying. We would particularly like that you report in a table what the assumptions are and model competing risks.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=46d23f52607f4645a1194ab649c6d968

**Report from The BMJ's manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.
Members of the committee were: John Fletcher (chair), Gary Collins (statistician), Daoxin Yin, Georg Roggla, Rubin Minhas, Jose Merino, Amy Price, Tiago Villanueva, Elizabeth Loder

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
  For a modelling study – this seems reasonably well done and reported – the Methods in the paper are a lay summary of what they did, with a good, more detailed description of the Methods in the supplementary material. However, these studies largely depend on their assumptions – and whilst I think they have this information in there (and in the supplementary material), it could be made much clearer. A clear summary box would be helpful.
  Observed dementia cases of by wave and sex-specific age groups are quite small (Supplementary figure 1, Table 2); I wonder whether some of this should be in the main paper, as this underpins the study.
  The validation seems to only include those aged 65-90+, why were those <65 omitted? Too few events? Or no data in CFAS II?
  One of the reviewers has indicated that Wave 7 (2015 data) are available - and they raise a good point to see how were their model predicts with this new 2015 data.

- One editor said that you are claiming to have a better prediction model than what has gone before. He was not sure you do. He made the following comments:
  1. One reason you say yours is better is that they model competing risks of death from CVD. But they don't model deaths from cancer or COPD to name the two next biggest killers.
  2. Dementia prevalence and crude incidence are largely dependent on survival to old age so any changes in mortality from other causes will have a knock on effect on dementia frequency and they don't appear to have modelled this.
3. They are predicting a long way out and with the large rise in frequency of diabetes it is by no means certain that CVD will decline further and may even increase again.
4. They should present a table of assumptions and starting values that drive their model. Without this we can't judge if the assumptions are reasonable. The methods are not sufficiently detailed to allow someone to repeat their study.
5. In their reporting they should stick to presenting the model and the results of the model. For example, the "conclusion" that incidence of dementia is falling is not based on the model but is input data from another study that drives the model.

- Another editor said that the finding that incidence is declining is not novel and has been shown in many studies from different countries. The fact that they estimate that prevalence will increase depends on the inputs to the model but he was not convinced that the assumptions hold.

- Another editor agreed that if you haven't modelled COPD and cancer that could be a problem.

- Another editor had two concerns: you should discuss the international context. Moreover, he wondered why changing lifestyle patterns including diet and physical activity don’t play a role in this paper.

- Several other editors were supportive.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

TO THE EDITOR
This is a very interesting study presenting data from the English Longitudinal Study of Aging (ELSA) on trends in dementia incidence and prevalence. Although previous studies already have shown that dementia incidence is declining, the present study used the Markov model IMPACT-
BAM to predict future dementia prevalence taking into account the effects of competing risks (cardiovascular disease, mortality). Yet, the study has some minor issues that should be addressed or at least discussed more critically. I expect the authors to be capable of making such minor revisions.

TO THE AUTHORS

GENERAL COMMENTS
In this manuscript, Ahmadi-Abhari and coworkers present the results of an estimation of dementia incidence and future dementia prevalence based on the ELSA dataset (2002-2013). A probabilistic Markov model was used that takes into account the effects of cardiovascular disease. The manuscript is well written and the topic seems relevant to this journal. Major strengths include the large population-based sample, and the validation of results against independent reports. I hope that the following comments help strengthening the manuscript further.

MINOR ESSENTIAL/DISCRETIONARY REVISIONS
1. Abstract (sentence 44): Try to avoid the use of ‘‘we’’. Perhaps change to: ‘A recent decline in age-specific dementia incidence was confirmed.’
2. Introduction: Information on the societal importance of this study is lacking in this section (e.g. policy implications, effects of health costs, healthcare burden, input for public health campaigns, etc.).
3. Introduction (sentence 14): check citation ‘‘12;13’’ should be ‘‘12 13’’ without the ‘‘;’’ (throughout whole manuscript)
4. Introduction (sentence 14) ‘‘Thus, vascular risk reduction is likely to drive...’’ Did you see the results of this 6-year multi-domain vascular care intervention to prevent dementia? (http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30950-3/fulltext?rss=yes). Results did not lead to reduced incidence of all-cause dementia. Perhaps rephrase sentence.
5. Methods: ELSA Wave 7 data (up to 2015) is available (https://discover.ukdataservice.ac.uk/catalogue/?sn=5050&ype=Data%20catalogue). Perhaps this can be used as a confirmation of your estimation of dementia incidence in 2015 (if available)?
6. Methods: participants were recruited around age 50-55: how was information collected regarding early life events/health outcomes (retrospectively?)? Is the ELSA
population a true representative of the general population in England and Wales (e.g. wealth, minority/race, and educational level)?

