Author’s response to reviews

Title: Educational inequalities in mortality associated with rheumatoid arthritis and other musculoskeletal disorders in Sweden

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Dear Editor-in-Chief,

Please find attached the revised version of our manuscript entitled, “Educational inequalities in mortality associated with rheumatoid arthritis and other musculoskeletal disorders in Sweden”.

We are pleased that you are willing to consider a revised version of the above-cited manuscript for publication in BMC Musculoskeletal Disorders. We are grateful for the time and effort and the valuable comments given by the expert reviewers. We have read through the comments carefully, and have revised the manuscript according to the reviewers’ suggestions (changes are marked with yellow color in the text) and present a point-by-point reply below.

Thank you for considering our paper for publication in BMC Musculoskeletal Disorders.

We look forward to hearing from you.

Reviewer #1

This manuscript reports results from an investigation of the association between education and RA/MSK-specific mortality after a median of 12 years follow-up. The manuscript is based on
results from data arising from 3 different types registries containing data on residents of the Skane region of Sweden. The manuscript is well-written but would benefit from a little more detailing of the methods and expanding the discussion to include how education impacts mortality in general, how that compares to what was observed for MSK deaths and what the implications are specifically for MSK. In addition, this manuscript could greatly benefit from a sample size flowchart showing the data sources and how they arrived at the final sample size.

Reply: We thank the reviewer for the comments.

Action: We have added the estimates for non-MSK disorders-related mortality to the manuscript. We have also revised our discussion. Moreover, we provided more details on sample size in the result section (since we did not have too many exclusion criteria, we rather report this as text instead of a graph): “We identified 1,091,548 people aged 30-99 years who were recorded as the Skåne resident at least once between 1998 and 2013. Of these, 21903 (2.0%) were excluded with missing follow up data (e.g., people who were registered only once in the register with no further information on place of residence or vital status), 70,409 (6.6%) had missing data on level of education, and 88 with missing information on country of birth”.

Methods:

1) How were you able to ascertain if/when someone moved into/out of the Skane region? How often are the registries updated? Also, what about people who were not Swedish born, how were they accounted for (i.e., how were they picked up by the registries)?

Reply: We thank the reviewer for the comment. All residents in Sweden (including those who move to Sweden and attend to live here for at least a year) are required to be registered in the Swedish Population Register. When they have been registered they will be given a Swedish personal identity number which is essential for living in Sweden because no public services (e.g. education, health, housing, bank, etc.) are available to those without a personal identity number. The Swedish Population Register is a national register containing statistics of vital events such as births, deaths, and place of residence. The register is administrated by the Swedish Tax Agency which receives most of the information from other public agencies. Moreover, one must notify the Tax Agency if, for example, she/he wants to report a change of address, change of name or getting married. This register is updated annually. The database LISA presently holds annual registers since 1990 and includes all individuals 16 years of age and older that were registered in Sweden as of December 31 for each year. The database integrates existing data from the labour market, educational and social sectors and is updated each year with a new annual register. The cause of death register contains data on date and causes of death and is updated annually. All these registers are merged using the personal identity number and used for research purposes.
Therefore, these registers capture both moving of individual within the country and also those who moved to the country. All these registers are national but for the current study we had only access to the Skåne population according to our ethical approval.

Action: We have added the following to the text: “The database LISA presently holds annual registers since 1990 and includes all individuals 16 years of age and older that were registered in Sweden as of December 31 for each year. The database integrates existing data from the labour market, educational and social sectors and is updated each year with a new annual register (https://www.scb.se)”.

2) Does LISA contain information for all people? Is it specific to those who lived in Skane? If so, how does it pick up people who moved to the region later?

Reply: Please see our reply to the comment #1.

3) Were the LISA data and Swedish Population Register data collected at roughly the same time? If not, how were they linked up and how was the differing data collection times accounted for?

Reply: These registers are updated annually and there is no difference in timing of data collection.

4) Were the subjects' education and other covariates assessed at study entry only or were they updated over time?

Reply: We thank the reviewer for the comment. Yes, we included covariates as measured at entry to study. It should be noted that age was our time scale and therefore was updated over follow up. The data on sex is coded as men and women and hence they are time-invariant in our database. Furthermore, we used education as our socioeconomic factor and included only people over 30 years in the study which implies that a large proportion of our study sample did not have any changes in their education over time.

