PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of undiagnosed stage 3 chronic kidney disease in France, Germany, Italy, Japan and the USA: results from the multinational observational REVEAL-CKD study
AUTHORS	Tangri, Navdeep; Moriyama, Toshiki; Schneider, Markus P.; Virgitti, Jean Blaise; De Nicola, Luca; Arnold, Matt; Barone, Salvatore; Peach, Emily; Wittbrodt, Eric; Chen, Hungta; Järbrink, Krister; Kushner, Pamela

VERSION 1 – REVIEW

REVIEWER	Jones, Julia Western Health, Department of General Practice
REVIEW RETURNED	05-Sep-2022

GENERAL COMMENTS	This study provides important insight into the underdiagnosis of stage 3 CKD across multiple countries. However, there are a few areas that would benefit from clarification. Could you please address the following issues? 1. Could you please define "non-extrapolated electronic medical records" used in France on page 7? 2. Could you please explain what is meant by "a representative sample of practices throughout Germany" on page 7? Are these a mix of public/private healthcare services? Are they all general practices or other specialist clinics? What makes them representative? Are the practices from metropolitan and rural areas? Do the catchment areas for the practices include patients from all socioeconomic groups? Once this has been defined, please also provide details as to whether the data from other countries also "representative"? 3. At the moment it is not clear what patient records are included in some of the databases. For each database could you please clarify whether electronic medical record data comes from general practice records, (private/public) hospital outpatient records, (private/public) hospital inpatient records, specialist clinics or other sources? And are the coded diagnoses entered by clinicians or by administrators who are coding based on clinical notes or both? Similarly, for the insurance data, is this data based on patients reporting their own medical conditions or based on doctors' reports of the patients' conditions or both? If based on patients' reports I would suspect this would lead to under-reporting of the CKD diagnosis. 4. Could you please provide more detail regarding how the diagnostic data needs to be entered by clinicians into electronic medical records in order to be extractable from databases? Is it data routinely entered during everyday practice into the electronic medical records? For example, would a diagnosis of CKD coded by a general practitioner into their practice's medical record during a consultation be detected in each of the databases? If any of the

	databases would not detect such a diagnosis, this needs to be explicitly stated, as it would likely lead to many patients' diagnoses not appearing in the database. 5. What statistical software was used?

REVIEWER	Bragg-Gresham, Jennifer University of Michigan , Internal Medicine – Nephrology
REVIEW RETURNED	19-Sep-2022

GENERAL COMMENTS	I am pleased to see the authors bringing attention to the problem of underdiagnoses of CKD, in multiple countries. Paper is well written and important, but I do have a few concerns about the current analyses. Suggestions that may make the paper stronger are below. 1. I worry that the sample is biased toward sicker patients by requiring the strict KDIGO definition of CKD (i.e., two consecutive measurements), within health systems. With the understanding that only requiring 1 measurement of eGFR < 60 may be biased also, I suggest the authors include both analyses and consider the estimates to be the likely boundaries of the "real" estimate. At a minimum this needs to be discussed in the discussion section and considered during interpretation of results. In the current analyses, the estimate of undiagnosed CKD among patients in Stage 3 in the US are much LOWER than published by the USRDS when using the representative NHANES sample. There report only required 1 measure of eGFR < 60 and showed approximately 90% undiagnosed, compared to your reported 65%. See figure 1.13a on page 25. https://usrds.org/media/1723/v1_c01_genpop_18_usrds.pdf. 2. My second concern is the choice to not include race in the estimates of CKD during the years where it was used in practice, as well as the findings in Supplemental Table 6, which seem to be reversed of what would be expected. During the study period Physicians would have only had the current (race included) estimates to use at the time when making their diagnosis of CKD. Thinking through the direction of bias, ignoring race would cause a potential overestimate of diagnoses among black patients and a potential underestimate of diagnoses among white patients, since Black patients would have had a higher eGFR estimated with the race modifier included. This assumes that physicians are more likely to diagnose at lower eGFR's. I worry that something is amiss in your supplemental tables 6 where you show that eGFR estimates were lower for Black patients with the race modifier. This should actually be in the opposite direction. eGFR estimates are higher in Black patients when the race modifier is employed. This means that some of the Black patients you are including in your study population (eGFR 30-59) would have had eGFR > 60 if the Race equation was used…meaning they would not even make it into your sample. Please see the table in our work on this topic: Bragg-Gresham J, Zhang X, Le D, Heung M, Shahinian V, Morgenstern H, Saran R. Prevalence of Chronic Kidney Disease Among Black Individuals in the US After Removal of the Black Race Coefficient From a Glomerular Filtration Rate Estimating Equation. JAMA Netw Open. 2021 Jan 4;4(1):e2035636. Note that we published this before the

