PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Understanding ethnic inequalities in stillbirth rates: A UK population based cohort study
AUTHORS	Matthews, Ruth; Draper, Elizabeth; Manktelow, Bradley; Kurinczuk, Jennifer; Fenton, Alan; Dunkley-Bent, Jacqueline; Gallimore, Ian; Smith, Lucy

VERSION 1 – REVIEW

REVIEWER	Doug Wilson University of Calgary, Obstet Gynecol
REVIEW RETURNED	04-Oct-2021

GENERAL COMMENTS	1. I enjoyed reading this research work but just have a few thoughts or questions. 2. Administrative data is difficult as you restricted at certain questions or times. 3. Abstract and Key Summary: OK 4. Introduction was appropriate and concise. 5. Methods were summarized. 6. Results: Table 1 and 2 clearly presented 7. Page 12 congenital anomalies results are you able to consider gravidity G1 to G5 ; whether the anomalies were isolated or multiple as this may be important re consanguinity which is only briefly mentioned on page 15 but has a very important impact for the groups identified with an increased likelihood. Within the study time period were women only counted for the first SB or were there recurrences considered. As this again may show genetic risk for recessive and X-linked genetic conditions. Can you enhance the placental and cord contribution / assymetric insertion / vasa previa / two vessel cord / abruption / IUGR contribution etc as this is also important. 8. Discussion: OK 9. Figures 1-3 clear and I assume they will be published in color. 10. Overall very good contribution to the SB topic.

REVIEWER	Russell Kirby University of South Florida, Community and Family Health
REVIEW RETURNED	13-Oct-2021

GENERAL COMMENTS	In this manuscript, the authors use data from six calendar years (2014-2019) of MBRRACE-UK to examine differences in stillbirth rates by ethnicity, how differences are mediated by socioeconomic status and maternal age, and how cause of stillbirth differs by ethnicity. The paper holds some interest, but there are several areas where improvements might be made. Starting with the abstract, the objective to examine stillbirth rates by

	ethnicity does not directly follow from the first sentence about more slowly declining rates of stillbirth in the UK. Make the connection to motivation more strongly. Also in the abstract, line 40, how were congenital anomalies ascertained? If this refers to cause of death, so indicate. Or if from a birth defects registry, let the reader know that. Throughout abstract, be consistent about how results are reported- sometimes 95% CI is indicated and sometimes not. Perhaps too much time is spent discussing proportion of stillbirths with unexplained cause - how much does this vary by ethnicity? If this is the main point, state it more clearly. Still in abstract, line 51, it should say 'persists' In the introduction, the material on p 6, starting with 'A greater impact...' would be better placed in the discussion than in the introduction. There's no need for more convincing the reader why you did the study after you've stated your objectives. In the methods, please state more clearly how ethnicity was ascertained. This is not clear from p 6 line 49 . . . are you reporting maternal ethnicity, or some composite of maternal and paternal ethnicity as ethnicity of the stillborn? It would make more sense (at least to this reviewer) to report on maternal ethnicity throughout this analysis. Not stated in the methods, was maternal nativity examined - that is, was the mother born in the UK or elsewhere? This reviewer appreciates the use of CODAC to classify cause of stillbirth, but a table showing the distribution of causes by ethnicity appears to be lacking in the manuscript. on p 7, line 18, there appears to be an extraneous 'a', but it might read better 'Multivariable models are reported on a complete case basis, ...' Also on this page, re this study, should PPI stakeholder group consultation be present or past tense (line 48). Related to exclusion of congenital anomalies (line 25), is cause of death the source of information about birth defects, or are these data acquired from a birth defects registry? Sometimes the birth defect in a stillbirth isn't identified until delivery. In text as well as abstract, be consistent with including 95% CI when reporting point estimates and confidence intervals. This is true both for prevalence rates and for odds ratios. In Table 1, where gestation is reported, it makes more sense to report this in terms of fetuses at risk if possible. Regarding Table 2 and the accompanying text, did the authors do any tests for interaction or effect modification? The change in estimate from base model to multivariable model is large enough that some evaluation should be done. It is also not clear from this table what is adjusted, and whether other covariates (for example nativity) were controlled. Given the nature of the findings, too much data are reported in the results, as well as in the tables. The authors should highlight key

