PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Increasing Age- and Gender-Specific Burden and Complexity of Multimorbidity in Taiwan, 2003-2013: A Cross-Sectional Study based on Nationwide Claims Data
AUTHORS	Hu, Rey-Hsing; Hsiao, Fei-Yuan; Chen, Li-Ju; Huang, Pei-Ting; Hsu, William

VERSION 1 - REVIEW

REVIEWER	Dragana Jovic Institute of Public Health of Serbia, Serbia
REVIEW RETURNED	26-Dec-2018

GENERAL COMMENTS	Dear Editor, Thank you for inviting me to review manuscript submitted under the title “The Increasing Age- and Gender- Specific Burden and Complexity of Multimorbidity in Taiwan, 2003-2013”. After careful reading, I got impression that manuscript did not provide enough evidence for meeting its main objectives, although highly representative data source was used in the study. Please find below major remarks for the Methods section. 1. Manuscript provides clear explanation of main data source (Taiwan’s National Health Insurance Research Database, NHIRD). However, description of two subsets (Longitudinal Health Insurance Database, Registry of Beneficiaries of the NHIRD), indicated as parts of main data source, and their role in the sampling strategy, is scarce. 2. Description of the process for random selection of respondents and criteria for random selection of respondents (including inclusion and exclusion criteria) is missing. 3. Authors mentioned they created 11-year panel (2003-2013) for the analysis. Later in the text, they indicate two subsets of main data source, for year 2005. and 2010, as data sources. This puts into question period for which analyses are valid. 4. Authors created 11-year interval for cross sectional study, but they: - report prevalence without indicating whether they were calculating point prevalence or period prevalence, - report prevalence without any confidence interval (95%CI), - report prevalence without any unit (%, etc).

	- report prevalence for 2003 and 2013, without showing statistics and types of statistical tests used, - report prevalence for 2003 and 2013, but do not report prevalence of multimorbidity in the total sample. 5. In the study aims authors mention estimation of trends, but the analyses of time series or usage of certain, even simple indexes, cannot be seen in the manuscript. According to my opinion one figure that presents data for 2003 and 2013 is not sufficient to underpin analysis of trend(s). 6. Page 10, line 55: Authors clam that ”they defined cases as patients who had at least three diagnoses with 20 common diseases or deficits upon outpatient visits during the study period”. Authors must indicate which conditions were considered as common diseases (chronic diseases?) and which were considered as deficits, because any ambiguity in terms may raise question whether authors understood definition of multimorbidity. Regarding outpatient visits for defining patients with multimorbidity, can authors please explain which visits served as marker for identifying patients with multimobidity? According to my knowledge, number of visits is not good marker for identifying such patients.

REVIEWER	Bruno Pereira Nunes Federal University of Pelotas
REVIEW RETURNED	04-Jan-2019

GENERAL COMMENTS	The paper is very interesting and has potential to publication due to its strengths. However, some important issues should be clarified to better inform the readers of the paper. A more comprehensive literature review of Asian publications and a more detailed explanation of multimorbidity definition and operationalization are essential. Abstract - Is there a paucity of studies on Asia region? Despite several original papers, two systematic reviews were conducted in Asia or Asian countries. They should be included in the review of the paper mainly on the discussion section. o Systematic reviews: https://bmjopen.bmj.com/content/5/10/e007235.long https://onlinelibrary.wiley.com/doi/full/10.1111/ggi.12340 o Original papers (examples): https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0197443 https://www.hindawi.com/journals/bmri/2016/6582487/ https://bmjopen.bmj.com/content/7/3/e013529.long - Results: the authors state that multimorbidity prevalence was “37.23 % in 2003 and 48.97 % in 2013” but in table 1 these frequencies are related to “Prevalence of at least one disease/deficit”. What is the prevalence of two or more morbidities (multimorbidity definition on methods section)? Strengths and limitations of this study - The authors stated: “Multimorbidity was defined using existing methods to classify and consider geographic or ethic

