PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Kidney disease and risk of dementia: a Danish nationwide cohort study
AUTHORS	Kjaergaard, Alisa; Johannesen, Benjamin; Sørensen, Henrik T.; Henderson, Victor; Christiansen, Christian

VERSION 1 – REVIEW

REVIEWER	Thorleif Etgen Kliniken Sudostbayern AG
REVIEW RETURNED	13-May-2021

GENERAL COMMENTS	This large population-based study evaluates the association of chronic kidney disease and future risk of dementia. Some points might help to further improve this interesting study: Introduction The authors claim that is presently uncertain whether kidney disease has an impact on the risk of dementia although several studies have been published demonstrating an association between dementia and cognitive dysfunction/chronic kidney disease. Please add and discuss the results some of these studies or meta-analyses, for example: Cognition in chronic kidney disease: a systematic review and meta-analysis. Berger I, Wu S, Masson P, Kelly PJ, Duthie FA, Whiteley W, Parker D, Gillespie D, Webster AC. BMC Med. 2016 Dec 14;14(1):206. doi: 10.1186/s12916-016-0745-9. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, Allman RM, Warnock DG, McClellan W. Am J Kidney Dis. 2008 Aug;52(2):227-34. doi: 10.1053/j.ajkd.2008.05.004. Epub 2008 Jun 30. Cognitive function in chronic kidney disease. Madero M, Gul A, Sarnak MJ. Semin Dial. 2008 Jan-Feb;21(1):29-37. doi: 10.1111/j.1525-139X.2007.00384.x. Methods The exclusion of participants with missing values (<11% of employment status and education level) might lead to a selection bias which should further be discussed. The adjusted Cox model includes “potential confounders” (page 10,

	line 43). How are “potential confounders” defined? Do “potential confounders” accord with all covariates listed in table 1? Table 1 Which of the characteristics are significantly different among the kidney disease and the comparison cohort? Please add another column showing the corresponding p-values, for example.

REVIEWER	Wisit Kaewput Phramongkutklao College of Medicine
REVIEW RETURNED	10-Jun-2021

GENERAL COMMENTS	The title of the article is “Kidney disease and risk of dementia: a cohort study”. The authors conducted a nationwide cohort study. This study aimed to determine whether the impact of kidney disease on risk of future dementia. You did a great job on data gathering and situation analysis. However, some of main important issues need to be verified to improve your work as following. Specific comments: 1. In the methods section, statistical analyses, please clarify, what method that used for adjusting in the multivariate analysis? Please provide a test for the interaction between variables, the goodness of fit, and multicollinearity in final adjusted Cox model in supplementary. 2. Include full details of how the authors handled missing data. 3. In “Methods” part, please clarify censor strategies e.g., right censor, left censor, etc 4. How did the authors assess the baseline Cox model? The Cox regression model should generate from the several proportional hazards’ assumptions. Please confirm these assumptions by provide proportional assignment test for both visualization and statistical analysis e.g. Schoenfeld residuals for a non-zero slope, etc., in supplementary. Reference: Stensrud MJ, Hernan M. Why Test for Proportional Hazards? JAMA. 2020; doi:10.1001/jama.2020.1267. PMID:32167523 [epub ahead of print] 5. The working definition of CKD by ICD10 are composed of N18 Chronic kidney disease (CKD) N18.1 Chronic kidney disease, stage 1 N18.2 Chronic kidney disease, stage 2 (mild) N18.3 Chronic kidney disease, stage 3 (moderate) N18.30 Chronic kidney disease, stage 3 unspecified N18.31 Chronic kidney disease, stage 3a N18.32 Chronic kidney disease, stage 3b N18.4 Chronic kidney disease, stage 4 (severe) N18.5 Chronic kidney disease, stage 5 N18.6 End stage renal disease N18.9 Chronic kidney disease, unspecified, Did the authors include these followings in the analysis? Additionally, please provide citations with published literature evaluating the accuracy of existing icd 8 codes and/or data sources related to chronic kidney disease. 6. Please provide full detail of population sampling technique from each hospital, region, and included both unweight sampling number, weight % and standard errors. 7. Finally, since I am not a native English user, I did not check for grammatical errors thoroughly. This should be done by an appropriate language reviewer.