7. Methods: the cognitive tests administered in ELSA are limited (as you already mention in the Discussion). In section 1.2 of the Supplement the cognitive domains are described. Orientation in time, day, month, year was used to assess concentration and the numeracy test as measure of executive function. This can be discussed/questioned of course. Are the studies that used the same procedure for establishing cognitive domains? Please cite these.

8. Methods: participants were compared with a reference population aged 50-80 with the same level of education regarding cognitive tests scores. Do you also have different reference groups for males and females? There are some differences regarding cognitive performance between men and women, especially in the older age groups.

9. Methods: the IQCDE was used to determine cognitive impairment in persons who were unable to take part in the study. A proxy informant is asked about the participant’s memory abilities, daily situations, etc. What was the relation between the participant and the proxy informants asked to complete this questionnaire? Partners, children, neighbors, nurses? I think this will make a difference. Additionally, are there any references that validate using this instrument for this purpose?

10. Methods: dementia cases were defined on either cognitive + functional impairment or self-reported doctor diagnosis of dementia. What was the overlap between both? Why not also using a combination (very sure cases of dementia) in a sensitivity analysis? Which % of dementia cases is based on “self-report of a doctor’s diagnosis” and which % is based on “objective” measurements of cognitive and functional abilities?

11. Methods: definition of cardiovascular disease? No information available on atrial fibrillation given it association with cognitive impairment (http://www.ncbi.nlm.nih.gov/pubmed/23460057)? It’s debatable whether stroke should be included in a cardiovascular compound, perhaps better to exclude persons with stroke to have a more clearly compound of cardiovascular disease. What is you rationale behind this? How was death from cardiovascular disease established? Is it based on death certificate data or from the ONS data, and what is the accuracy?

12. Statistical methods (sentence 32): ‘we assumed the decline”; perhaps not entirely clear for the reader which
decline you are referring to.
13. Results: decline in the future prevalence of dementia in women is reported and in the Discussion (page 9, sentence 39) you mention “as the current narrowing of the life expectancy gap between the sexes continues”. Can you hypothesize or explain why this is about to occur?
14. Results/Discussion: Changes over time in available risk factors accounted for about 22% of the calendar effect in dementia incidence (Supplement Table 3). Why did you choose for these risk factors? Why not also include depression? Depression is well-known risk factor of cognitive impairment or dementia (http://www.ncbi.nlm.nih.gov/pubmed/23637108; http://www.ncbi.nlm.nih.gov/pubmed/25504093). Other possible risk factors to include are healthy diet and socio-economic status/wealth (both available in ELSA based on the study website)
15. Results/Discussion: check the correct use of abbreviations CFAS and ELSA throughout the manuscript (e.g. Discussion, page 10, sentence 9
16. Discussion: “Cognitive decline starts at a younger age than the 65+ or 70+ age-groups recruited in previous studies”. I agree with this point, but some of these studies only look at dementia as an outcome and therefore focused on a group >60/65 due to limited number of people with dementia under age 60/65. This leads directly to the following question: How many people (%) in the ELSA cohort showed significant cognitive decline before the age of 60?
17. Discussion, sentence 12; which CFAS study? 1, 2 or both? Provide reference as evidence
18. Discussion: you mention “declining cardiovascular disease incidence” and “Improvement in vascular risk factors”. Please elaborate on this important matter (e.g. better cardiovascular disease management programs)
19. Supplement Table 1 (page 5): Do you have an explanation why the number of people from Wave 1 and Wave 4 with diabetes and cardiovascular disease increase with almost 100%? These are substantial changes.

