PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The prevalence of multimorbidity and its associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation
AUTHORS	Saito, Yoshiyuki; Igarashi, Ataru; Nakayama, Takeo; Fukuma, Shingo

VERSION 1 – REVIEW

REVIEWER	Wang, Xiao-Wen Peking University Health Science Center
REVIEW RETURNED	19-Apr-2022

GENERAL COMMENTS	This manuscript showed the prevalence and health burden of multimorbidity in Japan by using a large health insurance database. The manuscript is well written, interesting and easy to follow. I have some concerns regarding the study. 1. I was wondering how the diagnosed disease prevalence from the health insurance data was standardized to the Japanese total population. Please make it clear in the method. Also, since the database is nationally representative, I suppose the prevalence rate is more important than the number itself, therefore, is it necessary to show the estimated prevalence of the Japanese total population in table 1? 2. The cox regression, which was used to estimate the associations between multimorbidity and 5-year hospitalisation and/or death events, did not adjust for any other potential confounders, including sex. 3. Abstract: Line 61-62 “The standardised prevalence of multimorbidity was approximately 5% (ages 20-29), 10% (30-39), 20% (40-49), 30% (50-59), 50% (60-69), and 60% (70-74).” The estimation was from the health insurance data or the total Japanese population? Which part of this manuscript does this result correspond to? 4. Discussion: Line 270-274 The prevalence of multimorbidity was similar to other high-income countries, so how about other developing countries? Does it make any difference?

REVIEWER	Jürisson, Mikk Tartu Ulikool Arstiteaduskond, Institute of Family Medicine and Public Health
REVIEW RETURNED	20-Apr-2022

GENERAL COMMENTS	This is a well-written informative manuscript about the emerging

	public health issue. However, I have some comments. Major 1. What is the rationale for selecting the diseases of interest for assessing MM? Looks like you chose those from the Charlson index only, and left out the rest. There are three major concerns regarding this: a. your results are difficult to compare to the previous research, b. You have left out a significant proportion of the disease burden, c. The Charlson index was developed for a different purpose, to assess the comorbidities that are associated with a significant risk of death. However, we know that disease burden consists of two variables, risk of death AND loss of health-related quality of life, and some diseases that have a major burden from the quality of life loss are not associated with limited survival. Exclusion of those will result in underestimating the MM prevalence and burden. In addition, comorbidity and MM are two different concepts and using one for assessing another needs clarification. This question needs to be addressed either by redefining the list of diseases or by explaining the Methods. Please take a look at the alternatives https://pubmed.ncbi.nlm.nih.gov/22579043/ https://bmjopen.bmj.com/content/11/10/e049045 2. Your analysis used administrative data. We know that these data are collected for a different purpose, and not for research purposes. Do you have any results from validation studies that have assessed the data quality of the Insurance database? You should address this issue in the Methods or Discussion. 3. What was your rationale for selecting a working-age population database for assessing MM? Your title „assessing MM across generations“ infers that all generations are included. However, older people have been left out. It is somewhat surprising accounting for the high life expectancy of the Japanese. The title is misleading and should be replaced. You should specify your target group in the title and throughout the text. 4. Your title refers to MM prevalence only and leaves out the association with clinical outcomes. Can it be adjusted to sharpen the focus? 5. What was the relationship between the two cohorts used in the study? The description (lines 131-139) is not quite clear. 6. The administrative database might contain some single incident diagnoses (suspected diagnoses) but not necessarily the final diagnosis. What was the minimum number of claims and over which period for the claim to be included in the analysis? How was the prevalent condition defined? 7. Results. Lines 207-210, you indicate the prevalence of MM in the total population and refer to Table 1, but there are no MM prevalence numbers in Table 1. 8. Along the same lines, the prevalence of MM increased with age, referring to Figure 1A, but there are several lines at the bottom of Figure 1, and difficult to discriminate between them. In addition, the numbers are quite low, which indicates the insufficient number of conditions included in the analysis. 9. Then, your second objective was to assess the association between MM and outcome events (hospitalization, deaths). You have a short section of „Effect of MM by age group“ where you bring several HR-s but it is not clear from the text what those are referring to. You have shortened the text so that it becomes difficult to understand what you say. Minor. 1. Suggest replacing „historical cohort“ with „retrospective cohort“

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This manuscript showed the prevalence and health burden of multimorbidity in Japan by using a large health insurance database. The manuscript is well written, interesting and easy to follow.

