PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Excess mortality in adults with documented diabetes in Germany – Routine data analysis of all insurance claims in Germany 2013-2014
AUTHORS	Schmidt, Christian; Reitzle, Lukas; Heidemann, Christin; Paprott, Rebecca; Ziese, Thomas; Scheidt-Nave, Christa; Baumert, Jens

VERSION 1 – REVIEW

REVIEWER	Hiroshi Yokomichi University of Yamanashi, Japan
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	Paper by Dr. Schmidt C et al treated all-cause mortality in having and not having diabetes, using health insurance data of Germany. I would like to provide comments to increase impact of the manuscript. [Major] 1. Introduction: Mortality rate by 5 years of age in Caucasian country may have been already published. The researchers could introduce it and explain why they need to analyse it in Germany. Also, they could present the rates of representative Caucasians, Orientals and Africans as global epidemiologic data. 2. Analysis: If it is possible, instead of index of MMR, excess mortality rate may have more impact for readers in medical science. 3. The outcome is single as all-cause mortality. Having diabetes results in CVD and cancer. Isn't it possible to utilise the other major death causes? 4. Diabetes types: Generally, patients with type 1 and 2 diabetes have difference prognoses. Is it possible to analyse mortality rate by diabetes types? There also exists gestational diabetes and the other diabetes. 5. Table 1: If it is possible, instead of mortality rate, expected life-span at each age group may have more impact; The index would be more useful. This may be difficult for researchers. I wonder that integration of the inverse of the presented mortality by 5 age may enable presenting expected life-span. 6. Figure 2: The exponential increase in mortality with advanced age may not be new finding in epidemiology of diabetes. This figure may ensure the data accuracy. However, I consider that a single figure could independently contain new finding. What is the new finding in the figure 2? Is it difference between datrav and destatis? I may be able to propose drawing the exponential curve of the two sexes in a single figure to compare the sex difference in Germany, or inserting the exponential curves from data of another nation.

	7. Figure 3: Transposition of longitudinal and horizontal axes may increase understandability of the data. [Minor] 8. Table 1 and 2: M and MMR need to be spelled out. Tables and figures need to stand alone with understandability. Although I requested many points, I consider that this manuscript would contribute to epidemiology of diabetes, when it would be revised.

REVIEWER	Rosa Sicari CNR, Institute of Clinical Physiology, Pisa, Italy
REVIEW RETURNED	04-Dec-2020

GENERAL COMMENTS	This is a very well conducted analysis on the mortality rate of patients with and without diabetes using the dataset of health insurance claims in Germany. Authors' conclusions is that the public system for diabetes surveillance should be improved, especially for the higher risk groups (younger people). There are some, minor issues that need to be addressed: 1.In the abstract please avoid to use expressions such as "for the first..." 2.The discussion is quite long and should be more focused on the use of these results to improve diabetes surveillance. 3. No data are reported on the impact of therapy. It would be interesting to link mortality to type of therapy and adherence.

VERSION 1 – AUTHOR RESPONSE

REVIEWER(S) COMMENTS:

General note to the reviewer and editorial team:
We would like to thank Dr. Sicari and Dr. Yokomichi for their helpful comments and recommendations. As you can see, we have discussed every point and made changes were possible. We chose blue marking for discussion and red marking for change.

Reviewer: 1

Reviewer Name: Hiroshi Yokomichi
Institution and Country: University of Yamanashi, Japan Competing interests: None declared.

Comments to the Author
Paper by Dr. Schmidt C et al treated all-cause mortality in having and not having diabetes, using health insurance data of Germany. I would like to provide comments to increase impact of the manuscript.

[Major]
1. Introduction: Mortality rate by 5 years of age in Caucasian country may have been already published. The researchers could introduce it and explain why they need to analyse it in Germany. Also, they could present the rates of representative Caucasian people, Oriental people and African people as global epidemiologic data.

Reply:
First, regarding the commentary on already published results of other Caucasian countries: We already present studies from Sweden, Scotland and Denmark (line 87 to 91) and from Australia (line 96 to 98).
Second, to emphasize the novelty and potential contribution of our study to public health, we clarify our objectives by underline the potential of the study data:
Lines 111-113: Due to partly conflicting findings stated above, further research is needed to increase knowledge on diabetes-related excess mortality, especially with respect to differences in magnitude by age, sex, region and time trend.
Lines 116-118: As almost 90% of the population is covered by statutory health insurance, this data source has enormous potential for public health research, including detailed analyses of mortality patterns.
Lines 122-128: Up to now, diabetes-related MRRs from the age of 30 years in 5-years age bands have not been available for the German population. Against this background our main aim was to provide for the first time estimates of MRRs related to diabetes within strata of narrow age bands and sex for Germany and thus adds important knowledge in diabetes-related excess mortality. Deeply stratified mortality rates based on valid data are important for the surveillance of diabetes in Germany, as they allow a comparison over time and with other countries.
Third, Dr. Yokomichi's last point concerns the presentation of mortality rates, particularly for Caucasian people. This is very important because we know that ethnicity is a potential factor in the development and progression of diabetes. Due to the missing information about the ethnic origin in the study data, this issue can not be addressed in our study. Clearly, it is a further limitation of routine data. But we take the ethnicity into consideration from line 402 onwards: In general, another limitation of routine data is that this data cannot identify the ethnicity of individuals. An ethnic risk profile is being discussed for diabetes in particular (https://doi.org/10.1136/bmj.k1497). This reference is a paper published in BMJ 2018 which estimated prevalence in the US population and categorized ethnicity into Hispanic, non-Hispanic white, non-Hispanic black, non-Hispanic Asian, and other. For example, type 2 diabetes was higher among non-Hispanic Asians.
2. Analysis: If it is possible, instead of index of MMR, excess mortality rate may have more impact for readers in medical science.
Reply:
One important application of the mortality rate ratios provided in our paper is to calculate excess deaths related to diabetes for Germany. We adapted the methods from a study conducted by Jacobs et al. (https://doi.org/10.2337/dc17-0954), who calculated excess deaths for Germany, by taking mortality rates from Denmark 2007. Using the same methodological approach, our estimates are considerably lower because of the differences in mortality rates between Denmark and Germany.
From line 324 onwards: The study by Jacobs et al. calculated, on the basis of the DaTraV dataset as well, the excessive deaths for women and men over 40 years of age in Germany. As such data were not available for Germany at that time, Jacobs et al. used the mortality rates from the Danish National Diabetes Register instead. This study estimated absolute excess deaths related to diabetes of 81,703 for women and 92,924 for men. In contrast, using the same methods but the estimated MRRs for Germany in our study, we found considerably fewer absolute excess deaths of 49,136 for women and 53,872 for men.
The outcome is single as all-cause mortality. Having diabetes results in CVD and cancer. Isn’t it possible to utilise the other major death causes?
Reply:
3. We analyzed all-cause mortality to derive excess mortality on the common assumption that diabetes is related to mortality via various paths. Certainly, CVD is one of the main death causes. In contrast to register data as used for example by Tancredi et al., our study data do not include the cause of death. In future work, we will process queries to address certain comorbidities together with diabetes to estimate all-cause mortality in diabetes associated with different comorbidities.