	findings, and refer the reader to tables and graphics for details. The figures are hard to read, and might be more effective converted into tables. This will also convey more statistical information to the reader. The discussion section length seems appropriate. A greater focus on how nativity contributes, independent of ethnicity or in concert, would be helpful. on p 15 line 42, its not clear how this study truly disaggregates groups by culture, religion and other characteristics. In the last paragraph of the discussion, its nice to see a call out to ISA and the CODAC classification, but given it was published in 2009 its no longer a 'new' classification system - just not that widely used. Finally, in the author contributions, it should read 'principal' rather than 'principle', and in the references, its not necessary to list when items were first published online unless they do not yet have formal publication volume and page numbers.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Doug Wilson, University of Calgary
Comments to the Author:
1. I enjoyed reading this research work but just have a few thoughts or questions.
2. Administrative data is difficult as you restricted at certain questions or times.
3. Abstract and Key Summary: OK
4. Introduction was appropriate and concise.
5. Methods were summarized.
6. Results: Table 1 and 2 clearly presented
7. Page 12 congenital anomalies results are you able to consider gravidity G1 to G5 ; whether the anomalies were isolated or multiple as this may be important re consanguinity which is only briefly mentioned on page 15 but has a very important impact for the groups identified with an increased likelihood.
Within the study time period were women only counted for the first SB or were there recurrences considered. As this again may show genetic risk for recessive and X-linked genetic conditions.

We thank the reviewer for these helpful comments and have tried to address them as follows. We were unable to consider gravidity or parity as while this information was available for stillbirths it was not available for all births throughout the time period covered in the study.

We recognise additional information on congenital anomalies regarding whether they were isolated or multiple would be helpful, but unfortunately, these data were limited. However, deaths were only attributed to congenital anomalies where this was thought to be the primary cause of the stillbirth.

Within this large national data set over 6 years, there may be recurrences of stillbirth. The dataset did not facilitate linkage of recurrent births or stillbirths to the same woman. We have acknowledged these limitations in the last paragraph on p14, by mentioning that we don't have information on previous stillbirths.

Can you enhance the placental and cord contribution / assymetric insertion / vasa previa / two vessel cord / abruption / IUGR contribution etc as this is also important.

More detailed information within the reported CODAC cause of death codes is available but would be difficult to explore within the required word limit and we believe may distract from the already large amount of information we have presented surrounding trends in inequalities and the relationships between ethnicity, deprivation and maternal age. The paper focuses on smaller more homogeneous ethnicity groups, so we also need to consider the size of our sample as we try to break down further *by more detailed cause of death as well. However, going forward as more surveillance data becomes available we hope to have the numbers available to look at this in more detail within a separate paper with a more specific focus on cause of death.*

8. Discussion: OK
9. Figures 1-3 clear and I assume they will be published in color.
10. Overall very good contribution to the SB topic.

Reviewer: 2
Dr. Russell Kirby, University of South Florida Comments to the Author:
In this manuscript, the authors use data from six calendar years (2014-2019) of MBRRACE-UK to examine differences in stillbirth rates by ethnicity, how differences are mediated by socioeconomic status and maternal age, and how cause of stillbirth differs by ethnicity. The paper holds some interest, but there are several areas where improvements might be made.

Starting with the abstract, the objective to examine stillbirth rates by ethnicity does not directly follow from the first sentence about more slowly declining rates of stillbirth in the UK. Make the connection to motivation more strongly.

We thank the reviewer for highlighting this and have shortened the objective to focus on the ethnic inequalities (P2).

