PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Population characteristics, mechanisms of primary care and premature mortality in England: a cross-sectional study
AUTHORS	Baker, Richard; Honeyford, Kate; Levene, Louis; Mainous III, Arch; Jones, David; Bankart, M. John; Stokes, Tim

VERSION 1 - REVIEW

REVIEWER	Mark Ashworth King's College London
REVIEW RETURNED	01-Oct-2015

GENERAL COMMENTS	This is a strong paper. Firstly, the study comes to a clear conclusion reminiscent of the findings of a Barbara Starfield study, in identifying the role of primary care as a determinant of (reducing) premature mortality. Two organisational primary care factors were identified: supply (GPs per 1000 population) and access (patient reported); one clinical factor was identified: detection of hypertension. There is a need for primary care research which, in essence, updates the earlier findings of Starfield. Secondly, this study conducts a cross-sectional analysis but then tests the stability of the regression model over three different years. One quibble is the selection of diabetes as the sentinel LTC chosen to represent the burden of morbidity within a practice. This is reasonable as far as it goes. But DM prevalence is not really representative of all morbidity prevalence. A better indicator of morbidity would have been a composite indicator of 8 LTCs which can be obtained from one of the QOF indicators (one of the Smoking domain indicators combines the number of patients registered with one or more of 8 selected LTCs). No reanalysis is required but it might be worth including this alternative in the Discussion as a potential limitation. Similarly, the selection of QOF indicators to describe the 'prevention, detection and management' of primary care seemed limited (pg6). For 'detection', the only conditions included were AF and Hypertension. The Association of Public Health Obervatories publish data on each GP practice in England, and estimates of prevalence shortfalls for several LTCs (observed vs expected prevalence) but it is unclear why just two conditions were included. Also why only two prevention activities were included. Similarly, the selection of jsut 4 'intermediate outcome' indicators seems rather arbitrary (pg6, line 35). Again, I dont consider further analysis is required but these potential limitations should be included in the Discussion. Statistical methods: the authors are to be congratulated for their

	careful construction of regression models including use of a log transformed outcome variable (distribution of premature SMR) (Pg7, line 10) and the use of regression diagnostics. However, I did not understand the phrase: 'no formal adjustment of multiplicity was made'. Does this mean that the authors opted not to conduct multi-level modelling? This should be clarified. Ideally a there should at least be adjustment for clustering at CCG level since many public health measures which could affect premature mortality rates are promoted at CCG level. Results: details about the sample of 8290 practices but inclusion of just 7858 in the final analysis are repeated in both Methods and Results section. This need only be stated once. Discussion: I think the authors could explain the counter-intuitive finding that white ethnicity was associated with higher mortality, once adjusted for deprivation. This is surprising considering excess DM and CVD morbidity in ethnic minority populations. The authors comment that their measure of 'efficiency', practice size, did not predict mortality (line31, pg9). Practice size is a dubious measure of efficiency. And the relationship is hardly likely to be linear - there is probably an optimal sized practice with smaller or larger sizes than the optimal size being relatively less efficient. It is likely that the employment or level of skill of a practice manager is a more direct measure of efficiency although this data is not readily available. Tables: distortions can be introduced into regression equations by outliers. Some of the variables included as predictor variables contain extreme outlier practices. For example, some practices had zero GPs per 1000 registered patients (Table 1) and I would have thought those practices should be excluded; similarly some had zero patients with AF (diagnosed since 2008) which is plausible but should be dealt with by inclusion in the regression equation as 'block variables', or similar. A similar consideration applies to the practices with zero patients achieving the CKD03 indicator. I would prefer re-analysis of the regression models based on these issues (or independent consultation with a statistical referee). Table 2: regression coefficients. The Beta values for the predictor variables are presented. The Beta of 0.000159 should be presented as Beta <0.01 (otherwise a false impression of accuracy to 5 decimal places is conveyed). Similarly other coefficients should only be displayed to 2 decimal places. If the authors do agree to minor modifications of their regression modelling, I would ask them to consider including a different measure of practice morbidity. Table 2 highlights the problem: the Beta value is high for DM prevalence. But it begs the question, what about the prevalence of other LTCs. The denominator for the Smoking 5 indicator, a composite measure of 8 LTCs really would be far preferable. Table 2: Achievement of 3 of the 4 selected clinical management indicators are paradoxically associated with worse premature mortality. In some ways, this is very disappointing. It appears that the achievement of demanding clinical QOF targets has resulted in increased premature mortality. The authors offer only one explanation: "The measures of clinical management had only small

