Author’s response to reviews

Title: Association of diabetic kidney disease with cardiovascular and non-cardiovascular outcomes: A retrospective cohort study

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Re: BEND-D-19-00090

Association of diabetic kidney disease with cardiovascular and non-cardiovascular outcomes: A retrospective cohort study

Dear Dr. Pan,

Thank you for your letter of April 17, 2019, in which you indicated that addressing the reviewer concerns would improve the above-referenced manuscript and may allow a revised version to be published in BMC Endocrine Disorders. We carefully considered the comments we received, revised the manuscript accordingly, and believe it is improved as a result. Point-by-point responses to each reviewer comment follow below.

Thank you for your interest in our work.
Reviewer reports:

Yunfei Liao (Reviewer 1): This is a retrospective cohort study. The authors clarified the association of diabetic kidney disease with cardiovascular and non-cardiovascular outcomes. The study is well designed and the results are clearly shown, however, I have some questions to be answered.

We thank the Reviewer for these comments.

1. Cardiovascular (CV) complications are the leading cause of morbidity and mortality in patients with diabetes. The additive CV hazard between diabetes and diabetic kidney disease (CKD) has been shown in several settings. Among medically treated patients with diabetes undergoing percutaneous coronary intervention (PCI), the presence of CKD has been associated with a significantly higher in-hospital and 1-year mortality rate. Some studies have shown that both diabetes and CKD are risk factors for the development of atrial fibrillation and are associated with an increased risk of stroke. What is the differences between your study and other research?

Prompted by the Reviewer, we carefully re-read our Introduction section, which of course is designed to set forth the rationale for the study. We agree with the Reviewer that our study rationale, and by extension our explanation of the specific knowledge gap we hoped to fill, was not clearly stated. In general, it is quite clear, as the Reviewer states, that CKD is associated with adverse CVD outcomes. However, we perceive several knowledge gaps. First, the stage at which putative DKD is diagnosed has not (to our knowledge) been studied in a large administrative database. Second, although DKD-related mortality has been studied in large datasets, we perceived a gap in studies examining the epidemiology of DKD-related morbidity using large administrative datasets; as such, we wanted to examine how CKD stage in DKD patients was
associated with morbidity outcomes (both CV- and non-CV-related). We reasoned that a large administrative dataset was an appropriate way to draw initial epidemiologic conclusions.

Reflecting the comments of the Reviewer, to better explain our study rationale, we rewrote, reordered, and rephrased the Introduction. We now say, on page 4, the following (where the new text is in italics): “In patients with type 2 diabetes, the association of kidney disease with mortality has recently been quantified.5 However, determination of the stages at which DKD is detected and how DKD stage is associated with major cardiovascular and non-cardiovascular events has not, to our knowledge, been quantified in a large administrative dataset. To investigate these questions, we created a large retrospective cohort of patients enrolled in an employer group health plan (EGHP) to calculate incidence and prevalence of DKD and the associated risks of ESRD, myocardial infarction (MI), congestive heart failure (CHF), stroke, and infection.”

2. In this study, there is a close relationship between CV and CKD in diabetic patients. What do you think which is the cause and which is the result?

This is an excellent question, as there are clear bidirectional relationships. As the Reviewer suggests, vascular disease can contribute to renal disease, and renal disease can contribute to cardiovascular events. The most forthright answer is that one cannot know based on an observational study such as ours, as causality cannot be determined. However, considering the Reviewer’s question, we now think it appropriate to add a “disclaimer,” or admonishment, about the inability to draw causal inferences using a study design such as ours. We added text to this effect in the limitations section on page 14 (the new proposed text is in italics): “As an observational study, our analysis cannot determine causality. Preexisting vascular disease could contribute to kidney disease development in diabetic patients, while DKD could contribute to cardiovascular events; we suspect both mechanisms are operative. Further, it is unclear whether prevention of DKD advancement would actually result in attenuation of the risks of the outcomes we studied, although this hypothesis is highly plausible.”

3. There are many diabetic patients combined with other kidney diseases (such as chronic glomerulonephritis, hypertensive nephropathy), not diabetic nephropathy. How to define diabetic nephropathy instead of other chronic kidney disease? How to eliminate these confounding factors?

The Reviewer is correct that there is a range of kidney disease in patients with diabetes: DKD alone, DKD with another superimposed cause of kidney disease, or even non-diabetic kidney disease alone. Perhaps a third of patients with diabetes have evidence of non-diabetic kidney disease (Bermejo et al. Clin Kidney J. 2017;10(2):255-256), and others have a combination of
DKD and non-diabetes-related kidney disease. The challenge is that, to our knowledge, all such studies rely on case series of biopsies that were performed for the purposes of clinical care. In other words, “protocol” or surveillance biopsies were not performed. As such, it is likely that most diabetic patients biopsied in these case series were biopsied because they were unusual in some way, often because the physician wanted to rule-out coexisting non-diabetic kidney disease. If all diabetic patients with CKD were routinely biopsied, it seems likely that far more than 2/3 of patients would have DKD as the predominant finding given that only highly selected diabetic patients are biopsied. Until a large series of protocol biopsies is published, it seems unlikely we will understand the true epidemiology of DKD.

