Author's response to reviews

Title: Deaths from heart failure: Using coarsened exact matching to correct cause of death statistics

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Author's response to reviews: see over
Dear Ms. Houtz:

Attached please find the revised version of our manuscript titled “Deaths from heart failure: Using coarsened exact matching to correct cause of death statistics”, for consideration in Population Health Metrics.

We appreciated the constructive reviews and have adopted the comments in the revised manuscript, with responses to specific comments provided below. We have enclosed a version of the manuscript with all changes in redlines, as well as a clean version. The page numbers, table and figure numbers, and reference numbers provided below refer to the revised manuscript.

**Reviewer 1**

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1. At the least, add to argument for the matching method in the Discussion that ideally regression and matching methods would be compared head-to-head—how do they compare with one another (equivalency) and which produces the most consistent results across different populations?

*The matching method is in fact equivalent to a fully saturated multinomial regression (considering all higher-order terms and interactions). The main benefits of matching (as described on p. 10) are: 1) speed (the equivalent multinomial takes up to a week to converge on the desktop PC used for these analysis); 2) it eliminates the need to select disease groups, which can be data driven using the matching method; 3) it eliminates the need to test higher-order and interaction terms; and 4) unlike the logistic regression model, it does not make functional form assumptions, avoiding potential source of bias. Once the relevant disease groups were determined from the data, fitting a multinomial regression with the final match variables yields a very similar result (which we confirmed by running the regression). The discussion has been clarified to reflect this on page 10.*

2. Explain better how the matching categories chosen in the Methods. Data driven, based on prior experience?

*The following sentence was added on page 5: "Because the algorithm was not sensitive to how the variables in Table 2 were coarsened, we coarsened the variables until most treatment deaths could be matched to at least one control death.”*

3. State clearly if the average relative error was meant to be descriptive or the basis of decisions regarding valid or invalid.

*The text on p. 6 was clarified to indicate that the ARE is meant to be descriptive.*
- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Consider adding a description or small Table 1 with main etiologies of heart failure (ie hypertension, IHD, valvular disease, infections (including Chagas), idiopathic cardiomyopathies, etc), perhaps in the Introduction.

   The following text was added on page 4: "Heart failure is a leading ill-defined cardiovascular cause of death in the US and in many other countries [11]. Coronary heart disease is the primary cause of heart failure in the US, but in developing countries infections such as Chagas disease can play an important role (Krum 2009). Hypertension, diabetes, and overweight increase the risk of developing heart failure [15]. Determining heart failure etiology is often complicated by the presence of multiple co-morbid conditions [16]."

2. While discussing this, under what underlying cause of death listed in the present Table 1 does valvular disease fall? Can you confirm in the text that Chagas belongs under Cardiomyopathy?

   Chagas disease (B57) is included in "other diseases" and valvular disease (I08) is included in "other cardiovascular disease". Aside from Chagas in Brazil, few deaths are certified to these causes and few were redistributed to these causes. Thus, they were not shown separately. A statement about Chagas in Brazil was added to the text on page 7.

3. Background page 3: “Causes such as heart failure…violate standard protocols” not strong or clear enough, state “in the ICD system, heart failure is not allowed to be an underlying cause of death”

   The text on p. 3 states: "...the certifying physician often lists only the mode of dying, such as cardiac or respiratory arrest, shock, or heart failure. The World Health Organization’s International Statistical Classification of Diseases and Related Health Problems (ICD) rules specify that the mode of death should never be designated as the UCD, if another plausible cause is listed on the death certificate. Yet, certifying physicians regularly list only the mode of dying due to uncertainty about the UCD or lack of knowledge or interest in correct procedures for completing a death certificate."

4. Methods first full paragraph on page 7. Assume that authors meant something like:

   “US deaths with heart failure listed as the UCD were matched with...2888 deaths with death certificate mention of heart failure but another disease as the UCD”

   The text was clarified as suggested.