5) Is there any other information on covariates? All that is mentioned is sex, marital status and country of birth.

Reply: We thank the reviewer for the comment. It should be noted that age was also another covariate which was included as our time scale.
We have data on employment and income and it is possible to obtain data on comorbidity. However, we didn’t include employment and income for several reasons: 1) we were interested in total effect of education on MSK mortality and we considered employment and income as mediator not confounder in this relationship, that is one’s education determines her/his employment status and income, 2) education is less likely than occupation and income to be the result of ill-health (reverse causation), 3) education is a more stable proxy for socioeconomic status compared with income or employment (i.e., employment/income are more probable to change overtime compared with education particularly in those aged>30), and 4) there were higher proportion of missing values on income and employment in our dataset than education.

Regarding comorbidity, we assumed comorbidity as a mediator not confounder in relationship between education and MSK mortality and since we were interested to estimate the total effect of education, we didn’t control for mediators including comorbidity.

Action: No further action has been taken.

6) Is anything known about healthcare utilization and treatment for their condition? What about treatment for other conditions like high blood pressure or heart conditions? I’m thinking of these in terms of comorbid conditions to be used as covariates.

Reply: We thank the reviewer for the comment. Please see our reply to previous comment. We didn’t consider comorbid conditions as confounder in our study. Of course, we aware that some comorbid condition can be confounder (i.e. those which occurred early in life and influenced educational achievement of people). However, we lack data on these conditions and this is a limitation.

Action: We acknowledged the limitation of our study due to lack of data on some important confounders including early life health status: “Due to the lack of data, we did not control for several important confounders of the education-MSK mortality association (e.g., early life socioeconomic and health status, cognitive ability)”.

7) Bottom of page 6, top of page 7: It is mentioned that the age strata refer to “attained age". Is this attained age at study entry or final point (death/censoring)?

Reply: The attained age refer to the subject’s age over follow up.

Action: We have added an example to clarify what we mean by attained age: “For instance, if someone entered the study at age 68 and was followed until age 82, s/he contributed for 2 years to the age stratum 30—69 years, for 10 years to the age stratum 70—79 years, and for 2 years to the age stratum 80+ years”.
8) There needs to be more detail for how the 'any mention' method of assigning mortality was carried out. For example, in your analyses was each subject contributing other causes of death? If so, was the number of contributions accounted for? All of this needs to be described in the methods.

Reply: We thank the reviewer for the comment. As we explained in the text, any mention approach considers any mention of the disease of interest (RA and other MSK disorders in our study) on a death certificate as an event. We identified mention of RA/other MSK disorders using ICD-10 codes. We do not consider number of contributing causes as a confounder in relationship between education and mortality and hence we didn’t adjust for it.

Action: We have added the following to the text: “For cause-of-death attribution, we used “any mention” approach where a death certificate with any mention of the disease of interest (RA and other MSK disorders in our study) on any part of the death certificate (i.e., underlying or contributing cause) is considered as an event”.

9) MSK and RA are associated with many factors that have a much higher risk of death including CVD and diabetes. Was a competing-causes approach considered in sensitivity analyses? If so, what were the results? That might be a good addition to the appendix.

Reply: We thank the reviewer for the comment. There are two main regression approaches to analyse competing events: 1) models based on cause-specific hazard, and 2) models based on the cumulative incidence function (e.g., the Fine-Gray model). Both these approaches “are valid and the choice of the appropriate approach depends on the research question” [Wolbers M, et al. Competing risks analyses: objectives and approaches. European Heart Journal 2014, 35:2936–2941]. In our study, we were interested in the aetiological question of how education influence the rates of mortality from MSK and other causes and hence we applied cause-specific Cox regression model. However, we didn’t estimates the association for non-MSK causes and to comply with the reviewer suggestion and also recommendation from the literature (“A complete description of competing risks data should include the modelling of all event types and not only of the event of main interest”), we have treated death certificates with no mention of RA/other MSK disorders as competing event and have added the estimates of hazard ratio (HR) and relative index of inequality (RII) for these causes to the manuscript.