Additional Questions:
Please enter your name: Kay Deckers

Job Title: PhD student

Institution: Maastricht University
The authors analyzed data from the ELSA to explore whether the incidence of dementia in the UK has changed in recent years, and to estimate how this would impact on the projections of dementia prevalence in the country in the next decades.

The aging of societies is expected to lead to catastrophic increases in the number of people with dementia under the assumption that the age- and sex-specific prevalence of dementia will not vary over time. Recent epidemiological
studies in Europe and the US suggested that this assumption may not hold, but results are not unequivocal. Despite this research is extremely important for policy makers and clinicians, it is not ‘POEM’.

Changes over time, or trends, in prevalence and incidence of dementia have been reported in recent years in the MRC-CFAS study. The MRC-CFAS was purposely designed and powered to detect any such changes. Further evidence is warranted, but the present study is not original and has important limitations.

Previous studies have been conducted in the UK on larger and better defined samples, using more advanced research protocols; in previous papers the potential issues related to differential attrition and the variability of response rates were also addressed (the latter was not explicitly addressed by the authors of the present study) [See Matthews F et al. The Lancet 2013].

There are several important limitations in the study design and in the presentation and interpretation of the results, the internal validity of the study itself may be not adequate.

MAIN COMMENTS

Constant methods and diagnostic criteria to ascertain dementia in community dwelling samples are required to explore changes over time in dementia incidence and prevalence. Although the criteria to establish dementia caseness were kept constant in the present study, they were not formally validated, and they were not equal for all participants. Cognitive assessment was limited to questions on time orientation (but not space) and two cognitive tests, one of memory and one of verbal fluency. The informant questionnaire consisted in the short version of the IQCODE, which was used only in a subsample of those with no cognitive assessment. The outcome of the present study is probably best defined as cognitive impairment (objective or reported by a next of kin) rather than dementia, because cognitive assessment was too limited and “evidence of significant decline from a previous level of performance [...] (DSM)” was not sought. Further, learning effects in cognitive tests between the 2-year intervals were likely. This could have introduced bias in outcome ascertainment through the study follow-ups, with repercussions on the validity of the comparisons of incident cognitive impairment over time.

The paper does not comply with the standards of reporting
recommended in the STROBE Statement.

Descriptive data of dementia prevalence are reported as supplementary materials only; and the statistical methods used to model the expected projections of dementia prevalence, which do not increase the validity of the diagnosis itself, seem unnecessarily complicated (probably more appropriate for a set of sensitivity analyses). These techniques apparently relied on a number of assumptions that may not hold, including the posited 2.7% annual reduction in dementia incidence, which is somewhat unsupported (below). In addition, the internal validation of this statistical method is likely prone to circularity, and it is confusing (below).

The research question of the present study is not clearly stated. It is not clear whether the authors set out to explore whether potential differential attrition may explain the variability in dementia incidence over one decade in the ELSA, or to present descriptive data of a potential competing scenario, with the current one supported by Alzheimer’s Disease International and the UK Alzheimer Society, regarding trends of dementia prevalence based on that evidence to inform policy makers and relevant stakeholders.

Title
The title is unfocused and somewhat misleading and does not reflect the content of the paper, rather it unnecessarily overemphasizes the statistical model used (presumably) to calculate ‘dementia trends’, with no specifications on whether these trends refer to incidence or prevalence or both.
Several implicit claims in the title are inaccurate or confusing. What does ‘recent’ mean in this context, recent birth cohorts or findings? Further, because this study cannot count on a validated dementia diagnosis, the authors should refrain from making such claim in the title (see comments above).
Finally, the use of an acronym (i.e. IMPACT), and the fact that it refers to a statistical technique should be discouraged.

Introduction
Prevalence depends on (and is actually proportional to) incidence and disease duration, and in the case of dementia the latter equals survival with the disease. This important consideration is absent in the introduction, is not considered
in the methods, nor are its implications adequately considered in the Discussion and to interpret and contextualize the study’s main findings, that is the future numbers of those affected by dementia. It is obvious that the numbers presented in the paper would be greatly affected by any proportional increment in survival in people with dementia compared to cognitively healthy counterparts in the UK population. This is key for policy makers, because improvements in care and more timely diagnosis of dementia are highly recommended [See the Lancet Neurology Commission: “Defeating Alzheimer’s Disease and Other Dementias”, by Winblad et al.], which would presumably lead to significant longer survival in people with dementia.