	discrepancies between Western and Asian countries." How is this performed? Introduction - The section should be more complete by including the above papers. A more widespread explanation of how the paper will fill the literature gap. Methods - The explanation of cases (multimorbidity?) is not clear: "We defined cases as patients who had at least three diagnoses with 20 common diseases or deficits upon outpatient visits during the study period." What is the multimorbidity definition? The authors should clarify this part of the methods section. - The study has a huge potential by using claim data which provide more widespread and detailed information of morbidities than the majority of cross-sectional studies, for example. However, the selection of morbidities is poorly justified. Why authors didn't use some proposals of definition as presented in the below papers? o https://academic.oup.com/biomedgerontology/article/72/10/1417/2731241 o https://bjgp.org/content/68/669/e245 - What are the deficits? Why the authors use this definition? - Are they acute and chronic diseases included on the definition? There is an important discussion on multimorbidity area regarding this topic. Authors can explain their definition or selected just chronic diseases to use on the paper. Discussion There is an importation limitation of the study which should be more discussed: "We identified multimorbidity based on the diagnoses recorded in the outpatient or inpatient visit. However, only up to three and up to five diagnoses were allowed to be recorded in each outpatient or inpatient visit in the NHIRD, the prevalence of multimorbidities may be underestimated". For example, for patients who had three diseases, there is no underestimation but there are for them who have more than five diseases. The implication of this should be more detailed and discussed as a central point of the paper. Tables and figures - Figure 1 is showing prevalence or absolute numbers? - The legend of Figure 2 (which is very interesting) should be formatted. Extra - Authors use different forms to write multimorbidity. They can standardize the term. Moreover, multimorbidities is not a common term because multi is already related to many diseases.

REVIEWER	Jennifer St. Sauver Mayo Clinic Division of Epidemiology USA
REVIEW RETURNED	22-Jan-2019

GENERAL COMMENTS	Hu and colleagues present a detailed description of multimorbidity in the Taiwanese population. As such, they provide important information on a large, Asian population, and fill a needed gap in the literature describing multimorbidity throughout the world. Strengths of the study include use of Taiwan's National Health Insurance Research Database (NHIRD) for population-level data,

	and the availability of data from both 2003 and 2013. The authors found a striking increase in the prevalence of multimorbidity during that time frame, much of which seems to be driven by fairly dramatic increases in prevalence of many of the 20 conditions in all age groups. I would expect overall prevalance of multimorbidity to increase as an increasing proportion of the population ages; however, the increases in multimorbidity seem to be present in all age groups. Could the authors comment on possible health changes at the population level that could be driving this change? Improvements in treatment and management could explain the increased prevalence in the older population, but I was surprised by the significant increases in the young and middle aged population as well. Minor comments: Discussion- please comment briefly on how the prevalence of multimorbidity in this population compares to data from other population-based studies in other parts of the world. Limitations section- what proportion of the population opts out of the national insurance system? Do they differ from the population in the NHIRD?

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments:

Reviewer #1:

After careful reading, I got impression that manuscript did not provide enough evidence for meeting its main objectives, although highly representative data source was used in the study. Please find below major remarks for the Methods section.

Comment 1:

Manuscript provides clear explanation of main data source (Taiwan's National Health Insurance Research Database, NHIRD). However, description of two subsets (Longitudinal Health Insurance Database, Registry of Beneficiaries of the NHIRD), indicated as parts of main data source, and their role in the sampling strategy, is scarce.

[REPLY: Thank you for the comment. We have added detailed descriptions regarding the two subsets (i.e. LHID) based on the official statements provided by the maintence agency of NHIRD, the National Health Research Institute (NHRI), Taiwan, in the revised manuscript (the Data source section) for better clarity.

