PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The risk and incidence of cognitive impairment in patients with chronic kidney disease and diabetes: The results from a longitudinal study in a community cohort of patients and an age and gender matched control cohort in North Wales, United Kingdom.
AUTHORS	Hobson, Peter; Kumwenda, Mick; Shrikanth, Siva; Nair, Hari; Wong, Stephen

VERSION 1 – REVIEW

REVIEWER	Tsuruya, Kazuhiko Nara Medical University
REVIEW RETURNED	08-Jun-2021

GENERAL COMMENTS	To estimate the incidence and risk for neurocognitive disorders (NCD) in a chronic kidney disease (CKD) cohort with diabetes, compared to an age and sex matched control cohort, the authors conducted a longitudinal study. Cognitive function was assessed in 92 CKD patients and 143 control cohort at baseline and at approximately 36 months. The CKD cohort had a twofold increased risk for the development of an NCD compared to the controls, adjusted for age and sex. According to the finding, the authors concluded that CKD patients have a twofold increased risk for the development of an NCD, and suggested that neuropsychological screening and assessment should be incorporated into normal CKD clinical practice and management. The theme of this study is intriguing and the manuscript is well-written; however, there are some concerns to be addressed. 1. It is difficult to understand because the main findings are only presented as sentences in the results section. It will become easier to understand if they are presented as figures and/or tables. 2. Because of a small number of participants in the group of eGFR 45 to <60 mL/min/1.73m2 (“45 <60 group”), the statistical balance is not good in Table 1. If the “45 to <60 group” is combined with “30 <45 group” into a new group “30 <60 group”, the number of participants in the new group becomes 48 and the balance will be improved. 3. The authors should show data in which demographic, clinical, and cognitive assessment outcomes are compared between all CKD patients (eGFR <60, n = 92) and the controls (n = 143) in Table 1.

	4. I suggest the authors to cite the following paper: Takae K, et al. J Am Heart Assoc. 2018 Jan 20;7(2): e006693. 5. There are many misspellings to be corrected. Page 8, line 54: 1.9 (1.0-3.5) → 1.9 (95% CI; 1.0-3.5) Page 5, line 29; page 12, line 33: μmol/l → mL/min/1.73m2 Page 11, lines 5-8: interleukin (IL)-1β and interleukin (IL)-1β and fibrinogen → interleukin (IL)-1β and fibrinogen Page 18, lines 23 and 26: BP mmHG → BP mmHg Page 18, line 32: eGFR ml/min → eGFR mL/min/1.73m2

REVIEWER	Zhang, Bing The Afliated Hospital of Nanjing University Medical School, Radiology
REVIEW RETURNED	16-Jun-2021

GENERAL COMMENTS	This study explored the incidence and risk of neurocognitive disorders (NCD) among patients with chronic kidney disease (CKD) and diabetes in a three-year longitudinal follow-up cohort. The study found that the CKD cohort had a twofold increased risk for the development of an NCD compared to the controls. The author highlighted the need of neuropsychological screening and assessment in normal CKD clinical practice and management. The study is well conceived and focuses on an area that has received little attention to date. However, I have a number of concerns about this manuscript, as described below. Major concerns 1. Something like a flowchart demonstrating the process of participants enrollment would help readers quickly understand the study implementation process, grouping information, inclusion and exclusion criteria and other information, although add in supplementary materials. 2. Methods (page7, line 42): Please confirm that you have complied with all relevant ethical regulations for work with human participants, and that informed consent was obtained. The author should state this in the Methods section, including the name of the board and institution that approved the study protocol. These are necessary for publication. 3. Methods (page 7, line 5): How accuracy of the diagnosis of Who made the diagnosis of “NCD” and “mild NCD” and how professional is this person in diagnosing cognitive impairment? Was he/she a neurologist? Was the diagnosis given by one person or several people at the same time? What happens if two people disagree on the diagnosis? Please add details about this, as the outcome of NCD has a key influence on the results of this study. 4. Methods (page8, line 30): Overall, although the selection of covariates can be said sound, the design of the study flaws. Considering that this is a study on cognitive tests and their association with an outcome, controlling for major covariates like depression scores and stroke history is mandatory. The Table1 reported depression scores but did not mention stroke history. 5. Results (page9, line50): The incidence and RR value of NCD in CKD patients were main findings of this study, considering relatively small sample size, please add some analyses of the sample size and power regarding the main findings. 6. Results: The title of this study is “the incidence and risk of NCD in CKD patients” but the main results only about the incidence and relative risk of the NCD. In fact, the exploration of risk factors for