	and inconsistent relationships to mortality, and were not stable over the three years investigated. A potential explanation is the only limited variability in performance between practices that the QOF has engendered." But the Beta values in Table 2 really were very small: all <0.09. This highlights though another issue with the interpretation of the findings. The authors emphasise the importance of the finding concerning access even though the Beta value was just 0.06. They they discount the findings about 'clinical management' because the Beta values were 'small'. This is inconsistent. It would be better to take the approach that any Beta <0.1 may well be statistically significant but the effect size is so small that it should be discounted. If we adopt this approach, Supply of GPs is the strongest predictor by a long way (Beta -4.31), followed by Deprivation (Beta 1.81), followed by the DM prevalence indicator (Beta 1.30) (but see comments above about this variable). These are the three strongest predictors of premature mortality. The other factors are much, much less powerful predictors. Finally, this brings me to the theoretical model. Its a good model. It has already been tested. But these results appear to have been interpreted in a way which provides too much support for the original model. The model has not been rejected. But the strength of the predictors of premature mortality is mainly confined to just three factors: GP supply, deprivation, morbidity burden. A story built around these three factors would be a stronger story than one built on the various components of the original model.

REVIEWER	Davide Rasella Fiocruz - Brasilia. Brazil
REVIEW RETURNED	27-Oct-2015

GENERAL COMMENTS	This is an interesting and relevant paper which uses a relatively simple study design to assess the impact of several aspects of primary care and of socioeconomic variables on amenable mortality in England. Considering its usefulness, a journal such as BMJ open can be a right place for this kind of paper, having this manuscript relevance in particular for epidemiologists and policymakers. Very interesting and meaningful the estimation of impact at the national level. The main limitation of the study is related to the study design. QOF and patient survey data from 2009/10 were used as explanatory variables for mortality data from the period 2006-2010 (the average mortality rate of the period). The cross-sectionality of the analysis is acceptable with no option for longitudinality, but here the outcome is - for the 50% - before the period of the exposure. This limitation has been discussed, but in order to convince the reader some additional explanations should be given: should the explanatory variables be considered constant during the period 2006-2010 (so the 2009-10 values are similar to 2006-08 values)? Even if data from the 2007/8 cannot be used, maybe some other ecologic-level data can suggest that there were not relevant trends which could have biased the analysis. Another option could be a sensitivity analysis using as outcome the mortality from 2009 to 2010, which is probably less stable but can suggest similar estimates.

	Other minor revisions are the following: p.5 line 2: please better explain MSOA. p.5 line 14. I cannot find Figure 1, is the one in the appendix section? It seems to have a table format with some empty compartment, could it be made a little bit more clear/simple? Maybe dividing some elements in separate compartments? p5.line 34. Please better explain why for health outcomes data at the MSOA level have been considered and for IMD at the LSOA level. p6 line 54. Please explain: No formal adjustment for multiplicity was made . p7. line 5. Please delete the phrase: Counts of deaths were not available, and it was not possible to use a count model. A Poisson or Negative Binomial model - with the denominator of the rate as offset - could have been used. This is discussed in the limitations session as well. Linear regression is a reasonable choice, and considering that regression diagnostics were positive, can be considered correct as well. p8. line 36. not clear how "The SMR is the ratio of the observed to expected number of deaths, the expected number of deaths being calculated using age-specific death rates for England" can be 103, is it expressed in terms of percentages (103%?). Please also provide a reference of some paper which uses this measure of preventable mortality , as others lists of amenable mortality are available (Nolte and McKee (2008) and Tobias and Yeh (2009) - see http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DELSA/HEA/WD/HWP(2011)1&docLanguage=En).

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a strong paper.

Firstly, the study comes to a clear conclusion reminiscent of the findings of a Barbara Starfield study, in identifying the role of primary care as a determinant of (reducing) premature mortality. Two organisational primary care factors were identified: supply (GPs per 1000 population) and access (patient reported); one clinical factor was identified: detection of hypertension. There is a need for primary care research which, in essence, updates the earlier findings of Starfield.