"We used a subset of the NHIRD, which contains claim data for 2 million of randomly selected beneficiaries to create an 11-year (2003-2013) panel of claims for analysis. In this study, we used two subsets of the NHIRD, the Longitudinal Health Insurance Database (LHID) 2005 and 2010 as our data source. These two datasets were made up of claims data on one million beneficiaries that were randomly sampled by the National Health Research Institute (NHRI), Taiwan. The one million beneficiaries in LHID 2005 were randomly selected from the year 2005 Registry for Beneficiaries of the NHIRD, which includes registration data of approximately 25.68 million beneficiaries of the National Health Insurance (NHI) program during the year 2005. The one million beneficiaries in LHID 2010 were randomly selected from the year 2010 Registry for Beneficiaries of the NHIRD, which

includes registration data of approximately 27.38 million beneficiaries of the NHI program during the year 2010. According to the statistics provided by the NHRI, there were no significant differences in the gender distribution between patients in the LHID 2005 and the original NHIRD ($\chi2=0.008$, df=1, p-value=0.931), and between those in the LHID 2010 and the original NHIRD ($\chi2=0.067$, df=1, p-value=0.796)23. Therefore, the two subsets were thought to be representative enough of the original NHIRD, and the results obtained suggested generalizability to the whole Taiwanese population."

Reference (the official statements provided by the NHRI)

23. National Health Research Institute, Taiwan. National Health Insurance Research Database, Taiwan. Available from: https://nhird.nhri.org.tw/en/Data_Subsets.html. Accessed August 22 2018.

]

Comment 2:

Description of the process for random selection of respondents and criteria for random selection of respondents (including inclusion and exclusion criteria) is missing.

[REPLY: Thank you for the comment. Please see our replies to your Comment 1. We have added the process for random selection in the revised manuscript. As the two subsets are served to represent the original NHIRD (only in a smaller scale to provide confidentiality of beneficiaries and efficiency of data analyses), there were no other inclusion and exclusion criteria in addition to random sampling to guarantee the representativeness of LHID to the NHIRD.]

Comment 3:

Authors mentioned they created 11-year panel (2003-2013) for the analysis. Later in the text, they indicate two subsets of main data source, for year 2005. and 2010, as data sources. This puts into question period for which analyses are valid.

[REPLY: Thank you for the comment. We would like to clarify for the reviewer that the "2005" and "2010" only indicate these subjects were randomly sampled from the year 2005 and 2010 Registry for Beneficiaries. However, we have retrieved 11 years of claims data (2003-2013) for these selected subjects.]

Comment 4:

Authors created 11-year interval for cross sectional study, but they:

- report prevalence without indicating whether they were calculating point prevalence or period prevalence,
- report prevalence without any confidence interval (95%CI),
- report prevalence without any unit (%, etc).
- report prevalence for 2003 and 2013, without showing statistics and types of statistical tests used,
- report prevalence for 2003 and 2013, but do not report prevalence of multimorbidity in the total sample.

[REPLY: Thank you very much for these comments.

We have strengthened the descriptions of prevalence in both the Methods and Results sections for better clarity.

- We reported descriptive data on the prevalence of multimorbidity in different age groups (categorized into eight groups including 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, and 90+) and both sexes (men and women) in the years 2003 and 2013 (annual point prevalence).

- The individual prevalence was the estimated fraction (percentage, %) with the number of patients with each disease or deficit in each age and sex group as the numerator and with population size in each group and sex as the denominator. We have added the unit of prevalence (%) in all the tables and figures for better clarity.

- We also have added chi-square tests to compare prevalence for 2003 and 2013 based on the reviewer's comment.

We also would like to clarify for the reviewer that as we report the prevalence as percentage, it usually goes without 95% confidence interval. In addition, as we intended to investigate the changes of prevalence of multimorbidity between 2003 (annual point prevalence) and 2013 (annual point prevalence), reporting prevalence of the total sample was not our main focus.]

Comment 5:

In the study aims authors mention estimation of trends, but the analyses of time series or usage of certain, even simple indexes, cannot be seen in the manuscript. According to my opinion one figure that presents data for 2003 and 2013 is not sufficient to underpin analysis of trend(s).

