PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effect of Socio-demographic Factors on the Association between Multimorbidity and Healthcare Costs: A Population-based, Retrospective Cohort Study
AUTHORS	Thavorn, Kednapa; Maxwell, Colleen; Gruneir, Andrea; Bronskill, Susan; Bai, YuQing; Koné Pefoyo, Anna; Petrosyan, Yelena; Wodchis, Walter.

VERSION 1 – REVIEW

REVIEWER	Lars Borgquist Department of Medical and Health Sciences, Linköping university, Sweden
REVIEW RETURNED	25-Apr-2017

GENERAL COMMENTS	This is a well performed study of in the field of public health and health services research. Multimorbidity is a growing field of interest not the least from a clinical point of view but also from a health policy perspective. Alternative measures of multimorbidity, burden of illness, could be discussed. The amount of individual data used in the study is imposing and the statistical analyses are adequate. Results presented were fairly expected and not very interesting. However, it is good to know that the welfare system works in Canada and that the most deprived persons get most of the resources. I miss some more detailed analyses taking into account associations between specific clusters on chronic conditions based on medical knowledge. E.g. there are medical knowledge concerning associations between stroke and some of the other conditions;the risk of having a stroke is related to combinations of hypertension, diabetes, chronic heart failure, cardiac arrhythmia (and also age and being a woman). Hence, it should be of interest to analyse the costs of more specific combinations of conditions in order to make health policy recommendations in preventing for instance stroke (by means of anticoagulants). Maybe socio-demographic factors will be of minor importance in certain of these combinations of chronic conditions? It would be interesting to know when socio-economic factors are not so important. Other medical associations are related to depressions and dementia. And what about associations between rheumatoid arthritis and arthritis? Results with the costs of these more specific combination of conditions could be presented in a new table and replace table 3. I have difficulties to classify AMI as a chronic condition.

REVIEWER	Andrea L. Lorden University of Oklahoma Health Sciences Center Oklahoma City, OK USA
REVIEW RETURNED	11-May-2017

GENERAL COMMENTS	Page 7, lines 7-21. The authors' citations (14 & 15) are for the methodological issues described, and do not provide evidence that previous studies, especially recent studies, have failed to account for skewed cost data and log transformation issues when analyzing and interpreting cost data. To strengthen the paper, I recommend one of the two following changes: 1) additional references that support the assertion that other (recent) studies have not accounted for skewed data or interpretation of transformed data, or 2) rephrase to more accurately reflect the importance of accounting for skewed cost distributions or the interpretation of transformed cost data. Page 8, lines 14-16. This sentence is confusing, and does not accurately convey the meaning associated with the references provided. The references discuss the validation and validity of the data source, but that is not coming across as clearly as it should. Also, it would be beneficial if the authors described the "multiple provincial health administration databases" and database contents before discussing the validity of the data source. Page 8, lines 38-40. The authors identify certain conditions within a "two-year" period, which is inconsistent with the one-year study period and data description. Please clarify. The authors should explicitly state how "two-years" are applied. Page 8, lines 33-49 Currently, the case identification description is too vague to replicate. While references are provided for 5 of the conditions used in the study, there is a lack of coding information for the remaining 11. Cancer is a particularly broad category that has not been described sufficiently to replicate identification. Supplemental materials that include specific codes would facilitate replication by other researchers. Also, other information is missing from the case identification such as reasons for exclusions, i.e. missing evaluation variables. Page 9, lines 48-50 – While patient costs at an average cost per hour for home health visits make sense, it does not make sense for long-term care. Do the authors mean per diem? Please provide an explanation as to why per hourly costs were selected for long-term care? Page 12, lines 33-48 and Table 3 – The authors' description of testing interaction terms is unclear. For example, were interactions tested separately ("at a time" line 40) or in the presence of the other interactions ("full model with interaction terms" line 45). The results presented in Table 3 suggest one model was evaluated that included all variables and all interactions. If multiple models were evaluated, this should be clarified by the authors, and table 3 should report coefficients for the independent variables included in all models, such as age and sex, for each model evaluated.

	Page 19, lines 6-20 – The interpretation of the rates is difficult to follow, and potentially the most interesting finding. It would be helpful if the authors were to reiterate the rates with SEs in the text to aid dissemination. Page 24, lines 46-48 – This is your most interesting finding, so please elaborate on the implications. Page 25, lines 22-27 – While your effects were significant, this is not surprising given your n was large. Additionally, most of your effect sizes were very small. Therefore, to say that the association between cost and number of conditions "depended" on neighborhood may be overstating its influence on the relationship.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
This is a well performed study of in the field of public health and health services research. Multimorbidity is a growing field of interest not the least from a clinical point of view but also from a health policy perspective. Alternative measures of multimorbidity, burden of illness, could be discussed.

