PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality of ethnic minority groups in the United Kingdom: a systematic review protocol
AUTHORS	Stanaway, Fiona; Noguchi, Naomi; Mathieu, Erin; Khalatbari-Soltani, Saman; Bhopal, Raj

VERSION 1 - REVIEW

REVIEWER	Tani Martins University of Exeter, UK
REVIEW RETURNED	24-Oct-2019

GENERAL COMMENTS	Thank you for inviting me to referee this paper, which sets out a protocol to investigate ethnic variation in all-course mortality. In the UK, this is an important subject but significantly under-researched. Compared to the majority, ethnic minorities in the UK have higher rates of illnesses and poor access to care and are more likely to report a less positive experience of care. All of these may impact disease mortality; authors may want to comment on how these factors might have influenced the findings of potential studies, and by extension, their review findings. Also, the authors considered the limitation of using country of birth as a proxy measure of ethnicity, but they omitted generational differences in ethnic minority groups. For instance, mortality rates among second-generation migrants (classified as ethnic minorities) may be similar to the British White majority, and so the findings of studies that used combined ethnic groupings (e.g., Black or Asian) may be inaccurate. How do the authors intend to deal with this potential source of noise in ethnicity data? My main concern for this paper is whether authors will find enough UK studies to achieve their objective. Other comments • Under research question line 51, "…how do all-cause mortality rates differ between major ethnic groups and the White majority population…" The phrase 'major ethnic groups' as used here is misleading. • Under eligibility criteria line 30, could the authors justify the exclusion of populations with a specific disease? • Ethnic categories listed in either column of Table 1 are slightly different from the official groupings for the 2011 national census for England and Wales (please check UK Office for National Statistics website clarification). • Line 46 "Where possible, we selected ethnic group classifications from the three UK censuses". Suggest using definitions from one of the three censuses as there are subtle differences. You may notice

	that the 2001 census definition appears more in research and electronic medical records. • Page 6 line 7 “Studies that group multiple and extremely diverse ethnic groups together as one single category (such as all non-white ethnic minorities) will be excluded” Could this exclusion limit authors findings? • Few ethnic groups are missing in Appendix 2, notably White British, Irish and other Whites

REVIEWER	David Walsh Glasgow Centre for Population Health, Scotland
REVIEW RETURNED	29-Oct-2019

GENERAL COMMENTS	This protocol, for a systematic review of mortality of ethnic minority groups (compared to the majority White population) in the UK, is very clearly written, comprehensive and detailed. It is also an extremely important topic, not least because of the rapidly changing ethnic profile of the UK (and elsewhere). Generally, the authors should be congratulated on the clarity of their approach. My one, slightly nagging, concern relates to the weight given to reviewing the evidence for the mortality differences per se between ethnic minority groups and that given to the reasons for those differences. The review seems to be more about the former than the latter which, although understandable, worries me slightly. We already know, from very large, longitudinal UK studies, that place of birth (UK-born vs non-UK born) is enormously important in explaining differences among non-White UK populations (see, for example, Wallace 2016, and Bhopal et al 2018). SEP is also, obviously, extremely important. And both issues are clearly highlighted in the protocol, which is to its credit: in relation to place of birth, it states that relevant sub-group analyses will be undertaken, and additional quantitative analyses of SEP are also mentioned. However, the sense I have from the protocol is that they will be “add-ons”, subject to the availability of appropriate data. The ‘nagging concern’ I have, therefore, is that if such relevant explanatory data cannot be analysed, the review will, by default, highlight differences between groups without explaining them. And that can then lead to misinterpretation: there is a good, fairly recent, example of this from work in Scotland where a (robust, well-analysed and well-written) paper highlighting differences in life expectancy between ethnic groups was unfortunately accompanied by a misleading press release suggesting a principally behavioural explanation. Later work from the same (excellent) programme of research showed instead the importance of place of birth (UK vs non-UK) in understanding those differences. Of course a review of all the many potentially relevant explanations for differences in mortality rates between ethnic groups would be a different exercise completely – not least because of the sheer complexity of the subject matter. Reviews by Davey Smith and many others have highlighted this over the years. However, I think it would still provide some reassurance if more weight was able to be given in the protocol (even in the title? Or in stating how results will be presented?) to the importance of issues such as place of birth and SEP in terms of emphasising the likely influences on mortality