Secondly, this study conducts a cross-sectional analysis but then tests the stability of the regression model over three different years.

One quibble is the selection of diabetes as the sentinel LTC chosen to represent the burden of morbidity within a practice. This is reasonable as far as it goes. But DM prevalence is not really representative of all morbidity prevalence. A better indicator of morbidity would have been a composite indicator of 8 LTCs which can be obtained from one of the QOF indicators (one of the Smoking domain indicators combines the number of patients registered with one or more of 8 selected LTCs). No reanalysis is required but it might be worth including this alternative in the Discussion as a potential limitation.

The choice of diabetes prevalence as a measure of the burden of morbidity in a practice is indeed a limitation. Alternative measures of morbidity include the response to the patient survey regarding self-reported long term conditions, but unfortunately this question was not included until 2012. The denominator of the smoking indicator also gives an estimate of the practice population who have one of 8 chronic conditions. However, the most prevalent chronic condition in this set of conditions is hypertension, which is included in the model as a measure of detection. The percentage of the practice population who have a chronic condition as determined by the smoking indicator and hypertension prevalence based on QOF registers are highly correlated ($R_p=0.94$, $p<0.0001$). Including this measure in the model introduces multicollinearity. We accept the limitation of using diabetes as a measure of morbidity burden and have highlighted this in the text, but in the model we

have used do not feel there is a useful alternative. We have added a comment on this issue to the limitations section of the discussion. We now also quote Barnett et al, Lancet 2012, which shows the high incidence of co-morbidity among people with diabetes.

Similarly, the selection of QOF indicators to describe the 'prevention, detection and management' of primary care seemed limited (pg6). For 'detection', the only conditions included were AF and Hypertension. The Association of Public Health Obervatories publish data on each GP practice in England, and estimates of prevalence shortfalls for several LTCs (observed vs expected prevalence) but it is unclear why just two conditions were included. Also why only two prevention activities were included. Similarly, the selection of jsut 4 'intermediate outcome' indicators seems rather arbitrary (pg6, line 35). Again, I dont consider further analysis is required but these potential limitations should be included in the Discussion.
We took the indicators for prevention and management from Ashworth et al. The Public Health Impact score: a new measure of public health effectiveness for general practices in England. Br J Gen Pract 2013; DOI: 10.3399/bjgp13X665260. We selected those indicators predicted in this paper to have the highest mortality effect (see table 1 of this paper). We have now included more details about this in the paper (page 6). We also state that we limited the number of indicators in order to reduce the risk of finding spurious associations. Our previous studies had shown that hypertension detection predicted coronary heart disease and stroke mortality rates in England (see Levene et al. Association of features of primary care with coronary heart disease mortality. JAMA 2010;304:2028-2034, & Levene et al. Association of Primary Care Characteristics with variations in mortality rates in England: An Observational Study. PLoS ONE 2012;7(10): e47800. doi:10.1371/journal.pone.0047800, & Honeyford et al. Modelling factors in primary care quality improvement: a cross-sectional study of premature CHD mortality. BMJ Open 2013;3:e003391 doi:10.1136/bmjopen-2013-003391).

Statistical methods: the authors are to be congratulated for their careful construction of regression models including use of a log transformed outcome variable (distribution of premature SMR) (Pg7, line 10) and the use of regression diagnostics. However, I did not understand the phrase: 'no formal adjustment of multiplicity was made'. Does this mean that the authors opted not to conduct multi-level modelling? This should be clarified. Ideally a there should at least be adjustment for clustering at CCG level since many public health measures which could affect premature mortality rates are promoted at CCG level.
We have not made formal corrections for there being multiple p-values and confidence intervals cited,and have therefore aimed to avoid over-interpretation of the uncorrected values. We have added adjusted the wording in the text to improve clarity (page 7).
A multi-level model approach was not considered in this case as the role of PCTs was not considered to be key in the theoretical model. We accept the reviewer’s comments that the clustering effect of PCTs (CCGs came in after the period of study) and have modified the statistical model to take this into account. We have used the same approach as Calderon-Larranga et al (2014).
Results: details about the sample of 8290 practices but inclusion of just 7858 in the final analysis are repeated in both Methods and Results section. This need only be stated once.
We have removed the reporting of the exclusions from the methods section.