	race free equation was created. We simply removed the race adjustment, but the direction of change would remain the same, although the magnitude would be smaller. I would suggest the authors show the prevalence results using both equations for Black patients. I think you may find higher estimates of undiagnosed CKD among this group. 3. Lastly, urine testing is often missing for the vast majority of patients. I am assuming the authors set missing urine testing to 0. Could this be added to the methods if it is not already there. Also, if there is room, I would like to see missing rates by country. As a small comment, I would remove the work retrospective from the study design, since you did not choose your sample based on the outcome and look backward for exposure. I would simply call this an observational study or prospective observational study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1		
#1	Could you please define "non-extrapolated electronic medical records" used in France on page 7?	On their website, THIN Cegedim describes the database using the term “non-extrapolated”, which in this instance simply means raw data. The term “non-extrapolated” was employed to differentiate this database from another healthcare database by the same provider which contains extrapolated THIN data. We have removed the term “non-extrapolated” from the manuscript, as it is unnecessary in this context.
#2	Could you please explain what is meant by "a representative sample of practices throughout Germany" on page 7? Are these a mix of public/private healthcare services? Are they all general practices or other specialist clinics? What makes them representative? Are the practices from metropolitan	We thank the reviewer for their comment. An analysis of the representativeness of this database (Rathmann *et al*, *Int J Clin Pharmacol Ther* 2018;56:45

	and rural areas? Do the catchment areas for the practices include patients from all socioeconomic groups? Once this has been defined, please also provide details as to whether the data from other countries also "representative"?	9–66) concluded that the German Disease Analyzer contained data on patients that were similar to the overall German population, with a good agreement of the incidence or prevalence of major chronic diseases in the database compared with German reference data; this study is referenced in the Methods section. Information on specific clinics and settings are unavailable, as the databases used in REVEAL-CKD were selected based on the availability of the required laboratory/claims linkage to perform the analysis. Indeed, analysis of the true representativeness of each of these databases is out of the scope of this manuscript. We have changed the description of the German Disease Analyzer database to remove the word “representative” and align with the description of the database from the German Federal Health Monitoring System website. “Data for Germany were extracted from the German Disease Analyzer, a database of anonymised longitudinal data on drug prescriptions, diagnoses and medical and demographic data contributed by a panel of more than 2500 physicians in Germany.”

#3	At the moment it is not clear what patient records are included in some of the databases. For each database could you please clarify whether electronic medical record data comes from general practice records, (private/public) hospital outpatient records, (private/public) hospital inpatient records, specialist clinics or other sources? And are the coded diagnoses entered by clinicians or by administrators who are coding based on clinical notes or both? Similarly, for the insurance data, is this data based on patients reporting their own medical conditions or based on doctors' reports of the patients' conditions or both? If based on patients' reports I would suspect this would lead to under-reporting of the CKD diagnosis.	We thank the reviewer for their comment. We have created a new table in the supplement (Supplementary Table 1) which includes a breakdown of the data sources by country, database type (electronic medical records, claims data, or both) and the coverage of the databases. Diagnosis codes for CKD were clinician-reported and did not rely on patient self-reporting of their conditions.
#4	Could you please provide more detail regarding how the diagnostic data needs to be entered by clinicians into electronic medical records in order to be extractable from databases? Is it data routinely entered during everyday practice into the electronic medical records? For example, would a diagnosis of CKD coded by a general practitioner into their practice's medical record during a consultation be detected in each of the databases? If any of the databases would not detect such a diagnosis, this needs to be explicitly stated, as it would likely lead to many patients' diagnoses not appearing in the database.	The databases used in REVEAL-CKD collected diagnostic data that is entered by clinicians into patient electronic medical records during routine clinical practice. Diagnosis codes for CKD will be identified if they appear in a patients' medical record in the setting captured by each database. This potential limitation is addressed in the Discussion section: "Lastly, there is a risk of misclassification if CKD diagnoses were made in clinical settings that do not contribute to the databases, or if patients had CKD that was recognised by their healthcare providers but was not recorded with an appropriate ICD-9/10 code in the databases. Although a lack of such codes may not always indicate that a patient's CKD is undiagnosed, this definition of CKD diagnosis has been