	differentials. My other two points are more minor. First, although the study quality assessment tool (Supplementary Appendix 3) mentions representativeness of samples, it doesn't explicitly talk about sample size which I would have thought would have been important. The same is true of response rates. (It does mention 'participation rates' but without an indication of what level would be deemed to be prone to potential bias). Second, the protocol mentions data analysis being undertaken separately for sub-UK studies (English, Scottish, N. Irish) because of – it is stated – the poorer health of (for example) White Scottish compared to White English and the resulting comparability issues that this may present. However, it's worth adding that although it is changing rapidly, the profiles of the non-White minority groups (in terms of SEP, and also mortality experience of UK-born) in Scotland has been shown to be quite different to those in England. So this should also be borne in mind in the data synthesis part of the project.

REVIEWER	Stephen J Tregear Booz Allen Hamilton, USA
REVIEW RETURNED	12-Jan-2020

GENERAL COMMENTS	This is an interesting protocol that for the most part is well written and reproducible. My comments, which are minor, pertain to the Data Synthesis section. There is a general lack of citation use in the section. For example, one should add a citation or two after the first sentence so that readers unfamiliar with random effects meta-analysis can research this for themselves. The same applies to the use of cumulative meta-analysis. What software will be used for the meta-analysis? I think that subgroup Analysis 4 is really a sensitivity analysis since you state that you expect that the three measures of effect should be comparable further up in the protocol. This analysis is testing that assumption. Consider the use of meta-regression models if the number of articles identified is sufficient. This will allow for multiple factors to be considered in a single model. Of course, this will not be possible

REVIEWER	Tao Chen Liverpool School of Tropical Medicine
REVIEW RETURNED	16-Jan-2020

GENERAL COMMENTS	I did not have particular comments on this system review. One point is that this article missed the start date of this review. Another point is the reason of including the cross-sectional study given that this study is to assess the relationship between ethnicity and all-cause mortality.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Tani Martins

Institution and Country: University of Exeter, UK Please state any competing interests or state ‘None declared’: There are no competing interests

Thank you for inviting me to referee this paper, which sets out a protocol to investigate ethnic variation in all-course mortality. In the UK, this is an important subject but significantly under-researched. Compared to the majority, ethnic minorities in the UK have higher rates of illnesses and poor access to care and are more likely to report a less positive experience of care. All of these may impact disease mortality; authors may want to comment on how these factors might have influenced the findings of potential studies, and by extension, their review findings. Also, the authors considered the limitation of using country of birth as a proxy measure of ethnicity, but they omitted generational differences in ethnic minority groups. For instance, mortality rates among second-generation migrants (classified as ethnic minorities) may be similar to the British White majority, and so the findings of studies that used combined ethnic groupings (e.g., Black or Asian) may be inaccurate. How do the authors intend to deal with this potential source of noise in ethnicity data?

We agree that country of birth and ethnicity are both important considerations and that there may be differences in members of the same ethnic group depending on whether they are born overseas (migrants) or have been born in the UK (second-generation). As a result, we have specified a subgroup analysis where we will compare the health of UK-born versus overseas-born members of each ethnic group if the data permits. We have moved this sub-group analysis to a more prominent position and emphasised more the importance of examining this point in the introduction. Please refer to the highlighted text at the end of the second paragraph of the introduction on page 4 as well as the subgroup analyses listed on page 12 and copied below.