Prompted by the Reviewer’s appropriate concerns, we now specifically call out this vexing issue in the Discussion in a dedicated paragraph on page 14, where we say, “A major challenge in studying kidney disease etiology in large administrative datasets is lack of detailed clinical information, such as that derived from a kidney biopsy. This is a particularly vexing issue in the case of DKD. While studies have shown that perhaps a third of biopsied patients with diabetes have non-diabetes-related kidney disease (Bermejo et al. Clin Kidney J. 2017;10(2):255-256; Sharma et al. Clin J Am Soc Nephrol. 2013;8(10):1718-1724), these findings are derived from case series of patients undergoing real-world clinical care. The vast majority of diabetic patients with CKD are not biopsied, suggesting that only atypical cases of putative DKD are biopsied (and thus reported on in biopsy studies). Because of this, for the purposes of this study, we attributed CKD in patients with diabetes to DKD, but we acknowledge that, in some cases at least, non-diabetic kidney disease was likely the primary cause of kidney disease. A more complete understanding of DKD epidemiology awaits more comprehensive biopsy studies.”

4. Noncardiovascular outcomes of diabetes refer to a series of diseases, including infection, DKA, Diabetic neuropathy, et al. Why this article only study infection?

The Reviewer is correct that a wide range of potential diabetes-related outcomes could possibly have been studied. Diabetic neuropathy is poorly detected in administrative datasets using billing claims. We did strongly consider amputation, but were concerned that amputations could occur not only from diabetes, but also from vascular disease. Further, in the particular dataset we examined, an Employer Group Health Plan, amputations are relatively rare (although amputation rates are likely much higher in other datasets, such as US Medicare).

We were primarily interested in cardiovascular outcomes and, of course, ESRD, since the pathophysiologic link between diabetes and cardiovascular disease, and between diabetes and ESRD, is so strong. We elected to study infection as a hypothesis-generating exercise. We also wanted to study a non-cardiovascular disease-related outcome, and so we concentrated on a major one—infection. To clarify our rationale, we now say, in the Introduction on page 4, “We elected to study infection specifically because of evidence that diabetes is associated with this
outcome; as such, we reasoned that it would serve as an informative counterpoint to cardiovascular disease-related outcomes.”

5. The age of onset and course of disease are very important risk factors of diabetic complications. Correlation analysis should be performed. The impact of these two factors should be ruled out in statistical analysis.

We agree with the Reviewer that the clinical course of diabetes plays a major role in the development of diabetes-related complications, including DKD. Age of onset, duration of diabetes, and level of diabetic control are all important.

Unfortunately, upon re-reading our description of our study design, we realize that this was unclear. The problem is that, confusingly, we used the term “diabetes index date” and “DKD index date” throughout the manuscript, and in at least one case we referred to the “index date” when it was not clear what we meant. Our specific goal was to examine outcomes once DKD developed, not from the time DM developed. As such, we should use the term “index date” only for DKD; it is misleading for us to use the term “index date” when talking about diabetes. We removed the term “diabetes index date” throughout, and we now refer to “index date” only when referring to DKD, the date of which is the true “time zero” for the study.

Because complications related to diabetes take years and, more typically, decades to develop, it was not practical for us, using employer group health plan data, to ascertain when, precisely, diabetes started for most patients. Most patients were likely longstanding prevalent diabetes patients, so all we can be reasonably sure of is the start date of DKD. Thus it is not correct for us to designate a diabetes index date. Given that complications of diabetes result only after many years, that we could not accurately determine onset of diabetes in our dataset, and that we specifically wanted to study outcomes timed from the beginning of DKD (not diabetes), we cannot include a “diabetes duration” term in our model, nor can we know the age at diabetes onset.

To improve the manuscript, we have eliminated the term “diabetes index date” (reserving the term “index” only for DKD),” altered Figures S1 and S2 to remove this confusing term, and added the following clarification in the limitations on page 14: “Duration of diabetes, a disease that patients often have for many decades, was unknown, and therefore could not be specifically controlled for in the analysis, nor could age at time of diabetes onset.”
Xiong-Fei Pan (Reviewer 2): The manuscript examines the associations of diabetic kidney disease (DKD) with cardiovascular and non-cardiovascular outcomes using a commercial database that including 2.2 million patients with diabetes. It found elevated risks of both cardiovascular and non-cardiovascular outcomes among patients with DKD and those with only diabetes. The study is well designed with adequate statistical analyses and appropriate interpretation. There are, however, a few issues to address before it is publishable.