REVIEWER	Donal Sexton Trinity College Dublin, School of Medicine
REVIEW RETURNED	09-Jul-2021

GENERAL COMMENTS	Thank you for the opportunity of reviewing this large study by Kjaergaard et al looking at the association between kidney disease and incident dementia. I fell the study is important and adds to the literature evolving on the link between chronic kidney disease and dementia.. The introduction and discussion are well written and there is an extensive exploration of possible limitations of the study which is welcomed. However I feel some clarifications are need from the authors 1. In the abstract the design is not stated – I think its important to clearly define this study as a retrospective registry based study (rather than a prospective cohort study) 2. why 1:5 controls, some data suggests a threshold benefit of matching at 1:3 cases: control without much additional benefit beyond that, did the results change by different number of controls to cases? 3. The study focuses on cumulative incidence but is there any account of competing risks for example mortality ? perhaps the date of death is not available which hinders competing risk modelling. Another limitation that should be acknowledged is the lag between dementia onset and diagnosis – presumably the time to event models are using date of dementia as the outcome? 4. Relying on hospital records to define kidney disease can lead to confounding since when patients are unwell they may have an acute kidney injury and return to baseline kidney function afterward but could be coded as having kidney disease. Also it should be referenced in the paper that the traditional metric of kidney disease is defined by the KDIGO criteria and represents eGFR and urinary albumin excretion criteria on 2 occasions at least 3 months . Use of coding as the definition of kidney disease has limitations. 5. “Using a large nationwide registry-based cohort study in a universal healthcare system with individual-level data on all participants and a complete follow-up largely eliminated selection bias.” I don’t agree, and I think this statement should be removed through the manuscript - unfortunately without a dedicated prospective cohort study based on stratified random sampling with pre-defined assessment intervals (such as NHANES) you cannot eliminate such bias completely. I do agree that the registry is sufficiently large as to create the possibility of random errors in coding etc balancing out on each side of Y/N but even large registries will be susceptible to possible systematic biases for example the tendencies of different individuals filling out the registry information documents. 6. a limitation of the study is the lack of competing risk assessment but this may have been due to absence of data on date of death. 7. f mild cognitive impairment were capable of being included this might have been interesting rather than the more extreme end of the spectrum dementia but I realise the difficulties with teasing this out based on registry data. 8. Can the authors explain their choice of matching with

	replacement? with such a big cohort would matching without replacement not make more sense? 9. The authors mention throughout the manuscript hospital derived diagnosis of CKD but in the methods they also reference specialist clinics so there is some outpatient data included also. The absence of lab data precludes use of eGFR obviously, so this is more of a code based CKD based on labelling for admission codes etc. But could the authors clarify how they mixed the hospital data and outpatient data or when they say "hospital" are they referring to the outpatient specialist clinics rather than hospitalisations? 10. One issue with coding for ckd might be that the underlying primary disease may effect the outcome - for example renovascular disease may be more likely associated with vascular dementia than for example igA nephropathy. With such large numbers this registry may have had adequate numbers of each primary disease, however those with lower risks for dementia may confound the results – for example a young person with a single kidney being coded as CKD. Etc 11. I think the authors should also acknowledge the possible biases induced from coding comorbidities/covariates for example CVD etc 12. The authors mention the incorporation of prescriptions for example for blood pressure meds etc – how complete is this data in the registry? 13. In the statistical analysis section - the hazard ratio approach this suggests there was a date of diagnosis of dementia, as referred to above one issue is that there can be a lag from onset to diagnosis. 14. I think the authors should specifically explain why competing risk models were not used – is it because the dates of death were not available? 15. were conditional models used to account for the matched methodology? please elaborate in the methods section 16. what proportion of the cohort had kidney failure/dialysis? 17. The longer term risk of dementia appears lower in CKD - was this due to higher mortality in those with kidney disease (in addition to the reasons explored by the authors in the discussion)- this is why competing risks important for this study. 18. Line 37 – page 16/35 – "albuminuria has a better sensitivity…" please include a reference. it could also be argued that albuminuria is more specific than sensitive for kidney disease. 19. "The major strength of our study is its design: large nationwide registry-based cohort study in a universal healthcare system with individual-level data on all participants and a complete follow-up thus largely eliminating selection bias" page 18/35 – again with respect I think this statement may mislead the reader and this cant be achieved without a prospective cohort with nationally representative random sampling (example NHANES) and I think the authors ought to mention that. 20. There can be some mislabeling when patients have an acute kidney injury in hospital and on follow up in outpatient clinic their kidney function returns to normal and they are discharged from the specialist clinic – how does the registry

