**Author’s response to reviews**

**Title:** Sulfonylurea Use and the Risk of Hospital Readmission in Patients with Type 2 Diabetes

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**Author’s response to reviews:**

Reviewer #1:

The authors estimated the readmission risk in the two cohorts of SU-monotherapy group and noSU-monotherapy group cox proportional hazard regression predicting time to readmission recruiting data from MEPS database. The found that SU monotherapy patients have about 30% increased risk for readmission compared to other-AHA use and also found that average readmission expenditure of SU users was higher than that of other oral AHA users. Their findings may be important for the management of treatment using AHAs, there are some points in this manuscript to be revised as follow.

As stated in Discussion, this study includes limits to estimate causal relationship between drug use and the risk of readmission. Because these limits are important and essential of this study, the authors should mention the limits in the abstract to prevent the misunderstanding of their results.

We have added the following sentence to the Methods section of the Abstract: “The lack of clinical data on disease severity and progression limited our ability to estimate causal relationships between drug use and risk of hospital readmission.”

They found that average readmission expenditure of SU users was higher than that of other oral AHA users. The finding about the cost of admission is interesting and important. Therefore comments especially about what makes the difference should be discussed and stated in the discussion.

In the revised Discussion, we interpret the finding that hospital readmissions are, on average, more costly for those patients on SU monotherapy than for those in the other cohort: “In this study, the patients in the SU cohort were on average 8 years older than
those taking a non-SU AHA, a fact that helps to explain the difference in readmission cost between the two cohorts. Older patients were both more likely to have additional comorbidities, requiring attention during the hospitalization, as well as more advanced diabetes. Moreover, as seen in Table 2, the SU cohort, before propensity-score adjustment, had a significantly higher percentage of patients with fair or poor perceived health status than those in the other cohort of patients, potentially lengthening and/or complicating their hospital stay.”

Reviewer #2:

Heaton, et al. compared the risk for diabetes-related hospital readmission in patients with type 2 diabetes treated with sulfonylureas (SUs) compared to those treated with other oral antihyperglycemic agents (AHAs). In this study, they concluded that SU use is associated with an approximately 30% increased risk for hospital readmission compared to other oral AHAs. This large retrospective cohort analysis is important with respect to showing that SU use is related to a higher risk for hospital readmission. However, the serious problem with this study is that there are many mistakes in data of this study.

Specific comments

Criticism 1: (Results) Page 8, line 56: "Of these patients, 5.7 million patients were on SU therapy (SU or SU+), and the remaining 7.8 million were on non-SU oral agents (noSU and noSU+) as shown in Table 1." This sentence is not consistent with the data of Table 1.

We apologize for this error. The values in Table 1 were correct, but our sentence was not. In the revised manuscript, we write the following: “Of these patients, 7.87 million patients were on SU therapy (SU or SU+), and the remaining 5.67 million were on non-SU oral agents (noSU and noSU+) as shown in Table 1.”

Criticism 2: (Discussion) Page 11, line 23: "(23.2% versus 16.1; p=0.003)". Authors should change this into "(23.2% versus 16.1%; p=0.003)"

Done and thank you.

Criticism 3: (Table 2): Authors should fill in a blank of total all patients.

Done and thank you.

Criticism 4: (Table 2): The sum of patients classified by race is not consistent with total patients in the SU cohort.

We apologize profusely for this error. In the revised manuscript, all of the values for race have been replaced with the correct values. In addition, we checked over all other values in Table 2 and found no additional errors.
Criticism 5: Table 3 shows that eye disease is also significant predictor of readmission. However, there was no description about this in the Results or Discussion sections.

We added the following to the Results section: “Other significant predictors of readmission were being single (HR 1.44, 95% CI: 1.04–1.99; p=0.030) and having eye disease (HR 1.45, 95% CI: 1.06–2.00; p=0.022).” We also added the following paragraph to the Discussion: “Unmarried patients had a statistically significant higher risk of hospital readmission than patients who were married. This result is consistent with a number of studies showing that marriage has a protective effect on mortality and hospitalization. The statistically significant effect of eye disease makes sense given that the strongest predictor for development and progression of retinopathy is duration of diabetes. Patients suffering diabetes for longer are more likely to develop eye problems as well as other complications leading to hospitalizations.”

Reviewer #3:

The largest component of medical expenditures for patients with diabetes is hospital inpatient care. Many hospitalizations of patients with diabetes result from hypoglycemia due to SU.

The objective of this study is to compare the risk for diabetes-related hospital readmission in patients with type 2 diabetes treated with SU compared to those treated with AHAs.