I have some concerns regarding the study.

1. *I was wondering how the diagnosed disease prevalence from the health insurance data was standardized to the Japanese total population. Please make it clear in the method. Also, since the database is nationally representative, I suppose the prevalence rate is more important than the number itself, therefore, is it necessary to show the estimated prevalence of the Japanese total population in table 1?*

We appreciate your thoughtful comment. For a simpler presentation of results, we moved the standardized prevalence rates and the estimated numbers from Table 1 to Supplementary eTable 3. To clarify how to estimate those results, we added explanations as follows ("Estimation of diagnosed disease prevalence to nationwide scale" in the method);

"We calculated prevalence rates according to groups by 5-year age brackets and sex. Then, we estimated the prevalence rates standardized to Japanese total population (age-sex standardized prevalence rate), using the number from the vital statistics 2014 in Japan."

2. *The cox regression, which was used to estimate the associations between multimorbidity and 5-year hospitalisation and/or death events, did not adjust for any other potential confounders, including sex.*

We apologize for our vague explanation in the manuscript. Although we did adjust for sex in the Cox model, we did not write it correctly in our previous manuscript. To clarify this point, we added the following sentences ("The association of multimorbidity with outcome by age group " in the method);

"To examine the association of multimorbidity with the outcome by age group, we performed Cox regression analysis adjusted by sex using cohort data from four consecutive years (FY2015 to FY2018)."

We showed all results of Cox regression In supplementary eTable4.

Supplementary eTable 4. Hazard ratios in multimorbid individuals based on hospitalisation and death rates in a 5-year cohort of *n* = 111 088 men and *n* = 70 871 women. Cox regression analysis

Overall[a]												
	Full Model			**20-39 years**			**40-59 years**			**60-71 years**		
	HR	95%CI		HR	95%CI		HR	95%CI		HR	95%CI	
Age	1.02	1.01	1.02									
Sex	0.97	0.95	0.99	0.36	0.34	0.37	1.29	1.25	1.33	1.44	1.38	1.51
≥2 diseases	2.17	2.12	2.21	2.17	2.05	2.29	2.31	2.24	2.38	2.05	1.97	2.14
Men[b]												
Age	1.03	1.03	1.04									
≥2 diseases	2.04	1.98	2.10	2.81	2.56	3.07	2.25	2.17	2.34	1.94	1.84	2.04
Women[b]												
Age	0.99	0.99	1.00									
≥2 diseases	2.22	2.15	2.30	1.91	1.78	2.04	2.42	2.30	2.54	2.28	2.12	2.44

[a]References are female for sex, no disease for morbidity variables

[b]Reference is no disease for morbidity variables

HR; hazard ratio, CI; confidence interval

3. *Abstract: Line 61-62*
   "The standardised prevalence of multimorbidity was approximately 5% (ages 20-29), 10% (30-39), 20% (40-49), 30% (50-59), 50% (60-69), and 60% (70-74)."The estimation was from the health insurance data or the total Japanese population? Which part of this manuscript does this result correspond to?

As we described in our previous response (comment 1 of the reviewer 1), we moved standardized prevalence rates from Table 1 to Supplementary eTable 3A. Therefore, we removed those results from the abstract and added prevalence rate from the study population from Figure 2A.

"The prevalence rate of multimorbidity increased with age, i.e., approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of diseases as well as below results are shown in eTable 3 in the Supplement)."

4. *Discussion: Line 270-274*
   The prevalence of multimorbidity was similar to other high-income countries, so how about other developing countries? Does it make any difference?

