PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of chronic kidney disease and cardiovascular comorbidity on mortality in a multi-ethnic population: a retrospective cohort study
AUTHORS	Jesky, Mark; Lambert, Amanda; Burden, AC Felix; Cockwell, Paul

VERSION 1 - REVIEW

REVIEWER	Rohini Mathur Research Fellow Centre for Primary Care & Public Health QMUL
REVIEW RETURNED	02-Aug-2013

THE STUDY	Patient Selection 1. The study sets out to explore the relationship between CKD, cardiovascular comorbidity and mortality. The background covers the relevant literature, however it might be useful to explicitly state any hypotheses the authors have about the expected results, if they have any. 2. The population of interest excludes all individuals without a renal function test in the previous 12 months. Is there any reason that a longer time period was not used (ie/ renal function tests in the past 2 years for example). It may be that individuals with normal kidney function (eGFR>60) results may not be tested as frequently, and thus be excluded from your eligible population and limit the representativeness of the study population. 3. Though it is likely that all patients with CKD will have had a renal function test in this time period, did any patients have a CKD code but no renal function test in the previous year? 4. Did the ethnic breakdown of patients with renal function tests match the ethnic breakdown of the source population? If not, what are the hypothesized reasons for differential testing between groups. 5. It is unclear from the flow diagram whether patients on renal replacement therapy/dialysis were excluded from the study cohort? What happened to patients who started RRT during the follow up period? 6. Were all patients included at the beginning of the study in May 2008 present for the entire period of follow up? Did the proportion of patients censored (if any) vary by ethnic group.

	7. The authors should specify whether diabetes was Type 1 and Type 2 combined, or just one of the two.
RESULTS & CONCLUSIONS	1. The prognostic value of the cumulative multimorbidity on mortality risk is very interesting. If time and resources permit, it would be very interesting to know if certain combinations of co-morbidities drive the ethnic differences in mortality. For example the relationship between diabetes and CKD is well established- it would be valuable to have some commentary how your study adds to the literature in this area. 2. If the data you have has dates of first diagnosis for the co-morbidities, it would be valuable to explore the relationship between the duration of the co-morbidities and mortality risk. This may yield a pattern as important as that of the cumulative burden. We know that South Asian groups have earlier onset of diabetes, incorporating a measure of this may further explain the relationships shown in the paper. 3. The study has shown a lower risk of mortality in non-white ethnic groups as suggested in previous literature, however the discussion does not expand on reasons as to why this finding may be. In addition to the genetic factors suggested by the authors, are there any health system level factors which may may cause this difference (ie/ more timely treatment of severe CKD in certain ethnic groups). 4. Did the dataset include any information on medication prescribing for the patients- treatment with non-steroidal drugs or ACE/ARB for example may impact on the relationship of interest between CKD, co-morbidity and mortality. 5. The discussion highlights that the lack of differences by deprivation are unusual, however recent studies across London which serve similarly ethnically diverse and deprived communities have also shown very little relationship with deprivation in similar primary care based studies.

REVIEWER	Dietrich Rothenbacher, MD, MPH Institute of Epidemiology and Medical Biometry Ulm University
REVIEW RETURNED	06-Aug-2013

THE STUDY	The representativeness of the patients is difficult to assess yet. Further analysis necessary to clarify this point.
RESULTS & CONCLUSIONS	Needs further evaluation - how representative is the analysis population?
GENERAL COMMENTS	Jesky and colleagues used data of an inner-city primary care trust in West Midlands, UK, to investigate the prognostic value of estimated CKD on all cause-mortality and especially investigated the influence of ethnicity. They found lower risk for South Asian and black individuals compared to white after adjustment for various cofactors. The results were quite stable also after adjustment for CKD, eGFR, and comorbidity. Surprisingly, they found no association with SES. eGFR as well as ACR should an association with mortality after adjustment for covariates. The study is important as it covers a population of which we usually do not have much data and of which the health related issues are not well studied yet. The following points deserve further specification:

	Introduction - The introduction should also provide some basic information related to the performance of the estimating equations in various ethnic groups – alternatively this issue can be considered and examined in the discussion section in the context of the findings of the study. Methods - Figure 1 should separate the two categories “Individuals below 40 years or no renal function within previous 12 months = 238,954” and indicate how many subjects were excluded because of the one and because of the other factor. This is a very critical issue as from the population for included practices with n = 278,749 only 39,795 were included. It is very important to show how many were excluded because of age, an exclusion criterium, or how many had no renal function measured. This step is critical for the validity of the study and therefore the population should be compared also with respect to main sociodemographic and other influential factors. - What was the reason to measure GFR – can this be explained in more detail. Which role may “confounding by indication” play? - How was ethnicity evaluated (which categories and explanations were given)? - Please spell out how the eGFR was estimated. Which estimating equation was used? - Please specify how the proportionality assumption was assessed? - According to which criteria were the variables chosen into the models? How was the model validity assessed? - The authors should also consider other measures quantifying the prognostic value of specific factors by means of model fit, discrimination, reclassification, and calibration measure. E.g. what added value has ethnicity beside the demonstrated measures of association in the fully adjusted models? Results - Please specify how long the follow-up time was? - It is unclear to me why table I is in the supplement. Isn’t this the main table? - Figure 2 should also display a table below the plot that indicates how many subjects are still included during the FU-timer. Discussion - The value of self-reported ethnicity should be discussed further. What do the authors believe is mainly measured? Sociocultural or biological factors? The concept and the way to measure it accurately should be discussed further. An important issue is the attrition from the overall sample size to the analysis sample. It should be discussed in more detail how the populations differ and what the possible bias on the overall results may be. - Please also discuss the implications of the findings.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Rohini Mathur
Research Fellow
Centre for Primary Care & Public Health
QMUL

Patient Selection
1. The study sets out to explore the relationship between CKD, cardiovascular comorbidity and mortality. The background covers the relevant literature, however it might be useful to explicitly state any hypotheses the authors have about the expected results, if they have any.

Authors' reply
Thank you for the comment. There were two key hypotheses:
There are differences in mortality risk between the ethnic groups.
Any differences in mortality risk between the ethnic groups are explained by known risk factors including comorbidities, renal function, demographic and socioeconomic factors

2. The population of interest excludes all individuals without a renal function test in the previous 12 months. Is there any reason that a longer time period was not used (ie/ renal function tests in the past 2 years for example). It may be that individuals with normal kidney function (eGFR>60) results may not be tested as frequently, and thus be excluded from your eligible population and limit the representativeness of the study population.

Authors' reply
The twelve month period chosen is a reflection of the National Institute of Health and Clinical Excellence Guidelines [http://www.nice.org.uk/cg73] for CKD for the period during which the study was carried out. Extending the period to 2 years identified an additional 164 (<0.1%) people for the analysis. A comment regarding people with a higher eGFR perhaps having renal function tested less often has been added to the discussion.

3. Though it is likely that all patients with CKD will have had a renal function test in this time period, did any patients have a CKD code but no renal function test in the previous year?

Authors' reply
An interesting question which our dataset was unable to answer, as having one's eGFR checked was necessary to be included in the dataset. We have looked at this in a later 2011 dataset (unpublished) and have found that 1543/6501 (19.2%) people on the CKD register for the population under study had not had their renal function recorded in the last 12 months. We have emphasised this (together with the relative paucity of literature on the accuracy of risk registers) in the discussion.

4. Did the ethnic breakdown of patients with renal function tests match the ethnic breakdown of the source population? If not, what are the hypothesized reasons for differential testing between groups.

Authors' reply
The ethnic background in the source population was different to the ethnic breakdown of individuals with renal function tests done. This suggests individuals of white ethnicity are relatively under-represented in the data. We have added possible reasons for this to the discussion section.

Ethnicity, aged 16 years and over.

n (in thousands) Percent

White 86.8 41.0
Asian 79.8 37.7
Black 29.7 14.0
Mixed 6.7 3.2
Other 8.7 4.1
Total 211.7 100

Source: [http://www.ons.gov.uk/ons/taxonomy/index.html?nscl=
Population+Estimates+by+Ethnic+Group]

5. It is unclear from the flow diagram whether patients on renal replacement therapy/dialysis were excluded from the study cohort? What happened to patients who started RRT during the follow up period?

Authors' Reply
We excluded people with an eGFR ≤ 15ml/min (stage 5 CKD) as this will have included people receiving dialysis treatment. Analysis of the data identified 98 people with stage 5 CKD. The mean eGFR at commencing dialysis in the UK in 2011 was 8.7 ml/min [renal registry data: http://www.renalreg.com/Reports/2012.html]. We excluded this group due to the different and competing mortality risk of this population.

6. Were all patients included at the beginning of the study in May 2008 present for the entire period of follow up? Did the proportion of patients censored (if any) vary by ethnic group.