		validated by previous real-world studies,[8,11,12,27] and provides an appropriate surrogate measure for rates of diagnosis in large epidemiological studies such as REVEAL-CKD."
#5	What statistical software was used?	The analysis used Python 3.7 and R 4.0.2. This information has been included in the Methods section.
	Reviewer 2	
#1	I am pleased to see the authors bringing attention to the problem of underdiagnoses of CKD, in multiple countries. Paper is well written and important, but I do have a few concerns about the current analyses. Suggestions that may make the paper stronger are below.	We thank the reviewer for this comment.
#2	I worry that the sample is biased toward sicker patients by requiring the strict KDIGO definition of CKD (i.e., two consecutive measurements), within health systems. With the understanding that only requiring 1 measurement of eGFR < 60 may be biased also, I suggest the authors include both analyses and consider the estimates to be the likely boundaries of the "real" estimate. At a minimum this needs to be discussed in the discussion section and considered during interpretation of results.	As stated by the reviewer, the decision to classify stage 3 CKD based on a minimum of two consecutive eGFR measurements was made to ensure that patients were selected based on the KDIGO criteria, wherein kidney disease must have a duration of 90 days or more to be considered "chronic". For this reason, analysis of patients with only a single eGFR measurement within the boundaries for stage 3 CKD was not performed. Additionally, patients with stage 3 CKD required multiple readings in order to avoid misclassification of patients with a single spurious value which may have been the result of, for example, transient dehydration

		or acute kidney injury. We have clarified this point in the Methods: "Patients aged ≥18 years were included in the analyses if they had at least two consecutive estimated glomerular filtration rate (eGFR) measurements that fell within the range indicative of stage 3 CKD (≥30 and <60 mL/min/1.73 m^2) and were recorded >90 and ≤730 days apart, taken on or after 1 January 2015. The decision to require at least two eGFR measurements with a gap of at least 90 days between each measurement was made to ensure that patients met the KDIGO definition for CKD,[5] and to avoid potential misclassification of patients based on single spurious eGFR measurements <60 mL/min/1.73 m^2." We acknowledge that there may be a degree of selection bias in the limitations section, given that patients required at least two creatinine values for inclusion: "…there may be a degree of selection bias present in these results toward patients who are being routinely monitored for other conditions, or who are actively seeking healthcare."
#3	In the current analyses, the estimate of undiagnosed CKD among patients in Stage 3 in the US are much LOWER than published by the USRDS when using the	A higher prevalence of undiagnosed stage 3 CKD based on a single eGFR measurement

	representative NHANES sample. There report only required 1 measure of eGFR < 60 and showed approximately 90% undiagnosed, compared to your reported 65%. See figure 1.13a on page 25. https://usrds.org/media/1723/v1_c01_genpop_18_usrds.pdf.	is expected for the reasons outlined above. Use of an isolated eGFR measurement <60 mL/min/1.73m^2 to identify patients with stage 3 CKD risks misclassifying patients with single spurious values <60 mL/min/1.73m^2 stemming from other causes. Furthermore, in the USRDS report, only 10% of patients with stage 3 CKD report an awareness of their condition: patient awareness is likely to be significantly lower than true diagnosis rates, especially in early-stage CKD which is often asymptomatic. We have clarified the decision to use multiple eGFR measurements as opposed to a single measurement in the discussion: "REVEAL-CKD used the internationally recognised CKD-EPI equation to calculate eGFR values from available serum creatinine measurements.[23] Multiple consecutive eGFR measurements indicative of stage 3 CKD were required to confirm the presence of chronic kidney disease, in line with KDIGO recommendations suggesting a threshold of >90 days to consider the condition to be chronic.[5] Estimates of the prevalence of undiagnosed stage 3 CKD based on a single measurement are likely to be higher, owing to the potential for the inclusion of patients with

