PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | PREVENTING RENAL AND CARDIOVASCULAR RISK BY RENAL FUNCTION ASSESSMENT: INSIGHTS FROM A CROSS-SECTIONAL STUDY IN LOW-INCOME COUNTRIES AND THE US |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Remuzzi, Giuseppe; Cravedi, Paolo; Kumar Sharma, Sanjib; Flores Bravo, Rodolfo; Islam, Nazmul; Tchokhonelidze, Irma; Ghimire, Madhav; Pahari, Bishnu; Thapa, Sanjeev; Basnet, Anil; Tataradze, Avtandil; Tinatin, Davitaia; Fwu, Chyng-Wen; Kopp, Jeffrey; Eggers, Paul; Ene-Iordache, Bogdan; Carminati, Sergio; Perna, Annalisa; Chianca, Antonietta; Couser, William; Perico, Norberto |

VERSION 1 - REVIEW

| REVIEWER           | Li Zuo, M.D.  
| Institute of Nephrology,  
| Peking University First Hospital  
| China  
| I have no competing interests. |

| REVIEW RETURNED    | 30-May-2012 |

| THE STUDY          | 1. Is the research question clearly defined? No. the authors described the prevalence of CKD among 5 countries. But they did not tell the reader what their real aim of the study.  
|                    | 2. Is the overall study design appropriate and adequate to answer the research question? No. Becasue the sampling methods are difference in the 5 countries. and the prevalence is not comparable.  
|                    | 3. Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described? No. they participants were not clearly desceibed.  
|                    | 4. Are the patients representative of actual patients the evidence might affect? No. Because the sampling method is not clear.  
|                    | 5. Are the methods adequately described? No. we do not know how the participants were included or excluded.  
|                    | 6. Is the standard of written English acceptable for publication? No. Because of a few spelling mistake. |

| GENERAL COMMENTS   | This is a descriptive report. The authors descripted CKD in 5 nations. But the design of the report is problematic in that:  
|                    | (1) The method used to sample from the two general populations from low income countries is not clear. We do not know whether the samples were representative of the two countries. Also, the high risk population sampling method is not clear; they might also not representative of the two countries.  
|                    | (2) The authors had plenty of data in hand, but this descriptive analysis reporting the prevalence of CKD of the five countries in general population and in risk population is far away from reader’s interest.  
|                    | (3) A few spelling mistake. |
THE STUDY

The CONSORT checklist does not contain any information that should be better reported in the manuscript, and does not raise questions about the work. It is appropriate.

GENERAL COMMENTS

The authors report on their assessment of the prevalence of albuminuria and reduced kidney function based on screening programs in Nepal, Bolivia, the US, Bangladesh and Georgia. This is a well-written manuscript, based on a commendable effort to assess prevalence of kidney disease in both developed and developing countries. I have but a few comments and questions grouped by section of the manuscript.

Title: Would recommend revising to read, “…and the US”.

Summary/Key Messages: First sentence that begins, “We found that about a half of high-risk patients in has some…”. Please revise for clarity.

Methods: The authors state that diabetes status was defined based on history or current treatment for diabetes. Were medication lists of the participants available/reviewed? If so, it would be interesting to know what proportion of the subjects in each country were taking ACE inhibitors or ARBs.

Were serum creatinine measures calibrated in the same, standard manner in the different programs?

There appears to be significant differences in the age distributions of the programs examined; and the outcome data by age category is appreciated. Did the authors consider performing age-adjusted prevalence estimates (or age adjusted predicted probability estimates) of the examined markers of kidney disease? This might strengthen the conclusion that certain programs yielded similar prevalence estimates, and I suspect this is the reason the prevalence of eGFR<60 appears so much higher in the U.S. when compared to Nepal, for example.

Table 2: The low proportion of married individuals in Bangladesh was striking (4.2%). Was this a typographical error? If not, this should be mentioned in the Discussion. Was a measure of fruit/vegetable intake considered for NHANES? Given the availability of such rich nutritional data in NHANES, it is unclear why similar data is only noted for the non-US programs.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Li Zuo, M.D.

i. The method used to sample from the two general populations from low income countries is not clear. We do not know whether the samples were representative of the two counties. Also, the high risk population sampling method is not clear; they might also not representative of the two countries.
Major information on sampling strategies was already included in Table 1. However, as properly suggested by the Reviewer, we provided here (and included in the revised version of the manuscript) more details on how participating subjects were selected and how the programs were implemented in the two general population screenings in Nepal and Bolivia.

- Nepal

The program established in Nepal included subjects ≥18 years old and was conducted in the community in Dharan, a city in eastern Nepal as follows. Dharan has 19 wards and the screening started from ward one and progressed sequentially to ward 2, ward 3 and so on. The demography of each ward was mapped and each member of the family was listed in a card. The members of the survey team visited each household and collected the data. Each person screened received a particular identification number (Identification number: Country code - Survey area/unit code - VDC/health care worker – patient number (e.g. 977 – 01 – 11-00001).