Discussion: I think the authors could explain the counter-intuitive finding that white ethnicity was associated with higher mortality, once adjusted for deprivation. This is surprising considering excess DM and CVD morbidity in ethnic minority populations.
All minority ethnic groups are more likely to live in deprived neighbourhoods (Jivraj S, Khan O. Ethnicity and deprivation in England: How likely are ethnic minorities to live in deprived neighbourhoods? Centre on Dynamics of Ethnicity (CoDE). University of Manchester, 2013). The effect of adjusting for deprivation on the mortality of different ethnic groups has been noted in other studies, and is thought, potentially, to be explained by characteristics of the IMD, and possibly, inconsistencies in the recording of ethnicity (Association of Public Health Observatories. Indications of

Public Health in the English Regions. 4: Ethnicity and Health. http://www.apho.org.uk/resource/view.aspx?QN=IND_SERIES (accessed 11/11/15). We have added a comment on this issue to the text, plus a reference.

The authors comment that their measure of 'efficiency', practice size, did not predict mortality (line31, pg9). Practice size is a dubious measure of efficiency. And the relationship is hardly likely to be linear - there is probably an optimal sized practice with smaller or larger sizes than the optimal size being relatively less efficient. It is likely that the employment or level of skill of a practice manager is a more direct measure of efficiency although this data is not readily available.
We did not have a good variable for efficiency; there has been little research into efficiency of general practice, and practice size may not be a good indicator of efficiency (see Ala Szczepura Carol Davies Joy Fletcher Aziz Boussofiane, (1993),"Efficiency and Effectiveness in General Practice", Journal of Management in Medicine, Vol. 7 Iss 5 pp. 36 – 47). Nevertheless, the numbers of small practices is declining, and the size of practices is increasing, and a recent review of the quality of general practice recognised that 'general practice will need to operate at a scale commensurate with the demands placed upon it' (The King's Fund. Improving the quality of care in general practice Report of an independent inquiry commissioned by The King's Fund. London: The King's Fund, 2011).
We accept that the relationship between practice size and efficiency may not be linear, and sensitivity analysis suggests that when practice size is included as a categorical variable, indicating the smallest 10%, there is a significant association with premature mortality. We have included a short description of this in the results section.

Tables: distortions can be introduced into regression equations by outliers. Some of the variables included as predictor variables contain extreme outlier practices. For example, some practices had zero GPs per 1000 registered patients (Table 1) and I would have thought those practices should be excluded; similarly some had zero patients with AF (diagnosed since 2008) which is plausible but should be dealt with by inclusion in the regression equation as 'block variables', or similar. A similar consideration applies to the practices with zero patients achieving the CKD03 indicator. I would prefer re-analysis of the regression models based on these issues (or independent consultation with a statistical referee).
The challenge of determining a cut off for the exclusion of practices based on GP supply was discussed between the authors extensively. Excluding practices with zero GPs per 1000 patients has no impact on model results; this is now included in the sensitivity analysis. 30 practices have zero GPs per 1000 patients, although it could be argued that these could justifiably be excluded from the analysis a decision would then need to be made as to whether other practices with exceptionally low or high GPs per 1000 patients should be included in the analysis and an arbitrary cut off would need to be determined. Since we were unable to identify a justifiable cut off point, we decided that the most transparent approach was to include all practices in the principal analysis, a similar approachwas used by Soljak et al (2011) [Does higher quality primary health care reduce stroke admissions? a national cross-sectional study. Michael Soljak, Amaia Calderon-Larrañaga, Pankaj Sharma, Elizabeth Cecil, Derek Bell, Gerrard Abi-Aad, Azeem Majeed Br J Gen Pract Dec 2011, 61 (593) e801-e807; DOI: 10.3399/bjgp11X613142].

Some practices did have zero underlying achievement for some QOF indicators; we made the decision to include all general practices that had valid data for all the explanatory variables included in the model. There is no suggestion that zero underlying achievement for these indicators is an error in the data. Practices which had no patients to which the indicator applied and therefore had zero underlying achievement were excluded as this did not indicate low care. An alternative modelling approach would be to divide the practices into quintiles for each QOF indicator (high achieving, middle achieving, low achieving etc.), but there are disadvantages in converting continuous variables into categorical variables and this option would introduce between 7 and 28 additional variables dependent on the modelling approach used.