[REPLY: Thank you very much for the comment.

We did have estimated data for each of the year between 2003 and 2013. However, reporting annual prevalence for each year would make our tables very lengthy. That is why we choose to report the 10-years changes in prevalence of multimorbidity between 2003 (annual point prevalence) and 2013 (annual point prevalence) to reveal the increasing burden of multimorbidity. However, we totally agree with the reviewer that we should added statistics to assess whether these changes are statistically significant. We thus used chi-square tests to compare the prevalence of multimorbidity between 2003 (annual point prevalence) and 2013 (annual point prevalence) and found they are all statistically significant ($p<0.05$), except for prevalence of osteoporosis between 2003 and 2013 in Table 2.

We have added these statements in the Methods and Results section. We also have added footnotes in Table 1 and 2 for better clarity.]

Comment 6:

Page 10, line 55: Authors clam that "they defined cases as patients who had at least three diagnoses with 20 common diseases or deficits upon outpatient visits during the study period". Authors must indicate which conditions were considered as common diseases (chronic diseases?) and which were considered as deficits, because any ambiguity in terms may raise question whether authors understood definition of multimorbidity. Regarding outpatient visits for defining patients with multimorbidity, can authors please explain which visits served as marker for identifying patients with multimobidity? According to my knowledge, number of visits is not good marker for identifying such patients.

[REPLY: Thank you very much for the comment. The term “deficit” was adopted from the cumulative deficit approach used in previous studies 25 to define multimobidity. Deficits were defined by variables for disease state, signs and symptoms and disability. However, as we mainly use ICD-9-CM codes to define the 20 common diseases, we feel using the term “deficit” is confusing. We thus have deleted the term “deficit” in the revised manuscript.

In addition, we would like to clarify for the reviewer that to ensure the specificity of every disease, only those who had at least 3 outpatient or 1 inpatient claims record of that specified diagnosis code in one year were considered as having the specified disease. This algorithm was adopted from many published studies using NHIRD to identify comorbidities 24-26. For example, one individual must at least have three different visits for hypertension (e.g. March 1, May 2, and July 15, 2003) to be considered as having hypertension in that year. Same algorithm was applied to other diseases. Therefore, if this person also has at least three different visits for diabetes mellitus then he or she was defined as having two diseases (multimorbidity) in that year. We have strengthened statements with proper references 24-26 in the Identification of common diseases section for better clarity.

References:

24. Chen CY, Wu VC, Lin CJ, et al. Improvement in Mortality and End-Stage Renal Disease in Patients With Type 2 Diabetes After Acute Kidney Injury Who Are Prescribed Dipeptidyl Peptidase-4 Inhibitors. Mayo Clin Proc 2018;93(12):1760-74.

25. Wen YC, Chen LK, Hsiao FY. Predicting mortality and hospitalization of older adults by the multimorbidity frailty index. PLoS One 2017;12(11):e0187825.

26. Dai YX, Wang SC, Chou YJ, et al. Smoking, but not alcohol, is associated with risk of psoriasis in a Taiwanese population-based cohort study. J Am Acad Dermatol 2019;80(3):727-34.]

Reviewer #2:

The paper is very interesting and has potential to publication due to its strengths. However, some important issues should be clarified to better inform the readers of the paper. A more comprehensive literature review of Asian publications and a more detailed explanation of multimorbidity definition and operationalization are essential.

Comment 1:

Is there a paucity of studies on Asia region? Despite several original papers, two systematic reviews were conducted in Asia or Asian countries. They should be included in the review of the paper mainly on the discussion section.

- Systematic reviews:

https://bmjopen.bmj.com/content/5/10/e007235.long

https://onlinelibrary.wiley.com/doi/full/10.1111/ggi.12340

- Original papers (examples):

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0197443

https://www.hindawi.com/journals/bmri/2016/6582487/

https://bmjopen.bmj.com/content/7/3/e013529.long

[REPLY: Thank you for providing several important studies. We have added these papers in the Introduction section.