		isolated eGFR measurements within the threshold for stage 3 CKD (as a result of, for example, transient dehydration or acute kidney injury)."
#4	My second concern is the choice to not include race in the estimates of CKD during the years where it was used in practice, as well as the findings in Supplemental Table 6, which seem to be reversed of what would be expected. During the study period Physicians would have only had the current (race included) estimates to use at the time when making their diagnosis of CKD. Thinking through the direction of bias, ignoring race would cause a potential overestimate of diagnoses among black patients and a potential underestimate of diagnoses among white patients, since Black patients would have had a higher eGFR estimated with the race modifier included. This assumes that physicians are more likely to diagnose at lower eGFR's.	We calculated eGFR values for this study from available inputs (age, sex, creatinine) and did not rely on lab-generated eGFR values from databases. This enabled us to have a consistent method for the calculation of eGFR, and also to align with contemporary practice (not using the race modifier). We appreciate the reviewers' concern that the use of a race modifier when calculating eGFR at the time creatinine values were originally taken may have classified Black patients as having stage 2 CKD (and therefore less likely to be diagnosed), and have addressed this concern in the limitations section of the Discussion: "Because data were collected from between 2015 and 2020, physicians may have still been using the race modifier for Black patients. Therefore, some Black patients may have been classified as having stage 2 CKD and have been less likely to receive a diagnosis as a result."
#5	I worry that something is amiss in your supplemental tables 6 where you show that eGFR estimates were lower for Black patients with the race modifier. This	In Supplementary table 6 (now Supplementary table 7), the inclusion of the race modifier in

	should actually be in the opposite direction. eGFR estimates are higher in Black patients when the race modifier is employed. This means that some of the Black patients you are including in your study population (eGFR 30-59) would have had eGFR > 60 if the Race equation was used…meaning they would not even make it into your sample. Please see the table in our work on this topic: Bragg-Gresham J, Zhang X, Le D, Heung M, Shahinian V, Morgenstern H, Saran R. Prevalence of Chronic Kidney Disease Among Black Individuals in the US After Removal of the Black Race Coefficient From a Glomerular Filtration Rate Estimating Equation. JAMA Netw Open. 2021 Jan 4;4(1):e2035636. Note that we published this before the race free equation was created. We simply removed the race adjustment, but the direction of change would remain the same, although the magnitude would be smaller.	black patients did increase eGFR estimates. This is shown through the reclassification of approximately 46% of Black patients to stage 2 CKD (i.e. eGFR >60 mL/min/1.73m^2) when the race modifier is used. We have restructured the discussion of this Supplementary table to improve the clarity of this point: "When calculating eGFR, race was not included as a modifier in line with recent trends among physicians[24 25] and guidance from expert recommendations.[26] Inclusion of the race modifier may have been expected to inflate eGFR in Black patients. Indeed, in a sensitivity analysis performed on the US TriNetX database which included data on race (**Supplementary Table 7**), we saw that a substantial proportion of Black patients (46.1%, corresponding to 9.2% of the overall TriNetX cohort) were reclassified as having stage 2 CKD (eGFR between 60–89 mL/min/1.73m^2) when the race modifier was included in the calculation of eGFR." We agree with the reviewers' assessment that the eGFR formula used in practice at the time would often have included the race modifier, and that this may have led clinicians to classify Black patients as having

