Author’s response to reviews

Title: Factors Associated with Type 2 Diabetes in Patients with Vascular Dementia: A Population-Based Cross-Sectional Study

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Author’s response to reviews:

Reviewer reports:

Andrew Smyth, MB PhD (Reviewer 1):

1. You state that this is a cross-sectional study but in the abstract describe incident dementia - this is not possible in a cross sectional study. You also describe that you 'retrospectively investigated the factors associated with type 2 diabetes'. Is this a cross-sectional study or retrospective cohort study? In the background you then discuss 'prevalence of DM-related complications. Which is it - incidence or prevalence?

Ans: We apologized using these inaccurate words to result in your misunderstanding. To avoid confusion, we have deleted the inappropriate word and rewritten the sentence. As your valuable suggestions, prevalence should be used in this cross-sectional study.

2. Do you think that it is adequate to base the presence/absence of diagnoses of diabetes and mellitus on administrative data? Just because a random sample of administrative data are checked each years and false reports are associated with a penalty - who does this check? Would it not be better to have actual clinical criteria to make these diagnoses?

Ans: Thank you the comments. High validity of disease diagnosis codes in this claim data can be expected because Taiwan National Health Insurance Program (TwNHIP) has performed a well
medical review system to prevent waste, safeguard quality, and maintain the public’s healthcare safety and quality[1]. This review process follows two tracks: a procedural review track and a professional peer review track. Procedural review has been carried out through physician’s order automated review and profile analysis by computer. Professional peer review is regularly performing monthly based on unusual volumes of medical services in the different types of reimbursement methods. In addition, the highly accuracy of DM diagnosis on this administrative data had been demonstrated by previous study[2]. The results of further sensitivity analysis that changeing definitions of DM confirmed our expectation.

3. What is the primary research question - prevalence of diabetes in those with dementia? Why not the prevalence of dementia in those with diabetes? I’m not sure I understand why it is important to look at the prevalence of diabetes in those with dementia. Surely it would be more relevant to see what the rate of dementia is in all of those with diabetes – if the contention is that dementia is a potential complication of diabetes?

Ans: The prevalence of dementia in DM population can reflect the load of cognition disorder in clinical DM care. It is interesting, particularly in how to avoid dementia case occurring or to recognize care burden of dementia in DM population. Our study, on the other hand, would like to emphasized the important burden and associated factors of DM in dementia population who usually lose their self-care ability or lack effective care supportive system. These findings from our results should be important to physician to arrange glucose screening and monitoring procedures based on patient’s characteristics and provide appropriate knowledge of DM management to care giver.

4. Please explain and justify why chronic pulmonary disease is considered a cardiovascular disease?

Ans: We put them into the same group of systematic disease because it has been considered as novel risk factor of ischemic heart disease [3]. Chronic pulmonary disease usually causes chronic inflammatory process. Several inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, C-reactive protein (CRP), and fibrinogen can directly result in vascular damage, an early stage of cardiovascular disease.

5. Please justify the appropriateness of combining renal disease and an abnormal lipid profile.

Ans: Past large observational studies had demonstrated that lipid abnormal would increase risk of renal dysfunction[4, 5]. In addition, lipid metabolism is highly influenced by chronic renal
disease[6, 7]. We put them into together to highlight the important of co-management of both diseases.

6. Is there any data on how reliable the Charlson comorbidity index is, when calculated based on administrative data? Given the distribution of the Charlson Comorbidity Score in participants in this cohort, it is not appropriate to compare with t-test, suggest that you review this.

Ans: The reliable of the Charlson comorbidity index on administrative data has been explored by a previous study. Dale M. Needham et al. systematically reviewed literatures using admission diagnosis and comorbid disease information available from Canadian administrative databases to be risk adjustment[2]. They found that highly agreement of disease diagnosis between the database and chart review, and mortality prediction did not differ between the two methods. Therefore, we believe that Charlson comorbidity index can represent as disease severity index on this national administrative database. Furthermore, we have changed the statistical method to Mann-Whitney U test and the result has no significant change (table 1).

7. What is meant by 'multivariable logistic regressions'? What was adjusted for?

Ans: In our study, there were two models using multivariable logistic regression. One is adjusted for demographic factors, comorbidities, and disease severity. The other one is adjusted for demographic factors, various systematic comorbidities, and disease severity. We have added this information “Multivariable logistic regressions adjusted for sex, age, income, area of residence, urbanization, and comorbidities were run to identify the independent factors associated with type 2 diabetes mellitus.” on footnote of table 2 and “Multivariable logistic regressions adjusted for sex, age, income, area of residence, and urbanization, and various systematic comorbidities were run to identify the independent factors associated with type 2 diabetes mellitus.” on footnote of table 3 in the new edition.