“Based on two systematic reviews conducted by Pati S et al 17 and Hu X et al 18 and other studies 19-21, available evidence of multimorbidity in Asian countries were limited to specific area in one country 19-21 (i.e. no population-based data were available), limited by sample size (mostly including only hundreds of people) 19-21 and limited to the method that measure multimorbidity (mostly were self-reported). Similarly, they mainly focused on the prevalence of multimorbidity in the elderly 17 18 20 . In addition, most of existing studies were cross-sectional one-time measurement of the prevalence of multimorbidity 17 18 20 and were not presented the time changes of burden of multimorbidity.”

We also have added the two review articles in the Discussion section.

First paragraph of the Discussion section:

“Our study also fills the knowledge gap of existing studies conducted in Asian countries 17 18 by providing the nationwide estimates of multimorbidity across different age groups and by providing the 10-years changes of burden of multimobidity, which have not been done in existing studies.”

Sixth paragraph of the Discussion section:

“Thirdly, as there is no consensus of the number of diseases used to identify multimorbidity, comparisons of epidemiology of multimorbidity in different countries were very difficult. For example, a systematic review conducted by Pati S et al 17 revealed that among 13 studies included in their systematic review, the number of health conditions analyzed per study varied from 7 to 22 with prevalence of multimorbidity varied from 4.5% to 83%.”

References:

17. Pati S, Swain S, Hussain MA, et al. Prevalence and outcomes of multimorbidity in South Asia: a systematic review. BMJ Open 2015;5(10):e007235.

18. Hu X, Huang J, Lv Y, et al. Status of prevalence study on multimorbidity of chronic disease in China: systematic review. Geriatr Gerontol Int 2015;15(1):1-10.

19. Ge L, Yap CW, Heng BH. Sex differences in associations between multimorbidity and physical function domains among community-dwelling adults in Singapore. PLoS One 2018;13(5):e0197443.

20. Mini GK, Thankappan KR. Pattern, correlates and implications of non-communicable disease multimorbidity among older adults in selected Indian states: a cross-sectional study. BMJ Open 2017;7(3):e013529.

21. Pati S, Hussain MA, Swain S, et al. Development and Validation of a Questionnaire to Assess Multimorbidity in Primary Care: An Indian Experience. Biomed Res Int 2016;2016:6582487.]

Comment 2:

Abstract

- Results: the authors state that multimorbidity prevalence was “37.23 % in 2003 and 48.97 % in 2013” but in table 1 these frequencies are related to “Prevalence of at least one disease/deficit”. What is the prevalence of two or more morbidities (multimorbidity definition on methods section)?

[REPLY: Thank you very much for pointing these out. We have corrected the statement with prevalence of two of more diseases.

“The prevalence of multimorbidity (2+ diseases) was 20.07% in 2003 and 30.44% in 2013. In 2013, the prevalence varied between 5.21 % in patients aged 20-29 years and 80.96% in those aged 80-89 years.”]

Comment 3:

Strengths and limitations of this study

- The authors stated: “Multimorbidity was defined using existing methods to classify and consider geographic or ethic discrepancies between Western and Asian countries.” How is this performed?

[REPLY: Thank you for the comment. We have illustrated the approach identifying the list of common diseases in the Identification of common diseases section.

“…… Three epidemiologists with clinical and research expertise in chronic diseases and multimorbidity took part in the discussions to identify the list of diseases based on literature review of existing definitions of chronic disease across scientific papers. Since there was a lack of consensus over what diseases should be included in the definition of multimorbidity, we sought the union of the diseases included in two of the previous studies investigating multimorbidity6 27 and those in a Taiwanese study (our previous study with a geriatric specialist involved) evaluating the association between frailty and unplanned hospitalization, admission to intensive care units, and mortality25.”]

Comment 4:

Introduction

- The section should be more complete by including the above papers. A more widespread explanation of how the paper will fill the literature gap.

[REPLY: Thank you for providing several important studies. We have added these papers in the Introduction section.

