Author’s response to reviews

Title: Relationship Between Multimorbidity, Demographic Factors and Mortality: Findings from the UK Biobank Cohort

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Version: 2 Date: 21 Jan 2019

Author’s response to reviews:

Reviewer reports:

Reviewer #1: Dexter Canoy

Many thanks for addressing queries and comments that I have previously raised. This current version is a substantial revision to the original submission. I only have few remaining suggestions which I think will be useful for the scientific community to know.

1. In the abstract, the last sentence should read "...greater relative impact..." to be consistent with the findings reported in the study.

Authors’ Response: Thank you for your comments, we agree with this suggested change.

Changes to Manuscript<-Abstract<-Conclusion: Multimorbidity had a greater relative impact on all-cause mortality in middle aged as opposed to older populations, particularly males, which deserves further exploration.
2. In the descriptive section of the results, it would be useful to report the mean ages of death (all-cause, cancer and vascular). It's interesting to note that there are more cancer-related than vascular deaths presumably because of the relatively short follow-up. (The authors may wish to additionally report the mean ages of death in men and women if these ages are vary greatly between them.)

Authors’ Response: Thank you for this suggestion, we have added the mean ages for deaths (all-cause, cancer and vascular), separately for men and women, as suggested.

Changes to Manuscript<-Results<-Multimorbidity and Mortality<-Page 12: At the end of the follow-up period, 14,348 participants (2.9%) had died; the mean age for those who died was 61.3 years (61.7 years for males, 60.7 years for females).

Changes to Manuscript<-Results<-Multimorbidity and Mortality<-Page 12: The mean age for those who died due to cancer related causes was 61.4 years (62.1 years for males and 60.6 years for females); the mean age for those who died due to vascular causes was 61.8 years (61.7 years for males, 61.8 years for females).

Reviewer #2: Harm van Marwijk

Thanks for the extensive rebuttal. The paper is now clearer but I am still not entirely convinced by the novelty of the data.

Authors’ Response: Although the relationship between multimorbidity and adverse health outcomes have been studied previously, we strongly believe that this work advances the current understanding in following aspects:

1. The association between multimorbidity and cancer mortality has never been studied in a general population (previous work has been in cancer populations only). This is highlighted in the manuscript, in the introduction and discussion section.

2. The association between multimorbidity and vascular mortality has never been done in a general population (previous work has been undertaken in patients with pre-existing cardiometabolic conditions only). This has been described in the introduction and discussion section of the manuscript.
Introduction: However, there are many evidence gaps in understanding the relationship between multimorbidity and mortality, for example, cancer and vascular mortality are the top two causes of mortality but the potential impact of multimorbidity on these outcomes has not been investigated [7].

Discussion<Comparison with other literature<Page 23: However, while there is data to show multimorbidity is associated with lung and ovarian cancer mortality, this is the first study we know of to examine the relationship of multimorbidity with all-cause and cancer mortality [31, 32].

Discussion<Comparison with other literature<Page 23: Whilst the effect of multimorbidity on vascular mortality has been studied elsewhere, it has only been studied in populations using a selective sample of pre-existing cardiometabolic conditions [36, 37].

3. There is no previous literature comparing the relationship of multimorbidity and mortality across different age groups. Again, this has been discussed in the manuscript.

Discussion<Comparison with other literature<Page 24: Our findings suggest that the impact of multimorbidity on survival may vary significantly across different age groups with relative mortality risk higher among younger male adults with multimorbidity, hence future life expectancy algorithms using multimorbidity need to take this into account. Secondly, the majority of interventions for the management of multimorbidity to date have been targeted towards relatively older adults [39, 40], and these findings suggest there is need for future research to develop interventions for managing multimorbidity in middle-aged populations and to explore whether multimorbidity should be noted as a risk factor within cancer referral pathways.

4. Our paper describes which clusters of long-term conditions have the strongest association with all-cause mortality across different levels of multimorbidity. This work is extremely novel, and we have added changes to the manuscript to reflect the novelty of this work. The Academy of Medical Sciences 2018 report highlights this as a particular gap in knowledge worthy of investigation.
Changes to Manuscript: Discussion: Comparison with other literature: Page 23: We identified clusters of long-term conditions with the strongest association with all-cause mortality across different levels of multimorbidity. This is a key research gap highlighted in the recent Academy of Medical Sciences Report [1]. Our findings highlight the most impactful combinations of LTCs and highlight the need for further research to better understand the relationships between these conditions and how they might interact.

Changes to Manuscript: Discussion: Comparison with other literature: Page 24: We have identified clusters of LTCs associated with the highest risk of mortality; clinicians can use this information while risk stratifying patients with multimorbidity in routine practice.

Reviewer #3: Mette Nørgaard

The authors have revised the manuscript appropriately and the manuscript has improved substantially by this revision, but I have a few remaining comments.

