

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Secular Trends of Epidemiologic Patterns of Chronic Kidney Disease Over Three Decades: An Updated Analysis of the Global Burden of Disease Study 2019
AUTHORS	Feng, Xiaojin; Hou, Ningning; Chen, Zhenna; Liu, Jing; Li, Xue; Sun, Xiaodong; Liu, Yongping

VERSION 1 – REVIEW

REVIEWER	Hansson, Erik University of Gothenburg Sahlgrenska Academy, School of Public Health and Community Medicine
REVIEW RETURNED	05-Aug-2022

GENERAL COMMENTS	<p>The authors are undertaking a very large task of characterizing the global burden of CKD incidence and deaths. They use the Global Burden of Disease dataset for this.</p> <p>Even though the exact methodology of the GBD dataset cannot be described here, some minimal description of this methodology is needed in order to make it possible for the reader to understand potential limitations of this analysis. The key question for understanding the validity of this study is how accurate CKD data from low and middle income countries are likely to be. The authors make no attempt to consider or address this question, neither in the methods or conclusions section. I was not able to find any text mentioning any possible limitation of this study to be found anywhere in the manuscript text. Poor reporting in LMICs is acknowledged as a limitation in a “highlight” bullet, but this needs to be much more thoroughly discussed and considered. Is this likely to have changed over time? What implications does it have for the analysis of risk factors and comparisons between countries and geographical regions? Give some examples of the actual original data being fed into these estimates - what does it come from: verbal autopsies, prevalence surveys, hospital or mortality records? Does these sources differ between countries?</p> <p>Researchers interested in studying variation in CKD burden have developed a protocol for standardized prevalence surveys, the DEGREE protocol which I encourage the authors to consider. A reason for developing this was the absence of adequate data on CKD, which largely is a silent disease needing laboratory analyses which in many cases are unavailable. It also contributes to mortality before onset of clinical disease. Studies of accuracy of verbal autopsies of CKD are uncommon, but a Chinese study among that even among relatives of CKD patients dying at hospital, only about half specified CKD as the cause of death.¹ That mortality registers are not well functioning in many LMICs is well-known, and there is other research from IHME on this.</p>
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	<p>Estimates are provided with extreme precision, e.g.: “Globally, there were 697.29 million CKD cases and 18.99 million incident cases”, i.e. down to 10000 individuals at a global level. The authors also do not formulate these as estimates but as “there were”. This type of results reporting combined with an absence of limitations and background information on the methodology raises questions on how literally the authors themselves interpret the estimates.</p> <p>The analysis of temperature abnormalities is not well described. As I understand this analysis from the main GBD study, heat abnormalities are considered to give immediate or short-lag effects on mortality. Even though extreme temperatures at short time spans may cause CKD patients to die, short time extreme heat does not lead to CKD death within a few days in previously well as per definition CKD cannot develop so quickly. What is really being analyzed here? What is the time lag between abnormal temperature and CKD death? How are abnormal temperatures being measured? CKDnt/CKDu which is discussed at the end of the paper is considered to be caused by repeat excessive heat exposure combined with heavy physical work. Low temperatures are according to figure 4 a much larger risk factor than high temperatures, yet it is not all mentioned in the text while high temperatures receive a very large amount of written text. Likewise, lead exposure, is not mentioned in the text but is identified as a rather important risk factor in the figure.</p> <p>The first conclusion in the abstract “Public awareness of CKD prevention measures is insufficient” completely lacks basis in the analysis or main text - nowhere is any data on public awareness of CKD prevention described.</p> <p>1. Yang G, Rao C, Ma J, et al. Validation of verbal autopsy procedures for adult deaths in China. Int J Epidemiol 2006;35(3):741-8. doi: 10.1093/ije/dyi181 [published Online First: 2005/09/08]</p>
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REVIEWER	Hockham, Carinna Imperial College London, The George Institute for Global Health
REVIEW RETURNED	30-Sep-2022