Introduction:

“There has also been very little exploration and as a result, limited consensus on what the underlying drivers of mortality differences by ethnicity in the UK might be. Place of birth (in particular being born overseas compared to being born in the UK) is likely an important predictor of mortality differences as well as socioeconomic status (SES).”

Subgroup analyses:

1. “UK-born versus overseas-born within each ethnic group to examine the contribution of early life environment to observed differences in mortality by ethnicity.”

My main concern for this paper is whether authors will find enough UK studies to achieve their objective.

We agree that there is a possibility that there will be insufficient studies available to be able to conduct all of the planned analyses. However, we do not believe that this is a reason not to do the review or to pre-specify important analyses that should be conducted if available data permit. This is an important topic where summarised evidence is needed and if it is found that research has been insufficient, particularly the number of studies that have collected both country of birth and ethnicity data, then this will in itself be an important finding for the review and a clear message that further primary studies/adequate data collection are needed.

Other comments

- Under research question line 51, "…how do all-cause mortality rates differ between major ethnic groups and the White majority population…" The phrase 'major ethnic groups' as used here is misleading.

We have changed this to 'ethnic minority groups' which is line with the title of the protocol.

- Under eligibility criteria line 30, could the authors justify the exclusion of populations with a specific disease?

Our research question is interested in differences in all-cause mortality between ethnic minority groups and the White majority population in the United Kingdom at the population level. Those with specific diseases such as diabetes will have different (higher) mortality rates to the general population and therefore the mortality rates from such studies would not be able to be meaningfully combined with those from studies looking at mortality rates in the overall population. Therefore, we consider that mortality in particular sub-groups of the population is outside of the scope of this review. We have added the following text to this effect on page 5 under eligibility criteria:

"Studies restricted to populations with a specific disease such as diabetes will be excluded as mortality rates in these population sub-groups would be higher and not able to be meaningfully combined with those based on the whole population."

• Ethnic categories listed in either column of Table 1 are slightly different from the official groupings for the 2011 national census for England and Wales (please check UK Office for National Statistics website clarification).

Our ethnic categories are based on those used in not just the England and Wales census but also the Scottish and Northern Ireland censuses as our review encompasses the entire United Kingdom. We used the smallest subcategories available for example Indian/British Indian/Indian Scottish rather than Asian/Asian British as long as the specific ethnic group represented at least 0.5% of the population in at least one of the three censuses. For example, in the England and Wales census the category of Asian has the subcategories of Indian or British Indian, Pakistani of British Pakistani, Bangladeshi or British Bangladeshi, Chinese, and other Asian.

• Line 46 “Where possible, we selected ethnic group classifications from the three UK censuses”. Suggest using definitions from one of the three censuses as there are subtle differences. You may notice that the 2001 census definition appears more in research and electronic medical records.

We agree that there is a lot of inconsistency between ethnic group classifications both between the three UK censuses as well as over time. We have provided Table 1 so that regardless of the specific nomenclature that is used, ethnic groups can be grouped and analysed in a way that is most meaningful. For example, those grouped according to the England and Wales census as British Indian and those grouped according to the Scottish census as Indian Scottish will be considered as belonging to the same ethnic group for the purposes of the review. Many of the conceptual underpinnings of our protocol, including the terminology around ethnicity have been guided by the book ‘Migration, Ethnicity, Race, and Health in Multicultural Societies’ by R.S. Bhopal (reference 15).

• Page 6 line 7 “Studies that group multiple and extremely diverse ethnic groups together as one single category (such as all non-white ethnic minorities) will be excluded” Could this exclusion limit authors findings?

We believe that this is an important exclusion criterion in order for the results to be meaningful. There is considerable diversity in health outcomes between different ethnic minority groups and by grouping all ethnic minority groups together this diversity is lost and can result in misleading findings and interpretations.