Using a retrospective cohort analysis, the authors demonstrate that patients treated with SU compared to those not treated with SU experienced higher rates of readmission and higher readmission costs. It's important to estimate relationships between SU use and risk of hospital readmission. Although the findings are of interest, this study still has some problems to be improved as indicated below.

My major comments are as follows.

1) Clinical information of patients treated with SU is not enough to compare the characteristics of patients. This study investigates the difference in the treatment of diabetes. So clinical information (such as blood glucose level, HbA1c, duration of diabetes, daily dose of an SU, number of hospitalizations etc) is required to understand the quality of treatment of diabetes.

Table 2 shows Perceived health status. However, it's difficult to estimate glycemic control in patients treated with SU.

Unfortunately, the MEPS database is lacking in clinical data that could be very useful in helping to predict hospital readmission. We have discussed this problem in the Limitations section of the manuscript. Moreover, in the revised version, we have added
the following sentence to the Abstract: “The lack of clinical data on disease severity and progression limited our ability to estimate causal relationships between drug use and risk of hospital readmission.”

2) There are lots of reasons of hospitalization. So it's difficult to assess the effect of SU.

Is hypoglycemia mainly associated with hospital admission?

It's better to describe the distribution of primary causes of hospitalization in this manuscript.

Thank you for this comment. We have added the following paragraph to the Results section of the manuscript: “For all of the cohorts identified in Table 1, cardiovascular disease was the most frequently occurring diagnosis at readmission. The second and third most common diagnoses were hypoglycemia and diabetes, respectively. Renal disease and eye disease accounted for very low percentages of readmission diagnoses (&lt; 10% and ≈ 1%, respectively).”

3) What kinds of patients take SU?

The authors should discuss such an issue to prevent hospital admission and reduce the costs.

In response to your comment as well as to a comment from another reviewer, we have added some more detail to the revised manuscript about the difference between SU and non-SU cohorts. The following text now appears in the Discussion: “In this study, the patients in the SU cohort were on average 8 years older than those taking a non-SU AHA, a fact that helps to explain the difference in readmission cost between the two cohorts. Older patients were both more likely to have additional comorbidities, requiring attention during the hospitalization, as well as more advanced diabetes. Moreover, as seen in Table 2, the SU cohort, before propensity-score adjustment, had a significantly higher percentage of patients with fair or poor perceived health status than those in the other cohort of patients, potentially lengthening and/or complicating their hospital stays.”

Here are the minor comments.

1) Figure legend is lacking in this manuscript.

Figure and Table legends should be explained in more detail.

For the revised manuscript, we have written the following detailed legends:

Figure 1. Kaplan-Meier Curves for Time to Readmission within One Year for Patients Receiving Sulfonylurea Monotherapy versus Monotherapy with another Oral Antihyperglycemic Agent. Each data point along the two curves represents the
proportion of patients not readmitted to the hospital after a specified length of time following their first diabetes-related hospitalization. At the end of one year, approximately 72% of patients taking a sulfonylurea remained out of the hospital, whereas over 80% of patients not taking a sulfonylurea had not been rehospitalized.

Table 1. Hospital Readmission Rates and Average Readmission Costs for Medication-Based Patient Cohorts: 1999-2010. The readmission percentage is found by dividing the number readmitted to the hospital by the total number of patients who experienced an initial diabetes-related hospitalization. Readmission cost is expressed in 2010 U.S. dollars.

Table 2. Baseline Characteristics for Patients Receiving Antidiabetic Monotherapy. Characteristics include demographic characteristics; insurance coverage; period of first hospital admission; comorbidities; medical care received; and disease severity. In order to achieve balance between the cohorts in characteristic distributions, propensity scores were estimated and used as a covariate in the Cox proportional hazard regression following a statistical check to see whether balance was achieved.

Table 3. Estimated Hazard Ratios from a Cox Proportional Hazard Regression with Time to Hospital Readmission as the Dependent Variable. After propensity-score adjustment, and controlling for demographic and other patient characteristics, patients on a sulfonylurea were 29% more likely to be readmitted to the hospital than patients on another oral antihyperglycemic agent. Unmarried patients and patients with eye disease were also more likely to be readmitted.

2) Please insert a p-value after ‘95% CI 0.93-1.52’ (line 22, page 10).

Done and thank you.

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

We have added the following sentence to the Methods section of our manuscript: “Because of the public nature of the MEPS database, the research did not require review and approval by the Institutional Review Board at the University of Cincinnati.”
Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation. If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

Not applicable, thank you.

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

Not applicable, thank you.

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.

Done and thank you.