PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Observational study of vascular dementia in the Spanish elderly population according to type 2 diabetes status: trends in incidence, characteristics and outcomes (2004-2013)
AUTHORS	Jimenez-Garcia, Rodrigo; Muñoz-Rivas, Nuria; Mendez-Bailon, Manuel; de Miguel-Yanes, Jose; Hernandez-Barrera, Valentin; de Miguel-Diez, Javier; Lopez-de-Andres, Ana

VERSION 1 - REVIEW

REVIEWER	Sunil Kumar Raina Department of Community Medicine Dr. RP Govt. Medical College, Tanda (Kangra) Himachal Pradesh (India)
REVIEW RETURNED	11-Mar-2017

GENERAL COMMENTS	1. The research question is not completely answered. Trend indicates a direction, upward or otherwise; which is not clear in the abstract although has been answered in results in the main manuscript. The statistical analysis mentions use of using $\chi 2$ linear trend analysis (proportions); which is appropriate. However, trends have not been described (in text) as linear or otherwise. 2. The method section has not been detailed adequately and requires a review of supplementary data to understand the methods. Some detail of how calculation each missing years were arrived is needed. Given the fact that all adjustments in incidence were made for year 2013 for a trend study conducted over 10 years(with attempt to reflect on yearly trend through tables) period with variables (Diabetes/ Hypertension) of interest apparently on the increase in last decade or so across the world, I would like to interpret the results with caution without a detail in these calculation. 3. Issues related to ethics need to be evaluated in view of the prevailing laws regarding conduct of study in that country. 4. Calculation of incidence on the basis of a database (with missing records for some years), without any access to socio-demographic variables is another limitation.

REVIEWER	Oskar Hansson Lund University, Sweden
REVIEW RETURNED	14-Mar-2017

GENERAL COMMENTS	In the manuscript by Muñoz-Rivas et al, the authors found that the incidence of VaD was higher among people with T2DM over the study period, especially in men. They also found that pneumonia and parenteral nutrition were associated with mortality. The manuscript is relevant and generally well written, but there are some

	concerns: 1) Did the authors study have the possibility to validate the VaD diagnosis? For example, could they select a random smaller set of study participants and study the medical records of these cases to estimate the accuracy of the VaD diagnosis according to the Spanish National Hospital Database. 2) Similarly, the diagnosis of T2DM could maybe be studied in a random smaller set of study participants, using the medical records. Here the medications at discharge from hospital would quite easily reveal whether the patient have T2DM or not. 3) In the abstract the authors write “T2DM was positively associated with VaD hospitalization (IRR 2.14, 95%CI 2.11-1.16).” But this does only seem to be true for men, and not women (see page . Please clarify. Further, the CI for men might be wrong (2.11-1.16, maybe it should be 2.11-2.16?). 4) The authors could also include “previous stroke” as confounding variable in the statistical analyses to be able to study whether T2D is a risk factor of VaD independent of stroke, i.e. via microvascular damage. This could be done in the Poisson regression models when studying the time trend in the incidence due to VaD. 5) Finally, the impact of the paper would be much higher if the authors also investigated whether the incidence of “discharge from hospital with VaD” is more frequent among all individuals in Spain with T2D versus those in Spain with no T2D. In order to do that all T2D cases in Spain could be matched with 1:1 (or 1:2) to non-T2DM cases in Spain based on e.g. age, gender and where they live. Then occurrence of VaD could be compared between the two groups. But maybe this is out of the scope of the present study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

COMMENT
1. The research question is not completely answered. Trend indicates a direction, upward or otherwise; which is not clear in the abstract although has been answered in results in the main manuscript. The statistical analysis mentions use of using $\chi 2$ linear trend analysis (proportions); which is appropriate. However, trends have not been described (in text) as linear or otherwise.

ANSWER
Thank you for this comment. The abstract has been corrected to indicate the trend direction in the incidence with the following sentence.
“We found a significant upward linear trend in the incidence of vascular dementia for men and women with and without diabetes from 2004 to 2013.”
Following your suggestion we have clarified that the trends are linear in the text of the manuscript.

COMMENT
2. The method section has not been detailed adequately and requires a review of supplementary data to understand the methods. Some detail of how calculation each missing years were arrived is needed. Given the fact that all adjustments in incidence were made for year 2013 for a trend study conducted over 10 years(with attempt to reflect on yearly trend through tables) period with variables (Diabetes/ Hypertension) of interest apparently on the increase in last decade or so across the world, I would like to interpret the results with caution without a detail in these calculation.