• Few ethnic groups are missing in Appendix 2, notably White British, Irish and other Whites

These ethnic groups were not included as search terms as they are mostly the comparison populations and it is common practice to include only search terms based on the P (population) and I (intervention or risk factor of interest) terms from the PICO research question in order to keep the search as broad and sensitive as possible. In addition, when planning the search terms with the medical librarian it was discovered that due to the use of country terms, adding ethnicity terms closely related to the country term did not increase the search sensitivity (e.g. adding ‘White British’ in addition to ‘Britain’ or Irish in addition to ‘Northern Ireland’).

Reviewer: 2

Reviewer Name: David Walsh

Institution and Country: Glasgow Centre for Population Health, Scotland Please state any competing interests or state ‘None declared’: None declared

This protocol, for a systematic review of mortality of ethnic minority groups (compared to the majority White population) in the UK, is very clearly written, comprehensive and detailed. It is also an

extremely important topic, not least because of the rapidly changing ethnic profile of the UK (and elsewhere).

Thank you for this comment.

Generally, the authors should be congratulated on the clarity of their approach. My one, slightly nagging, concern relates to the weight given to reviewing the evidence for the mortality differences per se between ethnic minority groups and that given to the reasons for those differences. The review seems to be more about the former than the latter which, although understandable, worries me slightly.

We already know, from very large, longitudinal UK studies, that place of birth (UK-born vs non-UK born) is enormously important in explaining differences among non-White UK populations (see, for example, Wallace 2016, and Bhopal et al 2018). SEP is also, obviously, extremely important. And both issues are clearly highlighted in the protocol, which is to its credit: in relation to place of birth, it states that relevant sub-group analyses will be undertaken, and additional quantitative analyses of SEP are also mentioned. However, the sense I have from the protocol is that they will be “add-ons”, subject to the availability of appropriate data. The ‘nagging concern’ I have, therefore, is that if such relevant explanatory data cannot be analysed, the review will, by default, highlight differences between groups without explaining them. And that can then lead to misinterpretation: there is a good, fairly recent, example of this from work in Scotland where a (robust, well-analysed and well-written) paper highlighting differences in life expectancy between ethnic groups was unfortunately accompanied by a misleading press release suggesting a principally behavioural explanation. Later work from the same (excellent) programme of research showed instead the importance of place of birth (UK vs non-UK) in understanding those differences.

Of course a review of all the many potentially relevant explanations for differences in mortality rates between ethnic groups would be a different exercise completely – not least because of the sheer complexity of the subject matter. Reviews by Davey Smith and many others have highlighted this over the years. However, I think it would still provide some reassurance if more weight was able to be given in the protocol (even in the title? Or in stating how results will be presented?) to the importance of issues such as place of birth and SEP in terms of emphasising the likely influences on mortality differentials.

We agree that the misinterpretation of ethnic differences in health is important to avoid. We have added some additional text to the second paragraph of the introduction to highlight the importance of country of birth and SEP as underlying determinants of mortality differences. We have also rearranged the section on subgroup analyses so that it is clear that consideration of country of birth is a central part of the work. (The subgroup analysis of country of birth had been initially placed at the end under additional analyses only because we were planning to do this subgroup analysis regardless of heterogeneity whereas the others listed are only for investigation of heterogeneity.) For SEP, it is most likely that where this data is available it will be in the form of mortality rates for each ethnic group that have been adjusted for differences in SEP (as opposed to presentation of results stratified by each category of SEP in each ethnic group). Therefore, we will not conduct subgroup analyses by differences in SEP but will provide a quantitative synthesis where possible of SEP

adjusted results. We have mentioned this point in the first paragraph under data synthesis. We have also added a dotpoint under the strengths and limitations section at the start of the protocol that emphasises the importance of examining the impact of country of birth and socio-economic status in our analysis. These additions are also summarised below.