5. Limitations—suggest mentioning that the 13% of heart failure assigned to diabetes in Mexico may be due to cause of death assignment problems related to diabetes itself.

   While we strongly suspect that too many deaths are certified to diabetes in Mexico, to our knowledge there is no study that specifically demonstrates that. The paper by Murray et al.
did indicate that those individuals who had access to better health care were less likely to be assigned diabetes as an underlying cause of death. Nevertheless, this is another example of the problem discussed in the 2nd paragraph on page 11 -- it could reflect an epidemiologic difference or a problem with certification of deaths. A statement was added to the discussion highlighting this possibility.

6. Is the high rate of cardiomyopathy as heart failure UCD in Brazil due to Chagas? Can you check how often Chagas is mentioned on death certificate part 2 of “cardiomyopathy” UCDs in Brazil?

Chagas is only mentioned on a handful of death certificates certified to cardiomyopathy, however, like you, we suspect that the higher rate of cardiomyopathy in Brazil is related to Chagas disease. The text added in response to comment #2 clarifies that deaths certified to Chagas disease are not included in the cardiomyopathy category.

7. “Table 2” mentioned second paragraph of page 7 should be Table 3.
8. typo (backslash) in the first full paragraph, first sentence of page 10

The reference and typo have been fixed.

9. Same paragraph, page 10, more attribution to HF in Egypt may not just be “physician culture” but also more diagnostic uncertainty (unable to identify the UCD).

We do consider this physician culture: Egyptian physicians may be more likely to use heart failure when there is uncertainty about the underlying cause of death. The text was clarified to reflect this.

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
10. As stated above, the final paragraph of the Discussion, and perhaps a few words in the Conclusion could be devoted to: How the ICD be structured to better capture multiple causes of death/multiple underlying causes of death? What would improve death certificate reporting? Should heart failure be designated an underlying cause?

A section was added discussing cause-of-death classification at the end of the discussion section.

11. For external validity, brief description in the Discussion of prevalence and/or incidence of hypertension, ischemic heart disease, smoking in each nation (this is available for the U.S. (NHANES), should be for Mexico, but may be unavailable for Brazil. The pattern of more stroke, less IHD mortality in Brazil in Mexico—would expect reflective of more hypertension-related disease.

The reviewer is asking a more general question about overall death certification in these countries, which is out of the scope of this current analysis. This analysis considers only
the associate of heart failure with various causes, which may be related to the underlying epidemiology, but may also have to do with physician practice.

12. The authors do not state how often one of the heart failure causes is listed in death certificate part 2 (multiple cause) alongside a heart failure UCD. For instance, how often is hypertension listed in a part 2 below IHD as the UCD? Could this information be used to establish some uncertainty bounds around the allocations, and give a hint of overlapping multiple causes of heart failure?

We agree with the reviewer -- we did perform the analysis mentioned above but decided that considering only causes listed in part 1 of the death certificate was more defensible, and therefore chose not to present the results that considered causes listed in part 2 of the death certificate.

Reviewer 2

Details comments:
1- In the Methods heading (page 4), the authors mentioned that underlying causes of death is selected typically using the automated coding system developed by the U.S. National Center for Health Statistics (line 24-26). This system is not used in many countries, particularly developing countries. Hence, it should be clarified that the two countries in study (except U.S) are used the automated coding system or not.

This was clarified on p. 6.

2- It seems that there are some mistakes to reference tables in the text, for instance, in page 7 (line 9) should be Table 3 and also in the title of table 3 (page 16) match variables are shown in Table 2 not in Table 1.

The references have been fixed.

3- In page (10) it has been mentioned that 18% of recorded deaths were certified to heart failure in Egypt in 2007 (line 14), but reference for this estimation has not been mentioned.

The reference has been added.

Thank you for having managed the review of the paper. We look forward to your and the Editorial Board’s response and would be glad to answer any further questions you may have on the manuscript.

Sincerely,

Gretchen Stevens, D.Sc.