GENERAL COMMENTS	<p>General comments</p> <p>Thank you for the opportunity to review this manuscript. Using data from the GBD Study, the authors have provided a comprehensive overview of the current state of play with regards to the death burden of CKD across the globe. They have created some really nice figures, but I think effort needs to be taken to decide which of these figures are the most pertinent, and to use these to build a clearer story, as the manuscript currently reads a little disjointed and it is quite hard, as a reader, to extract the main takeaways. Whilst I appreciate that the authors have gone into much more detail than was possible in Bikbov et al. (2020), there is a need to be more focused in their objectives and subsequent commentary.</p> <p>Minor comments</p> <p>1. Abstract, Objectives: The stated objective is that the characteristics of the global death burden will “provide a framework for policy discussions, resource allocation, ...” I therefore expected some sort of explicit framework to have been constructed and</p>
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presented by the authors themselves, but this was not the case. Would change it just to say “to help inform...” or similar to better reflect the content of the manuscript.

2. Abstract, Main outcome measures: “We estimated the death burden...” – The death burden estimates came from the GBD Study, so I think it is misleading to say this as it suggests that the authors generated the estimates themselves.

3. Materials and methods, page 5, line 97: 5 categories for SDI regions = “quintiles” not “quartiles”

4. Materials, and methods, page 6, line 105: Should it be 2.5th and 97.5th percentiles?

5. Results: Suggest reporting numbers to 1 decimal place.

6. Results, line 148: “Of the total DALYs, which is consisted of years of life lost prematurely (YLLs) and years lived with disability (YLDs), YLLs accounted for 78.94%, while YLDs accounted for 21.06% in 2019. As the overall death burden was mainly attributed to disease-related deaths, we focused subsequent analyses mainly on the CKD-related death burden.” – I don’t understand this sentence. Are the “total DALYs” all DALYs irrespective of cause? You’ve already focused on CKD-related measures in the previous paragraph so it doesn’t make sense to then go back to overall DALYs and back to CKD....

7. The figures are illegible in their current format and are in slightly confusing order. Please amend. I think some of the panels could probably be dropped as per my comment in the “General comments” section above.

Major comments

8. For me, there isn’t a clear rationale for this study, given that Bikbov et al published their study on the same topic in 2020 using data from 1990 to 2017. I appreciate that these authors have focused on mortality and so have been able to do into more depth in their description but I think it still warrants a clear rationale. I should also flag our recent publication (doi: 10.1016/j.xkme.2022.100535), in which we used GBD Study data to describe sex difference in CKD-associated mortality between 1990 and 2019. Again, I think the authors have included plenty else in this manuscript to justify it, but the rationale should be clearly laid out in the manuscript.

9. I think the authors need to be clearer about what is their contribution and what is not. The generation of the mortality estimates used in this study was done by the GBD Study team and so the language used in the manuscript needs to convey that clearly and consistently. The authors do say that the data were obtained from the GHD Exchange but then there are times where it sounds like they have performed the modelling to generate the estimates themselves – for example, much of what is included in the “statistical analyses” section is misleading (to me, anyway). All it needs is a slight changing of the wording to make it crystal clear that, for example, the 95% UIs were available from the GHDx and not generated by the authors.

	<p>10. There is a lot of jumping around between different metrics, geographical scope, and so on. I would urge the authors to spend time creating a clearer story that is easy to follow. For example, I suggest removing any mention of DALYs given that this was not the stated objective of the paper.</p>
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VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer 1, Dr. Erik Hansson, University of Gothenburg Sahlgrenska Academy:

1. Even though the exact methodology of the GBD dataset cannot be described here, some minimal description of this methodology is needed in order to make it possible for the reader to understand potential limitations of this analysis. The key question for understanding the validity of this study is how accurate CKD data from low and middle income countries are likely to be. The authors make no attempt to consider or address this question, neither in the methods or conclusions section. I was not able to find any text mentioning any possible limitation of this study to be found anywhere in the manuscript text. Poor reporting in LMICs is acknowledged as a limitation in a “highlight” bullet, but this needs to be much more thoroughly discussed and considered. Is this likely to have changed over time? What implications does it have for the analysis of risk factors and comparisons between countries and geographical regions? Give some examples of the actual original data being fed into these estimates - what does it come from: verbal autopsies, prevalence surveys, hospital or mortality records? Does these sources differ between countries?