	deal with this data? 21. Tables and graphs appear appropriate – the graph on page 29 – the labelling of the outcome for which the HR apply probably needs to be clearer. 22. For supplementary table 1 – If I am interpreting the table correctly it seems that the majority of the kidney disease cases are labeled as diabetic nephropathy or unspecified – the large proportion listed as unspecified would make we concerned about the general completeness of the record filling. 23. Has the registry ever done any analysis in general to compare the information listed for the registry in comparison to hospital records in a subset of participants ? for example I believe for the United States Renal Data System (USRDS) at some stage researchers looked at claims data in a subset of people to see how accurate the information was – for example for someone listed as having coronary artery disease in the registry files has a corresponding coronary angiogram documenting that this is accurate?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Prof. Thorleif Etgen, Kliniken Sudostbayern AG Comments to the Author:

This large population-based study evaluates the association of chronic kidney disease and future risk of dementia. Some points might help to further improve this interesting study:

Response: Thank you for the positive evaluation of our manuscript.

Introduction

The authors claim that is presently uncertain whether kidney disease has an impact on the risk of dementia although several studies have been published demonstrating an association between dementia and cognitive dysfunction/chronic kidney disease.

Please add and discuss the results some of these studies or meta-analyses, for example:

Cognition in chronic kidney disease: a systematic review and meta-analysis.

Berger I, Wu S, Masson P, Kelly PJ, Duthie FA, Whiteley W, Parker D, Gillespie D, Webster AC.

BMC Med. 2016 Dec 14;14(1):206. doi: 10.1186/s12916-016-0745-9.

Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study.

Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, Allman RM, Warnock DG, McClellan W.

Am J Kidney Dis. 2008 Aug;52(2):227-34. doi: 10.1053/j.ajkd.2008.05.004. Epub 2008 Jun 30.

Cognitive function in chronic kidney disease.

Madero M, Gul A, Sarnak MJ.

Semin Dial. 2008 Jan-Feb;21(1):29-37. doi: 10.1111/j.1525-139X.2007.00384.x.

Response:

Thank you for these suggestions. Since the focus of these three studies is not on dementia, but cognitive impairment, we decided to only cite and discuss the most recent systematic review that includes a meta-analysis, Berger et al 2016, and not the review by Madero et al from 2008 or the paper by Kurella-Tamura et al from 2008. We have now added the following to the Discussion section (page 14):

"A meta-analysis of cross-sectional and cohort studies including more than 50,000 participants showed an association between kidney disease (eGFR<60 ml/min/1.73 m2) and cognitive impairment. The cognitive domains predominantly affected (i.e., orientation, attention, concept formation and reasoning) differed from those affected by dementia, suggesting that kidney disease may be more closely linked with other cognitive impairment than with dementia. Unfortunately, we did not have data on cognitive performance."

Methods

The exclusion of participants with missing values (<11% of employment status and education level) might lead to a selection bias which should further be discussed.

Response:

We have now added missing values as a limitation in the Discussion section (page 16):

"Limitations of our study include selection, survival and surveillance bias. As we did not perform multiple imputations for income, employment status and education level, the exclusion of participants with missing values may have biased our estimates. However, this would only bias the estimates if the missing values were not random. The unbiased assocation may be even larger if the missing values are linked to lower levels of income, employment and education."

The adjusted Cox model includes “potential confounders” (page 10, line 43). How are “potential confounders” defined? Do “potential confounders” accord with all covariates listed in table 1?

Response:

We have now rephrased the Covariates paragraph in the Methods section (page 9) and clarified that the potential confounders were identified through a literature review and in accordance with the covariates listed in table 1: “We identified cardiovascular disease (CVD), CVD risk factors, (any) cancer and socioeconomic status as potential confounders due to their reported associations with kidney disease and dementia (listed in table 1)."