Strengths and limitations of the study:

- We will examine the extent to which country of birth and socio-economic status contribute to ethnic inequalities in mortality

Introduction:

There has also been very little exploration and as a result, limited consensus on what the underlying drivers of mortality differences by ethnicity in the UK might be. Place of birth (in particular being born overseas compared to being born in the UK) is likely an important predictor of mortality differences as well as socioeconomic status (SES). However, results can be conflicting for the influence of socioeconomic status on the health of ethnic minority persons, particularly in terms of the relationship between SES and mortality in migrants4,6.

Subgroup analyses:

The first two subgroup analyses listed below will be conducted regardless of the presence or absence of statistical heterogeneity.

Subgroup analyses

1. UK-born versus overseas-born within each ethnic group to examine the contribution of early life environment to observed differences in mortality by ethnicity.

2. Published versus unpublished results within each ethnic group to examine the presence of publication bias.

My other two points are more minor. First, although the study quality assessment tool (Supplementary Appendix 3) mentions representativeness of samples, it doesn't explicitly talk about sample size which I would have thought would have been important. The same is true of response rates. (It does mention 'participation rates' but without an indication of what level would be deemed to be prone to potential bias).

Whilst sample size is an important consideration, this is usually considered in the context of lack of power (leading to wide confidence intervals around estimates) rather than as a cause of bias per se. Hence, it is not commonly included as an item in risk of bias tools such as the Newcastle Ottawa scale. The issue of the small number of ethnic minority persons in individual studies and resulting lack of power will be addressed to some degree by combining these small studies together in a meta-analysis where possible.

Response rates/participation rates are considered under the question on representativeness. This question is mostly based around the method of recruitment (volunteers vs census-based studies of the whole population) but if cohort studies not based on data linkage are included, we will consider

participation rates. Rather than choosing a specific cut-point we will consider both the participation rate but also the difference in participation rates between ethnic groups. We have also not provided a cut-off for what level of loss to follow up indicates bias in the question on 'adequacy of follow up' as the risk of bias is a result of both the response rate and the event rate. I.e. when event rates are low even very small lack of participation/losses to follow up could result in bias. As a result, we will make a judgement for each study based on consideration of differences in participation/response rates between the ethnic groups being compared in relation to the mortality rate observed in the study.

Second, the protocol mentions data analysis being undertaken separately for sub-UK studies (English, Scottish, N. Irish) because of – it is stated – the poorer health of (for example) White Scottish compared to White English and the resulting comparability issues that this may present. However, it's worth adding that although it is changing rapidly, the profiles of the non-White minority groups (in terms of SEP, and also mortality experience of UK-born) in Scotland has been shown to be quite different to those in England. So this should also be borne in mind in the data synthesis part of the project.

Thank you for this comment. We have added this consideration into the Methods section of the protocol (last paragraph under data synthesis on page 12).

"In addition, there is some evidence that the health of non-White minority groups can differ between countries in the UK."

Reviewer: 3

Reviewer Name: Stephen J Tregear

Institution and Country: Booz Allen Hamilton, USA Please state any competing interests or state 'None declared': None declared

This is an interesting protocol that for the most part is well written and reproducible. My comments, which are minor, pertain to the Data Synthesis section. There is a general lack of citation use in the section. For example, one should add a citation or two after the first sentence so that readers unfamiliar with random effects meta-analysis can research this for themselves. The same applies to the use of cumulative meta-analysis.

Thank you for this comment. We have added references to the data synthesis section as recommended. Please refer to references 17 and 22.

17. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2008;1(2):97-111. https://doi.org/10.1002/jrsm.12

22. Lau J, Antman EM, Jimenez-Silva J, et al. Cumulative meta-analysis of therapeutic trials for myocardial infarction. NEJM 1992;327:248-254.

What software will be used for the meta-analysis?

Analyses will be conducted using STATA version 16.0. We have added this information to the methods section of the protocol.

“Analyses will be conducted in STATA version 16.0 (StataCorp, College Station, TX).”

I think that subgroup Analysis 4 is really a sensitivity analysis since you state that you expect that the three measures of effect should be comparable further up in the protocol. This analysis is testing that assumption.