Action: We have clarified that we used cause-specific Cox regression model for estimating HR and RII in the method section. We have also added the estimates for non-MSK disorders mortality to our manuscript in Table 3.
Results:

1) It would be informative to have a table of frequencies of other causes of death that were also listed on the death certificates.

Reply: We fully agree with the reviewer.

Action: We have added two supplemental tables describing contributing causes when RA/other MSK disorders were recorded as underlying cause (Table S1) and vice versa (Table S2).

Discussion:

1) There needs to be something in the discussion about women having more RA and MSK than men and therefore would probably be more likely to have one of those listed in their death record.

Reply: We thank the reviewer for pointing this out.

Action: We have added a paragraph to the discussion where we discussed educational inequalities across sex and age groups as follow: “The greater absolute educational inequality in RA-related mortality in women than in men might be partially explained by higher RA-related mortality among women. However, while women had higher mortality rate of other MSK disorders, among people aged ≥70 years the absolute educational inequality in other MSK disorders-related mortality was larger in men. The similar finding was found for the relative educational inequalities in both RA- and other MSK disorders-related mortality (i.e., higher RIIs in men than in men among those aged ≥70 years). These findings might reflect that compared with older women, older men experience larger educational inequalities in prevalence of MSK risk factors, in management of MSK disorders, and in use of health care”.

2) Also, as can be found in many published manuscripts, those with low education have higher rates of mortality in general. How do the numbers in this study compare to death in general? What are the implications for the results of this study in light of previous literature? I did not see that in the discussion.

Reply: We thank the reviewer for the comment. As we mentioned in reply to comment #9 above, we have added the estimates for non-MSK causes to the manuscript and in result we have added a paragraph to the discussion to explain these estimates.

Action: We have added the following to our discussion: “Our results showed that the magnitude of relative inequality was greater in deaths with mention of MSK disorders compared with those with no mention of MSK disorders. Furthermore, we assessed the relative educational
inequalities in fracture-related mortality in this sample in a previous study (16) and found smaller RII compared with MSK disorders-related mortality. While the reasons for these differences are not obvious and warrant further investigation, this result may reflect larger educational gradient in prevalence of MSK disorders risk factors than in prevalence of other causes risk factors. It should be noted that we pooled all other causes together and hence our finding might not generalizable to specific-causes of death (e.g., neoplasms, cardiovascular diseases, etc.)”.

3) Some mention needs to be made of the limitation of predicting MSK mortality without considering other contributing causes.

Reply: We thank the reviewer for the comment. As we explained in previous comments, we were interested in association between education and MSK disorders mortality and since we assumed other causes do not influence educational attainment, we do not consider the lack of control for contributing causes as a limitation. Furthermore, in this revised version, we have reported educational inequalities in death certificate with no mention of MSK disorders which might partially account for the reviewer comment.

Action: No further action has been taken.

4) While this is a nice first pass at looking at education as a predictor of MSK deaths, I think a more sophisticated analysis using other MCD approaches may give us a better idea of how much impact MSK causes of death are more likely to be due to, in part, having lower levels of education.

Reply: We thank the reviewer for the comment. As we are aware, there are three approaches for cause-of-death attribution: 1) “underlying cause”, 2) “any mention”, and 3) “weighted multiple-cause”. Of these, the last two approaches are based on multiple cause of death (MCD) data and the last one is the most appropriate. However, to apply “weighted multiple-cause” approach to study a disease, there should be enough number of death certificates with mention of the disease of interest as sole cause of death, as these are informing about the actual potential for the disease to cause death by itself (“pure hazard”). However, MSK disorders are very unlikely to be mentioned as sole cause of death on death certificate (in our study, there were only 16 death certificates with a MSK disorder as sole cause of death). Furthermore, we have used “weighted multiple-cause” to study cause-specific mortality among people with gout (manuscript under review) and unfortunately, the R package to run this approach is extremely slow. It took about 2 hours for each estimate in a sample of 25000, meaning that using it in a sample as large as our
study (n=900000) it would take at least a day for each model to run (54 models were run in the current study).

Action: No further action has been taken.

Reviewer #2

I have no issues with the manuscript which is well written & clearly set out, with a sound methodology and statistical analysis.

The only novel aspect of this research was the use of actual underlying cause of death due to MSK conditions in exploring the association between mortality and educational level in MSK patients. The results were not unexpected.