We thank the Reviewer for these comments.

1. It is expected to have more detail about the study population (Page 5). The scope of the commercial database is not clearly defined. Why were only 2010-2014 datasets selected? It would be beneficial if earlier data were used with a longer follow-up.

The Reviewer raises three issues here. The first involves a description of the database. We appreciate that an international audience is likely to be less familiar with this than US investigators, and we should take pains to avoid a US-centric approach. We now provide additional detail in the Methods, on page 5: “This database, which derives from a selection of more than 350 large employers, health plans, and government and public organizations, includes information on person-specific clinical utilization, expenditures, and enrollment across inpatient and outpatient services. The database links paid claims and encounter data to detailed patient information across sites and types of providers and over time. These data represent the medical experience of insured employees and their dependents for active employees, early retirees, and Medicare-eligible retirees with employer-provided Medicare Supplemental plans, among others. At the time we undertook the study, 2014 was the most recent year of data available for purchase.” We would be happy to provide additional information if requested, but more detailed information would probably best be left to a supplemental section.

The second is the timing of the data. Unfortunately, employer group health plan data are expensive to purchase from the commercial insurer. When conducting studies, our philosophy is to purchase the most data that we possibly can, and the most recent data that we can. The study budget allowed us to purchase 5 years of data. At the time this analysis commenced, 2014 data were the most recent available. We therefore entered into a Data Use Agreement for 2010-2014 data. We now state this in the Methods as above.

Third is the issue of duration of follow-up. We agree that had there been a longer follow-up, more outcomes would have accrued. We now acknowledge this as a limitation on page 14, “A longer follow-up period would have been beneficial to strengthen the estimates of the association between exposures and outcomes, but we purchased the most data possible within the study budget (as well as the most recent data available at the time the study commenced).”
2. The exposure of interest, DKD was defined as chronic kidney disease in diabetes patients (Page 6). The authors might need to acknowledge this limitation. It is possible that chronic kidney disease occurs before diabetes in certain patients, while after diabetes in other patients.

The Reviewer is correct that there is a range of kidney disease in patients with diabetes. This important point was also brought up in the third critique from Reviewer 1. Perhaps a third of patients with diabetes have evidence of non-diabetic kidney disease (Bermejo et al. Clin Kidney J. 2017;10(2):255-256), and others have a combination of DKD and non-diabetes-related kidney disease. All such studies, however, seem to rely on case series of biopsies that were performed for the purposes of clinical care; “protocol” (surveillance) biopsies were not performed, which is not unexpected. As such, it is likely that most diabetic patients biopsied in these case series were biopsied because they were unusual some way (often because the physician likely wanted to rule out coexisting non-diabetic kidney disease). If all diabetic patients with CKD were routinely biopsied, it seems likely that far more than 2/3 would have DKD as the predominant finding, given that only highly selected diabetic patients are biopsied in routine clinical care.

We have now specifically called out this issue in a dedicated paragraph page 14, where we say, “A major challenge in studying kidney disease etiology in large administrative datasets is lack of detailed clinical information, such as that derived from a kidney biopsy…The vast majority of diabetic patients with CKD are not biopsied, suggesting that only atypical cases of putative DKD are biopsied (and thus reported on in biopsy studies)...A more complete understanding of DKD epidemiology awaits more comprehensive biopsy studies.”

3. The follow-up was short in this study (Page 6). It is highly possible that certain outcomes occur before the DKD. Reverse causality cannot be ruled out. The authors need to discuss this.

We agree with the Reviewer that the follow-up is short. Unfortunately, this is characteristic of employer group health plans in the US. As result, we agree that reverse causality cannot be ruled out. This point, also, was noted in the second critique from Reviewer 1.

The most forthright answer is that in an observational study such as ours, causality cannot be determined. In response to both Reviewers’ concerns, we added a warning about the inability to draw causal inferences using a study design such as ours. We added text to this effect in the limitations section on page 14 (the new proposed text is in italics): “As an observational study, our analysis cannot determine causality. Preexisting vascular disease could contribute to the kidney disease development in diabetic patients, while DKD could contribute to cardiovascular events; we suspect both mechanisms are operative. Further, it is unclear whether prevention of DKD advancement would actually result in attenuation of the risks of the outcomes we studied, although this hypothesis is highly plausible.”
4. Table 1: the sum of percentages was over 100% in certain columns. The authors might need to check the data and add footnotes below the table.

The Reviewer is correct. We had not noticed this. Some columns do indeed sum to 100.1%. This is due to slight rounding. We now say, below Table 1, “Note: Due to rounding, some column percentage totals may slightly exceed 100%.”