	the development of NCD is also a meaningful topic. Therefore, if authors can provide additional knowledge or results related to risk factors, I believe this would add potential information for future clinical practice. 7. Discussion: The manuscript does lack of a good paragraph on limitations of this study. Minor issues 1. Tables / Figures: As there are so many abbreviations used throughout the manuscript, I suggest to explain them again in each table legend. Such as “EQ-5D”, “PDQ-9”... 2. The grouping categories of CKD patients in the table should be more specifically described, similar to G3a/G3b/G4, etc., rather than the statement such as 45 < 60.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kazuhiko Tsuruya, Nara Medical University
1. It is difficult to understand because the main findings are only presented as sentences in the results section. It will become easier to understand if they are presented as figures and/or tables.

Response: We have included a flow chart with the outcomes as a supplemental figure XX

2. Because of a small number of participants in the group of eGFR 45 to <60 mL/min/1.73m2 (“45 <60 group”), the statistical balance is not good in Table 1. If the “45 to <60 group” is combined with “30 <45 group” into a new group “30 <60 group”, the number of participants in the new group becomes 48 and the balance will be improved.

Response: We edited Tables 1 & 2 as suggested by the reviewer.

3. The authors should show data in which demographic, clinical, and cognitive assessment outcomes are compared between all CKD patients (eGFR <60, n = 92) and the controls (n = 143) in Table 1.

Response: We have changed the title of Table 1 to clarify that all of the variables in the table were compared between the CKD and control cohorts.

4. I suggest the authors to cite the following paper:
Takae K, et al. J Am Heart Assoc. 2018 Jan 20;7(2): e006693.

Response: We have added the above paper as suggested by the reviewer: Ref 28 in the revised manuscript.

5. There are many misspellings to be corrected.
Page 8, line 54: 1.9 (1.0-3.5) → 1.9 (95% CI; 1.0-3.5)
Page 5, line 29; page 12, line 33: μmol/l → mL/min/1.73m2
Page 11, lines 5-8: interleukin (IL)-1β and interleukin (IL)-1β and fibrinogen → interleukin (IL)-1β and fibrinogen
Page 18, lines 23 and 26: BP mmHG → BP mmHg

Page 18, line 32: eGFR ml/min → eGFR mL/min/1.73m2

Response: We have corrected the typos.

Reviewer: 2: Dr. Bing Zhang

1. Something like a flowchart demonstrating the process of participants enrolment would help readers quickly understand the study implementation process, grouping information, inclusion and exclusion criteria and other information, although add in supplementary materials.

Response: We have included a flowchart as a supplemental figure as suggested by the reviewer.

2. Methods (page7, line 42): Please confirm that you have complied with all relevant ethical regulations for work with human participants, and that informed consent was obtained. The author should state this in the Methods section, including the name of the board and institution that approved the study protocol. These are necessary for publication.

Response: The ethical statement was included in the original submission and can be found on page 19 of this revision.

3. Methods (page 7, line 5): How accuracy of the diagnosis of Who made the diagnosis of “NCD” and “mild NCD” and how professional is this person in diagnosing cognitive impairment? Was he/she a neurologist? Was the diagnosis given by one person or several people at the same time? What happens if two people disagree on the diagnosis? Please add details about this, as the outcome of NCD has a key influence on the results of this study.

Response: We have edited the methods section to clarify the points raised by the reviewer. For example, Dr Hobson the lead author, has over 30 years working in the field of neurosciences and neuropsychology. He has a wealth of expertise in the application, assessment and diagnosis of patients with neurological disorders.