8. Is the opening line of the results meant to convey that 22.5% of patients with dementia have diabetes? If so, then say so.

Ans: We have changed it based on this valuable suggestion.

9. Are the factors that are linked to DM in dementia similar to those linked to DM in the general population without DM?
Ans: Thank you for this suggestion. It is not easy to compare factors link to DM in both populations due to different main purposes. Most studies used general population to identify preventable factors associated with DM incidence. By contrast, most patients with dementia may accompany with multiple chronic diseases and DM. Dementia population is more suitable to investigate multiple chronic conditions interrelatedness, particular in DM, a disease need patient self-management. We added below information into our discussion to highlight this point. “These chronic diseases may share similar risk factors or etiology pathway. Although anthropometric, dietary, and life style factors have been considered in relation to developing type 2 DM in general population[8], most of these risk factors were not easily obtained in patient with dementia. Identification of disease factors associated with DM may be more intuitive and more efficient than traditional DM risk factors for physician providing optimal DM care for patients with dementia.”

10. What is meant by the phrase 'and younger (range of admitted OR: 0.55-1.13)’? Is this one OR with a confidence interval or to represent a number of different variables?

Ans: We categorized patient into age group of <65, 65-74, 75-84, and ≥85 years of age. The phrase 'and younger (range of admitted OR: 0.55-1.13) ' reflects the results in table 2. We observed that age 65-74 (adjusted OR: 1.13, 95%CI: 1.03-1.24), age 75-84 (adjusted OR: 0.86, 95%CI: 0.78-0.95), and age ≥85 (adjusted OR: 0.55, 95%CI: 0.49-0.62) were independently associated with DM compared to age <65 years.

11. Explain what is the difference between an association between DM and comorbidities etc, and then stating that you 'also analysed the associations of DM with income, etc'.

Ans: Thank you for this kind suggestion. We had rearranged the order in sequence of our paragraphs based on this suggestion. Please refer to discussion part in the new edition.

12. Is it surprising that DM prevalence was higher in those with more comorbitity? How many of those are established complications of diabetes?

Ans: Traditional DM-related complications include microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications (heart attack and stroke). Therefore, 3 comorbidities (myocardial infarction, cerebrovascular disease) can typically be listed as DM-related complications.
13. Explain the validity of the statement 'a greater number of renal/metabolic system related diseases' when there are only 2 disease included in that 'group'.

Ans: We had changed the phrase into “both with hyperlipidemia and renal disease” in the abstract.

14. Your statement that screening for dementia in patients with diabetes doesn't make sense – the way your paper is designed suggests that you should screen for diabetes in patients with dementia as 1/5 of them will have it. You have no estimate of the proportion of people with diabetes that will develop dementia.

Ans: Thank you for the valuable suggestion. These sentence have been changed by emphasizing the need for co-management of related metabolic system diseases to help prevent DM-relative complications in dementia.

15. Is it new information that lower income status is associated with diabetes? Surely not, as low socioeconomic status has been linked with higher rates of many chronic diseases. Your argument after the statement 'low income level to be associated with a higher prevalence of DM' is actually explaining the association between low income level and dementia, not diabetes.

Ans: We totally agree your point. The mechanism and association between low income, diabetes, and dementia are quite complex and may beyond the scope of this study. We believe further study is needed to clarify these relationships. As the discussion we mentioned that the findings from our results raising the importance of DM management especially in low-income patient who were usually short of sufficient supportive resources.

16. The grouping of comorbidities with similar pathophysiologies speaks more to the fact that those conditions are established complications of diabetes, rather than new mediators of the association between diabetes and dementia. Treatment of those disorders is primarily aimed at preventing worsening of those conditions, which may as a by product reduce the future risk of dementia, but to state that the reason for treating hypertension in diabetes is to prevent dementia is excessive.

Ans: We have changed similar pathologies to similar manageable risk factors, deleted inappropriate sentences, and rewritten the discussion part.
17. I don't understand Table 3 – how can CVD yes vs no have an OR or 3.93 but the number of CVD shows 1-3 is only 2.28 and 4-6 is only 2.33? This doesn't make sense. It also doesn't make sense to group the digestive disorders if there are only 2, and the renal/metabolic if there are only two. It looks like it doesn't matter if you have 2 vs 1 GI disease, but that there is an interaction between renal disease and hyperlipidemia. That analysis would be more interesting and appropriate. Also explain how the estimate for cancer in Table 2 and Table 3 are different? Is it not a single predictor variable?