The amount of individual data used in the study is imposing and the statistical analyses are adequate. Results presented were fairly expected and not very interesting. However, it is good to know that the welfare system works in Canada and that the most deprived persons get most of the resources.

I miss some more detailed analyses taking into account associations between specific clusters on chronic conditions based on medical knowledge. E.g. there are medical knowledge concerning associations between stroke and some of the other conditions; the risk of having a stroke is related to combinations of hypertension, diabetes, chronic heart failure, cardiac arrhythmia (and also age and being a woman). Hence, it should be of interest to analyse the costs of more specific combinations of conditions in order to make health policy recommendations in preventing for instance stroke (by means of anticoagulants).
Maybe socio-demographic factors will be of minor importance in certain of these combinations of chronic conditions? It would be interesting to know when socio-economic factors are not so important.

Other medical associations are related to depressions and dementia. And what about associations between rheumatoid arthritis and arthritis? Results with the costs of these more specific combination of conditions could be presented in a new table and replace table 3.

Response: Thank you very much for your insightful comments. We agree that it would be interesting to assess the association between particular disease clusters and healthcare costs. We chose to use disease counts because there is no standard or guidance on how to measure and define multimorbidity and the choice of measure would be subject to data availability and the outcome of interest , . A previous study conducted by our team has shown that there were no common clustering of diseases among individuals living with multimorbidity .

The number of disease clusters required to include 80% of the study population increased from 14 (among individuals with two conditions) to 2744 clusters of conditions (among individuals with 5 or more conditions). Moreover, a previous systematic review showed that 132 multimorbid definitions with 1,631 criteria were used to define multimorbidity in the published literature . Our decision to use

disease counts is also supported by a study by Islam et al indicating that the total number of chronic conditions were more predictive for out-of-pocket healthcare costs and high cost users than the clusters, dominant groups or dominant pairs .

I have difficulties to classify AMI as a chronic condition.

Response: Thank you. We have changed the term “chronic conditions” to “medical conditions”. It is suggested that the lingering effects of an MI are not unlike those of a chronic medical condition with ongoing treatment.

Reviewer: 2

Thank you for the opportunity to review this interesting paper on the relationship between multi-morbidity and health system costs as moderated by demographic factors. Any paper that illuminates the role of the social determinants in healthcare is important. While there are indications the evaluation was executed properly, the methods lack clarity. This translates to difficulties for interpreting and discussing the results (see specific comments below).

1. Page 7, lines 7-21. The authors’ citations (14 & 15) are for the methodological issues described, and do not provide evidence that previous studies, especially recent studies, have failed to account for skewed cost data and log transformation issues when analyzing and interpreting cost data. To strengthen the paper, I recommend one of the two following changes: 1) additional references that support the assertion that other (recent) studies have not accounted for skewed data or interpretation of transformed data, or 2) rephrase to more accurately reflect the importance of accounting for skewed cost distributions or the interpretation of transformed cost data.

Response: Thank you. To improve the clarity, we have revised sentences describing the limitations of Ordinary Least Square (OLS) and a log-transformed regression model. We have cited studies that used OLS and a log-transformed regression model.

2. Page 8, lines 14-16. This sentence is confusing, and does not accurately convey the meaning associated with the references provided. The references discuss the validation and validity of the data source, but that is not coming across as clearly as it should. Also, it would be beneficial if the authors described the “multiple provincial health administration databases” and database contents before discussing the validity of the data source.

Response: Thank you. We have removed the references and added a new paragraph describing data sources used for this study.

3. Page 8, lines 38-40. The authors identify certain conditions within a “two-year” period, which is inconsistent with the one-year study period and data description. Please clarify. The authors should explicitly state how “two-years” are applied.

Response: We have changed our description of the period used to identify medical conditions from “between April 1, 2009 and March 31, 2010” to “between April 1, 2001 and March 31, 2010”. A two-year period means that we looked for diagnosis codes included in hospitalization or physician records between April 1, 2001 and March 31, 2009.

4. Page 8, lines 33-49 Currently, the case identification description is too vague to replicate. While references are provided for 5 of the conditions used in the study, there is a lack of coding information for the remaining 11. Cancer is a particularly broad category that has not been described sufficiently to replicate identification. Supplemental materials that include specific codes would facilitate

replication by other researchers. Also, other information is missing from the case identification such as reasons for exclusions, i.e. missing evaluation variables.