Table 1

Which of the characteristics are significantly different among the kidney disease and the comparison cohort? Please add another column showing the corresponding p-values, for example.

Response:

The first paragraph in the Results section (page 11) describes the characteristics among the two populations as follows:

"Diagnoses of CVD and CVD risk factors were much more frequent in the kidney disease cohort than in the comparison cohort (Table 1). Furthermore, the kidney disease cohort had lower income, higher unemployment rate and lower education than the comparison cohort (table 1). Finally, the follow-up time was shorter for the kidney disease cohort than for the comparison cohort, with a median of 3.7 and 5.2 years, respectively."

We have purposly not included a column showing p-values in table 1 as significance tests should be avoided in descriptive tables according to the STROBE guidelines for reporting observational studies (https://pubmed.ncbi.nlm.nih.gov/17938389/).

Furthermore, p-values rely on both the strength of the association and the sample size, and dichotomization based on a p-value<0.05 is not a proof of a true difference, nor is a p-value>0.05 a proof of the opposite (https://www.nature.com/articles/d41586-019-00857-9).

Reviewer: 2

Dr. Wisit Kaewput, Phramongkutklao College of Medicine Comments to the Author:

The title of the article is “Kidney disease and risk of dementia: a cohort study”.

The authors conducted a nationwide cohort study. This study aimed to determine whether the impact of kidney disease on risk of future dementia.

You did a great job on data gathering and situation analysis. However, some of main important issues need to be verified to improve your work as following.

Response: Thank you for the positive evaluation of our manuscript.

Specific comments:

1. In the methods section, statistical analyses, please clarify, what method that used for adjusting in the multivariate analysis? Please provide a test for the interaction between variables, the goodness of fit, and multicollinearity in final adjusted Cox model in supplementary.

Response:

In the Statistical analysis paragraph in the Methods section (page 10), we have now specified the following: “However, to account for the matching methodology and due to the built-in selection bias

(see Discussion) as the matching could not be completely retained the adjusted Cox model therefore included adjustments for age (age groups listed in table 1), sex and calendar year of index date, as well as other potential confounders (as listed in table 1)."

We did not test for statistical interaction between covariates, because a p-value<0.05 is not a proof of a biological interaction (https://pubmed.ncbi.nlm.nih.gov/24452418/). Instead, we peformed stratification by all covariates (figure 3 and supplemental figure 2), and found no evidence of interaction.

As our aim was to examine the causal association in a model adjusting for potential confounders, and not to develop a prediction model that should fit the data, we did not provide model diagnostics like goodness of fit or multicollinearity.

2. Include full details of how the authors handled missing data.

Response:

In the Statistical analysis paragraph in the Methods section (page 10), we state: "Participants with missing values (<1% of personal gross income and <11% of employment status and education level each) were excluded from the adjusted analyses". In other words, these three covariates are the only covariates with missing values, as we had full information on all other covariates. Furthermore, in response to a comment by Reviewer #1, we have added this to the limitations paragrapg in the Discussion section as well.

3. In “Methods” part, please clarify censor strategies e.g., right censor, left censor, etc

Response: We included only incident patients with kidney disease in the study period. In the Statistical analysis paragraph in the Methods section (page 10), we have clarified that “Participants were followed from one year after index date until a diagnosis of dementia or censoring at December 31, 2016, emigration or death, whichever came first.”

4. How did the authors assess the baseline Cox model? The Cox regression model should generate from the several proportional hazards’ assumptions. Please confirm these assumptions by provide proportional assignment test for both visualization and statistical analysis e.g. Schoenfeld residuals for a non-zero slope, etc., in supplementary.

Reference: Stensrud MJ, Hernan M. Why Test for Proportional Hazards? JAMA. 2020; doi:10.1001/jama.2020.1267. PMID:32167523 [epub ahead of print]

Response:

We have now included the visualizations as a new supplemental figure 1 (the “old” supplemental figure 1 is now the supplemental figure 2) and the Statistical analysis paragraph in the Methods section (page 10) reads: "Proportional hazards assumption was tested graphically by log-log plots, and no violations were detected (supplemental figure 1)".