Ans: Thank you for this comment. We have carefully inspected these results and explained the possible differences by adding adjusted factors in the table footnotes. One reason that make the combining OR obviously larger than each separated ORs of related disease is different disease characteristics in the control groups. The patients in the control group of combining OR were healthier (neither having myocardial infarction or congestive heart failure or peripheral vascular disease or cerebrovascular disease or chronic pulmonary disease or hypertension) than who were in the control group of each separated related disease. For example, 30.8% of the patients in the non-MI group had cardiovascular disease, and 7.8% of them have congestive heart failure. Those comorbid diseases in the control groups may also associated with DM that causes the OR values toward to be one.

Ronan O’Caoimh (Reviewer 2): BEND-D-17_00274

Factors associate with Type 2 Diabetes in Patients with Dementia: A population-based cross sectional study

This paper examines differences in characteristics (demographic characteristics and co-morbidities) between diabetics and non-diabetics in Taiwanese adults with incident dementia (i.e. factors associated with incident dementia in the year to new diagnosis examining those with and without diabetes), showing that those with diabetes were more likely to be young, female and have multiple co-morbidities compared to non-diabetics with incident dementia.

1. Background:

A brief, targeted introduction. More discussion around what risk factors are associated with dementia in diabetes should be included. A few grammatical errors are also evident - P5 line 16-17 "in order TO identify...lines 22-23 and "linked WITH cognitive decline...."

Ans: We have added following information, “For the DM population, previous studies have found long-term poorly DM management and repeated serious glycemic episodes could result in
obvious cognitive impairment in overall older adults[9, 10].” in discussion to emphasize the importance of blood sugar management to prevent dementia. In addition, we have corrected grammatical errors you suggested.

2. Methods:

While it is likely that all the sample are incident cases, time of onset may be less certain given the challenges of diagnosis. Within the confines this is a limitation of the study. The ICD-9 code for 'Senile dementia, uncomplicated' should be elaborated. As a term this usually refers to only Alzheimer's (AD). Could other codes such as incident vascular or other dementia subtypes also be included in analysis?

Ans: We have added following limitation “Firstly, due to limited variables in the claim data, we were unable to obtained time of dementia onset.” to the discussion. We also believe that identification of types of dementia only using ICD-9-CM codes in our database could be inexact and could lead to misinterpretation of results due to misclassification. Therefore, we did not provide additional analyses for dementia subtypes. Furthermore, we further inspected number of patient diagnosed as 331 and found only 27 patients diagnosed as 331. We decide to remove these patients and redone our analyses in the new edition.

3. The association between vascular dementia (VaD) is stronger and it would be important to consider this. The paper should either be about AD only or VAD only or mixed or all dementia subtypes. This should be clarified. The title/text refer to dementia but this is a multi-faceted and multi-factorial heterogeneous condition, which should be clearly stipulated. The difficulty with diagnostic classification and rate of misclassification should be included as a limitation and the title changed if AD was the only dementia that was sought. My guess is that the authors meant all dementia or at least AD/VaD or mixed but not e.g. Lewy Body or Frontotemporal etc. Hence, the ICD codes included should be narrowed/widened and clarified for clinically minded readers.

Ans: Identification of types of dementia only using ICD-9-CM codes could be inexact and could lead to misinterpretation of results due to misclassification. We believe that dementia listed in Major Illness Certificate, Taiwan National Health Insurance is reliable, and it had covered patients with all types of dementia. We believe that most of cases in the study should belong to vascular disease. Furthermore, we further inspected number of patient diagnosed by ICD-9-CM 331 or 290 and found only 27 patients diagnosed as 331. Therefore, we have removed the patients diagnosed as 331 and redone all of analyses in the new edition. Similar results after removing these patients were represented in the new edition. For clarifying out target population, we have changed the title “~vascular dementia~”, and listed this limitation to our discussion.
4. Is this referring to Type 1 or 2 DM or both? - there are likely to be significant differences between these in terms of duration/co-morbidity etc. If only type 2 this should be included in the title/text for clarity. If both, I suggest doing a sensitivity analysis examining both separately and including the tables as appendices. Is it possible to determine when DM was diagnosed?

Ans: We were unable to correctly differentiate types of DM in the claim data. However, previous report had declared that life expectancy of an individual with type 1 diabetes is less than 15 years[11]. We believe that the type of DM in dementia population was most likely to be Type 2 DM. Thus, we have appropriately changed DM to type 2 DM in the text.

5. On P7, the authors refer to disease severity (line 23-24) - is this referring to diabetes or dementia or something else? Please clarify. The categories of co-morbidities should be expanded - I suggest separating cerebrovascular disease/stroke/tia from cardiovascular/PVD disease and renal disease from hypercholesterolaemia.

