Author's response to reviews

Title: Increased risk of hip fractures in patients with dementia: a nationwide population-based study

Authors:

Hao-Kuang Wang (ed101393@edah.org.tw)
Yi-Cheng Tai (ed106560@edah.org.tw)
Kang Lu (kanglu.1002@gmail.com)
Po-Chou Liliang (ed100172@edah.org.tw)
Chi-Wei Lin (ed104283@edah.org.tw)
Yi-Che Lee (pipijer@gmail.com)
Pei-Hsuan Fang (phoebe.phfang@gmail.com)
Li-Ching Chang (changlc@isu.edu.tw)
Ying-Chun Li (ycli@faculty.nsysu.edu.tw)

Version: 4 Date: 6 August 2014

Author's response to reviews: see over
Dear Dr. Shipley:

We would like to submit the revised manuscript entitled, “Increased risk of hip fractures in patients with dementia: a nationwide population-based study” for consideration of publication in BMC Neurology. We thank the reviewers for their kind comments and suggestions to improve our manuscript. We have responded to the reviewers' comments point by point and have revised the manuscript accordingly. The changes of our manuscript are listed. We believe that the findings reported in this study are relevant to the scope of your journal and will be of interest to its readership.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal. The study design was approved by the institutional ethics review boards. All the authors have approved the manuscript and agree with submission to your esteemed journal. There is no conflict of interest to declare.

Thank you very much for your review and for considering our manuscript for publication in BMC Neurology.

Sincerely,

Ying-Chun Li, Ph.D.
Institute of Health Care Management
National Sun Yat-Sen University
Kaohsiung 804
Taiwan.
Tel: 866-7-525-2000 ext 4875
Fax: 866-7-525-4698
Email: yeli@faculty.nsysu.edu.tw
Response to reviewers’ comments:

Reviewer 1:
Suggested major compulsory revisions – details of these suggestions are provided within the subsections below.

1. Restrict the inclusion criteria to older adults only

Author reply:
We completely agreed with the comments of reviewer 1. Our study is focused on dementia diagnosis, osteoporosis and fracture, the cohort should have included only older adults. Therefore, we excluded patients less than 60 years to recalculate the result. Fortunately, main result had similar power. We have revised the manuscript accordingly.

2. Add other fracture sites as outcome variables – e.g. wrist

Author reply:
We thank the reviewer 1 for his kind comments and suggestions to improve our manuscript. Decreased BMD at various skeletal sites has been associated with the occurrence of vertebral, hip and wrist fracture. Therefore, we added wrist fracture in our cohort study to recalculate the result. Main result had similar power. We have revised the manuscript accordingly.

3. Identify the osteoporosis ICD codes used

Author reply:
We used ICD-9-CM codes 733.0 to identify patients who had osteoporosis. We have revised the manuscript accordingly. (Amendment to Method, page 6, line 133, In addition to the abovementioned comorbidities, we also adjusted for osteoporosis (ICD-9-CM codes 733.0) and non-osteoporosis in the regression modeling.)

4. Strengthen the discussion section

Author reply:
We thank the reviewer 1 for his kind comments and suggestions to improve our manuscript. We add some discussion on this issue, and we have revised the manuscript. (Amendment to Discussion, page 10, line 210, According to our result, patients with dementia, especially the osteoporosis group, should be considered for special care to help prevent hip fracture. We suggest that health examinations that include cognitive, behavioral, or psychiatric assessment are needed, since early detection of cognitive dysfunction in patients with dementia may decrease the incidence of hip fracture. Moreover, the risk of hip fracture seems greatest in patients with dementia combined with osteoporosis, suggesting that early discovery and control of osteoporosis could decrease the risk of hip fracture [24, 25].

Amendment to Discussion, page 11, line 234, In addition, the adverse effect of wrist or vertebral fractures on most activities of daily living is not as severe as that of hip fractures. Thus, wrist or vertebral fracture are often not recognized and reported, leading
to under-diagnosis and under-treatment. Early radiographic diagnosis followed by appropriate therapy would help to prevent underreporting.)

