Author's response to reviews

Title: Time trends in socioeconomic inequalities in cancer mortality: results from a 35 year prospective study in British men

Authors:

Sheena E Ramsay (s.ramsay@ucl.ac.uk)
Richard W Morris (richard.morris@ucl.ac.uk)
Peter H Whincup (pwhincup@sgul.ac.uk)
A.O. Papacosta (o.papacosta@ucl.ac.uk)
Lucy T Lennon (l.lennon@ucl.ac.uk)
S.G. Wannamethee (g.wannamethee@ucl.ac.uk)

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Author's response to reviews: see over
Dear Editor,

We are very grateful to the Reviewers for reviewing our manuscript and for providing helpful comments. We address below each of the issues raised by the Reviewers point by point and outline changes made in the manuscript.

Response to Reviewers’ comments

Reviewer: Min Lian

Reviewer’s report:
Authors analyzed a cohort data with nearly 7500 British men to examine the socioeconomic disparity in cancer mortality.

Comments:
1. **Introduction**
The manuscript is lack of a strong justification in public health significance of the study. Insufficient literatures were reviewed in the introduction section.

Authors’ response:
We thank the Reviewer for this comment and accept that more justification for the study is needed in the introduction section of the paper.

Changes to the paper:
As suggested by the Reviewer, we have provided further justification for the public health significance of this study in the introduction section (page 3, paragraphs 1 and 2). The public health significance of our study is that whilst overall cancer mortality rates in the UK have improved, socioeconomic inequalities (or disparities) are present, such that those from lower socioeconomic groups are at increased risk of cancer mortality. An important aim of current public health policies is to reduce the increased risk of cancer mortality in lower socioeconomic groups. Therefore, it is important to monitor trends in inequalities to better understand the extent of inequalities to inform the development of public health policies. We have added this additional justification in the introduction section and have added more references for this background.

2. **Background/ methods**
Authors mentioned the data came from The British Regional Heart Study. More details are needed for this study. What was the original study purpose when this cohort was developed - for heart health, or for general health?

Authors’ response:
We agree and accept that more information is needed on the British Regional Heart Study, the cohort used in
this study. This study was established to investigate the epidemiology of CVD, but with appropriate data from primary care, mortality registers, and cancer registry it is well placed to explore time trends in cancer mortality.

**Changes to the paper:**

We have added more information on the British Regional Heart Study in the methods section of the paper (page 4, first paragraph). We have clarified that the Study was initially started to understand geographical variations in cardiovascular mortality in Britain, and we have added another reference to the cohort study.

3. Based on a long-term observation (35 years), there should be other important competing events happened, including cardiovascular diseases. Why are authors focusing on cancer? Ignoring competing risks of mortality, the findings might have been overestimated.

**Authors' response:**

We thank the Reviewer for this comment. Cancer mortality, a leading cause of death, was our main outcome of interest for this paper. Indeed, there are other causes of death in the cohort including cardiovascular-related diseases. However, we have already previously investigated trends in inequalities in all-cause and coronary disease mortality (Ramsay SE et al 2008, Journal of Epidemiology and Community Health). For the current paper under review, we were interested in investigating the same question on trends in inequalities for cancer mortality, which is another leading cause of death, and therefore, we focused on cancer mortality. We were interested in presenting evidence on ongoing trends in inequalities in cancer mortality in Britain – we believe our present paper builds on previous studies by providing long-term trends (over 35 years) until 2013 with participants from across Britain.

We accept that a longitudinal study like ours has the issue of competing risk for mortality. However, as mentioned above we have already applied similar methods to investigate inequalities in coronary disease (another leading cause of death) and observed similar results to those in the current paper on cancer mortality. Furthermore, competing risk, if anything, would underestimate the social class difference observed for cancer mortality, since participants of manual social class would be more likely to die of coronary disease before they could die of cancer. Moreover, this impact of competing risk, if present would be expected to be consistent throughout the follow-up period and therefore unlikely to affect the overall pattern in inequalities observed in the study, which is the focus of this paper. We therefore believe that competing risks are not likely to be an important issue in practice, but we agree that this needs to be addressed in the discussion section.
Changes to the paper:
As suggested by the Reviewer, we have now added clarification in the introduction section on the reason for focusing on cancer mortality in this paper (page 3, paragraphs 1 and 2). We have also added in the methods section that the statistical analyses have been previously used to investigate similar trends in all-cause and coronary disease mortality. We have also provided more information on total mortality in the cohort during the follow-up period (results section – page 6, paragraph 3). We have also now addressed the issue of competing risk for mortality in the discussion section as a limitation to acknowledge that competing risks may have underestimated the social class difference observed in our results (page 8, last paragraph; page 9, paragraph 1).