4. Methods (page8, line 30): Overall, although the selection of covariates can be said sound, the design of the study flaws. Considering that this is a study on cognitive tests and their association with an outcome, controlling for major covariates like depression scores and stroke history is mandatory. The Table1 reported depression scores but did not mention stroke history.

Response: We have revised the methods section to describe the inclusion/criteria for the study participants.

We feel that the controlling for covariates is adequately described in the statistical methodology and the results section.

5. Results (page9, line50): The incidence and RR value of NCD in CKD patients were main findings of this study, considering relatively small sample size, please add some analyses of the sample size and power regarding the main findings.

Response: We have included the original power calculation for the study that was submitted in the original Research and Ethics submission. We will let the editor decide if they want this added as a supplemental table.

Based upon a previous CKD cohort population, where a 12% and 7% incidence of dementia was reported in CKD and the general population respectively, we estimate a sample size of 143, assuming a □ level $p < 0.05$, and a power 80%.

$$N = \frac{P0Q0 \{z1 - \alpha/2 + z_1 - \beta \sqrt{P1\,Q1 / P0\,Q0}\}^2}{(P1 - P0)^2}$$

$Q0 = 1 - P0$

$Q1 = 1 - P1$

$$N = \frac{0.168 * 0.832 \{1.96 + 0.84 \sqrt{0.26*0.74/0.168*0.832}\}^2}{(0.26 - 0.168)^2}$$

$N = 143$

p0 = proportion (incidence) of population
p1 = proportion (incidence) of study group
N = sample size for study group
α = probability of type I error (usually 0.05)
β = probability of type II error (usually 0.2)
z = critical Z value for a given α or β

6. Results: The title of this study is “the incidence and risk of NCD in CKD patients” but the main results only about the incidence and relative risk of the NCD. In fact, the exploration of risk factors for the development of NCD is also a meaningful topic. Therefore, if authors can provide additional knowledge or results related to risk factors, I believe this would add potential information for future clinical practice.

Response: Whilst we agree that and exploration of related risk factors would be an invaluable source of information, we are aware that this study was never intended to investigate various risk factors and in addition, it was not powered enough to address this.

Our hope is that others (including ourselves) will take our initial findings forward and explore the potential risk factors in much larger adequately powered population samples. For example, the role of biomarkers and cognition is a rapidly evolving area of research interest and given the amount of biological samples CKD patients provide, we may be able to identify through an array of makers to identify the pathologic processes and possible synaptic dysfunction and neurodegeneration associated with CKD.

7. Discussion: The manuscript does lack of a good paragraph on limitations of this study.

Response: We have added two paragraphs (Page 14) as suggested to discuss the strengths and weaknesses.

Minor issues

1. Tables / Figures: As there are so many abbreviations used throughout the manuscript, I suggest to explain them again in each table legend. Such as “EQ-5D”, “PDQ-9”...

Response: We have added a table of abbreviations to address these concerns.

2. The grouping categories of CKD patients in the table should be more specifically described, similar to G3a/G3b/G4, etc., rather than the statement such as 45 < 60.

Response: We have also edited the Tables as suggested by the reviewer. However the first reviewer suggested a different editing of Tables 1 & 2: If the “45 to <60 group” is combined with “30 <45 group” into a new group “30 <60 group”, the number of participants in the new group becomes 48 and the balance will be improved”.

VERSION 2 – REVIEW

REVIEWER	Tsuruya, Kazuhiko Nara Medical University
REVIEW RETURNED	07-Nov-2021

GENERAL COMMENTS	Your manuscript has been properly revised. Some errors were found in Tables 1 and 2. Please correct them as follows. Table 1: 45<45 → 30<60 Table 2: 30<45 → 30<60 Alternatively, it might be better to change "30<60" and "<30" to "G3" and "G4+5", respectively, as suggested by the reviewer 2.

VERSION 2 – AUTHOR RESPONSE

I have made the changes as suggested by Reviewer 1. I have uploaded the changes on a Clean, Marked copies of the main manuscript and have changed Tables 1 & 2 in the clean and marked copies of the main document.