4. Diabetes types: Generally, patients with type 1 and 2 diabetes have difference prognoses. Is it possible to analyse mortality rate by diabetes types? There also exists gestational diabetes and the other diabetes.
Reply:
Type 1, type 2 and other forms may differ in terms of mortality. As we already stated out from line 422 onwards in our manuscript, there are difficulties in routine data (not exclusively there) to differentiate the types of diabetes in valid manner.
Because we see the reviewer's point we now emphasis this limitation as one of the five bullet points in the "strengths and limitations" just after the abstract.
We have not distinguished the type of diabetes because routine data contain implausible double diagnoses of type 1 and type 2 diabetes in the same person.
5. Table 1: If it is possible, instead of mortality rate, expected life-span at each age group may have more impact; The index would be more useful. This may be difficult for researchers. I wonder that integration of the inverse of the presented mortality by 5 age may enable presenting expected life-span.
Reply:
We would like to avoid such calculation in table 1. Instead, we quote in line 380 a suitable new reference (https://doi.org/10.1093/eurpub/ckaa165.814), which calculates life expectancy and healthy life years using the study data together with additional data sources.
6. Figure 2: The exponential increase in mortality with advanced age may not be new finding in epidemiology of diabetes. This figure may ensure the data accuracy. However, I consider that a single figure could independently contain new finding. What is the new finding in the figure 2? Is it difference between datrav and destatis? I may be able to propose drawing the exponential curve of the two sexes in a single figure to compare the sex difference in Germany, or inserting the exponential curves from data of another nation.
Reply:
Since we use the concept of all-cause mortality, a good match of counted deaths in the study data compared to all counted deaths in the official statistics is very important for validity. This match is not natural. Otherwise, if the match were not as good as shown in Figure 2, our mortality rates would be biased and the derived mortality rates would not be valid for the German population. Thanks to the advice of Dr. Yokomichi given in point 2 above, we calculated absolute excess deaths for woman and men for Germany and compare them with a former study using mortality rates coming from a different country. Obviously, using valid mortality rate ratios change the excess deaths related to diabetes. This example demonstrates how important a good match between official death statistics and the study data is.

7. Figure 3: Transposition of longitudinal and horizontal axes may increase understandability of the data.
Reply:
We tried several options but in the end concluded that changing the axes didn't help, but we did change the design and style to hopefully make Figure 3 easier to understand.

[Minor]
8. Table 1 and 2: M and MMR need to be spelled out. Tables and figures need to stand alone with understandability.
Reply:
We changed the headings in N in million (delete M in columns) and Mortality rate ratios.

Although I requested many points, I consider that this manuscript would contribute to epidemiology of diabetes, when it would be revised.

Thank you!

Reviewer 2 minor comments

1. In the abstract please avoid to use expressions such as "for the first..."
Even if it is true, we have followed the recommendation of the reviewer and deleted "for the first time" in our abstract: In line 52 we delete for the first time, and put We in front of the sentence.

2. The discussion is quite long and should be more focused on the use of these results to improve diabetes surveillance.
We agree with the reviewer that our discussion is quite long, but also think that this is due to the relatively short other parts of our paper. Moreover, we think that the discussion is the most important part of the paper, at least in our case. In the discussion, we emphasize the use of our results for surveillance purposes, not just diabetes. We think that our work is itself a contribution to diabetes surveillance and at the same time opens the perspective to use the presented data for other, mainly non-communicable diseases.
Therefore, we have not made any changes.

3. No data are reported on the impact of therapy. It would be interesting to link mortality to type of therapy and adherence.
This is a very important point. The study data are clearly limited and cannot cover concepts such as therapy and adherence. We have already discussed the point in calling for prospective population-based studies that can actively address both risk factors and adherence to prescribed therapy.
In line 366 we add: …., adherence to prescribed therapy

VERSION 2 – REVIEW

REVIEWER	Hiroshi Yokomichi University of Yamanashi, Japan
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	The researchers have addressed all of my comments. I have no more concern. I appreciate their efforts to report the important results.

REVIEWER	Rosa Sicari Institute of Clinical Physiology
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	Authors have addressed all the issues raised by this reviewer.