Also in the abstract, line 40, how were congenital anomalies ascertained? If this refers to cause of death, so indicate. Or if from a birth defects registry, let the reader know that.

We have altered the sentence relating to stillbirths caused by congenital anomalies to highlight that this is based on cause of death information not a congenital anomaly register (P2). This now reads: Exploring primary cause of death, higher stillbirth rates due to congenital anomalies were observed in babies of Pakistani, Bangladeshi and Black African ethnicities (range 0.63 to 1.05 per 1,000 births) and more placental causes in Black ethnicities (range 1.97 to 2.24 per 1,000 births).

Throughout abstract, be consistent about how results are reported- sometimes 95% CI is indicated and sometimes not.
We have amended the abstract to include 95% CI whenever a confidence interval is cited and "range" where an array of values is referred to (P2).

Perhaps too much time is spent discussing proportion of stillbirths with unexplained cause - how much does this vary by ethnicity? If this is the main point, state it more clearly.

We thank the reviewer for this helpful comment and have altered the sentence to make this more succinct and hopefully clearer: Over 40% of stillbirths were of unknown cause, but this was particularly high for babies of other Asian 60.2%), Bangladeshi (58.2%), and Indian (51.5%) ethnicities.
(P2).

Still in abstract, line 51, it should say 'persists'
Thank you for noticing this, we have amended as suggested by the reviewer (P2).

In the introduction, the material on p 6, starting with 'A greater impact...' would be better placed in the discussion than in the introduction. There's no need for more convincing the reader why you did the study after you've stated your objectives.
We agree this shouldn't be placed after the objectives and have moved this sentence to earlier in the introduction as we feel it is an important justification leading to our objectives (Last paragraph P4/5).

In the methods, please state more clearly how ethnicity was ascertained. This is not clear from p 6 line 49 . . . are you reporting maternal ethnicity, or some composite of maternal and paternal ethnicity as ethnicity of the stillborn? It would make more sense (at least to this reviewer) to report on maternal ethnicity throughout this analysis.

While mother’s ethnicity is available for stillbirths it is not available for all births and so analyses are based on the ethnicity of the baby. We have removed the sentence ”Ethnic group available from birth notification data is that of the baby, as defined by the mother” as we feel this is may cause confusion relating to how ethnicity was ascertained. (Last paragraph P5). We have also relabelled ethnicity in tables to refer to “baby’s ethnicity” to make this clearer.

Not stated in the methods, was maternal nativity examined - that is, was the mother born in the UK or elsewhere?

We don’t have this information for all births, so are unable to examine mother’s country of birth but we have highlighted this issue in the discussion (Last paragraph page 14)

This reviewer appreciates the use of CODAC to classify cause of stillbirth, but a table showing the distribution of causes by ethnicity appears to be lacking in the manuscript.

This information is portrayed in figure 2, which shows the rate of each cause of stillbirth, by ethnicity. We are happy to supply a supplementary table if further detail is required.

on p 7, line 18, there appears to be an extraneous 'a', but it might read better 'Multivariable models are reported on a complete case basis, ...'

Thank you for pointing this out. We recognise the “a“ should have been “are” and this has been altered.

Also on this page, re this study, should PPI stakeholder group consultation be present or past tense (line 48).
MBRRACE-UK undertake ongoing perinatal mortality surveillance and here present tense feels appropriate. We have left this as it is.

Related to exclusion of congenital anomalies (line 25), is cause of death the source of information about birth defects, or are these data acquired from a birth defects registry? Sometimes the birth defect in a stillbirth isn't identified until delivery.
The cause of death is assigned following death by the healthcare professionals reporting the stillbirth at each hospital based on the information available in the death certificate and additional information from the medical notes, the perinatal mortality review of the death and any investigations such as post mortem. This is detailed on page 6:

Cause of death was classified by local MBRRACE-UK reporters at each hospital using the Cause of Death and Associated Conditions (CODAC) classification system into the following first level categories: Infection, Intrapartum, Congenital Anomaly, Fetal, Cord Related, Placental Related, Maternal, or Unknown.