On page 16, the section "Type of Long-term conditions and Clinical Outcomes" would benefit from presenting HRs with 95% CI instead of simply writing statistically significant association. Statistical significance does not give the readers any information on the magnitude of the association or the precision of the estimate. Please see Rothman KJ. Six Persistent Research Misconceptions. J Gen Intern Med. 2014;29:1060-4.

Authors’ Response: Thank you for your suggestion, we agree with that. We have presented hazard ratios and confidence intervals to inform the reader of the magnitude of the association.

Changes to Manuscript: Results: Type of Long-term conditions and Clinical Outcomes: Page 16: We considered 24 individual LTCs, with the greatest individual statistically significant association with higher all-cause mortality in the whole cohort for possible combinations. These 24 LTCs were: dementia (HR 5.84; 95% CI 4.11-8.31), psychoactive substance addiction (HR 4.32; 95% CI 2.50-7.44), chronic kidney disease (HR 3.61; 95% CI 3.10-4.22), alcohol addiction (HR 3.32; 95% CI 2.75-4.00), Parkinson’s disease (HR 3.10; 95% CI 2.57-3.74), heart failure (HR 2.98; 95% CI 2.44-3.64), chronic liver disease (HR 2.99; 95% CI 2.44-3.65), previous history of cancer (HR 2.83; 95% CI 2.72-2.95), chronic obstructive pulmonary disease (COPD) (HR 2.07; 95% CI 1.93-2.23), peripheral vascular disease (HR 1.95; 95% CI 1.61-2.37), Schizophrenia/Bipolar disorder (HR 1.72; 95% CI 1.42-2.08), Pernicious anaemia (HR 1.66; 95% CI 1.34-2.07), Stroke/Transient Ischaemic Attack (TIA) (HR 1.67; 95% CI 1.54-1.80), Epilepsy (HR 1.65; 95% CI 1.43-1.90), diabetes (HR 1.61, 95% CI 1.53-1.70), coronary heart disease (CHD) (HR 1.60; 95% CI 1.52-1.69), bronchiectasis (HR 1.59; 95% CI 1.23-2.04), atrial fibrillation (AF) (HR 1.43; 95% CI 1.25-1.62), connective tissue disorders (HR 1.37; 95% CI
1.25-1.50), inflammatory bowel disease (HR 1.39; 95% CI 1.20-1.62), viral hepatitis (HR 1.38; 95% CI 1.06-1.79), osteoporosis (HR 1.30; 95% CI 1.16-1.45), depression (HR 1.25; 95% CI 1.17-1.34) and hypertension (HR 1.20; 95% CI 1.16-1.25).

In the conclusion "Multimorbidity had a greater impact on all-cause mortality in middle aged as opposed to older populations, particularly males, which deserves further exploration" it should be specified that it is a greater RELATIVE impact. In women aged 37-49 the 7-year mortality seems to be 0.4% in those without LTC and 2.2% in those with 4 or more, while the corresponding estimates in women aged 60-73 were 1.9% and 6.4% so the absolute difference is 1.8% in younger and 4.5% in older.

Authors’ Response: Thank you for your comments, we agree with this suggested change.

Changes to Manuscript<Abstract<Conclusion: Multimorbidity had a greater relative impact on all-cause mortality in middle aged as opposed to older populations, particularly males, which deserves further exploration.

In the tables, instead of only presenting the actual number of deaths, it would be relevant to also have the follow-up time specified. So either change number of deaths to the 7-year cumulative mortality or the mortality rate or simply give the follow-up time in a separate row.

Authors’ Response: The column heading has been changed to “7-year cumulative mortality” (table 2) and “7-year cumulative cancer/vascular mortality” (table 3).

When assessing the validity of self-reported long-term conditions, it would be relevant to present the positive predictive value of this information along with the completeness of registration if available. Have the authors or others formally examined this?

Authors’ Response: Unfortunately, it is not possible to validate the presence of self-report long-term conditions or to present any data on completeness in this cohort, as this information is not available. However, we have done sensitivity analysis using hospitalization records to define long-term-conditions but accept that it will not capture complete information. This was already acknowledged in our limitations, but we have expanded on this.

Changes to Manuscript<Discussion<Strengths and Limitations<Page 22: The use of self-reported health data is a potential limitation and it was not possible to validate the presence of these self-reported long-term conditions.
Editorial comments:

In addition to addressing the Reviewers comments, please also address the following editorial concerns:

a.) Please ensure author Ross McQueenie confirms authorship for this manuscript. We can resend the verification email.

Authors’ Response: I will be grateful if you can resend the verification email to Ross McQueenie please.

b.) Please add the following declarations: ‘Ethics approval and consent to participate’, Consent for publication’, ‘Availability of data and materials’, ‘Funding’, and ‘Authors contributions’. A full list of declarations is required, even if the response is 'Not applicable'.

Authors’ Response: All these declarations have now been completed and added to the manuscript.

c.) The order of the authors has now changed. Please complete a 'change of authorship' form (information included above) and include it with the revised manuscript.

Authors’ Response: This form has now been completed and attached with the revised manuscript.