Table 2: regression coefficients. The Beta values for the predictor variables are presented. The Beta of 0.000159 should be presented as Beta <0.01 (otherwise a false impression of accuracy to 5 decimal places is conveyed). Similarly other coefficients should only be displayed to 2 decimal places. We have not altered the presentation of the Beta values (see below).
If the authors do agree to minor modifications of their regression modelling, I would ask them to consider including a different measure of practice morbidity. Table 2 highlights the problem: the Beta value is high for DM prevalence. But it begs the question, what about the prevalence of other LTCs. The denominator for the Smoking 5 indicator, a composite measure of 8 LTCs really would be far preferable.
This has been discussed above. A composite measure would be preferable, but the inclusion of QOF based hypertension prevalence as a measure of detection in the model means any measure of morbidity that is based on a composite measure including hypertension prevalence introduces collinearity into the model.

Table 2: Achievement of 3 of the 4 selected clinical management indicators are paradoxically associated with worse premature mortality. In some ways, this is very disappointing. It appears that the achievement of demanding clinical QOF targets has resulted in increased premature mortality. The authors offer only one explanation: "The measures of clinical management had only small and inconsistent relationships to mortality, and were not stable over the three years investigated. A potential explanation is the only limited variability in performance between practices that the QOF has engendered."
The only additional explanation we have for the improvement in QOF clinical scores and increase in mortality is a volume outcome argument – an increase in volume is associated with an improvement in quality of care, in which case the indicators may reflect prevalence (Millett C, Car J, Eldred D, Khunti K, Mainous III AG, Majeed A. Diabetes prevalence, process of care and outcomes in relation to practice size, caseload and deprivation: national cross-sectional study in primary care. J R Soc Med 2007;100:275–283). We have now added a comment to this effect (page 10).
But the Beta values in Table 2 really were very small: all <0.09. This highlights though another issue with the interpretation of the findings. The authors emphasise the importance of the finding concerning access even though the Beta value was just 0.06. They discount the findings about 'clinical management' because the Beta values were 'small'. This is inconsistent. It would be better to take the approach that any Beta <0.1 may well be statistically significant but the effect size is so small that it should be discounted. If we adopt this approach, Supply of GPs is the strongest predictor by a long way (Beta -4.31), followed by Deprivation (Beta 1.81), followed by the DM prevalence indicator (Beta 1.30) (but see comments above about this variable). These are the three strongest predictors of premature mortality. The other factors are much, much less powerful predictors.
We do need to be consistent in how we discuss beta coefficients which are related to percentages, but the beta coefficient of GPs/1000 and deprivation with beta coefficients for percentage achieved cannot be compared as they are describing a different magnitude of effect. We didn't standardise the explanatory variables, and therefore cannot use a beta-coefficient cut off. We agree that there was too much emphasis on access given the size of the beta coefficient, and have deleted mention of the access finding from the abstract and qualified the mention of the finding in the discussion.

Finally, this brings me to the theoretical model. Its a good model. It has already been tested. But these results appear to have been interpreted in a way which provides too much support for the original model. The model has not been rejected. But the strength of the predictors of premature mortality is mainly confined to just three factors: GP supply, deprivation, morbidity burden. A story built around these three factors would be a stronger story than one built on the various components of the original model.
We have revised sections in the discussion section, removing the opening statement in the discussion on the model, removing the emphasis on access, and focusing more on deprivation, morbidity, and GP supply.

Reviewer: 2

This is an interesting and relevant paper which uses a relatively simple study design to assess the impact of several aspects of primary care and of socioeconomic variables on amenable mortality in England.
Considering its usefulness, a journal such as BMJ open can be a right place for this kind of paper, having this manuscript relevance in particular for epidemiologists and policymakers.
Very interesting and meaningful the estimation of impact at the national level.