“Based on two systematic reviews conducted by Pati S et al 17 and Hu X et al 18 and other studies 19-21, available evidence of multimorbidity in Asian countries were limited to specific area in one country 19-21 (i.e. no population-based data were available), limited by sample size (mostly including only hundreds of people) 19-21 and limited to the method that measure multimorbidity (mostly were self-reported). Similarly, they mainly focused on the prevalence of multimorbidity in the elderly 17 18 20. In addition, most of existing studies were cross-sectional one-time measurement of the prevalence of multimorbidity 17 18 20 and were not presented the time changes of burden of multimorbidity.”

We hope adding these statements could add more explanations of how the paper will fill the literature gap.

References:

17. Pati S, Swain S, Hussain MA, et al. Prevalence and outcomes of multimorbidity in South Asia: a systematic review. BMJ Open 2015;5(10):e007235.

18. Hu X, Huang J, Lv Y, et al. Status of prevalence study on multimorbidity of chronic disease in China: systematic review. Geriatr Gerontol Int 2015;15(1):1-10.

19. Ge L, Yap CW, Heng BH. Sex differences in associations between multimorbidity and physical function domains among community-dwelling adults in Singapore. PLoS One 2018;13(5):e0197443.

20. Mini GK, Thankappan KR. Pattern, correlates and implications of non-communicable disease multimorbidity among older adults in selected Indian states: a cross-sectional study. BMJ Open 2017;7(3):e013529.

21. Pati S, Hussain MA, Swain S, et al. Development and Validation of a Questionnaire to Assess Multimorbidity in Primary Care: An Indian Experience. Biomed Res Int 2016;2016:6582487.]

Comment 5:

Methods

− The explanation of cases (multimorbidity?) is not clear: “We defined cases as patients who had at least three diagnoses with 20 common diseases or deficits upon outpatient visits during the study period.” What is the multimorbidity definition? The authors should clarify this part of the methods section.

[REPLY: Thank you very much for the comment. We have clarified this part in the Methods section based on the reviewer’s comment.

“To ensure the specificity of every disease, only those who had at least 3 outpatient or 1 inpatient claims record of that specified diagnosis code in one year were considered as having that specified disease. This algorithm was adopted from many published studies using NHIRD to identify comorbidities 24-26.

For example, one individual must at least have three different visits for hypertension (e.g. March 1, May 2, and July 15, 2003) were considered as having hypertension in that year. Same algorithm was applied to other disease. Therefore, if this person also has at least three different visits for diabetes mellitus then he or she was defined as having two diseases (multimorbidity) in that year.”

References:

24. Chen CY, Wu VC, Lin CJ, et al. Improvement in Mortality and End-Stage Renal Disease in Patients With Type 2 Diabetes After Acute Kidney Injury Who Are Prescribed Dipeptidyl Peptidase-4 Inhibitors. Mayo Clin Proc 2018;93(12):1760-74.

25. Wen YC, Chen LK, Hsiao FY. Predicting mortality and hospitalization of older adults by the multimorbidity frailty index. PLoS One 2017;12(11):e0187825.

26. Dai YX, Wang SC, Chou YJ, et al. Smoking, but not alcohol, is associated with risk of psoriasis in a Taiwanese population-based cohort study. J Am Acad Dermatol 2019;80(3):727-34]

Comment 6:

Methods

- The study has a huge potential by using claim data which provide more widespread and detailed information of morbidities than the majority of cross-sectional studies, for example. However, the selection of morbidities is poorly justified. Why authors didn't use some proposals of definition as presented in the below papers?

  https://academic.oup.com/biomedgerontology/article/72/10/1417/2731241

  https://bjgp.org/content/68/669/e245

[REPLY: Thank you for the very nice comment and two very important literatures.

We actually adopted the approaches similar to the methods used in the two literatures provided by the reviewer to select morbidities in this study. We have thus strengthened the statements in the Identification of common diseases section to incorporate the concept.