A: Thank you for your important comments. We are so sorry for the undetailed description of the GBD dataset. The data in the GBD database were based on literature studies, survey data, surveillance data, medical records, health insurance claims, and statistical model analysis. There may be inevitable heterogeneity among the data of the past thirty-years period referring to these confounding factors. We have added this part to the manuscript to make it clear. In addition, we also include the Limitation of this study at the end of the DISCUSSION section. We apologized for the omission of this part during preparing the manuscript. (See page 4, lines 86-89, and page 13-14, lines 372-382)

2. Researchers interested in studying variation in CKD burden have developed a protocol for standardized prevalence surveys, the DEGREE protocol which I encourage the authors to consider. A reason for developing this was the absence of adequate data on CKD, which largely is a silent disease needing laboratory analyses which in many cases are unavailable. It also contributes to mortality before onset of clinical disease. Studies of accuracy of verbal autopsies of CKD are uncommon, but a Chinese study among that even among relatives of CKD patients dying at hospital, only about half specified CKD as the cause of death.¹ That mortality registers are not well functioning in many LMICs is well-known, and there is other research from IHME on this.

A: Thank you for your important recommendation. The issue you mentioned is very important. CKD is characterized by a silent disease with a gradual decline in kidney function that eventually results in end-stage renal disease (ESRD), with little chance of reversal. The DEGREE protocol has been widely used in clinical practice and clinical study. By searching the literature, the DEGREE protocol has been reported by Caplin B et al. (DOI: 10.1186/s12882-016-0417-1.) to estimate glomerular filtration rate (EGFR) epidemiological studies by vulnerable populations. It provides key information to inform hypotheses and guide further research into the causes of CKDu. This exploratory study has strengths, including appropriate sample size, high response rate, representativeness, and laboratory validation of international references. However, there are some limitations. First, this is a cross-sectional study and we cannot confirm that the relevant exposure factors occurred prior to the

outcome of interest (low EGFR). Second, only one EGFR measurement was performed, so this does not confirm CKD cases, as we could not demonstrate the chronicity of CKD. Third, recall bias may be a concern because we collected information by using self-reports about current and past behaviors and other exposures.

3. Estimates are provided with extreme precision, e.g.: “Globally, there were 697.29 million CKD cases and 18.99 million incident cases”, i.e. down to 10000 individuals at a global level. The authors also do not formulate these as estimates but as “there were”. This type of results reporting combined with an absence of limitations and background information on the methodology raises questions on how literally the authors themselves interpret the estimates.

A: Thank you very much for your vital suggestion. We are so sorry for our inaccurate description, and we have revised the relevant part. (See page 5, lines 128)

4. The analysis of temperature abnormalities is not well described. As I understand this analysis from the main GBD study, heat abnormalities are considered to give immediate or short-lag effects on mortality. Even though extreme temperatures at short time spans may cause CKD patients to die, short time extreme heat does not lead to CKD death within a few days in previously well as per definition CKD cannot develop so quickly. What is really being analyzed here? What is the time lag between abnormal temperature and CKD death? How are abnormal temperatures being measured? CKDnt/CKDu which is discussed at the end of the paper is considered to be caused by repeat excessive heat exposure combined with heavy physical work. Low temperatures are according to figure 4 a much larger risk factor than high temperatures, yet it is not all mentioned in the text while high temperatures receive a very large amount of written text. Likewise, lead exposure is not mentioned in the text but is identified as a rather important risk factor in the figure.