5. The working definition of CKD by ICD10 are composed of

N18 Chronic kidney disease (CKD)

N18.1 Chronic kidney disease, stage 1

N18.2 Chronic kidney disease, stage 2 (mild)

N18.3 Chronic kidney disease, stage 3 (moderate)

N18.30 Chronic kidney disease, stage 3 unspecified

N18.31 Chronic kidney disease, stage 3a

N18.32 Chronic kidney disease, stage 3b

N18.4 Chronic kidney disease, stage 4 (severe)

N18.5 Chronic kidney disease, stage 5

N18.6 End stage renal disease

N18.9 Chronic kidney disease, unspecified, Did the authors include these followings in the analysis? Additionally, please provide citations with published literature evaluating the accuracy of existing icd 8 codes and/or data sources related to chronic kidney disease.

Response:

Analyses restricted to ICD-10 code N18 (including all subcodes of CKD stages) was examined in a sensitivity analysis, while the main analysis additionally included several other persistent kidney diseases, dialysis treatment, and kidney transplant. This is explained in the Kidney disease paragraph in the Methods section (page 8):

"In the main analysis, we used an extended definition of kidney disease including chronic kidney disease as well as several other persistent kidney diseases, dialysis treatment and kidney transplant (for ICD codes, see supplemental table 1). Importantly, this extended kidney disease definition did not include acute and/or potentially reversible kidney injury. In a sensitivity analysis, we used chronic kidney disease (restricted to ICD-8 792 and ICD-10 N18) as the exposure for all-cause dementia only."

In the limitations paragraph in the Discussion section (page 16), we state:

"The positive predictive value of kidney disease coded in the Danish National Patient Registry has been reported to be 100%, whereas completeness may only be 37%; i.e., not all individuals with kidney disease are captured."

6. Please provide full detail of population sampling technique from each hospital, region, and included both unweight sampling number, weight % and standard errors.

Response:

We identified every single Danish resident with a hospital-diagnosed kidney disease from 1995-2016. This was possible due to the universal health care system, where all hospital contacts including diagnoses (during admissions and out-patient clinic visits) are registered in the Danish National Patient Registry (https://pubmed.ncbi.nlm.nih.gov/31372058/). Thus, the study population included all patients with hospital-diagnosed kidney disease as stated in the Methods section. For each patient with kidney disease, we used the Danish Civil Registration System of all Danish residents to identify

five comparison cohort members matched on age, sex and calendar year (https://pubmed.ncbi.nlm.nih.gov/24965263/) In order to further clarify this, we changed the second bullet point of the "Article summary" to:

"We conducted a nationwide registry-based cohort study of all Danish residents with kidney disease and a 1:5 matched general population comparison cohort without kidney disease during a study period from 1995-2016."

7. Finally, since I am not a native English user, I did not check for grammatical errors thoroughly. This should be done by an appropriate language reviewer.

Response: Done.

Reviewer: 3

Dr. Donal Sexton, Trinity College Dublin

Comments to the Author:

Thank you for the opportunity of reviewing this study. I believe it is an important study based on a large registry which does add to growing literature on Dementia and cognitive impairment in Chronic kidney disease. However, I feel there are certain methodological limitations that need to more fully acknowledged to reflect the fact that it is essentially a retrospective registry study rather than a prospective cohort study and the diagnosis of kidney disease is not the typical KDIGO definition but rather coded from hospital records. Therefore, I am recommending revision.

Thank you for the opportunity of reviewing this large study by Kjaergaard et al looking at the association between kidney disease and incident dementia. I fell the study is important and adds to the literature evolving on the link between chronic kidney disease and dementia. The introduction and discussion are well written and there is an extensive exploration of possible limitations of the study which is welcomed. However, I feel some clarifications are need from the authors.

Response: Thank you for the positive evaluation of our manuscript.

1. In the abstract the design is not stated – I think its important to clearly define this study

as a retrospective registry-based study (rather than a prospective cohort study).