4. Measure of socioeconomic position

The definition of socioeconomic condition is questionable. Although authors applied the longest-held occupation of subjects at study entry, that occupation might not be long enough and might not be representative, especially for subjects with frequent job changes. Additionally, occupation is only an aspect of socioeconomic status. Why wasn’t the family income used?

Authors' response:
We appreciate the Reviewer’s question about the measure of socioeconomic position used in the study and agree that more information is needed to justify its use and stability over time. This occupation-based measure of socioeconomic position was based on the longest-held occupation which was assessed at the age of 40-59 years. We have previously shown that over a 20-year period, very few participants (8%) changed their status using this definition of social class (Emberson JR et al 2004, International Journal of Epidemiology). This confirms the stability of this measure, the purpose of which was to examine the relation of socioeconomic position and cancer mortality in a defined and stable population. We do not have data on family income, and therefore we were unable to use income in our analysis. But we do have data on other socioeconomic measures, including housing tenure and years of education, which are strongly associated with occupational social class and validate its use as a measure of socioeconomic position.

Changes to the paper:
As suggested by the Reviewer, we have added more information in the discussion section on the measure of socioeconomic position used in the study. In particular, we have highlighted the stability of the measure in the discussion section, and have added a reference to the standard measure of occupational social class used (page 8, last paragraph). We have also added a comment in the methods section on the previous use of this measure to investigate inequalities in other health outcomes including all-cause mortality, coronary disease and disability (page 6, paragraph 1).
5. Adjustment for confounders

The statistical analysis did not control for important confounders besides age. Many factors could significantly impact on mortality outcome, including individual health behaviors, lifestyle factors, chronic comorbid conditions, health care coverage, cancer or other chronic condition-relevant treatment and management, etc. This is major issue of this study; therefore, evidence is not enough to draw the conclusion.

Authors’ response:

We thank the Reviewer for this comment. We agree with the Reviewer that we have not explored the possible causes underlying the trends observed in inequalities in cancer mortality as this was not the aim of the study. The purpose of this study was to investigate whether inequalities in cancer mortality remained unchanged over a 35 year period in Britain – our conclusions, therefore, are based entirely on the results of this aim. Since we have not investigated factors underlying trends in inequalities, and indeed, since we did not observe any particular trend in inequalities over time (remained unchanged), there was little to explore in terms of factors that might explain any trends (narrowing or widening) of inequalities. We agree that there are numerous factors that contribute to inequalities in cancer mortality. However, investigating these was not the purpose of our study. We accept that this issue needs to be clarified in the manuscript.

Changes to the paper:

As suggested by the Reviewer, we have clarified in the discussion section that the purpose of this paper is to investigate changes in inequalities in cancer mortality over time in Britain (page 9, paragraph 2). We have discussed possible factors contributing to inequalities in cancer mortality based on evidence from previous studies – this was part of the general discussion and implications not as a conclusion from the results.

Reviewer: Sandi Pruitt

Reviewer’s report:

This manuscript presents results of an analysis of a large, ongoing prospective study of British men (n=7489) who have been followed for 35 years. The large sample size and length of follow-up are a strength of this study. The goal of this study was to investigate whether socioeconomic differences in cancer mortality have persisted over this time, from 1978-80 to 2013.

6. Overall, this is a clearly written manuscript reporting that social class inequalities have persisted over 35 years. My primary concern with the manuscript is that it is written in the style of a government report. The authors could greatly improve the impact of their manuscript by providing more context regarding...
inequalities in Britain and why they persist, and being more thoughtful regarding the causes of observed inequalities, and potential future research directions and/or policy to address observed inequalities. Alternatively, they could address inequalities in cancer vs. other mortality or suggest some future research ideas. Currently, I’m left wondering why the literature needs another study saying inequalities aren’t going away. Adding some thoughtful discussion of the above would help with this problem.

Authors’ response:
We are grateful to the Reviewer for this comment and helpful suggestions to strengthen the paper. We agree that more information in the introduction and discussion is needed on further directions of research and thank the Reviewer for the helpful suggestions provided.