- Bolivia

All subjects older than 18 years were considered eligible for the evaluation. The screening program was conducted in the community in the city of La Paz and El Alto that it are located in Murillo province of the same department. The screening camp was organized in the Unit Nephrology Service at Hospital Juan XXIII. On the day of screening people were asked to come to the center. Each person screened received a particular identification number.

Before beginning the screening program, educational campaigns were carried out in the public of Dharan and La Paz. The focus of education was on the objective, procedures and the benefit of the program to the community. Educational materials on chronic kidney diseases, hypertension, diabetes, and cardiovascular disease were distributed to promote public awareness and participation in this program. This awareness program has been supplemented through local newspapers, posters, pamphlets, and by organizing local meetings with the heads of the villages, religious leaders, students and teachers of the schools and colleges and administrative officers in the locality. This helped to sensitize people on kidney diseases and their risk factors. Simultaneously, a continuing medical education program to educate the primary and secondary health care force on early detection and prevention of kidney disease was organized in the local areas. The day of the screening, the subjects were enrolled after being informed on the objective of the survey, the procedures, the information that could be drawn for the survey and the potential benefits of such screening. The physician or the nurse provided a full explanation of the procedures of the screening and obtains a verbal consent for the screening. These programs are still actively screening subjects.

We included most of the above information in the revised version of the manuscript. We also further emphasized in the limitations of the study that different sampling strategies do not allow any formal comparison on disease prevalence across countries. Nonetheless, presenting face-to-face data of large cohorts of subjects in different countries with different incomes represents, in our view, a unique opportunity to appreciate the relevance of kidney disease worldwide. This was actually the primary aim of our study.

ii. The authors had plenty of data in hand, but this descriptive analysis reporting the prevalence of CKD of the five countries in general population and in risk population is far away from reader’s interest.

We respectfully disagree with the Reviewer. Indeed, information on the prevalence of chronic kidney disease is of crucial importance for the implementation of prevention and treatment programs. Epidemiological data on kidney disease are scanty for Western countries and virtually inexistent for the developing world. Our present large study provides the crucial information that renal diseases are widely frequent, both in high- and in low-income countries. This information is of particular relevance, since mounting evidence is revealing that renal function is a major determinant of cardiovascular risk. Consistently, a recent population-level cohort study showed that the rate of myocardial infarction was lower in patients with diabetes but no chronic kidney disease than in those with chronic kidney disease without diabetes (Tonelli M, et al., Lancet; epub ahead of print; doi:10.1016/S0140-6736(12)60572-8). This
evidence in fact led to the idea that chronic kidney disease should be added to the list of criteria defining people at highest risk of future coronary events. Therefore, knowing the prevalence of chronic kidney disease and relative risk factors in low- and high-income countries is instrumental for setting up prevention programs.

We carefully fixed the spelling mistakes along the manuscript. Moreover, the paper was already revised by the three American Authors, namely Jeffrey B. Kopp, Paul Eggers, and William G. Couser.

**Reviewer #2: Deidra C. Crews, MD, ScM**

i. Title: Would recommend revising to read, “…and the US”.

We modified the title accordingly.

ii. Summary/Key Messages: First sentence that begins, “We found that about a half of high-risk patients in has some…”. Please revise for clarity.

We revised the sentence that now reads as follows: “We found that about a half of high-risk patients in has some degree of renal impairment, but …”.

iii. Methods: The authors state that diabetes status was defined based on history or current treatment for diabetes. Were medication lists of the participants available/reviewed? If so, it would be interesting to know what proportion of the subjects in each country were taking ACE inhibitors or ARBs?

We agree with the Reviewer that having information on the number of diabetic patients receiving ACE inhibitor or ARB therapy in developing countries would be of utmost interest to assess if evidence-based treatments routinely used in Western countries are regularly employed also in poorer nations. Unfortunately, due to the limited resources and challenges in implementing screening programs in developing countries, we had to restrict the number of information collected in the database that does therefore not include data on the use of RAS inhibitors. On the other hand, information is available of the number of patients that were actively treated or not for chronic kidney disease, hypertension, diabetes, or cardiovascular disease. Though data on specific treatments are not available, the table below summarizes the proportion of subjects receiving treatment for these conditions. Not unexpectedly, a larger fraction of subjects were on active treatment in the high-risk population cohorts from Bangladesh and Georgia, compared to general screening programs in Nepal and Bolivia.

Importantly, most subjects with a previous diagnosis of diabetes were on treatment (73.8% in Nepal, 58.6% in Bolivia, 91.0% in Bangladesh, 83.2% in Georgia).