Response: It is correct that the study is conducted using historical (retrospective) data, but data were collected prospectively in the registries and we therefore prefer not to denote the study as a retrospective study. Instead, we have now clarified in the abstract that the study was a "nationwide historical registry-based cohort study".

2. Why 1:5 controls, some data suggests a threshold benefit of matching at 1:3 cases:

control without much additional benefit beyond that, did the results change by different

number of controls to cases?

Response:

We agree that there may not be much additional benefit of matching beyond 1:3. The choice of exposed:comparison cohort ratio is therefore often a matter of personal preference and/or availabilty of subjects. As we sampled from the entire Danish population, we did have a sufficient number of subjects and therefore decided on a ratio of 1:5. We did not consider sensitivity analyses with other matching ratios, and we find it unlikely that matching 1:3 would change the results. However, we will of course do a new sampling with matching 1:3, if requested by the Editor/Reviewer.

3. The study focuses on cumulative incidence but is there any account of competing risks

for example mortality? Perhaps the date of death is not available which hinders

competing risk modelling. Another limitation that should be acknowledged is the lag

between dementia onset and diagnosis – presumably the time to event models are

using date of dementia as the outcome?

Response:

We did have the exact date of death. The first sentence in the Statistical analysis paragraph in the Methods section (page 10) states:

"We compared cumulative incidence (risk) of death as well as all-cause dementia (taking the competing risk of death into account) for the kidney disease and comparison cohorts."

We agree that the lag time between dementia onset and date of diagnosis is a limitation, and we have added the following to the limitations paragraph in the Discussion section (page 17): "Additionally, there is a variable lag time between dementia onset and the date of diagnosis".

4. Relying on hospital records to define kidney disease can lead to confounding since when

patients are unwell they may have an acute kidney injury and return to baseline kidney function afterward but could be coded as having kidney disease. Also, it should be referenced in the paper that the traditional metric of kidney disease is defined by the KDIGO criteria and represents eGFR and urinary albumin excretion criteria on 2 occasions at least 3 months. Use of coding as the definition of kidney disease has limitations.

Response:

We agree that acute kidney injury and return to normal kidney function should not count as persistent kidney disease. We did not include diagnoses of acute kidney injury nor acute dialysis in the study. The first sentence in the "Kidney disease" paragraph in the Methods section (page 8) states:

"In the main analysis, we used an extended definition of kidney disease including chronic kidney disease as well as several other persistent kidney diseases, dialysis treatment and kidney transplant (for ICD codes, see supplemental table 1)".

To further clarify this, we have added:

"Importantly, this extended kidney disease definition did not include acute and potentially reversible kidney injury".

We have also added the traditional KDIGO definition of chronic kidney disease as the last sentence under this paragraph (page 8):

" KDIGO (Kidney Disease Improving Global Outcomes) defines chronic kidney disease as persistent (>3 months) eGFR<60 ml/min/1.73 m^2 or kidney damage, often ascertained by the presence of albuminuria". [17]

We agree that using ICD codes for kidney disease has its limitations. Therefore, we included the following in the Discussion section (page 15): "Unfortunately, we did not have data on albuminuria or eGFR", and in the limitations paragraph in the Discussion section (page 17): "The positive predictive value of kidney disease coded in the the Danish National Patient Registry has been reported to be 100%, whereas completeness may only be 37; i.e., not all individuals with kidney disease are captured."

5. "Using a large nationwide registry-based cohort study in a universal healthcare system with individual-level data on all participants and a complete follow-up largely eliminated selection bias." I don't agree, and I think this statement should be removed through the manuscript - unfortunately without a dedicated prospective cohort study based on stratified random sampling with pre-defined assessment intervals (such as NHANES) you cannot eliminate such bias completely. I do agree that the registry is sufficiently large as to create the possibility of random errors in coding etc balancing out on each side of Y/N but even large registries will be susceptible to possible systematic biases for example

the tendencies of different individuals filling out the registry information documents.

Response: With this statement, we wanted to emphasize that the study included all Danish residents with a hospital-diagnosed kidney disease. However, we do agree that we cannot rule out selection bias from patients not being diagnosed and have therefore removed the sentence as suggested. Still, any misclassification of kidney disease should be related to dementia to cause a selection bias.

