

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of developing multimorbidity across all ages in an historical cohort study: differences by sex and ethnicity
AUTHORS	Rocca, Walter; St Sauver, Jennifer; Boyd, Cynthia; Grossardt, Brandon; Bobo, William; Finney Rutten, Lila; Roger, Verinique; Ebbert, John; Therneau, Terry; Yawn, Barbara

VERSION 1 - REVIEW

REVIEWER	Marjan van den Akker Maastricht University, School CAPHRI, dept of Family Medicine, Maastricht, the Netherlands. KU Leuven, dept of General Practice, Leuven, Belgium.
REVIEW RETURNED	02-Sep-2014

GENERAL COMMENTS	<p>This manuscript describes the analyses of the incidence of multimorbidity (as two or more, and as three or more new chronic diseases) in a large cohort over a considerable period of time.</p> <p>The authors use a database which was more or less founded in 1966. For this study the baseline was set at January 1, 2000. Why not take advantage of the extended time window available? This question relates to another of my comments: it is logical that - to calculate the incidence - only persons at risk at baseline are included in the analyses. As a result 14.3% of the population had to be excluded, because they already had two or more diseases at baseline, with a higher proportion in older age (up to 76% excluded among those aged 80 years and older). This implies that especially in the older groups, the population under study is not very likely to be representative (similar to the healthy survivor effect). Or as the authors optimistically put it “an ideal population to study successful aging and resiliency”, but that is not the focus of the current study.</p> <p>The authors conclude that the composition of the dyads and triads vary extensively across age and sex strata. Although this is very true, I’m surprised that the authors not mention in their discussion that this is a very obvious result. E.g. in 0 – 19 year olds, the most frequent dyad is depression – asthma. This is to be expected, because depression and asthma are the top-2 diseases with highest incidence in this age group. Hence, the expected co-occurrence (by chance) is also expected to be the highest. Since incidence rates for different diseases vary across age and sex groups, so will the dyads and triads found in the same groups.</p> <p>For future research, the authors express plans to “further analyse which combinations have the greatest impact on adverse outcomes”. In my opinion, for this type of questions, prevalence of multimorbidity is more relevant than incidence, because people experience the results of and need care not only for their new diseases, but also for</p>
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	<p>the existing ones.</p> <p>For further multimorbidity incidence analyses I would suggest to disentangle which groups are most at risk to develop multimorbidity and to look for unexpected dyads and triads (co-occurrence beyond chance).</p>
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REVIEWER	John E. Crews, DPA Centers for Disease Control and Prevention Atlanta, Georgia, USA
REVIEW RETURNED	

GENERAL COMMENTS	<p>This is an outstanding paper and a solid contribution to the emerging literature on multiple chronic conditions. It clearly advances the scientific agenda outlined by HHS.</p> <p>The strengths of the paper are detailed in the manuscript. Having a longitudinal cohort of people with reasonably complete medical records provides an opportunity to conduct this study.</p> <p>The incidence approach is very strong and creates a better understanding of conditions than prevalence measures that are typically employed.</p> <p>Grounding the 20 conditions examined in this study in the list of 20 conditions identified by HHS (Goodman paper) helps to illustrate the strengths and weaknesses of the list. I think the discussion section is particular strong and productive in terms of suggesting strategies to strengthen “The List.” I believe this paper is likely to contribute to discussions regarding what constitutes a standard list of conditions for MCC work.</p> <p>It might be useful to indicate which low incidence conditions do not appear in the dyads and triads. If some conditions do not appear in dyads or triads in this study, I would wonder when they would be addressed. Conditions might make The List, but seldom be examined. That tells us something.</p> <p>I think the point about the effects of pairs is important. Perhaps obvious, but needs to be said.</p> <p>In addition, “The List” contains no measure of vision or hearing—which are common and have grave effects on older people. Including sensory impairment in this model could be very useful down the line. Vision and hearing are generally measured by function and not disease in surveys, but diagnostic codes could get at that concern. The authors do not have to address this issue.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer Comments

Reviewer 1

1. “The authors use a database which was more or less founded in 1966. For this study the baseline was set at January 1, 2000. Why not take advantage of the extended time window available?”

We chose to study the incidence of multimorbidity in a fixed cohort followed over the most recent 14 years for several reasons. First, using a shorter time window makes the data easier to interpret, without having to consider the added dimension of secular trends or cohort effects. Second, we studied a recent cohort in order to make our data relevant to the present time, and interpretable in light of current medical practice. Finally, although a larger number of persons in each age group would have increased the precision of our incidence estimates, our examination of the entire population resulted in a significant number of persons at risk, even in the oldest age groups. Therefore, our incidence estimates were stable. However, we agree with the reviewer that by taking advantage of the entire dataset available we can address other interesting research questions. In particular, we can determine whether the incidence of multimorbidity has increased or decreased over time (secular trends and birth cohort trends). We are considering such analyses, but they are beyond the scope of the current study.

2. “This question relates to another of my comments: it is logical that - to calculate the incidence - only persons at risk at baseline are included in the analyses. As a result 14.3% of the population had to be excluded, because they already had two or more diseases at baseline, with a higher proportion in older age (up to 76% excluded among those aged 80 years and older). This implies that especially in the older groups, the population under study is not very likely to be representative (similar to the healthy survivor effect). Or as the authors optimistically put it “an ideal population to study successful aging and resiliency”, but that is not the focus of the current study.”