Authors' Reply
Due to the way the dataset was collected, using the primary care mortality database, individuals were censored if they had moved away from a participating general practice during the study period. 11.1% (9,907/89,392) of the population aged 40 or over left a participating practice during this period. This information has been added to Figure 1. We do not have the information to comment whether this varied by ethnic group.

7. The authors should specify whether diabetes was Type 1 and Type 2 combined, or just one of the two.

Authors' Reply
Type 1 and 2 diabetes are combined in the dataset.

1. The prognostic value of the cumulative multimorbidity on mortality risk is very interesting. If time and resources permit, it would be very interesting to know if certain combinations of co-morbidities drive the ethnic differences in mortality. For example the relationship between diabetes and CKD is well established- it would be valuable to have some commentary how your study adds to the literature in this area.

Authors' Reply
The impact of multiple comorbidities on mortality and whether it varies with ethnicity is interesting.

There are different frequencies of individual vascular risk factors within each ethnicity (see Table 1). We have analysed the individual comorbidities in a multivariate analysis (ie. rather than as a cumulative score) and split this analysis by ethnicity. This showed comorbidities convey different risks of death within different comorbidity groups (HF in the white cohort; HF, AF and CHD in South Asian

Cohort; and diabetes in the black cohort). However we found it was the cumulative effect of comorbidities that carried the greatest prognostic implication and therefore elected to focus on this and emphasise the message that increasing cardiovascular comorbidities were independent determinants of a higher mortality risk.

2. If the data you have has dates of first diagnosis for the co-morbidities, it would be valuable to explore the relationship between the duration of the co-morbidities and mortality risk. This may yield a pattern as important as that of the cumulative burden.

We know that South Asian groups have earlier onset of diabetes, incorporating a measure of this may further explain the relationships shown in the paper.

Authors' Reply
Unfortunately we do not have the date of first diagnosis and are unable to explore this further.

3. The study has shown a lower risk of mortality in non-white ethnic groups as suggested in previous literature, however the discussion does not expand on reasons as to why this finding may be. In addition to the genetic factors suggested by the authors, are there any health system level factors which may may cause this difference (ie/ more timely treatment of severe CKD in certain ethnic groups).

Authors' Reply
Thank you for this comment. We have expanded the discussion to include possible reasons for why this difference is not explained by the variables we analysed.

4. Did the dataset include any information on medication prescribing for the patients- treatment with non-steroidal drugs or ACE/ARB for example may impact on the relationship of interest between CKD, co-morbidity and mortality.

Authors' Reply
We have data for ACEi/ARB and statin use for the cohort. There are differences between use of ACEi/ARB between ethnicities, and we have included this as a possible reason for different outcomes in the discussion

5. The discussion highlights that the lack of differences by deprivation are unusual, however recent studies across London which serve similarly ethnically diverse and deprived communities have also shown very little relationship with deprivation in similar primary care based studies.

Authors' Reply
We have added to the discussion section on the subject of SES and mortality in predominantly deprived populations.

Reviewer: Dietrich Rothenbacher, MD, MPH
Institute of Epidemiology and Medical Biometry
Ulm University
89081 Ulm
Germany

No competing interests.

The representativeness of the patients is difficult to assess yet. Further analysis necessary to clarify this point.

Needs further evaluation - how representative is the analysis population?

Jesky and colleagues used data of an inner-city primary care trust in West Midlands, UK, to investigate the prognostic value of estimated CKD on all cause-mortality and especially investigated the influence of ethnicity. They found lower risk for South Asian and black individuals compared to white after adjustment for various cofactors. The results were quite stable also after adjustment for CKD, eGFR, and comorbidity. Surprisingly, they found no association with SES. eGFR as well as ACR should an association with mortality after adjustment for covariates. The study is important as it covers a population of which we usually do not have much data and of which the health related issues are not well studied yet.

Authors' Reply
Thank you for your comments regarding of study. We have attempted to address the points you raise below.

The following points deserve further specification:
Introduction
- The introduction should also provide some basic information related to the performance of the estimating equations in various ethnic groups – alternatively this issue can be considered and examined in the discussion section in the context of the findings of the study.