"These diseases were selected based on the disease burden that they may fall on the whole society regarding considerable cost, the requirement for long-term care, reduced health-related quality of life, hospitalization, or death illustrated in previous studies6 25 27. Three epidemiologists with clinical and research expertise in chronic diseases and multimorbidity took part in the discussions based on literature review of existing definitions of chronic disease across scientific papers based on literature review of existing definitions of chronic disease across scientific papers. Since there was a lack of consensus over what diseases should be included in the definition of multimorbidity, we sought the union of the diseases included in two of the previous studies investigating multimorbidity6 27 and those in a Taiwanese study (our previous study with a geriatric specialist involved) evaluating the association between frailty and unplanned hospitalization, admission to intensive care units, and mortality 25."]

Comment 7:

Methods

- What are the deficits? Why the authors use this definition?

[REPLY: Thank you very much for the comment. The term "deficit" was adopted from the cumulative deficit approach used in previous studies25 to define multimobidity. Deficits were defined by variables for disease state, signs and symptoms and disability. However, as we mainly use ICD-9-CM codes to define to 20 common diseases, we feel using the term "deficit" is confusing. We thus have deleted the term "deficit" in the revised manuscript.]

Comment 8:

Methods

- Are they acute and chronic diseases included on the definition? There is an important discussion on multimorbidity area regarding this topic. Authors can explain their definition or selected just chronic diseases to use on the paper.

[REPLY: Thank you for the comment. Based on our algorithm to define every disease (please see our replies to your Comment 5), the diseases we selected in this study were chronic diseases.

We have addressed this in the Methods section for better clarity.

“To ensure the specificity of every disease, only those who had at least 3 outpatient or 1 inpatient claims record of that specified diagnosis code in one year were considered as having that specified disease. This algorithm was adopted from many published studies using NHIRD to identify comorbidities 24-26…….. Based on our algorithm, the diseases we selected in this study were chronic diseases.”]

Comment 9:

Discussion

There is an importation limitation of the study which should be more discussed: “We identified multimorbidity based on the diagnoses recorded in the outpatient or inpatient visit. However, only up to three and up to five diagnoses were allowed to be recorded in each outpatient or inpatient visit in the NHIRD, the prevalence of multimorbidities may be underestimated”. For example, for patients who had three diseases, there is no underestimation but there are for them who have more than five diseases. The implication of this should be more detailed and discussed as a central point of the paper.

[REPLY: Thank you for the comment. We would like to clarify for the reviewer that the way we define a disease (as well as multimorbidity) was not based on diagnosis codes in record of one outpatient visit or admission.

To ensure the specificity of every disease, only those who had at least 3 outpatient or 1 inpatient claims record of that specified diagnosis code in one year were considered as having that specified disease. This algorithm was adopted from many published studies using NHIRD to identify comorbidities 24-26.

For example, one individual must at least have three different visits for hypertension (e.g. March 1, May 2, and July 15, 2003) were considered as having hypertension in that year. Same algorithm was applied to other disease. Therefore, if this person also has at least three different visits for diabetes mellitus then he or she was defined as having two diseases (multimorbidity) in that year.

We have clarified this part in the Methods section for better clarity.

Still, we felt there might be some underestimation even using such algorithm, and we thus added this in the Discussion section.]

Comment 10:

Tables and figures

- Figure 1 is showing prevalence or absolute numbers?
- The legend of Figure 2 (which is very interesting) should be formatted.

[REPLY: Thank you for the comment.

- Figure 1 is showing prevalence. We have added the unit of prevalence (%) in Figure 1 for better clarity.:

- To ensure the consistency of figure legends, we have modified the legend of Figure 2: Prevalence of multi-morbidity in Taiwan within common diseases, by sex and year.]

Comment 11:

Extra

- Authors use different forms to write multimorbidity. They can standardize the term. Moreover, multimorbidities is not a common term because multi is already related to many diseases.