Ans: The disease severity had been explained on the final sentence of the same paragraph. Thank you for the suggestions. The similar results based on the new grouping of the systematic disease you suggested were showing in the below table. We did not replace the table 3 by these results because it does not change our main conclusion. Certainly, we can replace it if it is necessary.

Table A. Association of systemic comorbidity with diabetes mellitus.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Univariable model</th>
<th>Multivariable-adjusted model*</th>
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<tbody>
<tr>
<td></td>
<td>OR 95%CI</td>
<td>OR 95%CI</td>
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<tr>
<td>Cardiovascular/Cerebrovascular-related diseases</td>
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<tr>
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<td>2.92 2.76-3.09</td>
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<td>1-3</td>
<td>3.85 3.64-4.07</td>
<td>2.93 2.76-3.10</td>
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<td>4-5</td>
<td>3.82 2.41-6.04</td>
<td>2.25 1.38-3.69</td>
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<tr>
<td>Yes</td>
<td>2.22 2.12-2.33</td>
<td>1.57 1.49-1.66</td>
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related diseases

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Number

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Renal disease

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Hyperlipidemia

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Cancer

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<tr>
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<td>1.26-1.56</td>
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</table>

Abbreviation: OR, odds ratio; CI, confidence interval.

1 Cardiovascular/ Cerebrovascular related diseases include myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, hypertension.

2 Digestive system related diseases include peptic ulcer disease, mild liver disease.

* Multivariable logistic regressions adjusted for sex, age, income, area of residence, and urbanization, and various systematic comorbidities were run to identify the independent factors associated with type 2 diabetes mellitus. P<0.05 was considered as statistically significant.

6. Results and discussion:

While the results are well presented, other analysis should be performed to improve the paper. Further analysis/sensitivity analysis should be performed in light of the diagnostic classification mentioned above.

Ans: Thank for the valuable suggestion. We have done sensitivity analysis using strict definition of DM by ICD-9-CM: 250.XX appeared on at least three ambulatory care claims records or at least one-time inpatient care claims record the one year leading up to dementia diagnosis. The similar results were shown in supplemental table s2-s3. We also added this information in the new edition.
7. The discussion also needs to be improved to, to discuss the finding in context of other relevant papers. Please consider the following:

Are other pertinent risk factors such as alcohol or smoking history available?

This could explain differences in liver disease or cancers.

It is known that diabetics develop dementia at an earlier age; likewise many of these co-morbidities are expected to be more common in diabetics.

The data presented here is similar to that found in other studies e.g. in a study in Western Australia by Zilkens et al., 2013 found that the mean time to incident dementia was 2.2 years younger in diabetics, which is very similar to this study.

The discussion should refer to other papers in this area and compare and contrast these findings - hence, while this is reassuring and reinforces what is known (and powered by a large sample), it is not novel.


Ans: Thank you for the valuable suggestions. Lack of personal life habitus information is major shortcoming in study only using claim data. It is not easy to clearly discuss the relationships of life habitus likes alcohol, liver disease, cancer, DM, and dementia. We also worry about over implications may mislead reader. On the other hand, we had rewritten our discussion based on you and the other reviewer’s options and added this important reference into our discussion.

8. Instead, it would be more interesting to look at the degree (strength of association) to which diabetes is independently associated with incident diabetes. Can the authors add this comparison? - it would really enhance the novelty and interest of this paper. Adjusting for all the other factors associated with dementia i.e. age, gender, vascular co-morbidities, renal disease to what degree is DM independently associated with the development of dementia. I appreciate that collinearity is a challenge but it should be explored.

Ans: Indeed, understanding factors associated with incident DM in dementia is interesting but may beyond the scope of this study. The study using claim data is more appropriate to understand disease associations that help physicians make up optimal clinical decisions. We recognize a large dementia registry cohort with comprehensive questionnaire information should be needed to explore factors associated with incident DM in future.
9. Also, is there any data on rate of progression i.e. is the stage of dementia known, recorded and followed in this data set? If so, what factors are associated with progression to end-stage etc. in diabetics compared to non-diabetics? Similarly can this dataset be used to examine if diabetes is associated with greater healthcare use or mortality in those with incident dementia? Surely, in such a dataset, some of these data are also available.

More discussion on what the significance/relevance of what individual associated factors mean is required for e.g. what is the significance of higher peptic ulcer disease - could this be a false association or a reflection of a general higher burden of medications/co-morbidities etc. Limitations as above should be included as above including the risk of effects of collinearity on the associations.

Ans: Thank you for these good ideas. We have been going to explore how was the medical care to be performed in dementia with type 2 DM, and how were the effects of different cares on patient outcomes likes glycemic adverse events, and mortality in further studies. We have also addressed your relevant suggestions in discussion.

Reference