Response: Thank you. The list of diagnosis codes used to define medical conditions is now included in Appendix 1.

5. Page 9, lines 48-50 – While patient costs at an average cost per hour for home health visits make sense, it does not make sense for long-term care. Do the authors mean per diem? Please provide an explanation as to why per hourly costs were selected for long-term care?

Response: The reviewer is correct. The costs of long-term care were based on a fixed per diem based on prevailing government payment rates. The sentence on Page 9 has been revised to read as follows:

"Patient costs for long-term care were estimated based on a fixed per diem based on prevailing government payment rates, and costs for home care were estimated using average cost per hour"

6. Page 12, lines 33-48 and Table 3 – The authors' description of testing interaction terms is unclear. For example, were interactions tested separately ("at a time" line 40) or in the presence of the other interactions ("full model with interaction terms" line 45). The results presented in Table 3 suggest one model was evaluated that included all variables and all interactions. If multiple models were evaluated, this should be clarified by the authors, and table 3 should report coefficients for the independent variables included in all models, such as age and sex, for each model evaluated.

Response: Thank you for these helpful comments. All interaction terms were tested at once. Only significant interaction terms were included in the final model. Page 12, lines 33 to 48 have been revised to read as follows:

"To investigate whether the relationship between the level of multimorbidity and healthcare costs was moderated by socio-demographic factors, we added all two-way interaction terms between the level of multimorbidity and each sociodemographic factor, including sex, age, income level, deprivation quintile, instability quintile, dependency quintile and ethnic concentration quintile. The significance of interaction terms was assessed by comparing the likelihood ratio of the full model with all interaction terms to the model without interaction terms using the likelihood ratio test".

We have sufficient power in the population database to include all interactions.
7. Page 19, lines 6-20 – The interpretation of the rates is difficult to follow, and potentially the most interesting finding. It would be helpful if the authors were to reiterate the rates with SEs in the text to aid dissemination.

Response: Thank you. We have revised lines 6 to 20 to read as follows:

"We also found that the association between number of medical conditions and healthcare costs was significantly modified by age and sex for both young and older adults [Table 3]. The positive association between healthcare costs and levels of multimorbidity was significantly stronger for older than younger adults. For individuals aged 65 years or younger, the increase in healthcare costs was more gradual in women than their male counterparts. For those aged 65 years or older, the increase in healthcare costs in women was significantly greater than for men"

We did not include the rates or coefficients and their SEs in text because including many coefficients and SEs of significant interaction terms may confuse readers. For example, the interaction between the number of medical conditions and age generated 8 coefficients and SEs, while the interaction

between the number of medical conditions and sex would add another 8 coefficients and SEs. Of these interaction terms, 15 terms were statistically significant.

8. Page 24, lines 46-48 – This is your most interesting finding, so please elaborate on the implications.

Response: We have revised Page 24, line 46 -48 to read as follows:

“The observed interaction effect may partly due to patterns in the healthcare use among an older population. There is generally a pattern of poly-pharmacy and use of continuing care services that are very costly.”

9. Page 25, lines 22-27 – While your effects were significant, this is not surprising given your n was large. Additionally, most of your effect sizes were very small. Therefore, to say that the association between cost and number of conditions “depended” on neighborhood may be overstating its influence on the relationship.

Response: Thank you. We have replaced the term “depended” by “varied” and added the following sentence to the end of the paragraph. Many of the effects are relatively small. At the same time there is a 3-fold difference in the proportion of people with 5+ conditions who live in the most deprived neighborhood compared to the people with 5+ conditions who live in the least deprived neighborhood. These are nontrivial differences.

“The effects of socioeconomic factors reported in this study should be interpreted with caution as there were derived based on neighborhood. Although the interaction terms between socioeconomic factors and levels of multimorbidity were statistically significant, some of estimated effect sizes were very small and might be a result of a large sample size used in this study.”