ANSWER
Sorry if this was unclear. The following paragraph has been included in the supplementary methods file.
“We calculated the adjusted incidence of discharge rates after vascular dementia (VaD) for men and women with and without type 2 diabetes (T2DM) per 100,000 inhabitants by age groups and overall. To do so we used the Spanish populations for each year studied according to the Spanish National Statistics Institute as reported on December 31 of each year. [1]. To stratify the population according to diabetes status we used data obtained from National Health Surveys (NHS) conducted in 2003/4, 2006/7, 2009/10 and 2011/12 and data from Di@bet.es Study.[2, 3] All these surveys allow us to have an accurate prevalence estimation of diabetes by sex and age groups.[4] Then we multiply the prevalence of diabetes for each sex- age group and year by the Spanish population that same year to obtain the people with and without diabetes.
From 2001 till 2012, Spanish NHS has been done every two or three years. We estimated a rate fitting model using linear regression with prevalences of diabetes from years 2003/4, 2006/7, 2009/10 and 2011/12 when NHS was available. Then we used this model to impute prevalences and to estimate the population suffering diabetes by sex and age groups for those years when NHS was not conducted, those are years 2005, 2008 and 2013.
Once this was done we used the direct standardization method to calculate the adjusted incidences for each diabetes status stratified by age groups and sex using the Spanish population for year 2013 as standard.
We only use standardization methods for incidences. The proportions of clinical conditions and diagnosis and therapeutic procedures are not adjusted. The values shown in the results are the observed prevalence, calculated by dividing the number of subject with these conditions or procedures by the number of observed vascular dementia admission for the year studied.”

COMMENT
3. Issues related to ethics need to be evaluated in view of the prevailing laws regarding conduct of study in that country.

ANSWER
The following paragraph related to ethics has been added to the main document
“Data confidentiality was maintained at all times in accordance with Spanish legislation. Patient identifiers were deleted before the database was provided to the authors in order to maintain patient anonymity. It is not possible to identify patients on individual levels, either in this article or in the database. Given the anonymous and mandatory nature of the dataset, it was not necessary to obtain informed consent according to the Spanish legislation. The study protocol was approved by the ethics committee of the Universidad Rey Juan Carlos.”

COMMENT
4. Calculation of incidence on the basis of a database (with missing records for some years), without any access to socio-demographic variables is another limitation.

ANSWER
Thank you for this comment. We agree that the lack of socio-demographic variables is another limitation. This comment has been added to the limitations section with the following sentence.
“Calculation of incidence on the basis of a database without any access to socio-demographic variables is another limitation.”

Reviewer: 2

COMMENT

In the manuscript by Muñoz-Rivas et al, the authors found that the incidence of VaD was higher among people with T2DM over the study period, especially in men. They also found that pneumonia and parenteral nutrition were associated with mortality. The manuscript is relevant and generally well written, but there are some concerns:

ANSWER

Thank you for your constructive comments that will surely improve the manuscript.

COMMENT

1) Did the authors study have the possibility to validate the VaD diagnosis? For example, could they select a random smaller set of study participants and study the medical records of these cases to estimate the accuracy of the VaD diagnosis according to the Spanish National Hospital Database.

ANSWER

Thank you for this comment. The following paragraph has been added to the limitations section to clarify this point

“Finally, as we state in the ethics section patient identifiers were deleted before the database was provided to us in order to maintain patient anonymity and it is not possible to identify patients on individual levels, either in this article or in the database. Therefore it is impossible for us to select a sample of study participant and to identify their medical records in order to validate the VaD and T2DM diagnosis because we don’t know in which hospital the participant was admitted.

Van de Vorst et al assessed the validity of the Dutch Hospital Discharge Register (HDR) for vascular dementia by comparing the ICD 9 MD codes with medical records. These authors concluded that the validity of using HDR codes to identify patients with dementia is high. For VaD the positive predictive Value (PPV) was of 91.3% (95% CI 72.0-98.8%) and there were no significant differences in PPV according to age, gender, setting of diagnosis, and comorbidity.[31]”

31. van de Vorst IE, Vaartjes I, Sinnecker LF, Beks LJ, Bots ML, Koek HL. The validity of national hospital discharge register data on dementia: a comparative analysis using clinical data from a university medical centre. Neth J Med. 2015;73:69-75.