[REPLY: Thank you for the nice comment. We have consistently used “multimorbidity” in the revised manuscript based on the reviewer’s comment.]

Reviewer #3:

Hu and colleagues present a detailed description of multimorbidity in the Taiwanese population. As such, they provide important information on a large, Asian population, and fill a needed gap in the literature describing multimorbidity throughout the world.

Comment 1:

Strengths of the study include use of Taiwan’s National Health Insurance Research Database (NHIRD) for population-level data, and the availability of data from both 2003 and 2013. The authors found a striking increase in the prevalence of multimorbidity during that time frame, much of which seems to be driven by fairly dramatic increases in prevalence of many of the 20 conditions in all age groups. I would expect overall prevalence of multimorbidity to increase as an increasing proportion of the population ages; however, the increases in multimorbidity seem to be present in all age groups. Could the authors comment on possible health changes at the population level that could be driving this change? Improvements in treatment and management could explain the increased prevalence in the older population, but I was surprised by the significant increases in the young and middle aged population as well.

[REPLY: Thank you very much for the comment. We did notice the increases in multimorbidity in all age groups, including the younger population. We have comment this phenomenon in the fourth paragraph of the Discussion section.

“As most researches in multimorbidity have focused on older adults33 34, evidence regarding this issue in young adults is very limited. In our study, the prevalence of multimorbidity (2+ diseases) in people aged 30-39, 40-49 and 50-89 were 11.18%, 21.76%, and 37.75%, respectively, in 2013. This indicates the need for early intervention in those who already suffer from multimorbidity in their middle-ages as the intensity of multimorbidity gradually increase as shown in our study. Lifestyle factors such as smoking, drinking, exercise or diet in middle ages were reported to be associated with multimorbidity35”]

Comment 2:

Discussion- please comment briefly on how the prevalence of multimorbidity in this population compares to data from other population-based studies in other parts of the world.

[REPLY: Thank you for the comment. We did try our best to comment briefly on how the prevalence of multimorbidity in this population compares to data from other population-based studies in other parts of the world, mainly in the second paragraph of the Discussion section.

“The prevalence of multimorbidity among Ontarians rose from 17.4% in 2003 to 24.3% in 2009, a 40% increase. In our study, the prevalence of multimorbidity rose from 20.07% in 2013 to 30.44 % in 2009, a 51.6% increase. Although the different magnitude of the increase could result from the various lists of diseases selected to count multimorbidity; the Ontario study includes 16 common chronic conditions6 while our study includes 20 common chronic conditions.”

However, we have added the following statement in the limitations (sixth paragraph of the Discussion section) that comparisons of epidemiology of multimorbidity in different countries were very difficult as there is no consensus of the number of diseases used to identify multimorbidity.

“Thirdly, as there is no consensus of the number of diseases used to identify multimorbidity, comparisons of epidemiology of multimorbidity in different countries were very difficult. For example, a systematic review conducted by Pati S et al 17 revealed that among 13 studies included in their systematic review, the number of health conditions analyzed per study varied from 7 to 22 with prevalence of multimorbidity varied from 4.5% to 83%.”]

Comment 3:

Limitations section- what proportion of the population opts out of the national insurance system? Do they differ from the population in the NHIRD?

[REPLY: Thank you for the comment. As the NHIRD were build up based on claims of our mandatory and single-payer National Health Insurance (NHI) system, which cover 99.9% of the total Taiwanese population, the proportion of the population opts out of the national insurance system is very minimal (less than 0.1%).]

VERSION 2 – REVIEW

REVIEWER	Bruno Pereira Nunes Universidade Federal de Pelotas, Brazil
REVIEW RETURNED	18-Mar-2019

GENERAL COMMENTS	The authors have answered and justified my questions.

VERSION 2 – AUTHOR RESPONSE

Reviewers' comments:

Reviewer #2: Bruno Pereira Nunes

Institution and Country: Universidade Federal de Pelotas, Brazil

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors have answered and justified my questions.

[REPLY: Thank you very much.]