We thank the Reviewer for bringing our attention to such an important issue. However, due to the incomplete dataset, we decided not to include the present information in the revised version of the manuscript. Nonetheless, online availability of the present revision will provide the readers with this potentially helpful information.

|                      | Nepal (n=20811) | Bolivia (n=3436) | Bangladesh (n=1518) | Georgia (n=1549) |
|----------------------|-----------------|------------------|---------------------|------------------|
| Chronic Kidney Disease | 136 0.65       | 9 0.26           | 13 0.88             | 133 9.49         |
| Hypertension         | 1924 9.25      | 97 2.82          | 571 38.95           | 853 58.38        |
| Diabetes             | 1007 4.84      | 52 1.51          | 146 9.95            | 273 19.24        |
| Cardiovascular Disease | 203 0.98      | 11 0.32          | 20 1.37             | 148 10.55        |
iii. Were serum creatinine measures calibrated in the same, standard manner in the different programs? Laboratories in developing countries were actually not calibrated according to the National Kidney Disease Education Program guidelines (NKDEP; available at: http://www.nkdep.nih.gov/lab-evaluation/gfr/creatinine-standardization/recommendations.shtml). This is an expensive and complex process hard to be implemented in resource-limited settings. Conversely, each laboratory made calibrations for creatinine measurement according to guidelines suggested by the manufacture producing the measurement kit. Though this procedure does not represent the goal standard, it should still provide a reliable evaluation of kidney function. Therefore, we believe that this issue could hardly have significantly biased our results that are based on major differences in creatinine levels. We discussed this point in the limitations of the study.

iii. There appears to be significant differences in the age distributions of the programs examined; and the outcome data by age category is appreciated. Did the authors consider performing age-adjusted prevalence estimates (or age adjusted predicted probability estimates) of the examined markers of kidney disease? This might strengthen the conclusion that certain programs yielded similar prevalence estimates, and I suspect this is the reason the prevalence of eGFR<60 appears so much higher in the U.S. when compared to Nepal, for example. As suggested by the Reviewer, we performed age-adjusted prevalence estimates of eGFR<60 ml/min/1.73m$^2$ and urinary albumin/creatinine ratio (ACR) >30. In particular, prevalence estimates were adjusted by the direct method to the year 2000 US Census population using the age groups 18 to 24 years, 25 to 34 years, 35 to 44 years, 45 to 54 years, and 55 years and older. 95% CIs were calculated using Taylor series linearization. This method is used to compare two or more populations. It allows removing the confounding effect of age, which can distort comparisons between populations with different age distributions, when age is related to the outcome of interest. As shown in the following table, the age-adjusted estimates were similar to the crude rates, which strengthens our previous conclusions. We included the results in the revised version of the manuscript. We thank the Reviewer for her insightful suggestion.

| Age-adjusted prevalence of eGFR<60 ml/min/1.73m$^2$ and ACR>30. | eGFR<60ml/min/1.73m$^2$ | ACR>30 |
|---|---|---|
| | % | % | 95% CI | % | % | 95% CI |
| NEPAL All | 19 | 22.1 | 21.5-22.7 | 7 | 7.8 | 7.2-8.4 |
| Gender | | | | | | |
| Women | 12792 | 21.3 | 26 | 25.2-26.8 | 6.4 | 7.1 | 6.3-7.9 |
| Men | 8019 | 15.3 | 16.8 | 16.0-17.6 | 8.1 | 8.8 | 7.8-9.8 |
| BOLIVIA All | 3436 | 3.2 | 4 | 3.0-5.0 | - | | |
| Gender | | | | | | |
| Women | 2192 | 2.6 | 3.4 | 2.2-4.7 | | | |
| Men | 1244 | 4.4 | 4.6 | 3.0-6.3 | | | |
| US All | 4299 | 7.0 | 6.6 | 5.8-7.6 | 10.4 | 10.2 | 9.1-11.3 |
| Gender | | | | | | |
| Women | 2091 | 8.6 | 8.1 | 6.8-9.6 | 11.5 | 11.3 | 9.7-13.2 |
| Men | 2208 | 5.3 | 5.1 | 4.2-6.1 | 9.2 | 9.0 | 8.0-10.2 |
iv. Table 2: The low proportion of married individuals in Bangladesh was striking (4.2%). Was this a typographical error? If not, this should be mentioned in the Discussion. Was a measure of fruit/vegetable intake considered for NHANES? Given the availability of such rich nutritional data in NHANES, it is unclear why similar data is only noted for the non-US programs.

As correctly pointed out by the Reviewer, the proportion of married individuals in Bangladesh was erroneously low, due to a typo. We corrected the mistake in the revised version of the manuscript. Other minor typos were present in the table and have been fixed. We thank the Reviewer for pointing this issue out.

Concerning the second issue, the NHANES uses 24-hour dietary recalls to estimate the number of daily fruit and vegetable servings in US. It indeed includes rich nutritional data. However, the estimated number of daily servings (mean daily serving intakes for fruits and vegetables in US is about 3) could not be comparable to the frequency of fruit/vegetable intake in other non-US countries (which responded ‘everyday, 3-5 times a week, once a week, or none’). Therefore, we did not include the NHANES fruit/vegetable intake data in the manuscript.

**VERSION 2 – REVIEW**

| REVIEWER | Li Zuo,  
| Institute of Nephrology,  
| Peking University First Hospital  
| Beijing,  
| China  
| No cometing interests. |
| REVIEW RETURNED | 05-Aug-2012  

| GENERAL COMMENTS | I have no more question. They had plenty of data in hands and will find a more moving way to report their data.  