The criticisms made to the current, and widely accepted, projections of dementia prevalence for the next decades is flawed. These projections are not “inaccurate”, they are based on demographic projections of changes in age structures due to population aging in all world regions, and on the assumption that age-specific prevalence of dementia will not change. There is insufficient evidence to support the use of varying age-standardized risks over time to calculate the future trends of dementia prevalence in the population (see Prince M et al. Alzheimer’s Research & Therapy 2016). The authors present an alternative scenario based on a 2.7% annual reduction in dementia incidence. As said, this should be presented as a possible scenario, because it is based on one possible model specification of the ELSA data only. For instance, in the MRC-CFAS study the incidence rates of dementia did not significantly change in men between CFAS I and II [Matthews F et al. 2016].

Further, even assuming that dementia incidence is truly declining in Western countries, the reasons and explanations of these secular trends are not clear. Thus, the argument of the potential competing effect of cardiovascular risk is speculative, and unsubstantiated. There is no evidence that changes in vascular risk profiles explained the observed reductions in dementia incidence in the past decades in both the Framingham and the MRC-CFAS studies (women only) (see Satizabal et al. NEJM 2016 and Matthews F et al. Nature Comm. 2016).

The final paragraph of the introduction is unfocused. Attrition is not defined, nor is it explained how it may impact trends in dementia incidence and/or prevalence.
The relevant literature is not appropriately cited, there is a continuing confusion between studies (and evidence) of dementia prevalence and incidence trends. A review of European studies is cited along with the original papers, this is redundant. Also, more recent and comprehensive reviews are not cited (i.e. Prince M et al. 2016). References 1 to 6 are mixed, prevalence and incidence studies are erroneously combined. Reference number 6 is redundant. Reference number 17 is not pertinent. References number 12 is about modelling the attributable risks of dementia to a selection of risk factors, not pertinent.

Methods
The major concern is about the validity of the ascertainment of dementia diagnosis. As said the validity of the diagnostic procedure was not previously demonstrated, cognitive assessment is very limited and learning effects very likely. The description of the ‘IMPACT-BAM’ models should be presented in the statistical methods section. In addition, the validation of this model is problematic, as it assumes adequate comparability between the ELSA and the MRC-CFAS studies, which have remarkably different designs, including sampling and outcome ascertainment. I am not a statistician, but the modelling of changes of dementia incidence across the waves of the study does not look adequate, and the results expressed in the form of HR are difficult to interpret.

Results
Numbers and reasons for non-participation at each stage are not reported, neither is there a flow-diagram of the analytic sample derivation. The characteristics of study participants should be presented in a comprehensive table and salient aspects reported in the text in the main paper not as supplementary materials. Differences in socio-demographic and health characteristics between wave 1 and 4 should be formally tested and reported using appropriate statistics. Dementia prevalence (not rates) should be reported providing the 95% CI intervals by gender and across the age groups; crude and age-, sex- and education-standardized prevalences could also be presented as the total for each wave of the study, to allow comparisons.

All non-statistically significant results should be clearly described as such in the text.
The trends in dementia prevalence (calculated with the IMPACT-BAM model) assume a 2.7% relative annual reduction in dementia incidence. The 95% CI of this decline are not reported in the main paper, while they are in the abstract.

Abstract
Numbers of participants in the analytic sample are not reported.
The methods used to calculate dementia prevalence and incidence are not described; and the actual criteria and procedures used to ascertain dementia are omitted.
Only results from one of the three model specifications used to calculate trends in dementia incidence are reported, the projected numbers of people with dementia are calculated accordingly.

Additional Questions:
Please enter your name: Emiliano Albanese
Job Title: Professor of public mental health
Institution: University of Geneva
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No
Funds for research?: Yes
Funds for a member of staff?: No
Fees for consulting?: No
Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No
Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests please declare them here: none to declare

Reviewer: 3

Recommendation:

Comments:
NOTES ON BMJ dem projcs..