We agree with the Reviewer’s observation that many individuals aged 60 years or older have already developed multimorbidity. Therefore, the population that remains at risk of subsequent multimorbidity in the older ages is healthier than the general population at the beginning of our window of study. On the other hand, although some individuals do reach older ages without multimorbidity, they are still at increased risk of developing subsequent multimorbidity compared to younger persons. Therefore, the population under study is representative, and using a longer study window would not change the situation. As suggested by the Reviewer, we have removed the language regarding successful aging and resiliency, and have added some language to the discussion section (lines 411-413).

3. “The authors conclude that the composition of the dyads and triads vary extensively across age and sex strata. Although this is very true, I’m surprised that the authors do not mention in their discussion that this is a very obvious result. E.g. in 0 – 19 year olds, the most frequent dyad is depression – asthma. This is to be expected, because depression and asthma are the top-2 diseases with highest incidence in this age group. Hence, the expected co-occurrence (by chance) is also expected to be the highest. Since incidence rates for different diseases vary across age and sex groups, so will the dyads and triads found in the same groups.”

We have added the words “as expected” in several places throughout the manuscript to highlight the fact that many of these results are not surprising. In addition, we have added language to the discussion section to address the Reviewer’s observation (lines 64-65, 198, 243, 253, and 432).

4. “For future research, the authors express plans to “further analyze which combinations have the greatest impact on adverse outcomes”. In my opinion, for this type of questions, prevalence of

multimorbidity is more relevant than incidence, because people experience the results of and need care not only for their new diseases, but also for the existing ones.”

We agree that clinicians must treat the patients who have prevalent conditions, and it is critical to provide data to help patients and clinicians forecast likely health outcomes (clinical point of view). However, the incidence approach is preferable when addressing mechanisms of multimorbidity in the general population (research point of view). Persons with prevalent conditions may be different from persons with incident conditions. First, they have survived long enough with their combination of conditions to visit a clinician. Patients with particularly harmful combinations of conditions may die more rapidly, and studying only survivors at one point in time may bias the findings. Second, the length of time in which a patient has had a condition may play an important role in the development of specific outcomes. Disentangling the effect of the presence of a condition from the effect of duration of a condition can be done more directly when using incident cases, but becomes more challenging when using prevalent cases. We have added language regarding the strengths of studying outcomes using an incidence design to our discussion (lines 400-404). See also the comment number 1 of Reviewer 2 about the advantages of the incidence approach.

5. “For further multimorbidity incidence analyses I would suggest to disentangle which groups are most at risk to develop multimorbidity and to look for unexpected dyads and triads (co-occurrence beyond chance).”

We have added these suggestions to our discussion regarding future directions and next studies (lines 446-452 and 462-466).

Reviewer 2

1. “This is an outstanding paper and a solid contribution to the emerging literature on multiple chronic conditions. It clearly advances the scientific agenda outlined by HHS. The strengths of the paper are detailed in the manuscript. Having a longitudinal cohort of people with reasonably complete medical records provides an opportunity to conduct this study. The incidence approach is very strong and creates a better understanding of conditions than prevalence measures that are typically employed. Grounding the 20 conditions examined in this study in the list of 20 conditions identified by HHS (Goodman paper) helps to illustrate the strengths and weaknesses of the list. I think the discussion section is particular strong and productive in terms of suggesting strategies to strengthen “The List.” I believe this paper is likely to contribute to discussions regarding what constitutes a standard list of conditions for MCC work.”

We thank the reviewer for the positive remarks regarding our manuscript.

2. “It might be useful to indicate which low incidence conditions do not appear in the dyads and triads. If some conditions do not appear in dyads or triads in this study, I would wonder when they would be addressed. Conditions might make The List, but seldom be examined. That tells us something. I think the point about the effects of pairs is important. Perhaps obvious, but needs to be said.”

Some of the conditions were relatively rare in the general population and contributed to dyads or triads in few persons. For example, autism and HIV infection were the least common conditions. Autism appeared as part of an incident dyad in only 31 persons (all 49 years of age or younger), and HIV infection appeared as part of an incident dyad in only 41 persons (all 59 years of age or younger). Therefore, as noted by the Reviewer, these conditions were included in the HHS list, but are not a substantial component of multimorbidity in the general population. On the other hand, they may be important in studies focusing on the population of children and young adults. We have added language to the manuscript regarding this observation (lines 299-304).

3. "In addition, "The List" contains no measure of vision or hearing—which are common and have grave effects on older people. Including sensory impairment in this model could be very useful down the line. Vision and hearing are generally measured by function and not disease in surveys, but diagnostic codes could get at that concern. The authors do not have to address this issue."

We agree with the reviewer that a number of conditions of great importance in older persons are not included in the HHS list. We have noted this limitation in our discussion section, and suggest that such conditions should be considered in future studies of multimorbidity (lines 295-299).

We believe that the manuscript has improved in response to the comments of the reviewers, and we hope that it is now acceptable for publication.

VERSION 2 – REVIEW

REVIEWER	John E. Crews, DPA Centers for Disease Control and Prevention USA
REVIEW RETURNED	06-Jan-2015

GENERAL COMMENTS	The authors have responded to the concerns I identified in the earlier review. I believe this is an outstanding contribution that advances inquiry regarding multiple chronic conditions, and the rich supplementary information will be of use to other investigators.
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