		stage 2. We have clarified our decision to not use the race modifier in the Discussion. "The decision to use the CKD-EPI equation without race was made in part to facilitate comparisons among countries and databases in which race was not available, and also to provide a consistent method of calculating eGFR for measurements taken across a time period where the inclusion of the race modifier was being actively debated.[48-52]"
#6	I would suggest the authors show the prevalence results using both equations for Black patients. I think you may find higher estimates of undiagnosed CKD among this group.	The above sensitivity analysis was performed to identify Black patients who may have historically been misclassified as having stage 2 CKD if the race modifier was included, rather than to explore the impact of the race modifier on the overall prevalence of undiagnosed CKD. Less than 10% of the total population of the TriNetX database would have been classified as having stage 2 CKD if the race modifier were included in the calculation, and therefore the impact on the overall prevalence of undiagnosed CKD would be very low. Furthermore, regardless of whether the race modifier was used at the time the measurements were taken, these reclassified patients would still have had stage 3 CKD based on the currently accepted

		CKD-EPI equation (without the race modifier). The key message of this manuscript would remain the same: the prevalence of undiagnosed stage 3 CKD is high.
#7	Lastly, urine testing is often missing for the vast majority of patients. I am assuming the authors set missing urine testing to 0. Could this be added to the methods if it is not already there. Also, if there is room, I would like to see missing rates by country.	The reviewer is correct that urine tests were often missing, as highlighted by the low availability of UACR testing shown in Table 1 and Supplementary table 5. This variable was not included in either of the multivariate analyses which adjusted for select baseline covariates (footnote for Supplementary figures 3 and 4) rather than every baseline covariate included in Table 1. We have clarified this by describing the adjustment as adjusting for "selected baseline covariates", and this potential limitation is now expanded upon in the Discussion: "Confirmatory UACR testing was not necessary to meet the study definition of stage 3 CKD owing to the extremely low levels of UACR testing in most of the cohorts. For the same reason, UACR testing was not included in the multivariate analyses which assessed factors associated with a lack of CKD diagnosis and factors associated with time to CKD diagnosis."
#8	As a small comment, I would remove the work retrospective from the study design, since you did not	We thank the reviewer for this comment and agree that

	choose your sample based on the outcome and look backward for exposure. I would simply call this an observational study or prospective observational study.	removing “retrospective” to describe the study simply as an observational study is more fitting. To minimize confusion, we have added the following in the Methods, to clarify that EMR/claims data were not generated for REVEAL-CKD and were rather collected from existing sources: “Existing secondary data were extracted from established, verified relevant databases containing electronic medical records and/or insurance claims in the countries of interest.”

VERSION 2 – REVIEW

REVIEWER	Jones, Julia Western Health, Department of General Practice
REVIEW RETURNED	13-Dec-2022

GENERAL COMMENTS	Thank you for addressing the issues raised during the peer review process. The changes that have been made improve the clarity of the manuscript. Thank you for addressing the important issue of undiagnosed CKD with your work.

REVIEWER	Bragg-Gresham, Jennifer University of Michigan , Internal Medicine – Nephrology
REVIEW RETURNED	10-Jan-2023

GENERAL COMMENTS	The added information on collection of data is very helpful, as well as the sensitivity work for the new CKD-EPI eGFR equation. I still have one major concern remaining, though. The inclusion of only individuals who have two measurements of eGFR (strict KDIGO guidelines) in the analyses is very likely to bias your results, especially in the US samples. I appreciate that you’ve added a short discussion to the limitations section, but I think more needs to be done for the readers to understand the potential magnitude of the potential effect. Looking at published data from the US Veterans population in 2014 (https://pubmed.ncbi.nlm.nih.gov/32890592/), the differences in CKD prevalence estimates is marked, based on the definition used. For example, using only diagnosis codes yielded a prevalence of 2.3%, using the strict KDIGO definition yielded a prevalence of 5.6%, and using any (single or multiple) indication of CKD yielded a prevalence