Authors' Reply
The performance of equations for estimated glomerular filtration rate with regards to ethnicity has been added to the discussion

Methods
- Figure 1 should separate the two categories "Individuals below 40 years or no renal function within previous 12 months = 238,954" and indicate how many subjects were excluded because of the one and because of the other factor. This is a very critical issue as from the population for included practices with n = 278,749 only 39,795 were included. It is very important to show how many were excluded because of age, an exclusion criterium, or how many had no renal function measured. This step is critical for the validity of the study and therefore the population should be compared also with respect to main sociodemographic and other influential factors.

Authors' Reply
We have added this information to Figure 1.
68.7% (195,829/285,221) individuals were below 40 years of age.
Of the 89,392 who were ≥ 40 years, 9,907 (11.1%) left a participating practice, 38,561 (43.1%) did not have their renal function checked within 12 months and an IDMS conversion for eGFR was not available in 1,129 (1.3%).

- What was the reason to measure GFR – can this be explained in more detail. Which role may "confounding by indication" play?

Authors' Reply
Thank you for this comment. Measurement of renal function is a key part of many of the QOF ('pay for performance') chronic disease registers within the UK primary care system and therefore individuals should have their eGFR checked. However, as you mentioned 'confounding by indication' may play a role with people with adverse health outcomes being seen more often and having more eGFRs. We have added this to the discussion section.

- How was ethnicity evaluated (which categories and explanations were given)?

Authors' Reply
Ethnicity was self reported and then amalgamated into five broad categories – Black, South Asian, White, Mixed, Other/not stated. We have used the first three in the analyses. One strength of our study lies with the high proportion of people with self-reported ethnicity stated (the 'gold standard' for classification) [ref: Saunders et al BMJ Open 2013].

- Please spell out how the eGFR was estimated. Which estimating equation was used?

Authors' Reply
eGFR was estimated using the MDRD equation and we have added this to the results section. As the serum creatinine was taken before IDMS standardisation, we have applied lab specific correction factors to take this into account.

- Please specify how the proportionality assumption was assessed?

Authors' Reply
Proportionality assumption was assessed and met for all covariates as the hazard of death was proportional over time. This was assessed using log(-log(survival function)) plots of all covariates. This has been added this to the manuscript

- According to which criteria were the variables chosen into the models? How was the model validity assessed?

Authors' Reply
The variables chosen in the models were based on those demographic factors and comorbidities that have been shown by other investigators as having associations with mortality in a primary care population and where that data was available in this the population that we have analysed in this study.

- The authors should also consider other measures quantifying the prognostic value of specific factors by means of model fit, discrimination, reclassification, and calibration measure. E.g. what added value has ethnicity beside the demonstrated measures of association in the fully adjusted models?

Authors' Reply
We have not used additional analyses to refine the prognostic value of specific factors (such as ethnicity) in this paper because the aim was not to develop a risk model for use in clinical practice focused on the additional prognostic value of each factor, but to describe overall relationships with outcomes in the cohort. We have made that more clear in the discussion section.

We are planning further work around developing a risk stratification tool from this model, however that would require an external validating population; we are currently in discussions around accessing such a population.

Results
- Please specify how long the follow-up time was?

Authors' Reply
The follow up period was from May 2008 until February 2011.

- It is unclear to me why table I is in the supplement. Isn't this the main table?

Authors' Reply
Thank you for the comment. Supplementary table I is looking at two different models for the Cox proportional hazards regression analysis. These tables were included to demonstrate the additional effect of eGFR and comorbidity prior to the final model including urinary ACR. We elected to place these in the supplemental data (rather than in the main body) with the aim of enhancing the readability.

- Figure 2 should also display a table below the plot that indicates how many subjects are still included during the FU-timer.

Authors' Reply
We have added this plot to Figure 2.

Discussion
- The value of self-reported ethnicity should be discussed further. What do the authors believe is mainly measured? Sociocultural or biological factors? The concept and the way to measure it accurately should be discussed further.

Authors' Reply
As you have highlighted, the research relies on self reported ethnicity. We have added the strengths and limitations of this to the discussion.

An important issue is the attrition from the overall sample size to the analysis sample. It should be discussed in more detail how the populations differ and what the possible bias on the overall results may be.
- Please also discuss the implications of the findings.

Authors' Reply
Attrition/ censored data due to people leaving the targeted primary care practices (and therefore not being identified from the primary care mortality database) have been included in the discussion section.

VERSION 2 – REVIEW

REVIEWER	Dietrich Rothenbacher Institute of Epidemiology and MEdical Biometry Ulm University
REVIEW RETURNED	23-Oct-2013

GENERAL COMMENTS	All my previous comments are addressed in an adequate manner.