We have changed this to a sensitivity analysis as advised. We have modified the section on sub-group and sensitivity analyses including changing this specific analysis to a sensitivity analysis. Please refer to the list of analyses on pages 12 and 13.

“Subgroup analyses

1. UK-born versus overseas-born within each ethnic group to examine the contribution of early life environment to observed differences in mortality by ethnicity.

2. Published versus unpublished results within each ethnic group to examine the presence of publication bias.

Subgroup analyses to explore heterogeneity

1. Method of ethnicity ascertainment between studies – country of birth vs self-reported ethnicity vs other methods.

2. Definition/included groups in one major ethnic group – e.g. South Asian vs subgroups of Indian, Pakistani, Bangladeshi.

3. Comparison population/geographic location – e.g. White majority population in England and Wales vs White Scottish population in Scotland.

Sensitivity analyses

1. Study design – non-cohort studies removed.

2. Risk of bias – within cohort studies only, studies with high risk of bias will be removed.

3. Measure of effect – hazard ratio vs relative risk or standardised mortality ratio.”

Consider the use of meta-regression models if the number of articles identified is sufficient. This will allow for multiple factors to be considered in a single model. Of course, this will not be possible

Thank you for this suggestion. We have added the use of meta-regression to the methods section as a potential method of exploring observed heterogeneity if sufficient studies are located. Please refer to the paragraph under 'Investigation of Heterogeneity' on page 12.

"If sufficient studies are available, we will consider the use of meta-regression in our exploration of causes of heterogeneity."

Reviewer: 4

Reviewer Name: Tao Chen

Institution and Country: Liverpool School of Tropical Medicine Please state any competing interests or state 'None declared': None declared

I did not have particular comments on this system review. One point is that this article missed the start date of this review.

We will commence the review once the protocol has been published. We will update the record in Prospero once we have commenced the review.

Another point is the reason of including the cross-sectional study given that this study is to assess the relationship between ethnicity and all-cause mortality.

We agree that cross-sectional studies are not ideal for answering questions of causality. However, even though not true cross-sectional studies, many vital statistics studies used to compare migrant mortality rates contain a cross-sectional analysis and we believe that these are important studies to include. In these studies, the mortality rate for each country of birth group is obtained by dividing the number of deaths (numerator) for a particular country of birth group from death records for a given time period by the total population (denominator) for a particular country of birth group based on the census. The census date closest to the period chosen for enumeration of deaths is selected (making the analysis cross-sectional) so that these two unlinked sources of data will as much as possible refer to the same population.

VERSION 2 – REVIEW

REVIEWER	Tanimola Martins University of Exeter, UK
REVIEW RETURNED	16-Feb-2020

GENERAL COMMENTS	The authors have now addressed my main concerns.

REVIEWER	David Walsh Glasgow Centre for Population Health, Scotland
REVIEW RETURNED	17-Feb-2020

GENERAL COMMENTS	Thanks you for your responses to my previous comments - I have no further comments. Good luck with the review.

REVIEWER	Stephen J. Tregear Booz Allen Hamilton USA
REVIEW RETURNED	27-Feb-2020

GENERAL COMMENTS	I believe this revised version of the protocol has addressed my previous comments. The document presents the protocol for the upcoming systematic review in a manner that is transparent and reproducible. The limitations of the protocol and their impact on any findings are discussed. Search criteria seem reasonable. Inclusion and exclusion criteria are provided. The method for assessing the quality of included studies is described. The processes for data synthesis are well described. Heterogeneity across study findings will be explored using appropriate methods.Meta-analytic methods described are appropriate. Supplementary materials support the main content of the protocol. There are no ethical concerns associated with this protocol since it is a systematic review of secondary data.

REVIEWER	Tao Chen Liverpool School of Tropical Medicine
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	The protocol article has been improved and addressed the comments properly. I have no comments on this