References

1. Stewart M, Fortin M, Britt HC, et al. . Comparisons of multi-morbidity in family practice—issues and biases. Fam Pract 2013;30:473–80.
2. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases—a systematic review on existing multimorbidity indices. J Gerontol A Biol Sci Med Sci 2011;66:301–11.
3. Kone Pefoyo AJ, Bronskill SE, Gruneir A, Calzavara A, Thavorn K, Petrosyan Y, et al. The increasing burden and complexity of multimorbidity. BMC Pub Health. 2015;15(1):415.
4. Le Reste JY, Nabbe P, Manceau B, et al. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. J Am Med Dir Assoc 2013;14:319–25.
5. Islam MM, Yen L, Valderas JM, McRae IS. Out-of-pocket expenditure by Australian seniors with chronic disease: the effect of specific diseases and morbidity clusters. BMC Pub Health. 2014;14:1008

VERSION 2 – REVIEW

REVIEWER	Lars Borgquist Linkoping university Sweden
REVIEW RETURNED	12-Jul-2017

GENERAL COMMENTS	The manuscript has improved quite a lot. It would be nice to see a sensitivity analysis concerning the effects

	on costs and the combinations of diagnosis. What happens to costs if arthritis is excluded in the calculations? (e.g.rheumatoid arthritis and arthritis are difficult to separate in the clinic). A sensitivity analysis for the variations in health care costs could also be of value. E.g. physician professional fees are not really costs related to resources used for physicians consultations.

REVIEWER	Andrea L. Lorden The University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City, OK, USA
REVIEW RETURNED	13-Jul-2017

GENERAL COMMENTS	The paper is generally well-written, but would benefit from one minor correction. Page 8, line 7 and Page 9, lines 36-43. Please be more explicit in the period definitions for study inclusion. For example, if all costs and case identification occurred between 2007-2010, why define population as individuals who participated between 2001 and 2010? What if an individual moved out to the system between 2001 and 2007, would they still be considered for inclusion in the study? Also, it is unclear how costs were aggregated into annual totals. I assume you used fiscal year, hence April 20yy to March 20yy+1. Would it have made more sense to aggregate for one year after the initial healthcare visit for a condition? Including a sentence or two explaining this would be helpful to the reader in interpreting your results.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Lars Borgquist
Institution and Country: Linkoping university, Sweden Competing Interests: None declared

The manuscript has improved quite a lot.
It would be nice to see a sensitivity analysis concerning the effects on costs and the combinations of diagnosis. What happens to costs if arthritis is excluded in the calculations? (e.g.rheumatoid arthritis and arthritis are difficult to separate in the clinic).

Response: Thank you for your suggestion. The authors agree that it would be very interesting and important to assess the impact of disease clusters and combinations on costs. However, this research question deserves a focus on its own and should be described in a separate paper. The selection and consideration of conditions must also be considered carefully as the number of disease clusters that commonly occur rises exponentially with the number of conditions that people experience (see Kone et al., 2015 where we show,for example, that 2744 combinations are required to represent 80% of the population with 5 or more conditions).

On Page 28 (second paragraph), we have added the suggestion that future studies should assess the plausible relationship between clusters of medical conditions and healthcare costs.
A sensitivity analysis for the variations in health care costs could also be of value. E.g. physician professional fees are not really costs related to resources used for physicians consultations.

Responses: We acknowledge that our measurement of cost captures the full expense incurred by the government payer is not only reflective of the resources used but also include the profit or return accrued by health care providers. While it would be interesting to better understand incremental costs, it would require a different methodology and we are unable to include this measurement in the current manuscript.

Reviewer: 2
Reviewer Name: Andrea L. Lorden
Institution and Country: The University of Oklahoma Health Sciences Center, College of Public Health, Oklahoma City, OK, USA Competing Interests: None to declare

Thank you for allowing me to review this paper regarding healthcare expenditures for multiple morbidity and social determinants of health. The paper is generally well-written, but would benefit from one minor correction.

Page 8, line 7 and Page 9, lines 36-43. Please be more explicit in the period definitions for study inclusion. For example, if all costs and case identification occurred between 2007-2010, why define population as individuals who participated between 2001 and 2010? What if an individual moved out to the system between 2001 and 2007, would they still be considered for inclusion in the study? Also, it is unclear how costs were aggregated into annual totals. I assume you used fiscal year, hence April 20yy to March 20yy+1. Would it have made more sense to aggregate for one year after the initial healthcare visit for a condition? Including a sentence or two explaining this would be helpful to the reader in interpreting your results.

Response: Thank you. We identified cases based on diagnoses occurring between April 2001 and March 2009 and measured an outcome (costs) between April 1, 2009 to March 31, 2010.

We excluded any individuals who moved out from the system during the case identification period, i.e. between 2001/02 and 2009/10. This clarification has been added to the Study Design and Sample section (Page 7 to 8).

For the total costs estimation, we have revised sentences on Page 10 (Line XX to XX) from:
“Annual total direct healthcare costs were the sum of costs across healthcare sectors for each patient for a one-year period, i.e. from April 2009 to March 2010.”
to
“Annual total direct healthcare costs were the sum of costs across healthcare sectors for each patient for a one-year period after the index date, i.e. from Apri