A: We apologize for the confusion caused by the unclear description in the text. We realize that you are correct in saying that we lack a description of low temperature and lead exposure, so we immediately made the relevant additions. (See page 11, lines 285-288 and page 13, lines 361-371)

5. The first conclusion in the abstract “Public awareness of CKD prevention measures is insufficient” completely lacks basis in the analysis or main text - nowhere is any data on public awareness of CKD prevention described.

A: Thank you for your important suggestion, we are concerned about the lack of clarity in the text description. Considering the rigor of the text, we have made relevant changes. (See page 2, line 46)

Responses to the comments of Reviewer 2, Dr. Carinna Hockham, Imperial College London, University of New South Wales

1. Abstract, Objectives: The stated objective is that the characteristics of the global death burden will “provide a framework for policy discussions, resource allocation, ...” I therefore expected some sort of explicit framework to have been constructed and presented by the authors themselves, but this was not the case. Would change it just to say “to help inform...” or similar to better reflect the content of the manuscript.

A: Thank you for your rigorous suggestion, we have revised it. (See page 2, line 27)

2. Abstract, Main outcome measures: “We estimated the death burden...” – The death burden estimates came from the GBD Study, so I think it is misleading to say this as it suggests that the authors generated the estimates themselves.

A: Thank you for your important suggestion, we agree that you are right, so we have corrected it. (See page 2, lines 32)

3. Materials and methods, page 5, line 97: 5 categories for SDI regions = “quintiles” not “quartiles”

A: Thank you for your careful review, we have corrected it. (See page 4, lines 99)

4. Materials, and methods, page 6, line 105: Should it be 2.5th and 97.5th percentiles?

A: Thank you for your rigorous suggestion, we have corrected it. (See page 5, lines 107)

5. Results: Suggest reporting numbers to 1 decimal place.

A: Thank you for your important suggestion, we have corrected it. (See the RESULTS section)

6. Results, line 148: "Of the total DALYs, which is consisted of years of life lost prematurely (YLLs) and years lived with disability (YLDs), YLLs accounted for 78.94%, while YLDs accounted for 21.06% in 2019. As the overall death burden was mainly attributed to disease-related deaths, we focused subsequent analyses mainly on the CKD-related death burden." – I don't understand this sentence. Are the "total DALYs" all DALYs irrespective of cause? You've already focused on CKD-related measures in the previous paragraph so it doesn't make sense to then go back to overall DALYs and back to CKD....

A: Thank you very much for your careful reading. We apologize for troubling you with our unclear description. Our aim is to further analyze in depth the composition of DALY caused by CKD, which is consisted of years of life lost prematurely (YLLs) and years lived with disability (YLDs), not all DALYs regardless of the cause. We have corrected it in the manuscript. (See page 8, line 151)

7. The figures are illegible in their current format and are in slightly confusing order. Please amend. I think some of the panels could probably be dropped as per my comment in the "General comments" section above.

A: We apologize for the lack of clarity in the figures and we have re-uploaded the figures.

8. For me, there isn't a clear rationale for this study, given that Bikbov et al published their study on the same topic in 2020 using data from 1990 to 2017. I appreciate that these authors have focused on mortality and so have been able to do into more depth in their description but I think it still warrants a clear rationale. I should also flag our recent publication (doi: 10.1016/j.xkme.2022.100535), in which we used GBD Study data to describe sex difference in CKD-associated mortality between 1990 and 2019. Again, I think the authors have included plenty else in this manuscript to justify it, but the rationale should be clearly laid out in the manuscript.