In addition, we have altered our sentence related to the exclusion of congenital anomalies on page 7 to make this clear:

Causes of death were examined before and after exclusion of stillbirths where the primary cause of death was congenital anomalies, because of the association with access and choices surrounding termination of pregnancy for fetal anomaly.

In text as well as abstract, be consistent with including 95% CI when reporting point estimates and confidence intervals. This is true both for prevalence rates and for odds ratios.

We thank the reviewer for noticing this inconsistency and have amended throughout.

In Table 1, where gestation is reported, it makes more sense to report this in terms of fetuses at risk if possible.

We agree with this statement but to avoid confusion with the other factors we have decided to remove the data on stillbirth by gestational age as it is less relevant to the messages of the paper and is not explored elsewhere (Table 1).

Regarding Table 2 and the accompanying text, did the authors do any tests for interaction or effect modification? The change in estimate from base model to multivariable model is large enough that some evaluation should be done.
It is also not clear from this table what is adjusted, and whether other covariates (for example nativity) were controlled.

Two-way interactions between covariates were explored and we have detailed this in the methods (P7) and also in the results section (P12). In Table 2 the base models are models fitted separately for each of the main factors but are all adjusted for country of residence and year of birth. The Multivariable model includes all of the main factors and country of residence and year of birth. We have tried to clarify this in the methods (P7) and in the footnote for Table 2.

Given the nature of the findings, too much data are reported in the results, as well as in the tables. The authors should highlight key findings, and refer the reader to tables and graphics for details.

We have gone through the results and reduced the results that are highlighted in the text to the key findings, referring the reader to tables and graphics where appropriate

The figures are hard to read, and might be more effective converted into tables. This will also convey more statistical information to the reader.

We believe that figures 2 and 3 display the overall patterns of the data which can be missed in a table but also provide detail that would be contained in an equivalent table (their clarity is welcomed by reviewer 1). However, we recognise that such data are limited for figure 1 and so have provided an additional table for the supplementary materials to display this statistical detail.

The discussion section length seems appropriate. A greater focus on how nativity contributes, independent of ethnicity or in concert, would be helpful. on p 15 line 42, its not clear how this study truly disaggregates groups by culture, religion and other characteristics.

We are unable to disaggregate data by country of birth or religion or culture but have recognised this limitation in the discussion. However, we feel that this analysis which allows more refined detail around ethnicity compared to previous studies does allow some increased, be it limited, awareness of differences that may arise from culture and religion. We have tried to clarify this in the section quoted by the reviewer (P14).

In the last paragraph of the discussion, its nice to see a call out to ISA and the CODAC classification, but given it was published in 2009 its no longer a 'new' classification system - just not that widely used.
We have clarified that this new system being developed is not CODAC itself but a new hybrid system and have highlighted appropriate references.

Finally, in the author contributions, it should read 'principal' rather than 'principle', and in the references, its not necessary to list when items were first published online unless they do not yet have formal publication volume and page numbers.

We have amended these.

VERSION 2 – REVIEW

REVIEWER	Russell Kirby University of South Florida, Community and Family Health
REVIEW RETURNED	17-Dec-2021

GENERAL COMMENTS	The authors have done a nice job in revising the manuscript to reflect reviewer and editor comments. I have no further comments on the text. I'm still not convinced that the graphical presentations (especially Figures 2 and 3) are needed - the data are also included in the figure and a table might make comparisons easier, but if the editor is ok with these, I am as well. If the authors plan additional work, it might be worthwhile to drill down to early and late preterm fetal mortality, as there could be some interesting differences by ethnicity and underlying cause. And I understand the inaccessibility of maternal nativity, but that is also a good area for additional research.