6. A limitation of the study is the lack of competing risk assessment but this may have been due to absence of data on date of death.

Response: We did account for competing risk by death as stated in the response to #3.

7. If mild cognitive impairment were capable of being included this might have been interesting rather than the more extreme end of the spectrum dementia but I realise the difficulties with teasing this out based on registry data.

Response:

We agree that mild cognitive impairment may be a more sensitive outcome, but given the threshold for referral to specialists we agree that it is probably not captured in registry-based data.

8. Can the authors explain their choice of matching with replacement? with such a big cohort would matching without replacement not make more sense?

Response:

We did matching with replacement, as it has been shown that matching without replacement may introduce bias (https://pubmed.ncbi.nlm.nih.gov/30310326/).

9. The authors mention throughout the manuscript hospital derived diagnosis of CKD but in the methods they also reference specialist clinics so there is some outpatient data included also. The absence of lab data precludes use of eGFR obviously, so this is more of a code based CKD based on labelling for admission codes etc. But could the authors clarify how they mixed the hospital data and outpatient data or when they say

“hospital” are they referring to the outpatient specialist clinics rather than

hospitalisations?

Response:
In Denmark, outpatient clinics for dementia and kidney disease are located at hospitals, and there are only few private practicing neurologists and no nephrologists working outside hospitals in Denmark. By including hospital-diagnoses, we included virtually all diagnoses made by specialists.

10. One issue with coding for CKD might be that the underlying primary disease may effect

the outcome - for example renovascular disease may be more likely associated with

vascular dementia than for example igA nephropathy. With such large numbers this

registry may have had adequate numbers of each primary disease, however those with

lower risks for dementia may confound the results – for example a young person with a

single kidney being coded as CKD. Etc

Response:
We agree. Despite the large study size, there were too few cases with some of the specific kidney disease subtypes to provide estimates for subtypes (supplemental table 1).

11. I think the authors should also acknowledge the possible biases induced from coding

comorbidities/covariates for example CVD etc.

Response:
We have added the following to the limitations paragraph in the Discussion section (page 16):
"Further limitations are misclassification bias (of kidney disease, dementia and covariates)…"

12. The authors mention the incorporation of prescriptions for example for blood pressure

meds etc – how complete is this data in the registry?

Response:
These data are complete from 1995 onwards for all outpatient prescriptions. Data are capted electronically for reimbursement at time of drug dipension at the pharmacy.
This is described in the Covariates paragraph in the Methods section (page 9): "…from the Danish National Prescription Registry, containing detailed individual-level data on prescriber, patient and products for all outpatient prescriptions dispensed since 1995."

13. In the statistical analysis section - the hazard ratio approach this suggests there was a

date of diagnosis of dementia, as referred to above one issue is that there can be a lag from onset to diagnosis.

Response: Please see answer to #3.

14. I think the authors should specifically explain why competing risk models were not used – is it because the dates of death were not available?

Response: Please see answer to #3.

15. Were conditional models used to account for the matched methodology? please elaborate in the methods section

Response: We adjusted for the matching factors in the Cox regression model to account for the matched methodology (Statistical analysis section, first paragraph). In that way, we conditioned on the matching factors at start of follow-up. We found that more appropriate than using a stratified Cox regression model conditioning on the matched pairs at time of kidney diagnosis.

16. What proportion of the cohort had kidney failure/dialysis?

Response: There were 245 first time cases of kidney transplant and 1,918 first time cases of dialysis (supplemental table 1).

17. The longer term risk of dementia appears lower in CKD - was this due to higher mortality in those with kidney disease (in addition to the reasons explored by the authors in the discussion)- this is why competing risks important for this study.

Response:
We agree that cumulative incidence of dementia was lower in CKD due to higher mortality.
In the Results paragraph in the Abstract, we state: "Five- and ten-year mortality rates were twice as high in patients with kidney disease compared to the general population. The five-year risk for all-cause dementia was 2.90% (95% confidence interval: 2.78%-3.08%) in patients with kidney disease and 2.98% (2.92%-3.04%) in the general population."
We did consider competing risk of death (please see response to #3).