5. The clarity and/or coherence of the paper need to be improved – editorial type concerns including clarity of writing must be attended to.

**Author reply:**
We had sent our manuscript to editing services.

**Specific comments**
1. **Is the question posed original, important and well defined?**
   • See my comments below about the use of the statement “newly diagnosed dementia”

**Author reply:**
We completely agreed with the comments of reviewer 1. Since the NHI program was initiated in 1995 in Taiwan, the LHID2000 only allows us to trace the use of medical services as far back as 1996; thus, we could not rule out the patients who were diagnosed with dementia before 1996. Therefore, a “new diagnosis” of dementia is not suitable. We have revised the manuscript accordingly.

2. **Are the data sound and well controlled?**
   • Data are sound – national data base used
   • Control group is appropriate

3. **Is the interpretation (discussion and conclusion) well balanced and supported by the data?**
   • The discussion is weak – I didn’t get a strong impression of what any future recommendations should be. I would suggest reducing the discussion that is currently presented and to add more related to recommendations based on the results. For example, we already know the rates of hip fractures are higher in the dementia group…what can we do about this? Other than lower detection rates for vertebral fractures, why else could there have been no differences in rates between the dementia versus control group?

**Author reply:**
We thank the reviewer 1 for his kind comments and suggestions to improve our manuscript. We add some discussion on this issue, and we have revised the manuscript.

(Amendment to Discussion, page 10, line 210, According to our result, patients with dementia, especially the osteoporosis group, should be considered for special care to help prevent hip fracture. We suggest that health examinations that include cognitive, behavioral, or psychiatric assessment are needed, since early detection of cognitive dysfunction in patients with dementia may decrease the incidence of hip fracture. Moreover, the risk of hip fracture seems greatest in patients with dementia combined with osteoporosis, suggesting that early discovery and control of osteoporosis could decrease the risk of hip fracture [24, 25].

Amendment to Discussion, page 11, line 234, In addition, the adverse effect of wrist or
vertebral fractures on most activities of daily living is not as severe as that of hip fractures. Thus, wrist or vertebral fracture are often not recognized and reported, leading to under-diagnosis and under-treatment. Early radiographic diagnosis followed by appropriate therapy would help to prevent underreporting.)

4. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?
   - Included subjects 20 years of age and older. As the study is focused on dementia diagnosis, osteoporosis and fracture, the cohort should have included only older adults – those less than 60 or 65 years should have been excluded. These are primarily diseases of age and it makes no sense to include a younger population.
   - The ICD-9 codes used to identify those with osteoporosis in the data set should have been included.
   - Specify the exact years of the follow-up time period
   - Figure 1 - The numbers should be added to the specific reasons for exclusion
   - Specify if the sample included only community dwelling individuals
   - Statistical analysis is adequate

Author reply:
We thank the reviewer 1 for his kind comments and suggestions to improve our manuscript. Our study is focused on dementia diagnosis, osteoporosis and fracture, the cohort should have included only older adults. Therefore, we excluded patients less than 60 years and recalculated the result. Fortunately, main result had similar power. Then we used ICD-9-CM codes 733.0 to identify patients who had osteoporosis. The primary endpoint of our study was the occurrence of hip fracture, wrist fracture or vertebral fracture as the main diagnosis during a 3-year period from their index use of health care. The numbers had been added to the specific reasons for exclusion in figure 1. We have revised the manuscript accordingly.

5. What are the strengths and weaknesses of the methods?
   - I am troubled the use of the term “new diagnosis of dementia”. Given that this is an administrative data base study, you really have no way of ensuring that these patients have a “new diagnosis” of dementia. I am not sure that having a new diagnosis really matters as it appears that the study is largely interested in fracture rates among those with and without a dementia diagnosis.
   - The paper could be strengthened by including other fracture sites. There have been a few other studies already published that are very similar to this study (dementia diagnosis predicting hip fracture as the sole outcome). See Tolppanen et al., (2013), PLOS One, 8(3). If you included other common fragility fracture sites such as wrist, this would strengthen the paper and would add to a gap in the existing body of knowledge in the area.