Thank you for your worthful comment. Following your comment, we added some other countries' reports in the manuscript.

"Also recently some Asian countries reported similar prevalence, Iran (13.4% in men, 25.0% in women), India, Bangladesh (53.7% - 56.5% in both gender, over aged 60)."

https://pubmed.ncbi.nlm.nih.gov/28490550/

https://pubmed.ncbi.nlm.nih.gov/26446164/

As we mentioned in manuscript, although it is not easy to directly compare each research due to using different multimorbidity definition, we found it is not far different to other studies in the manuscript.

Reviewer: 2

This is a well-written informative manuscript about the emerging public health issue. However, I have some comments.

Major

1. *What is the rationale for selecting the diseases of interest for assessing MM? Looks like you chose those from the Charlson index only, and left out the rest. There are three major concerns regarding this: a. your results are difficult to compare to the previous research, b. You have left out a significant proportion of the disease burden, c. The Charlson index was developed for a different purpose, to assess the comorbidities that are associated with a significant risk of death. However, we know that disease burden consists of two variables, risk of death AND loss of health-related quality of life, and some diseases that have a major burden from the quality of life loss are not associated with limited survival. Exclusion of those will result in underestimating the MM prevalence and burden. In addition, comorbidity and MM are two different concepts and using one for assessing another needs clarification. This question needs to be addressed either by redefining the list of diseases or by explaining the Methods. Please take a look at the alternatives*
   https://pubmed.ncbi.nlm.nih.gov/22579043/
   https://bmjopen.bmj.com/content/11/10/e049045

We are deeply grateful to your insightful comments. We agreed that multimorbidity and co-morbidity are different concepts.[ref1] Recent systematic review shows that there are variations in tools to assess multimorbidity and CCI is commonly used in previous studies.[17] We selected CCI because it is a validated tool to assess the diseases associated with a significant risk of clinical events.[20] We revised the follwoing sentence in the Method section ("Definition of diagnosed diseases and multimorbidity");

"There are a variety of definitions for chronic conditions in multimorbidity studies.[17-19] We used the Charlson Comorbidity Index (CCI) which is a validated tool to assess the diseases associated with a significant risk of clinical events.[20] The reason, we used CCI, was that we focused on describing the prevalence of each disease and also assessing the association of multimorbidity on hospitalisation or death."

17: https://pubmed.ncbi.nlm.nih.gov/33952533/

18: https://pubmed.ncbi.nlm.nih.gov/22579043/

19: https://pubmed.ncbi.nlm.nih.gov/34610934/

20: https://pubmed.ncbi.nlm.nih.gov/3558716/

Ref1: https://publichealthreviews.biomedcentral.com/articles/10.1007/BF03391611

As pointed out in the reviewer's comments, we were not able to assess diseases which may lead to QOL loss. We added those points in the limitation of Discussion section,

"With regard to limitations, the target population comprised regular employees and their families and might accordingly be healthier than the general population. Also, we defined multimorbidity by disease list included in CCI most likely to lead to death, hence, we were not able to consider other diseases associated with health-related quality of life loss. The presence of mental or psychosomatic disorders, which have been shown to be increasing, particularly in individuals already suffering from other chronic diseases,[27,28] younger people,[29] and people with a low socio-economic status. [30] Such diseases often remain undiagnosed or underreported in health records. [31] These limitations likely contributed to an underestimation of multimorbidity in our cohort. Further, because we did not manually verify the presence of disease using the physician's

medical records data or medication information, disease names extracted from the medical claims data might be incorrect in some cases. In particular, Japanese physicians sometimes change the name of the disease in the medical record to the "correct" disease name for the medication they wish to prescribe, a practice called "disease name for claims data"."

2. *Your analysis used administrative data. We know that these data are collected for a different purpose, and not for research purposes. Do you have any results from validation studies that have assessed the data quality of the Insurance database? You should address this issue in the Methods or Discussion.*

Thank you for your important comment. We added the following sentence in "Materials and Methods", regarding to recent review for Real World Data in Japan including a features of claims data.

