Author's response to reviews

Title: Modifiable Cardiovascular Disease Risk Factors as Predictors of Dementia Death: Pooling of Ten Cohort Studies

Authors:

David Batty (david.batty@ucl.ac.uk)
Tom Russ (tc.russ@ed.ac.uk)
John Starr (jstarr@staffmail.ed.ac.uk)
Manos Stamatakis (e.stamatakis@ucl.ac.uk)
Mika Kivimaki (mika.kivimaki@helsinki.fi)

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Author's response to reviews: see over
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Dr Ti-Fei Yuan
Editorial Team, Journal of Negative Results in Biomedicine

Dear Dr Ti-Fei Yuan,

MS: 1523829951122979 / Brief report / Modifiable Cardiovascular Disease Risk Factors as Predictors of Dementia Death: Pooling of Ten Cohort Studies / David Batty et al. / Journal of Negative Results in Biomedicine

Thank you for sending us the referees’ comments on this manuscript. We are delighted to respond, doing so in a point-by-point manner below.

Revisions to the manuscript, which we believe have improved its quality, are marked in red.

We look forward to hearing from you.

Yours sincerely,

David Batty
Reviewer number: 1
This is a comprehensive and well-constructed study. My only criticism would be (as the authors acknowledge in their discussion section) that dementia is not a single diagnosis. However, I imagine that given the data available to the authors it would not have been possible to limit the analysis to a particular form of dementia. Given that Alzheimer's disease is the commonest form of dementia one could probably infer that the results are most applicable to that disorder. Although the overall conclusions are ‘negative’ they are important and deserve to be published.

Our response: Thank you for these positive comments. The referee is correct on both counts: the type of dementia was not widely recorded but is, in around 70% of cases, likely to be Alzheimer's disease. As the referee indicates, this was a point we raised in the original manuscript; this has now been expanded in the revised version (see red text in the manuscript): “Additionally, comprising a series of subtypes (Alzheimer's disease, vascular dementia, AIDS dementia, and so on), dementia is not a single nosological entity. As it is likely that these subtypes do not have a unifying aetiology, using a composite dementia endpoint may mask some subtype-specific associations with CVD risk factors. It is also the case, however, that, with the majority of dementias being Alzheimer's, our finding are most applicable to this presentation.” (pg. 7).

Reviewer: Andre Pascal A Kengne
In this manuscript, the authors have investigated the association of a range of cardiovascular risk factors with death from dementia, and for comparison purpose with mortality from CVD. While CVD risk factors were associated with CV death as expected, only age, sex, non-HDL cholesterol and BMI were found to be associated with dementia death. This study is based on a large sample and large number of events, and accordingly a good statistical power to examine the study question.

Our response: Thank you for these positive comments. However, by focusing essentially on mortality, it is possible that the study failed to uncover some important associations. It is likely for instance that CVD risk factors are more associated with dementia occurrence than mortality in the context of dementia (which could be due to many other factors). The nature of the data does not allow the authors to investigate the association of CVD risk profile with dementia occurrence itself. They should probably acknowledge this as a limitation of the study.

Our response: We agree that not having dementia incidence data is a potential weakness. However, as we described in the original manuscript: “We have previously shown that in a cohort of Scottish individuals with psychiatrist-confirmed dementia, almost three quarters of those who subsequently died had dementia recorded on their death certificate.” (pg. 4). That is, in a cohort of patients diagnosed with probable Alzheimer’s disease, of the 502 who had died during 11 years follow-up, 72% had their dementia recorded as either a primary or contributing cause on their death certificate. This suggests that using dementia death approximates dementia incidence. We have added further information to the revised manuscript (see red text): “Finally, our outcome of interest was dementia death, not incidence; as such, our exposures are more distant from dementia event. This notwithstanding, in a separate study, we found that, in a cohort of patients diagnosed with probable Alzheimer’s disease, of the 502 who had died after 11 years of follow-up, 72% had their dementia recorded as either a primary or contributing cause on their death certificate. This suggests that using dementia death approximates dementia incidence.” (pg. 7)

Other points:
The choice of methods for pooling in meta-analysis based on the results of tests of heterogeneity is a fishing trip. While it is good for the investigators to perform the test of heterogeneity and report the results, the choice of the method for pooling the data should be pre-specified and dissociated from the results of the tests of heterogeneity. What happens if the authors allow the four significant risk factors for dementia in the same multivariable model? They should maybe run this analysis and report the results.
Our response: We chose a random effects meta-analysis for two reasons. First, many of the cardiovascular risk factors used in the present report (raised blood pressure, obesity, physical activity, smoking and so on) have been the subject of primary care-based modification during the period of follow-up of the included studies. Depending on the era of the study in question, this may therefore have had an impact on the risk factor-disease associations under scrutiny. Second, there have now been a series of papers from this collaboration in which the outcomes of interest have been the same as the present analyses – cardiovascular disease and dementia – although the predictor variables have differed. That these existing results suggest evidence of heterogeneity across studies, provided us with a second a priori reason to utilise the random-effects approach. The I² statistic we report was essentially an affirmation of this earlier work; this has now been moved to the results section. In short, we certainly do not regard our work as a ‘fishing trip’. We have now added our full justification for using a random-effects approach to the manuscript (see red text): “The study-specific effect estimates and their standard errors were pooled using a random effects meta-analysis. In contrast to a fixed-effects meta-analysis, a random-effects approach allows for variation in observed risk factor–disease estimates across studies because of real differences in the association in each study and/or sampling variability. We chose a priori a random-effects technique for two reasons. First, many of the CVD risk factors featured in the present report (raised blood pressure, obesity, physical activity, smoking and so on) have been the subject of primary care-based modification during the period of follow-up of the included studies. Depending on the era of the study in question, this may have had an impact on the risk factor–disease associations under scrutiny. Second, there have now been a series of papers from this collaboration in which the outcomes of interest have been the same as the present analyses – CVD and dementia – although the predictor variables have differed. That these existing results suggest evidence of heterogeneity across studies, provided us with a second a priori reason to utilise the random-effects approach.” (pg. 5).

The referee also asked us to provide age-, gender-, smoking-, and BMI-adjusted hazard ratios for each of these factors in relation to dementia death, analyses that would of course be post hoc. We have run these new analyses and added the new effect estimates to the text of the manuscript. In brief, the mutually-adjusted effects estimates were essentially unchanged relative to the age- and gender-adjusted hazard ratios.

Editorial requests:
1) Please include a statement in your Methods section explaining that you obtained informed consent from each participant.

Our response: This information was included in the original version of the manuscript.

2) Please include a competing interests section at the end of the manuscript, before the reference list. If the authors have no competing interests, please state: "The authors declare that they have no competing interests."

Our response: This has been done.

3) Please include an Authors? Contributions section at the end of the manuscript, before the reference list. Each author should be listed individually. We suggest the following kind of format (please use initials to refer to each author's contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Our response: This has been done.