This analysis of ELSA data is to estimate the trends in dementia by using combined joint models and time to event data to account for attrition and/or competing risk of death and risks for CVD v. dementia. Reduced risks of comorbidity from CVD, combined with general increases in life expectancy may lead to increases in dementia prevalence at older ages.

Dementia was defined using cognitive tests, IQCODE, ADLs, function. Not clinically screened or validated by diagnostic criteria.
A probabilistic Markov model takes into account the decreases in dementia and the increases in life expectancy at older ages, calendar time etc.

This is an interesting, well written and thoughtful paper that addresses the prediction of dementia prevalence over time. The key issue is whether dementia prevalence will change as influenced by changes in life expectancy and competing risk from CVD changes. Their conclusions are that dementia will increase due to reductions in CVD and increases in life expectancy. While this seems reasonable, there are a few caveats: (1) the assumption is that CVD declines will permit increase life expectancy, permitting more people to develop dementia. The model/paper ought to consider the possibility that other conditions could ‘take the place’ of CVD. For example, type 2 diabetes is epidemic at present and could rise to shorten life expectancy. (2) such a model is based on
an assumption about plasticity in maximum life span and in average life expectancy. This is not addressed in the paper. (3) similar to the ‘replacement’ of CVD as a cause, change in risk factors and environmental change may also affect these trends. (4) recent reports suggest that life expectancy is declining in the UK, at least for women. Presumably, a decline in life expectancy would lead to increase in dementia.

Additional Questions:
Please enter your name: Mary N Haan

Job Title: Professor/Vice Chair

Institution: UCSF Epidemiology

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </a>please declare them here: I have received NIH funds that are not related to this paper
Reviewer: 4

Recommendation:

Comments:
This is a very interesting manuscript addressed to estimate trends in dementia incidence and to project future prevalence rates for dementia in England and Wales. In order to determine trends in incidence rates the authors use the well known data from the English Longitudinal Study of Ageing (2003-2013 period). The future prevalence rate projections are based on a probabilistic discrete-time Markov model.
The introduction section is brief, concise and informative. The study objective is well described. The sample and methods are well characterized and the supplemental material (Section 1) is absolutely essential in order to fully understand the manuscript. The strategy adopted by the authors in order to check the validity of the methods, definitions and assumptions support the robustness of the study results. The authors report a large number of results, including 6 main figures, and 3 and 8 supplemental tables and figures respectively. The discussion is well focused, comparing the main results with the current literature. Study limitations also are well acknowledged. Taking into account that one the manuscript objectives was to describe recent trends in dementia incidence, I would suggest to the authors to include in the discussion section a new paragraph about the results offered in Supplemental table 3 regarding the relative annual change in incidence of dementia adjusted for change in level of risk factors.

Minor comments:
- Please, specify in the abstract that the setting corresponds to general adult population aged 50 years and over.
- Reference 19 is duplicated in reference 34.

Additional Questions:
Please enter your name: Josep Garre-Olmo

Job Title: Researcher

Institution: Girona Biomedical REsearch Institute

Reimbursement for attending a symposium?: No
Ahmadi-Abhari and colleagues present a manuscript focusing on modelling dynamically how dementia case numbers will change in the UK over the next three decades. They base their modelling study on results of ELSA, and set themselves apart from previous studies by implementing a competing risks approach. Although I think that this manuscript provides valuable insights for public health planning, there are several points that need to be clarified before the overall quality of the study can be assessed correctly.

Title:
- I would focus on the projections and not recent trends (as they have been shown before) and would remove the term IMPACT-Better ageing model since it’s not something well known established before, but part of the output of the paper.
Abstract:
- I would downplay the attrition part in the abstract and what the paper adds section because it primarily corrects for problems in your underlying data and doesn’t add per se anything good to your modelling approach. If you e.g. would have used health insurance data or CPRD data for estimating the trend in dementia incidence, you wouldn’t have needed it (although other limitations come with these types of data).

Introduction:
- There are now more studies available on dementia trends; e.g. Dodlhammer et al., A&D 2015 for Germany. Please update your references.