5. Table 2 and 3: It might not be helpful to list effect sizes for covariates if the authors were only interested in DKD. Particularly in Table 3, it is advisable to delete results for covariates. The authors may need to add footnote for the covariates and their variable types in the regression models. For example, was age treated as a continuous variable? The authors also need to acknowledge they only adjusted certain potential confounders available from the datasets. Confounders such as smoking and BMI were missing. It is not clear why patients with CHF were included for analyses regarding outcome of CHF. There are similar problems with stroke and other outcomes.

The Reviewer brings up several issues here. The first relates to the presentation of the data. We agree with the Reviewer that Table 3 is redundant with Figure 2, and also that the presentation of the effect sizes for the covariates in Table 3 is of limited value. We have therefore elected to eliminate Table 3. Table 2, however, merely shows unadjusted rates by important strata (age, sex, comorbidity burden), so we do think that it conveys valuable information. Our preference is to retain this table, but, if the Editor prefers, we will eliminate it.

For modelling, age was treated as a categorical values (four groups total). We now clarify this on page 6.

The Reviewer is correct that factors such as BMI and smoking were not used for adjustment. Unfortunately, these are not available in our administrative dataset. We revised our discussion of covariate adjustment in the Methods on pages 6-7 to say, “We also included age (treated as a categorical variable, divided into four groups), sex, and total hospital days during the baseline period as covariates; information on other potentially important covariates, such as race, smoking history, and body mass index, is not available in the MarketScan dataset.”

We have now conducted additional analyses, as requested. We examined the CHF outcome in a subgroup of patients without a history of CHF, and the stroke outcome in patients without a history of stroke. We elected not to show this for infection since few people, if any, are completely infection-free over the course of their lives, and one infection does not necessarily portend another. (We would have performed a similar analysis for MI, except that history of MI is not a category in the Elixhauser taxonomy, which is what we used to operationalize our covariates, as is commonly done). These are reported on page 10. We found that while CHF and stroke history at baseline were associated with future risk of CHF and stroke, respectively (as the
Reviewer was alluding to), the risk of these outcomes nevertheless increased sharply as stage of DKD worsened.

6. Figure 1 repeats results in Table 3. The authors should only keep one of them.

The Reviewer is correct. We have elected to retain Figure 1 and eliminate Table 3, thereby economizing the manuscript considerably.

7. Figure 1 and 2: The authors need to briefly introduce the main findings.

As suggested below, we added subgroup analyses to Figure 1, and we introduce these new findings (in conjunction with the overall findings) in the Results on page 9.

The Reviewer is correct that the findings presented in Figure 2 were not adequately explained in our previous manuscript version. We now describe representative findings on pages 9-10.

8. The authors might need to consider subgroup analyses by sex, age and other major covariates that may potentially modify the effect of DKD. This is more helpfully than listing results for covariates in Table 3.

This is a very helpful suggestion. We now provide additional analyses by sex, age group, and presence of hypertension. We report these new findings on page 9 and in Figure 1. The figure has been considerably expanded from the overall point estimates to include the point estimates by age (divided at age 55), sex, and presence/absence of hypertension. In addition, to make the information in the figure more understandable, we switched the x- and y-axes.

9. While the present study design does not permit us to make inferences about the relative importance of kidney disease in patients with diabetes compared with patients without diabetes, it does permit estimation of the extent of the association between DKD and risk of major cardiovascular and non-cardiovascular outcomes. While other studies have attempted to estimate costs associated with DKD and its progression, none, to our knowledge, have explicitly quantified risk of morbid events (Paragraph 2/ Page 11). These two sentences are not logically reasonable.

I believe we understand the Reviewer’s concern. We rewrote this section as follows (page 15):

“The present study, which was designed to estimate the associations of DKD (versus no kidney disease) in patients with diabetes, does not permit us to make inferences about kidney disease in
non-diabetic patients. As such, any findings regarding the association of kidney disease with outcomes is confined to DKD alone. Our study is unique because we have attempted to quantify the risks associated the DKD and morbid events, in contrast to other studies focusing on the costs associated with DKD and its progression.”

10. The logical flow of the discussion section can be improved, and the authors need to compare to results from other cohorts in the US and other countries.

We have substantially rearranged the organization of the Discussion, as can be seen by contrasting the marked (track-changed) and unmarked versions of the revised manuscript, and have economized it. Additionally, we added context by citing studies from the US using National Health and Nutrition Examination Survey data to determine DKD prevalence, as well as studies from Italy and China on DKD and the complications of diabetes. While direct comparisons are challenging to make, we attempted to better place our findings in the body of literature accumulated to date. These additions can be found on page 13.