	of 14.5%. The true estimate most likely lies between 5.6% and 14.5%, but is impossible to precisely estimate because not all patients receive 2 measurements of eGFR within the appropriate time frame (only 27.5% of the Veterans in the study cited above). The strict use of two measurements in the current work is most likely causing an overestimate of awareness in your study because the patients with two measurements of eGFR are inherently sicker and/or receiving more care within a health system, leading to a higher likelihood of detection of their CKD. Also, we don't know characteristics of the patients that have two measurements, compared to those that do not. The lack of this knowledge in your work examining the characteristics of individuals more likely aware of their CKD could have a large impact. I feel the only way to address this is to run a sensitivity analysis, examining awareness of individuals with CKD stage 3 identified by any measurement (even if just one eGFR or UACR). It would strengthen your findings if in the logistic modeling you find the same trends (i.e., older individuals and women are more likely to be aware). Awareness of kidney disease is such an important issue and I would hate to see the magnitude of your findings reduced by excluding individuals who very likely also have CKD and are unaware. Lastly, the methods section does not describe how the patient characteristics were defined. I would assume that the comorbidities were included using ICD codes, but I would state this and describe other adjustment/predictor variables.

VERSION 2 – AUTHOR RESPONSE

Comment

Response

Reviewer 1

#1

Thank you for addressing the issues raised during the peer review process. The changes that have been made improve the clarity of the manuscript. Thank you for addressing the important issue of undiagnosed CKD with your work.

We thank the reviewer for their comments.

Reviewer 2

#1

The added information on collection of data is very helpful, as well as the sensitivity work for the new CKD-EPI eGFR equation.

We thank the reviewer for this comment.

#2

I still have one major concern remaining, though. The inclusion of only individuals who have two measurements of eGFR (strict KDIGO guidelines) in the analyses is very likely to bias your results, especially in the US samples. I appreciate that you've added a short discussion to the limitations section, but I think more needs to be done for the readers to understand the potential magnitude of the potential effect.

Looking at published data from the US Veterans population in 2014(https://pubmed.ncbi.nlm.nih.gov/32890592/), the differences in CKD prevalence estimates is marked, based on the definition used. For example, using only diagnosis codes yielded a prevalence of 2.3%, using the strict KDIGO definition yielded a prevalence of 5.6%, and using any (single or multiple) indication of CKD yielded a prevalence of 14.5%. The true estimate most likely lies between 5.6% and 14.5%, but is impossible to precisely estimate because not all patients receive 2 measurements of eGFR within the appropriate time frame (only 27.5% of the Veterans in the study cited above).

The strict use of two measurements in the current work is most likely causing an overestimate of awareness in your study because the patients with two measurements of eGFR are inherently sicker and/or receiving more care within a health system, leading to a higher likelihood of detection of their CKD. Also, we don't know characteristics of the patients that have two measurements, compared to those that do not. The lack of this knowledge in your work examining the characteristics of individuals more likely aware of their CKD could have a large impact.

I feel the only way to address this is to run a sensitivity analysis, examining awareness of individuals with CKD stage 3 identified by any measurement (even if just one eGFR or UACR). It would strengthen your findings if in the logistic modelling you find the same trends (i.e., older individuals and women are more likely to be aware).

Awareness of kidney disease is such an important issue and I would hate to see the magnitude of your findings reduced by excluding individuals who very likely also have CKD and are unaware.

We agree that the requirement for two eGFR measurements may have caused an overestimate of awareness for the reasons the reviewer states. To investigate this, we have performed an additional sensitivity analysis on the TriNetX cohort, expanding the inclusion criteria to allow for patients with

only a single measurement of eGFR which indicates stage 3 CKD in the date range examined in the REVEAL-CKD study.

We have included the breakdown of these patients in a new Supplementary table 7. As the reviewer expected, in this cohort we found that an even larger proportion of patients were undiagnosed (82.2%) than in the main REVEAL-CKD cohort (64.3%).

The baseline characteristics of both groups were broadly similar, but there were some slight differences in the prevalence of comorbidities; for example, compared with the main TriNetX cohort, fewer patients in the sensitivity analysis cohort had type 2 diabetes (30.0% vs 38.0%, respectively), hypertension (69.8% vs 81.0%), heart failure (12.5% vs 18.7%) or established CVD (15.4% vs 19.8%). This aligns with the reviewers' suggestion that patients with two eGFR measurements may be sicker than those with a single eGFR measurement, because they are more likely to be receiving healthcare for other conditions.