Changes to the paper:
As suggested by the Reviewer, we have expanded the introduction section to provide more references to inequalities in cancer Britain and literature on possible reasons underlying these inequalities (page 3). We have also added comments in the discussion section on policy implications and further directions of research (page 9, paragraph 2) – in particular we have addressed that policies aimed at reducing inequalities in cancer mortality will need continuous evaluation to reduce cancer mortality in lower socioeconomic groups; further research is also needed to provide evidence for effective public health interventions to reduce socioeconomic inequalities in cancer mortality.

Major Compulsory Revisions
7. Statistical Analysis: No rationale is provided to describe why the authors collapsed social class into two groups. At a minimum, some description of what these categories include, how they were collapsed, and citations to other relevant literature regarding the validity of these two categories is needed. It is difficult to interpret the meaning of these categories without this additional information.

Authors’ response:
We thank the Reviewer for this comment. We accept that more information is needed to explain the justification for the use of the dichotomous social class classification. Social class groups were dichotomised into non-manual (I, II, IIInon-manual) and manual (IIImanual, IV, V) groups to provide a single overall summary of social inequalities and their trends. The first three groups of the Registrar General’s social class classification (I, II, IIInon-manual) comprise non-manual occupations, and the other three groups include manual occupations. This dichotomized social class grouping is a widely used approach in studies using the Registrar General’s social class classification (Smith GD et al 1998; Brown J et al 1997; Hart CL et al 2001; Shohaimi S et al 2004; Galobardes B et al 2007).

We used the categories of manual and non-manual groups in our analyses to provide a more stable indicator of
changes in the two main social class groups than would be possible with six groups. Using these stable and well-defined groups provides a useful summary of the extent of inequalities over time to obtain an overall direction of change of social inequalities over 35 years. Additional analyses using the detailed social class classification of six groups also showed similar results to that using the two broad groups of non-manual and manual. We have previously used the same dichotomous classification of social class in similar analyses to investigate changes in inequalities in all-cause and coronary disease mortality. A similar dichotomous grouping of social class has also been used in other studies.

Changes to the paper:
As suggested by the Reviewer, we have added more information on the social class measure and the categories used (page 5, paragraph 1). We have also added references to previous use of this social class measure by ourselves and other studies.

8. Statistical Analysis: Similarly to the above, no rationale is provided as to why the follow-up time was divided into three calendar periods. Without a clear rationale, I am left wondering why this was done. It is also not clearly addressed why the authors chose to fit Cox models separately by these time periods. Why didn’t the authors conduct time trend analyses, such as joinpoint regression? Joinpoint would provide a more robust test of trends over time and is not subject to the making of arbitrary stratifications over time; as these methods analyze trends over the entirety of the follow-up period.

Authors’ response:
We are grateful for this comment. We agree that further explanation is needed for the choice of dividing the follow-up time into three calendar periods. We chose to divide the follow-up time simply for a descriptive presentation of estimates according to three calendar periods instead of presenting an overall estimate comparing baseline to the end of the follow-up period. We have previously used a 5-year calendar periods for similar analyses on investigating inequalities over time for coronary disease mortality. However, given the smaller number of cancer deaths (compared to coronary deaths), particularly in the initial 5 year period, we decided to use 10-year calendar periods to present socioeconomic differences according to these 10-year periods.

We also accept that more explanation is needed on the statistical analyses used to test changes in inequalities over time. We would like to clarify that we did not use the 10-year periods for the formal assessment of trends over time (the 10-year periods were only for descriptive presentation of hazard ratios over time). We assessed trends over the entire follow-up period and estimated change in hazard ratio per year of the follow-up - this is in agreement with the Reviewer’s comment that trends need to be analyzed
over the entirety of the follow-up period. For the formal assessment of trends, we used Cox regression models to estimate the change in relative socioeconomic difference per year of the follow-up period – the Cox model included age, period, social class and an interaction term for social class*period. This model allowed us to formally test whether the effect of social class changed over time (or period). The model also provides an estimate of change in the hazard ratio per year over 35 years of follow-up – this estimate is a ratio of hazard ratios (comparing manual vs. non-manual) over the follow-up period, which is presented in the results section. We believe this method adequately assesses the change in relative risk (hazard ratio) over the entire follow-up, while also allowing for an interaction term. This method used to assess trends over time is one that we have previously used to investigate changes in inequalities over time for all-cause and coronary disease mortality (Ramsay et al 2008, Journal of Epidemiology and Community Health).

Changes to the paper:
As suggested, we have provided more information on the statistical methods used to formally test the change in inequalities over time in cancer mortality (see methods section, page 5, paragraph 2 and page 6, paragraph 1) – we have also added a reference in this section for the methods used previously.