The main limitation of the study is related to the study design. QOF and patient survey data from 2009/10 were used as explanatory variables for mortality data from the period 2006-2010 (the average mortality rate of the period). The cross-sectionality of the analysis is acceptable with no option for longitudinality, but here the outcome is - for the 50% - before the period of the exposure. This limitation has been discussed, but in order to convince the reader some additional explanations should be given: should the explanatory variables be considered constant during the period 2006-2010 (so the 2009-10 values are similar to 2006-08 values)? Even if data from the 2007/8 cannot be used, maybe some other ecologic-level data can suggest that there were not relevant trends which could have biased the analysis. Another option could be a sensitivity analysis using as outcome the mortality from 2009 to 2010, which is probably less stable but can suggest similar estimates.
This limitation is now highlighted in the text. Analysis has shown that care incentivised within QOF rapidly improved in the two years prior to the introduction of QOF and in the first two to three years after the introduction to QOF and that results have been relatively stable since then. See: Doran T1, Kontopantelis E, Valderas JM, Campbell S, Roland M, Salisbury C, Reeves D. Effect of financial incentives on incentivised and non-incentivised clinical activities: longitudinal analysis of data from the UK Quality and Outcomes Framework. BMJ. 2011 Jun 28;342:d3590. doi: 10.1136/bmj.d3590, and Doran Tim, Kontopantelis Evangelos, Reeves David, Sutton Matthew, Ryan Andrew M. Setting performance targets in pay for performance programmes: what can we learn from QOF? 2014; 348 :g1595.
Mortality data for 2009/10 only are not available.

Other minor revisions are the following:
p.5 line 2: please better explain MSOA.
We have revised the text and hope the explanation is now clearer.

p.5 line 14. I cannot find Figure 1, is the one in the appendix section? It seems to have a table format with some empty compartment, could it be made a little bit more clear/simple? Maybe dividing some elements in separate compartments?
Not sure what happened here – it appears to have reached reviewer 1.
p5.line 34. Please better explain why for health outcomes data at the MSOA level have been considered and for IMD at the LSOA level.
The IMD is reported by the Office for National Statistics at LSOA level, and these data were used by the Health and Social Care Information Centre to calculate the practice IMD scores. A LSOA has fewer people than a MSOA; whilst a unit of the size of a MSOA provides more stable mortality data, a LSOA can provide more detailed data on deprivation. We have added a comment to the text on this point.
p6 line 54. Please explain: No formal adjustment for multiplicity was made . See above.
See response above to reviewer 1.
p7. line 5. Please delete the phrase: Counts of deaths were not available, and it was not possible to use a count model. A Poisson or Negative Binomial model - with the denominator of the rate as offset - could have been used. This is discussed in the limitations session as well. Linear regression is a

reasonable choice, and considering that regression diagnostics were positive, can be considered correct as well.
We have deleted this text.
p8. line 36. not clear how "The SMR is the ratio of the observed to expected number of deaths, the expected number of deaths being calculated using age-specific death rates for England" can be 103, is it expressed in terms of percentages (103%?). Please also provide a reference of some paper which uses this measure of preventable mortality , as others lists of amenable mortality are available (Nolte and McKee (2008) and Tobias and Yeh (2009) - see http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DELSA/HEA/WD/HWP(2011)1&docLanguage=En).
The figure for SMR we give is a median, not a mean; it relates to the median SMR value of the 7858 practices in the study, and therefore may not be 100. We now include a reference to a paper from the Office of National Statistics that presents data for England and discusses which measure is most appropriate; the paper's authors concluded that an age threshold of 75 years was most useful in England for defining premature death (Levin Wheller, Allan Baker and Clare Griffiths,.Trends in premature mortality in England and Wales, 1950–2004. Heal th Stat i s t i c s Quarterly 2006;31:34-41).

VERSION 2 – REVIEW

REVIEWER	Mark Ashworth King's College London
REVIEW RETURNED	09-Dec-2015

GENERAL COMMENTS	This paper has been extensively revised, including re-working of the Results (further sensitivity analyses). The revisions address each of the points made by the Referees. I think that the revised manuscript is now a strong paper on an important subject - premature mortality rates in primary care, and the determinants of premature mortality. I am satisfied with the revisions.

REVIEWER	Davide Rasella Postdoctoral Researcher, Fiocruz Institute, Rio de Janeiro, Brazil.
REVIEW RETURNED	24-Dec-2015

GENERAL COMMENTS	My concerns have been adequately addressed by the authors in this manuscript review. I recommend the publication of the manuscript as it is.