Reply: We thank the reviewer for the comment. However, we would like to point out some issues: we used any mention of MSK disorders on death certificate as outcome not only underlying cause of death, and we examined the association between MSK mortality and educational level in the general population. In addition, while results might have not been unexpected, but there was a lack of knowledge on the magnitude of educational inequalities in MSK disorders mortality which was covered in our study. In other word, while one might expect educational inequality in MSK mortality, the magnitude of this inequality convey insightful information. In particular, in the revised version, we have added education inequalities for non-MSK disorders mortality which provide more useful information for policy making.

The issue is whether & how much this report adds anything to the extensive data we already have on this subject. The main weakness of the conclusions of the study is that the educational level variable used as the predictor is almost certainly a surrogate for more tangible & possibly correctable clinical and environmental features known to be associated with mortality, i.e. smoking, obesity, diet, exercise, type of employment, housing etc, none of which were available for this study.

Reply: We thank the reviewer for the comment. We would like to highlight that to our knowledge, only two previous studies quantified socioeconomic inequality in mortality due to MSK disorders in the general population. Actually, MSK disorders are rarely seen as a cause of death and even in the Global Burden of Diseases Study, most MSK disorders are not considered to be associated with mortality. Therefore, we disagree with the reviewer statement about “the extensive data we already have on this subject”.


On the other hand, we fully agree that the observed educational inequalities are possibly due to different factors, and access to data on these potential factors could have strengthen our study (as we have acknowledged in the discussion of our manuscript). However, similar to many studies in inequality research, quantifying the magnitude of inequality is a first step in explaining inequalities in any outcome. Therefore, our study should be considered as a starting point in determining pathways underlying educational inequalities (i.e., now researchers know that there are substantial educational inequalities in mortality related to MSK disorders which are larger than non-MSK disorders-related mortality and this might encourage them to determine pathways underlying these inequalities).

For this reason, therefore I adjudge the suggestions in the conclusions in both the abstract and in the discussion to be misleading: "Education was inversely associated with mortality from RA and other MSK disorders suggesting need for improvement of MSK disorders management in low-educated people". "This has important implications for healthcare resource allocation and disease management, for instance initiating specific interventions to target low educated people."

Surely it is more important that the underlying comorbidities & environmental/social aspects should be targeted, especially as some are correctable, rather than highlighting clinical management of RA. I feel the authors should acknowledge this and expand on the use of aspect of surrogate markers.

Reply: We thank the reviewer for the comment. We fully agree with the reviewer’s comment.

Action: We have revised the conclusions in both the abstract and in the discussion as follow: “We found substantial educational inequality in mortality from MSK disorders. Further research is needed to investigate underlying pathways driving these inequalities”; and “We also found that there were greater relative educational inequalities in MSK disorders-related mortality compared with non-MSK disorders-related mortality which warrant further investigation. We suggest that education should be considered in implementing preventive strategies targeting MSK disorders risk factors”.

Another possible weakness is the well-known variation in the reporting of MSK disorders on death certificates as a contributing cause of death. The authors allude to this but do not discuss this in any detail, given the very small percentages.

Reply: We thank the reviewer for the comment. We agree with the reviewer that this source of measurement error is of concern if it is associated with education.
Action: We have modified the limitations section in the discussion to account for this comment: “However, despite using MCD data, underreporting and diagnostic inaccuracy of MSK disorders on death certificates is a source of concern. In particular, if quality of cause of death data vary by education, then our estimates would be biased. However, a previous study reported no educational differences in the use of ill-defined causes of death in Sweden (17)”.

The manuscript would be improved if the authors provide robust reasoning for how this work would actually improve clinical care, the use of surrogate markers MSK conditions on death certification.

Reply: We thank the reviewer for the comment. To be honest, our aim was merely quantifying the magnitude of educational inequalities in deaths certificates with a mention of MSK disorders compared with those with no mention of MSK disorders. To be able to provide suggestions to improve clinical care or death certification, we need more detailed data on other variables including MSK disorders risk factors, type of treatment, adherence to treatment, etc. Therefore, without such data in our analyses, we rather not provide any suggestion on clinical care or death certification because it might be misleading.

Action: No further action has been taken.