Author reply:
We completely agreed with the comments of reviewer 1. Since the NHI program was initiated in 1995 in Taiwan, the LHID2000 only allows us to trace the use of medical
services as far back as 1996; thus, we could not rule out the patients who were diagnosed with dementia before 1996. Therefore, a “new diagnosis” of dementia is not suitable. We have revised the manuscript accordingly. Then decreased BMD at various skeletal sites has been associated with the occurrence of vertebral, hip and wrist fracture. Therefore, we added wrist fracture in our cohort study and excluded patients less than 60 years to recalculate the result. Main result had similar power. We add some discussion and four references on this issue, and we have revised the manuscript.

(Amendment to Discussion, page 10, line 210, According to our result, patients with dementia, especially the osteoporosis group, should be considered for special care to help prevent hip fracture. We suggest that health examinations that include cognitive, behavioral, or psychiatric assessment are needed, since early detection of cognitive dysfunction in patients with dementia may decrease the incidence of hip fracture. Moreover, the risk of hip fracture seems greatest in patients with dementia combined with osteoporosis, suggesting that early discovery and control of osteoporosis could decrease the risk of hip fracture [24, 25].

Amendment to Reference, page 18, line 381,

6. Can the writing, organization, tables and figures be improved?
• There are simple typos, grammatical - present vs. past tense, singular vs. plural, etc. issues throughout the paper – these detract from the overall quality of the work. The manuscript could be strengthened by having an editor review the paper prior to resubmission.
• Tables and data presentations are appropriate.

Author reply:
We had sent our manuscript to editing services.

7. Are there any ethical or competing interests issues you would like to raise?
• No concerns. Ethical clearance was obtained and the data are de-identified.

8. Are the included additional files (supplementary materials) appropriate?
• No additional files were included.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.
Reviewer 2:
this study found an increased risk of hip fracture in a 3 year follow up in people newly diagnosed with dementia and hip fracture.
the methods and analysis appear appropriate.
Interpretation of results is generally appropriate

Minor essential revisions
page numbers are missing making it difficult to review. Reference to patients in nursing homes and vitamin D does not seem relevant for a community sample. You need to be careful about comparisons with AD as your sample is dementia generally.

Author reply:
We thank the reviewer 2 for his kind comments and suggestions to improve our manuscript. We had added page numbers. Then we defined the dementia subtypes were AD (ICD-9-CM code 331.0), and unspecified dementia (ICD-9-CM codes 290.0 to 290.4, 294.1, and 331.1 to 331.2) in our study and recalculate the result. Fortunately, main result had similar power. A noteworthy finding of our study is that Patients who had AD were at the highest risk of hip fracture.

Amendment to Method, page 5, line 120, we further calculated different fracture incidence rates between cohorts depending on dementia subtypes. The dementia subtypes were Alzheimer’s Disease (AD) (ICD-9-CM code 331.0) and unspecified dementia (ICD-9-CM codes 290.0 to 290.4, 294.1, and 331.1 to 331.2).

Amendment to Result, page 7, line 158, Table 2 also shows the relative risk of different types of fracture depending on dementia subtype. It is noteworthy that the adjusted HRs for hip fracture in patients with AD was 2.19 (95% CI 1.43–2.88, p < 0.05).

the discussion needs careful review for readability and at times meaning. sentence are often asymptomatic that support ? does not make sense

Author reply:
We had sent our manuscript to editing services

Vertebral fractures may be underreported more accurate than is underreported ... in comparison to the general population. the is missing

Author reply:
We had revised the manuscript. (Amendment to Discussion, page 11, line 236, Thus, wrist or vertebral fracture are often not recognized and reported, leading to under-diagnosis and under-treatment.)

Sentence beginning In meta-anaylsis study does not make sense.

Author reply:
We had deleted this sentence.

Conclusion- patients not patient
Author reply:
We had revised the manuscript. (Amendment to Conclusion, page 13, line 263, In addition, the dementia group did not show an increased wrist or vertebral fracture risk when compared to the control group, even in patients with osteoporosis.)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare no competing interests