Methods:
- How were the response rates in ELSA (in both steps)? You assume representativeness but do not provide data to support it.
- You assume that there is no relevant migration over the next 30 years; that’s okay, but state it.
- Most of p.27 (p.4 of supplements) needs to go in the main text; How did you calibrate your model? What are the time steps you use in your Markov model? How did you model the demographic changes in the population and on which data this is based? It’s not enough to have that in the supplements.
- Using changes in CVD mortality as a proxy for CVD incidence is quite an assumption given that changes in treatment improve case fatality rates over time. I appreciate that you don’t have other data sources, but could you provide sensitivity analyses?
- Why do you only take into account CVD? There are other risk factors for death (cancer) which are also competing risks. I’m not too sure about the implications of this.

Results:
- People will not understand the results if the explanation of essential assumptions and input data is just in the supplement: Why do the results change from HR to OR between the approaches and what implications does this have for consistency? Moreover, do you assume a constant linear trend until 2040? Please discuss in the main text
- Figure 3/Supp Fig 5: How good is the fit of your model? It seems to perform badly in the oldest age groups, especially for CVD. What are the reasons? How can this affect the results?
- Figure 4: Please discuss why the incidence difference between sexes is removed until 2040
- Figure 6/7 can easily go to the supplement
- There are relevant spatial differences in demographic
dynamics, affecting resource planning on the relevant level of care. ELSA provides regional data

Supplement

- P. 25, 1.2: Do I understand correctly that the dimensions of cognitive testing changed over the different waves (i.e. literacy only available at 6, numeracy function at 1, 4 and 6)? How did you account for this? Does it counteract the rationale of using these data (see introduction – diagnostic criteria change over time)?
- You should provide in addition to Supplement Table 2 a table describing how many people were diagnosed based on which criteria/types of impairments/single tests
- P. 25, line 57: What happened to those in the last wave or those who were lost to follow up? How did you assess transient cognitive decline with them?
- P. 26, line 44: Why did you only use the cognitive function test and not in addition the ADL for the mixed model part of the joint model? Your rationale is not completely coherent at this point.
- P. 27, line 16: What did you calculate the ICC for? I don’t get it at the moment – sorry!

Additional Questions:
Please enter your name: André Karch

Job Title: Epidemiologist

Institution: Helmholtz Centre for Infection Research

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may
in any way
gain or lose financially from the publication of this paper?:
No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </a>please declare them here:

Reviewer: 6

Recommendation:

Comments:
The authors apply sophisticated modeling techniques to assess the effects of an increasingly well documented trend in developed nations toward reduced age-specific rates of incidence of dementia. As well, there is consideration of implications of a continued trend in the same direction (toward declining incidence rates) on future prevalence extending several decades.

The results here are clearly important and of considerable interest, even if there remain certain difficulties with predictions regarding future prevalence (burden) of dementia.

I am not as concerned as the authors seem to be about inadequacies or shortcomings in the methods used for the diagnosis of dementia. The reason is that, whatever method is used, it can be assumed it will persist into future epochs, so that time-trends should not be affected (even if, for example, present and future estimates for prevalence – important for services planning – may vary considerably depending on ascertainment methods.)

I think the authors have several opportunities to improve their paper. My principal concern is with their methods of estimating prevalence (not incidence). Prevalence will, of course, be influenced by incidence, and the authors have taken care of this nicely with their models, but it will be influenced as well by differential survivorship of cases once established. To estimate the latter requires more than looking at age-specific mortality projections, but must also consider differential effects of dementia "caseness". Some
consideration is given to this matter, for example, in the now-classic Brookmeyer papers (although these do not consider changes over time in incidence rates). I’m not sure whether it’s included here, but if it is you might “spell it out” a bit more clearly.

Also, it seems to me there is an opportunity here to examine age-by-sex interactions on incidence. Previous data have suggested that men and women have similar incidence rates until something like age 80, and then the rates diverge substantially. Do we see this also in the ELSA data? And what is the implication, if any, for projected rates.

I appreciate that the authors used several different assumptions in their projections of future incidence rates. It would be pleasant indeed if incidence did continue to decline each year through 2040 by 2.7%, but that seems to me a very strong assumption. The contrasting model that holds rates constant at current levels is probably unduly pessimistic, but the Discussion might dwell on this topic (as well as the vagaries in estimation of prevalence), with fewer words devoted to the shortcomings of the diagnostic methodology (for reasons given above.)