"Insured-based data base is used widely and one of the popular real-world data in Japan.[16]"

16: https://link.springer.com/article/10.1007/s40801-021-00266-3

3. *What was your rationale for selecting a working-age population database for assessing MM? Your title „assessing MM across generations" infers that all generations are included. However, older people have been left out. It is somewhat surprising accounting for the high life expectancy of the Japanese. The title is misleading and should be replaced. You should specify your target group in the title and throughout the text.*

We totally agreed with your suggestion and revised sentence in Title and Method as below.

Title :

"The prevalence of multimorbidity and it's associations with hospitalisation or death in Japan 2014-2019 - a retrospective cohort study using nationwide medical claims data in the middle-aged generation"

Research design and study population in Method :

"Since HIA2CE is a type of insurance for workers in Japan, database include only under 75 years individuals. Therefore, maximum age in this cohort was 74 years."

It means we did not exclude over 75 years population, it was limitation for using this type of insured data in Japan.

4. *Your title refers to MM prevalence only and leaves out the association with clinical outcomes. Can it be adjusted to sharpen the focus?*

Thank you for your careful comment. We revised Title and subtitle as shown in our previous response (comment 3 of the reviewer 2).

5. *What was the relationship between the two cohorts used in the study? The description (lines 131-139) is not quite clear.*

We appreciate your important comment. To clarify this point, we added some explanations in Method section ("Research design and study population");

"We prepared two data sets for analysis. The first was cross-sectional data set contained baseline data of FY2014, which we used to describe the diagnosed disease prevalence in FY2014. The study population for this baseline data set included individuals aged 20 to 74 years insured in FY2014 (April 2014 to March 2015). Since HIA2CE is a type of insurance for workers in Japan, database include only under 75 years individuals. Therefore, maximum age in this cohort was 74 years. Participants younger than 20 in FY2014 as well as participants who died during FY2014

were excluded (Fig.1). The cohort data set contained longitudinal data for a 5-year period, FY2014 to FY2018 (April 2014 to March 2019). Second data set contained participants insured in whole period. We used this cohort data set to conduct Cox regression analysis and calculate hazard ratios (HR)s for clinical events (Fig. 1).”

6. *The administrative database might contain some single incident diagnoses (suspected diagnoses) but not necessarily the final diagnosis. What was the minimum number of claims and over which period for the claim to be included in the analysis? How was the prevalent condition defined?*

We appreciate your important questions. Japanese claims data have codes to distinguish confirmed diagnoses from suspected diagnose. We only used confirmed diagnose. We added the following sentence in the end of Method section (“Definition of diagnosed diseases and multimorbidity”);

“We only used confirmed diagnoses, not including suspected diagnoses, in Japanese claims data.”

7. *Results. Lines 207-210, you indicate the prevalence of MM in the total population and refer to Table 1, but there are no MM prevalence numbers in Table 1.*

We are grateful to your important comment. We added row "Multimorbidity (≥2 diseases among CCI) “ on

Table1, Supplementary eTable 2, Supplementary eTable 3. (We showed Table1 below for example)

Table 1. Prevalence of diagnosed diseases in FY2014 applied to the Japanese total population