A: Thank you very much for your careful review of the manuscript. The article you recommended by Bikbov et al. in 2020 using data from 1990 to 2017 is a perfect and logical study and well worth the effort. But unfortunately, this article only contains data from 1990 to 2017 and lacks data from 2018 to 2019. This recent publication (DOI: 10.1016/j.xkme.2022.100535) using data from the GBD study to describe sex differences in CKD-related mortality between 1990 and 2019 is perfect. We regret that we did not cite it in our discussion of sex differences, and we have cited this study in the manuscript. (See page 12, line 314)

9. I think the authors need to be clearer about what is their contribution and what is not. The generation of the mortality estimates used in this study was done by the GBD Study team and so the language used in the manuscript needs to convey that clearly and consistently. The authors do say that the data were obtained from the GHD Exchange but then there are times where it sounds like they have performed the modelling to generate the estimates themselves -for example, much of what is included in the "statistical analyses" section is misleading (to me, anyway). All it needs is a slight changing of the wording to make it crystal clear that, for example, the 95% UIs were available from the GHDx and not generated by the authors.

A: First of all, thank you very much for your important suggestion, we would like to express our sincere apologies for the unclear description in the text and have made corrections accordingly. (See page 5, lines 105-106)

10. There is a lot of jumping around between different metrics, geographical scope, and so on. I would urge the authors to spend time creating a clearer story that is easy to follow. For example, I suggest removing any mention of DALYs given that this was not the stated objective of the paper.

A: Thank you for your important suggestion. After careful consideration, we concurred that the section on DALYs in the manuscript could not be removed. The description of the section on DALYs was not mentioned in a similar article, and we have added accordingly and noted that not only did the global growth of DALYs double from 1990 to 2019, but the total DALYs caused by CDK are also increasing. It facilitates the comparison of the overall impact of disease on population health and provides a multifaceted picture of the global burden of disease in chronic kidney disease.

Additional modifications:

1. Based on the efforts made during the revision process and with the agreement of all authors, we have adjusted the order of authors. (See the title page)

2. The grant project number was misspelled and the original text was corrected. (See page 14, lines 405-406)

VERSION 2 – REVIEW

REVIEWER	Hockham, Carinna Imperial College London, The George Institute for Global Health
REVIEW RETURNED	19-Dec-2022

GENERAL COMMENTS	<p>The authors have addressed most of my comments. However, there are a few things that I think still need considering.</p> <p>Note typo on the abstract: "Based on the CBD database...". Should be "Based on the GBD database"...</p> <p>Results: I'm sorry but I still don't understand this sentence in the results section: "As the overall death burden was mainly attributed to disease-related deaths, we focused subsequent analyses mainly on the CKD-related death burden. " Wasn't the whole purpose of your study to look at CKD-related death burden? Consider deleting?</p> <p>"At the SDI level, even though both showed increasing trends, the difference slightly narrowed with time, with the ratio of female deaths to male deaths changing from 0.9 in 1990 to 0.9 in 2019" -- this doesn't suggest that the ratio changed? Also, this wasn't something that we reported in our own study (Hockham et al., 2022) and so please consider removing "...but the difference narrowed over time.[2]" in the Discussion to ensure that you have accurately cited the findings of our paper? We reported that the sex difference narrowed with AGE but not over TIME.</p> <p>"In 2019, the female to male ASDR ratios ranged from 0.6 to 0.8 in all the SDI regions (figure 2b right), suggesting that the CKD-related death burden was unbalanced between sexes and age groups." Why have you mentioned "age groups" here? You haven't mentioned anything about age in this section of the manuscript.</p> <p>I still think that the manuscript would benefit from a revamp of the structure. I appreciate that the authors have divided the results</p>
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	into 4 broad sections already but I think further sub-headings would help to orientate the reader? Currently, the authors switch back and forth between different measures (deaths, ASRD, ASRI, DALYs, changes over time, etc.) and between global vs SDI vs regional results and I think that some of the key messages can get lost. Repeated sub-headings under each of the four main ones in the Results might help.
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VERSION 2 – AUTHOR RESPONSE

1. Note typo on the abstract: "Based on the CBD database...". Should be "Based on the GBD database"...

A: Thank you for your careful review of the manuscript, and we deeply apologize for our mistakes. We have corrected it. (See page 2, line 32)

2. Results: I'm sorry but I still don't understand this sentence in the results section: "As the overall death burden was mainly attributed to disease-related deaths, we focused subsequent analyses mainly on the CKD-related death burden. " Wasn't the whole purpose of your study to look at CKD-related death burden? Consider deleting?"