18. Line 37 – page 16/35 – “albuminuria has a better sensitivity…” please include a reference. it could also be argued that albuminuria is more specific than sensitive for

kidney disease.

Response:
We have rephrased this sentence as follows: "This finding suggests that albuminuria may be a better marker than eGFR of more advanced kidney disease."

19. “The major strength of our study is its design: large nationwide registry-based cohort study in a universal healthcare system with individual-level data on all participants and a complete follow-up thus largely eliminating selection bias” page 18/35 – again with respect I think this statement may mislead the reader and this cant be achieved without a prospective cohort with nationally representative random sampling (example NHANES) and I think the authors ought to mention that.

Response:
We have rephrased as suggested.

20. There can be some mislabeling when patients have an acute kidney injury in hospital and on follow up in outpatient clinic their kidney function returns to normal and they are discharged from the specialist clinic – how does the registry deal with this data?

Response:
We agree that there is a risk of mislabeling. In order to account for this (as much as possible), we only included ICD codes that should be used for persistent and not potentially reversible kidney injury (supplemental table 1).

21. Tables and graphs appear appropriate – the graph on page 29 – the labelling of the outcome for which the HR apply probably needs to be clearer.

Response:

The main outcome in figure 3 is all-cause dementia as stated in the legend. Therefore, this should be clear once the figure and legend are placed together which is why we did not label the figure.

22. For supplementary table 1 – If I am interpreting the table correctly it seems that the majority of the kidney disease cases are labeled as diabetic nephropathy or unspecified

– the large proportion listed as unspecified would make me concerned about the

general completeness of the record filling.

Response:

We agree that you are interpreting the table correctly. Diabetes is a common cause of CKD, and we were therefore not surprised that many are coded with diabetic nephropathy. To address the potential impact of unspecified kidney failure, we performed sensitivity analysis only focusing on CKD (N=41,925), coded as ICD-8 792 or ICD-10 N18. The estimates were similar in this sensitivity analysis (table 2, main analysis at the top and sensitity analysis at the bottom).

23. Has the registry ever done any analysis in general to compare the information listed for

the registry in comparison to hospital records in a subset of participants? for example I

believe for the United States Renal Data System (USRDS) at some stage researchers

looked at claims data in a subset of people to see how accurate the information was –

for example for someone listed as having coronary artery disease in the registry files has

a corresponding coronary angiogram documenting that this is accurate?

Response:

We agree that this is very important, and yes, this has been done for many different diagnoses. In a study validating diseases included in the Charlson Comorbidity Index, medical records were reviewed for 50 patients diagnosed with kidney diseases in the Danish National Patient Registry and was confirmed in all 50 patients corresponding to a positive predictive value of 100% (95% CI: 92.9-100) (https://pubmed.ncbi.nlm.nih.gov/26604824/). In another study, patient characteristics were compared between patients identified with kidney diseases using laboratory databases and by the Danish National Patient Registry. This study identified 27,947 patients diagnosed with kidney disease, while 75,031 patients had at least two eGFR measurements <60 ml/min/1.73m2 seperated by two months, corresponding to a completeness of 37% (https://pubmed.ncbi.nlm.nih.gov/33707181/).

This suggests that coding of CKD is similar or better in Denmark compared with a US study (https://pubmed.ncbi.nlm.nih.gov/16112040/).

We have clarified this In the Discussion section (page 17): "The positive predictive value of kidney disease coded in the Danish National Patient Registry has been reported to be 100%, whereas completeness may only be 37%; i.e., not all individuals with kidney disease are captured. While the positive predictive value of all-cause dementia and Alzheimer's disease in the Danish National Patient Registry is 86% and 81%, respectivelly, it is much lower for other dementia subtypes."

VERSION 2 – REVIEW

REVIEWER	Wisit Kaewput Phramongkutklao College of Medicine
REVIEW RETURNED	17-Aug-2021

GENERAL COMMENTS	The authors addressed all my previous concerns and significantly improved quality of the manuscript. I have no additional comment.

REVIEWER	Donal Sexton Trinity College Dublin, School of Medicine
REVIEW RETURNED	20-Sep-2021

GENERAL COMMENTS	Thank you. I am satisfied with the authors replies and modifications and have no further suggestions.