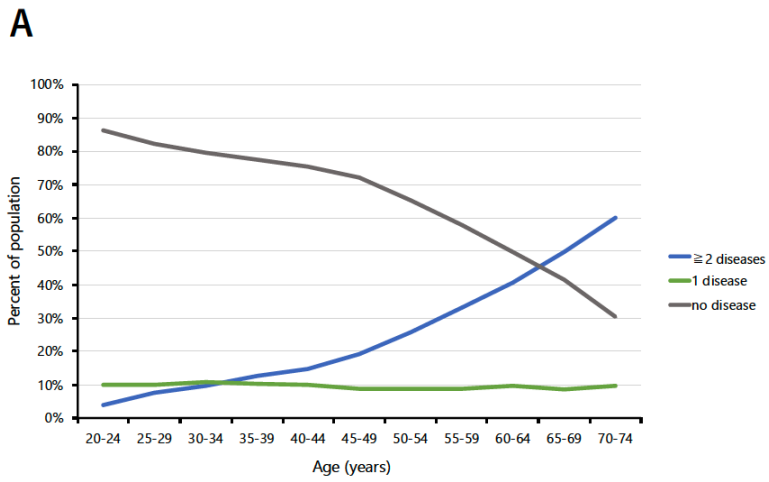
				Baseline data in FY2014			
		Overall		Men		Women	
		N=246,671	%	*N*=144,237	%	*N*=102,434	%
Men		144,237	58.5	-	-	-	-
Age (Mean, SD)		45.0	12.9	44.6	12.9	45.7	12.8
	20-24	18,524	7.5	11,315	7.8	7,209	7.0
	25-29	17,251	7.0	12,014	8.3	5,237	5.1
	30-34	18,093	7.3	11,104	7.7	6,989	6.8
	35-39	23,878	9.7	13,278	9.2	10,600	0.3
	40-44	39,721	16.1	21,640	15.0	18,081	17.7
	45-49	40,908	16.6	24,191	16.8	16,717	16.3
	50-54	29,466	11.9	17,577	12.2	11,889	11.6
	55-59	20,149	8.2	11,343	7.9	8,806	8.6
	60-64	21,278	8.6	12,706	8.8	8,572	8.4
	65-69	11,931	4.8	6,768	4.7	5,163	5.0
	70-74	5,472	2.2	2,301	1.6	3,171	3.1
AIDS/HIV		96	0.0	62	0.0	34	0.0
Any malignancy*		12,047	4.9	5,611	3.9	6,436	6.3
Cerebrovascular disease		10,866	4.4	6,510	4.5	4,356	4.3
Chronic pulmonary disease		43,216	17.5	22,484	15.6	20,732	20.2
Congestive heart failure		8,497	3.4	5,515	3.8	2,982	2.9
Dementia		447	0.2	210	0.1	237	0.2
Diabetes mellitus		27,344	11.1	17,881	12.4	9,463	9.2
Hemiplegia or paraplegia		813	0.3	533	0.4	280	0.3
Liver disease		27,127	11.0	16,954	11.8	10,173	9.9
Metastatic solid tumor		2,532	1.0	1,263	0.9	1,269	1.2
Myocardial infarction		1,628	0.7	1,325	0.9	303	0.3
Peptic ulcer disease		26,047	10.6	14,511	10.1	11,536	11.3
Peripheral vascular disease		10,407	4.2	5,723	4.0	4,684	4.6
Renal disease		2,573	1.0	1,751	1.2	822	0.8
Rheumatologic disease		4,146	1.7	1,397	1.0	2,749	2.7
≥1 disease among top 5		71,880	29.1	40,833	28.3	31,047	30.3
Disease no. among CCI							
	no disease	171,140	69.4	101,857	70.6	69,283	67.6
	1 disease	22,947	9.3	12,032	8.3	10,915	10.7
	2 diseases	17,120	6.9	8,994	6.2	8,126	7.9
	3 diseases	12,822	5.2	7,273	5.0	5,549	5.4
	4 diseases	9,588	3.9	5,874	4.1	3,714	3.6
	≥ 5 diseases	13,054	5.3	8,207	5.7	4,847	4.7
Multimorbidity (≥2 diseases among CCI)		52,584	21.3	30,348	21.0	22,236	21.7

Values are numbers (%) unless otherwise stated.
* Any malignancy includes leukemia and lymphoma.
FY; fiscal year
SD; standard deviation
CCI; Charlson Comorbidity Index

8. *Along the same lines, the prevalence of MM increased with age, referring to Figure 1A, but there are several lines at the bottom of Figure 1, and difficult to discriminate between them. In addition, the numbers are quite low, which indicates the insufficient number of conditions included in the analysis.*

Thank you for your important suggestion. To make the results more understandable and simple, we revised Figure 2A showing 3 groups of "no disease", "one disease", and "two or more diseases".