COMMENT

2) Similarly, the diagnosis of T2DM could maybe be studied in a random smaller set of study participants, using the medical records. Here the medications at discharge from hospital would quite easily reveal whether the patient have T2DM or not.

ANSWER

As commented in the previous point it is no possible for us to conduct a validation study given the anonymity of our data. As discussed in the limitations section the Spanish discharge data base does not include information on treatments.

The following paragraph has been added to the limitations section to discuss the validity of the diabetes diagnosis in discharge databases.

“Regarding the validity of diabetes diagnosis a recent review and meta-analysis found that a commonly-used administrative database definition for diabetes (2 physician outpatient billings and/or one hospitalization with a diabetes record on the discharge abstract summary within a two-year period) has a pooled sensitivity of 82.3% (95%CI 75.8, 87.4) and specificity of 97.9% (95%CI 96.5, 98.8%), based on the findings of six studies with complete data available. [32]

In Canada, Kokotailo et al found that, among patients with stroke, when compared with hospital

medical record the ICD 9 MD diagnosis of DM in the discharge report had a sensitivity of 94% (95%CI 69–99) and an specificity of 98% (95%CI 91–99). [33]"
32. Leong A, Dasgupta K, Bernatsky S, Lacaille D, Avina-Zubieta A, Rahme E. Systematic review and meta-analysis of validation studies on a diabetes case definition from health administrative records. PLoS One. 2013 Oct 9;8(10):e75256.
33. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. Stroke. 2005;36:1776-81.

COMMENT
3) In the abstract the authors write "T2DM was positively associated with VaD hospitalization (IRR 2.14, 95%CI 2.11-1.16)." But this does only seem to be true for men, and not women (see page . Please clarify. Further, the CI for men might be wrong (2.11-1.16, maybe it should be 2.11-2.16?).

ANSWER
Sorry for this mistake. The correct confidence interval is 2.11-2.16. This typing error has been corrected in the abstract and main text.
You are right, thank you very much for detecting this relevant mistake. There is a typing mistake in the IRR for women in page 15, the correct value is 2.22 (95% CI 2.19-2.25) not 0.75. So T2DM was positively associated with VaD hospitalization for men and women with T2DM.
The abstract and text have been corrected.

COMMENT
4) The authors could also include "previous stroke" as confounding variable in the statistical analyses to be able to study whether T2D is a risk factor of VaD independent of stroke, i.e. via microvascular damage. This could be done in the Poisson regression models when studying the time trend in the incidence due to VaD.

ANSWER
Thank you for this comment. We agree that previous stroke is a relevant confounding variable when vascular dementia is analyzed. Following your suggestion we have added new lines in tables 1 and 2 to describe the prevalence of "Previous stroke" among men and women with and without diabetes.
We did not include "Previous stroke" independently in the Poisson regression because it is one of the diseases included in the Charlson Comorbidity Index (CCI). We think that is better to use the CCI as a confounding variable rather that to introduce the different diseases one by one. However as can be seen in Table 1 and 2 the changes observed in the prevalence of "previous stroke" over time are of small magnitude and even not significant among diabetic women, so the confounding effect of this variable, if any, would be small.
The methods and results sections have been changed accordingly. The following sentences have been included:
Methods section
Page 5. "We specifically analyzed the presence of previous stroke (ICD 9MD codes 430.x, 431.x, 433.x1, 434.x1, 435.x, 436, and 362.3),"
Results section.
Page 9. "The prevalence of previous stroke was similar and near to 50% among men with and without diabetes in all years studied and rose significantly over time ($p<0.001$) from around 46% to 52% in both groups of patients."
Page 11. "Among women, the overall prevalence of previous stroke was significantly higher for diabetic than non-diabetics (49.12% vs. 47.71%). Only among women without diabetes a significant increase was found from 2004 to 2013. "

COMMENT
5) Finally, the impact of the paper would be much higher if the authors also investigated whether the incidence of “discharge from hospital with VaD” is more frequent among all individuals in Spain with T2D versus those in Spain with no T2D. In order to do that all T2D cases in Spain could be matched with 1:1 (or 1:2) to non-T2DM cases in Spain based on e.g. age, gender and where they live. Then occurrence of VaD could be compared between the two groups. But maybe this is out of the scope of the present study.

ANSWER
Thank you very much for your suggestion. Matching T2D cases in Spain to non-T2DM cases is surely a brilliant idea and we will do it in future investigations. However it is out of the scope of the present study and it would suppose to make new tables and a new results section.