We have added a description of this sensitivity analysis to the Methods:

> "The decision to require at least two eGFR measurements with a gap of at least 90 days between each measurement was made to ensure that patients met the requirements for the KDIGO definition of stage 3 CKD.[5] ~~and to avoid potential misclassification of patients based on single spurious eGFR measurements <60 mL/min/1.73 m^2.~~ In order to investigate the potential impact of requiring two eGFR measurements to classify patients, a sensitivity analysis was performed on data from the TriNetX database that included all patients with at least one eGFR measurement within the range of stage 3 CKD, taken within the same date range used for the main analysis."

We outline the main results of this sensitivity analysis in the Results:

> "In the sensitivity analysis of 532 921 patients in the TriNetX database who had at least one qualifying eGFR measurement, the prevalence of undiagnosed stage 3 CKD was 82.2% (**Supplementary table 7**)."

> "In the sensitivity analysis of patients in the US TriNetX database who had at least one qualifying eGFR measurement, the prevalence of comorbidities was lower than in the main cohort (**Supplementary table 7**)."

We have further addressed the potential overestimate of diagnosed CKD as a result of using a strict KDIGO definition based on the results of this sensitivity analysis in the Discussion:

> "REVEAL-CKD used the internationally recognised CKD-EPI equation to calculate eGFR values from available serum creatinine measurements.[23] Multiple consecutive eGFR measurements indicative of stage 3 CKD were required to confirm the presence of chronic kidney disease, in line with KDIGO recommendations suggesting a threshold of >90 days to consider the condition to be chronic.[5] This decision was made to conform to these widely used guidelines, and to avoid overestimating the prevalence of undiagnosed stage 3 CKD by including patients who had isolated eGFR measurements within the threshold of inclusion for stage 3 CKD (as a result of, for example,

transient dehydration or acute kidney injury). To investigate the potential impact of requiring two qualifying eGFR measurements for inclusion in REVEAL-CKD, a sensitivity analysis was performed using the TriNetX database that included patients with at least one eGFR measurement indicative of stage 3 CKD. Among these patients, the prevalence of undiagnosed stage 3 CKD was higher than in the main REVEAL-CKD cohort (82.2% versus 64.3%, respectively), whereas the prevalence of comorbidities was lower. This suggests that the requirement of multiple eGFR measurements may have biased the sample to select for patients with inherently poorer health status, because they may have been receiving more frequent healthcare visits than those with a single measurement, and therefore may have had more eGFR measurements taken. Although it is difficult to confirm which patients in this sensitivity analysis truly had stage 3 CKD and who were included as a result of transient eGFR dips, it should be noted that these findings suggest that the true prevalence of undiagnosed stage 3 CKD may be even higher than identified in the present study. ~~Estimates of the prevalence of undiagnosed stage 3 CKD based on a single measurement are likely to be higher, owing to the potential for the inclusion of patients with isolated eGFR measurements within the threshold for stage 3 CKD (as a result of, for example, transient dehydration or acute kidney injury).~~"

#3

Lastly, the methods section does not describe how the patient characteristics were defined. I would assume that the comorbidities were included using ICD codes, but I would state this and describe other adjustment/predictor variables.

We have added the following clarification to the Methods section:

"Comorbidities at index were identified using ICD-9/10 codes. Medication use at index was identified by the presence of at least one prescription for a given medication at or in the 12 months before index."

Editorial comments

#1

Table 1 should not exceed more than 9 columns. Otherwise, you will need to cite this as supplemental table and upload separately.

Table 1 (baseline characteristics of patients by country/database and CKD status [diagnosed/undiagnosed]) has now been swapped with Supplementary Table 5 (baseline characteristics of patients overall in each country/database), and manuscript text has been updated accordingly.

VERSION 3 – REVIEW

REVIEWER	Bragg-Gresham, Jennifer University of Michigan , Internal Medicine – Nephrology
REVIEW RETURNED	25-Apr-2023

GENERAL COMMENTS	The paper is much improved by the sensitivity analysis performed and as I had hoped, the results are even stronger. Thank you for bringing more attention to this important topic.