9. Relatedly, in the Discussion on Page 7, the authors state their results showed “no change in inequalities in cancer mortality.” I take issue with this statement as the authors did not conduct a formal test of this. They did clearly demonstrate that inequalities persisted; but they did not test the size of the inequality across the time periods.

Authors’ response:
We thank the Reviewer for pointing this out. We accept that further clarification of the methods used is needed. As explained in the response to the previous comment, we did carry out a formal test of whether the relative social class difference had changed over the 35-year period. We used Cox regression models to include age, period, social class and an interaction term for social class*period. This allowed us to test whether the effect of social class changed over the entire follow-up time. Furthermore, we used estimates from the Cox model to estimate the change in hazard ratio (or relative risk) per year over the 35-year period. Thus, we obtained an estimate which was a ratio of hazard ratios (comparing baseline and end of follow-up) to test if this had increased, decreased or stayed the same. This estimate is presented in the results section as – “...change in hazard ratio per year comparing manual vs. non-manual groups was 0.99 (95%CI 0.98-1.00, p=0.09), for all-cancer mortality...” This implies that there was no significant change in the hazard ratio (or relative risk) comparing social classes over time.
**Changes to the paper:**

We have now added clarification in the methods and results sections of the estimates used to quantify and formally test the change in inequalities over time (see page 5, paragraph 2; page 6, paragraph 1; page 7, paragraph 1).

10. **Results:** No Table 1 or other information is provided regarding characteristics of the sample. Even if this cohort has previously been described in other manuscripts, it is necessary to provide a table and description of the sample by manual vs. non-manual occupational status, because this is the primary independent variable of this study.

**Authors’ response:**

We thank the Reviewer for this helpful suggestion. We accept that an initial table with descriptive characteristics is needed.

**Changes to the paper:**

As suggested by the Reviewer, we have added a table (table 1) with descriptive characteristics of the cohort, overall, and according to non-manual and manual social class groups.

**Minor Essential Revisions**

11. **Introduction:** While I’m certain the authors had an a priori reason to examine smoking-related and non-smoking related mortality separately, it isn’t clear in the introduction. Moreover, it isn’t very thoughtfully discussed in the Discussion either.

**Authors’ response:**

We thank the Reviewer for pointing this out. We investigated inequalities in cancer mortality separately for smoking and non-smoking related cancers since smoking is one of the leading causes of cancers, and also because smoking has a strong socioeconomic gradient (with higher smoking rates in lower socioeconomic groups). Moreover, given the recent declines in smoking rates, we were interested in investigating whether changes in inequalities were more or less marked for smoking-related and non-smoking related cancer mortality.

**Changes to the paper:**

As suggested by the reviewer, we have added more information in the introduction section on the rationale for investigating smoking and non-smoking related cancer mortality separately (page 3, paragraph 2). We have also expanded on the discussion related to this issue (page 9, paragraph 2).
12. I think the fact that they had “imprecise data on exact date of diagnosis of cancers” should be explained in more detail. Why wasn’t the cohort data linked to cancer registries? This should be described as a clear limitation; as it also means that the authors could not analyze results by cause of death (all-cause or cause-specific).

Authors’ response:
We thank the Reviewer for raising this issue. We agree that clarification on the cancer data is needed. The cohort is linked to cancer registries. However, until the development of the current national UK Cancer Registries in 1992, the initial cohort follow-up did not have the possibility of a systematic linkage to cancer registries. This resulted in imprecise dates of diagnosis for the initial follow-up of the cohort, which limited us from assessing cancer survival (time from date of diagnosis to death). Nevertheless, the cohort has near complete follow-up for mortality, which is the key outcome of our analysis, along with precisely recorded dates of death – mortality data from death certificates (with dates and cause of death) have been obtained for the cohort annually from the National Health Service Central Register since the start of the study in 1978-80.

Changes to the paper:
As suggested by the Reviewer, we have added more detail in the methods section on mortality data for the cohort (page 4, paragraph 1). We have also now addressed the issue of imprecise dates of cancer diagnoses as a limitation of the study, as suggested by the Reviewer (page 8, paragraph 2).

13. Methods: clearly state the latest date of most recent follow-up used in this analysis.

Authors’ response:
We accept that the date of most recent follow-up needs to be clarified in the paper.

Changes to the paper:
As suggested by the Reviewer, we have added the date of the most recent follow-up used in the current paper which is from baseline until July 2013 (page 5, paragraph 2).