Fig2A.



9. *Then, your second objective was to assess the association between MM and outcome events (hospitalization, deaths). You have a short section of „Effect of MM by age group" where you bring several HR-s but it is not clear from the text what those are referring to. You have shortened the text so that it becomes difficult to understand what you say.*

We appreciate your worthful comment. We added the following sentence in the end of Method section ("Estimation of diagnosed disease prevalence to nationwide scale");

" This model was able to show HR for aging alone (e.g., HR for 40-59 ages without multimorbidity vs 20-39 ages without multimorbidity and complex of aging and morbidity(e.g., HR for 40-59 ages with multimorbidity vs 20-39 ages without multimorbidity)."

And also we revised subtitle in Result, "Effect of multimorbidity by age group" to "Association of multimorbidity with outcome by age group", and then we added below short sentence in the end of this section.

"The impact of multimorbidity on outcome exceeded that of aging (HR = 1.62 [95% CI, 1.56-1.69] ages ≥60 and HR = 1.10 [95% CI, 1.07-1.13] ages 40-59 without multimorbidity) (Fig. 3). That was to say, even in aged 20-39 with multimorbidity has a risk more than ages ≥60 without multimorbidity."

Minor.

1. *Suggest replacing „historical cohort" with „retrospective cohort"*

Thank you for your worthful comment. We accepted your suggestion and revised it in the manuscript.

REVIEWER	Wang, Xiao-Wen Peking University Health Science Center
REVIEW RETURNED	05-Oct-2022

GENERAL COMMENTS	The authors have answered all of my questions and the paper has been greatly improved. Therefore, it can be accepted for publication.

REVIEWER	Jürisson, Mikk Tartu Ulikool Arstiteaduskond, Institute of Family Medicine and Public Health
REVIEW RETURNED	10-Oct-2022

GENERAL COMMENTS	Thank you for the opportunity to review the interesting manuscript. The overall picture is very good. However. I still have some questions. 1. Abstract. Please explain why you chose the Charlson Index conditions and left out many others that might not impact mortality but might have a major impact on quality of life and well-being and thus contribute significantly to disease burden. 2. I don't understand how the total prevalence came to only 5% if almost all age groups presented much higher numbers. Please explain 3. The finding that MM patients have a higher risk of clinical events is well known. What is the scientific novelty there? 4. I would have expected to see the risk of death data as promised in the title, but it is not there. Please add. 5. Methods. What is the proportion of the population covered by the Insurance company that the data comes from? Can we extrapolate the results and call this a population-based study? Please justify. 6. How did you define the prevalent condition? Was one single claim sufficient for a patient to be included? What if that was an initial diagnosis that was not confirmed later? Did you account for prescription data as well? Sometimes people have multiple conditions but the claim (outpatient claims mostly) picks up only one or two. You did not account for the data from 2013 or 2012 to identify people who don't visit physicians too often, did you? Please describe the inclusion and exclusion in more detail and explain how they might have impacted the validity of the results (underestimation, overestimation). Sensitivity analysis using 2-year data or at least 2-3 claims per year might help. 7. Results. The primary outcomes are the prevalence of chronic diseases and MM but also hospitalizations and risk of death. In your analysis, the outcomes are clinical events. Please define what that is. Regardless, the primary outcomes need to be brought into the text as well. 8. Along the same lines: In Figure 3 you just say Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity. Hazard ratios for what? Clinical events, hospitalizations, deaths, all of those combined? Please be correct in presenting the results. 9. References. Please take a closer look at the references. Ref #19 Mikk, et al feature the first names and not the family names as should. The correct reference is Jürisson, et al… Please correct this.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Miss Xiao-Wen Wang

Comments to the Author:

The authors have answered all of my questions and the paper has been greatly improved. Therefore, it can be accepted for publication.