A couple of minor points: In the abstract, I think you should make it clear in your mention of ongoing decline in incidence that you are in fact considering further (not historical to date) declines (else, may be slightly confusing). What is ONS (please spell it out)?

- John Breitner

Additional Questions:
Please enter your name: John C. S. Breitner

Job Title: Professor

Institution: McGill University, Montreal, QC, Canada

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes
Funds for a member of staff?: No
Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) </A>please declare them here: My responses above relate specifically to the topic of epidemiology of dementia and Alzheimer's disease. The "funds for research" refers to past funding; I am not currently doing such research.

Reviewer: 7

Recommendation:

Comments:
This paper aims to provide an accurate estimate of trends in dementia incidence and to use adequate modeling to obtain projections for the prevalence of dementia up to 2040. This is a well-written paper, on a large population-based study, which tackles several issues from previous forecasts of dementia prevalence; in particular the trends in dementia incidence and the competing effect of cardiovascular risk. I have however some comments/questions.

Methods
One problem is the definition of "dementia", which is in fact not a dementia diagnosis. Even if using an algorithmic definition to evaluate trends in dementia incidence is probably better than using a clinical diagnosis (due to the changes in the way of making a clinical diagnosis with time), this point should be better pointed out in the paper (in the abstract and in the text), as both are not equivalent. Another problem is the definition used for classification of the
"dementia" cases (a combination of cognitive and functional impairment). The ADLs used here are only basic ADLs (walking, bathing, toilet, dressing, eating), which are not impaired at a mild stage of dementia, but only at a more severe one. Thus, this definition would probably only capture moderately severe to severe cases. This should be pointed out in the methods and in the discussion. Moreover, the authors should consider including other activities in their definition, such as Instrumental ADL; results could be presented for both definitions. Doing that will allow a better understanding of the extent of dementia in the future. Even in supplement methods, the study sample and the estimation of dementia incidence are not clear. In particular, as additional participants were added at several waves, I'm wondering which participants the dementia incidence estimate was based on? And between which time points? A flow chart and/or more explanations in the methods section could help.

Moreover, in the dementia incidence estimation, is interval censoring taken into account by the model? Or is taking attrition into account in the model the way to account for interval censoring?

Regarding the methodology, some previous papers already considered taking into account the evolution of disease incidence for projections; the methodology previously used could be discussed in comparison with the present paper (see for example Wanneveich M et al. Stat Methods Med Res. 2016).

Results
I'm wondering why there seems to be a peak in the number of incident cases in waves 4 for both men and women (Supplement-Table 2) and if it is significant? In Supplement results (Figure 4), you compare incidence in ELSA and CFAS II. However, if I'm right, incidence in CFAS II is only for a 2-year period. Could you consider also comparing results with a study providing incidence over a longer period of time (for example the Rotterdam - 5-year incidence- or another one)? Moreover I'm wondering why you specifically chose waves 4 to 6 in that figure. Finally although this paper is very interesting, there are probably too many results for a single paper (8 Figures and many more in the Supplemental results). Could you consider refining the results presented, in order to allow the reader to better absorb the main messages?

Minor points
p6 line 18-19: the word "decline" is written twice
Discussion p10, line 4: as MMSE explores global cognitive function, it does not only capture amnestic cognitive impairment.

Discussion p10, first paragraph: I agree that forecast for dementia is relevant to health and social policy; however, it is not only limited to individuals who would require 24-hour supportive care. Fortunately, before that phase, most individuals will require less intensive supportive care, for several months or years. Forecast is also necessary for these individuals. Please rephrase your sentence.

Discussion, p10, last line: Contrary to Lobo et al and Qiu et al, Grasset et al do not indirectly infer from comparing prevalence estimates, incidence is directly estimated. Thus, I would recommend moving this reference and including it in the introduction instead, with other references suggesting a declining incidence.

Additional Questions:
Please enter your name: HELMER Catherine

Job Title: Researcher

Institution: INSERM, U1219

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?:

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course, in the article's results section) the following terms, as appropriate:

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g. Footnotes and statements

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