A: Thank you for your important suggestion, we apologize for our ambiguous description. As we showed former, years of life lost prematurely (YLLs) account for 78.9% of the total DALYs caused by CKD in 2019, and hence, we focus our subsequent analysis on the death, but not other indexes. We have modified the sentence in the manuscript, hoping it may meet your approval.

3. "At the SDI level, even though both showed increasing trends, the difference slightly narrowed with time, with the ratio of female deaths to male deaths changing from 0.9 in 1990 to 0.9 in 2019" -- this doesn't suggest that the ratio changed? Also, this wasn't something that we reported in our own study (Hockham et al., 2022) and so please consider removing "...but the difference narrowed over time.[2]" in the Discussion to ensure that you have accurately cited the findings of our paper? We reported that the sex difference narrowed with AGE but not over TIME.

A: Thank you very much for your vital suggestion. We are so sorry for our mistake during the last revision. We mean '...with the ratio of female death to male deaths changing from 0.915 in 1990 to 0.925 in 2019', and we have corrected it in the manuscript. We apologize for not being able to accurately cite the paper's findings, and we have removed it.

4. "In 2019, the female to male ASDR ratios ranged from 0.6 to 0.8 in all the SDI regions (figure 2b right), suggesting that the CKD-related death burden was unbalanced between sexes and age groups." Why have you mentioned "age groups" here? You haven't mentioned anything about age in this section of the manuscript.

A: Thank you for your careful review. We apologize for our mistake and we have corrected it in the manuscript.

5. I still think that the manuscript would benefit from a revamp of the structure. I appreciate that the authors have divided the results into 4 broad sections already but I think further sub-headings would help to orientate the reader? Currently, the authors switch back and forth between different measures (deaths, ASRD, ASRI, DALYs, changes over time, etc.) and between global vs SDI vs regional results and I think that some of the key messages can get

lost. Repeated sub-headings under each of the four main ones in the Results might help.
 A: Thank you for your important comments, we think your proposal is very reasonable. We have added the relevant subheadings to the manuscript. (See page 5, line 128; page 8, line 152; page 9, lines 168, 186, and 199; page 10, lines 219, 230-231; and page 11, lines 248, 257, 267 and lines 283-284)

VERSION 3 – REVIEW

REVIEWER	Hockham, Carinna Imperial College London, The George Institute for Global Health
REVIEW RETURNED	28-Feb-2023

GENERAL COMMENTS	<p>I am satisfied that my comments have been addressed.</p> <p>A couple of very minor comments</p> <ol style="list-style-type: none"> 1. Be consistent in your use of "females/males" versus "women/men" 2. The only thing I would say is that the change in ratio of female deaths to male deaths from 0.915 in 1990 to 0.925 in 2019 is tiny, so I am not sure I would use this to conclude that the difference narrowed over time.
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VERSION 3 – AUTHOR RESPONSE

Response to reviewer(s):

1. Be consistent in your use of "females/males" versus "women/men"

A: Thank you for your important suggestion. We apologize for this mistake, and we have now made the correction to "females/males" throughout the manuscript. (See page 2, lines 48; page 10, lines 213 and 215; page 13, line 334; page 14, line 401)

2. The only thing I would say is that the change in ratio of female deaths to male deaths from 0.915 in 1990 to 0.925 in 2019 is tiny, so I am not sure I would use this to conclude that the difference narrowed over time.

A: Thank you for your important comments, we think your proposal is very reasonable.

We apologize for the inaccurate description in our manuscript. The ratio of female deaths to male deaths changed from 0.915 in 1990 to 0.925 in 2019, indicating that the CKD-related deaths burden was significantly higher for males than females during this time period, but not conclude that the gender difference is gradually decreasing. We have corrected this conclusion in the manuscript. (See page 9, lines 190-192; page 12, lines 327-328).