Reviewer: 2

Dr. Mikk Jürisson, Tartu Ulikool Arstiteaduskond

Comments to the Author:

Thank you for the opportunity to review the interesting manuscript. The overall picture is very good. However.

I still have some questions.

1. Abstract. Please explain why you chose the Charlson Index conditions and left out many others that might not impact mortality but might have a major impact on quality of life and well-being and thus contribute significantly to disease burden.

We appreciate your important comment. We agree with the opinion that not only death but also the effect of reduced quality of life should be taken into multimorbidity. As you pointed out, CCI originally includes comorbidities that have a strong impact on mortality. Unfortunately, we were unable to assess the impact on quality of life in this study. We added this limitation to the Discussion as appropriate(noted around line 280)

"Also, we defined multimorbidity by disease list included in CCI most likely to lead to death, hence, we were not able to consider other diseases associated with health-related quality of life loss. CCI originally includes comorbidities that strongly impact on mortality, not quality of life and well-being."

2. I don't understand how the total prevalence came to only 5% if almost all age groups presented much higher numbers. Please explain

Thank you for your worthful comment. To clarify this point, we added the below sentences in the result.

“The standardised prevalence of multimorbidity was estimated to 26.1% (26.1% in men, 26.0% in women) in the Japanese total population (eTable 3A in the Supplement). The prevalence rate with age was increased , i.e., approximately 5% (25-24 (3.9%), 25-29 (7.7%)), 10% (30-34 (9.7%), 35-39 (12.5%)), 20% (40-44 (14.6%), 45-49 (19.0%)), 30% (50-54 (25.9%), 55-59 (33.2%)), 50% (60-64 (40.7%), 65-69 (49.9%)), and 60% (70-74).(Fig. 2A. Details of the prevalence of diseases as well as below results are shown in eTable 3B in the Supplement). Figure 2B shows the types of disease and their prevalence across age groups.”

3. The finding that MM patients have a higher risk of clinical events is well known. What is the scientific novelty there?

We apologize for our vague explanation in the manuscript. We believe this study brought findings of the remaining knowledge gap in the following two points.

1. This is the first study in Japan to confirm the prevalence of MM by including in the denominator those who do not have the receipt of medical claims and to estimate the prevalence of MM in the general population.

2. Furthermore, we investigated an association between MM and generations. The point of clinical significance is that this study showed that MM has a clear effect from the middle-aged group.

To clarify this point, we added the below sentences in the conclusion.

"In conclusion, the present study confirmed the prevalence of MM by including in the denominator those who did not have the receipt of medical claims and to estimate the prevalence of MM in the general population. Furthermore, we revealed that the impact of multimorbidity is already clinically significant in middle-aged Japanese, with elevated adverse events such as hospitalisation or death. In addition, the risk posed by multimorbidity exceeds that of aging in all age groups. These results underscore the need to undertake healthcare intervention against the onset of multimorbidity before middle-age, and not to leave it as a problem for geriatricians. **"**

4. I would have expected to see the risk of death data as promised in the title, but it is not there. Please add.

Thank you for your important suggestion. We showed that data in Supplementary eTable2. We added this information to the Result.

" The composite outcome occurred 17.2% (death 0.8%, hospitalization 16.9%) in follow-up period (eTable2).**"**

5. Methods. What is the proportion of the population covered by the Insurance company that the data comes from? Can we extrapolate the results and call this a population-based study? Please justify.

Thank you for your important suggestion. Japanese total population is approximately 1,26 million and aged 20-74 are around 86.8 million. HIA2CE, which is the insurer of our source data covered 0.4 million

(0.3% of the Japanese total population). HIA2CE is not a big portion of the population however it is one of the large independent insurers in Japan. Also, the strong point of HIA2CE is to cover people nationwide in Japan.

HIA2CE published a paper that showed some statistical data about health-related expenditure. It mainly compared with national statistics of aggregated insurers of Society-Managed Health Insurance (SMHI)

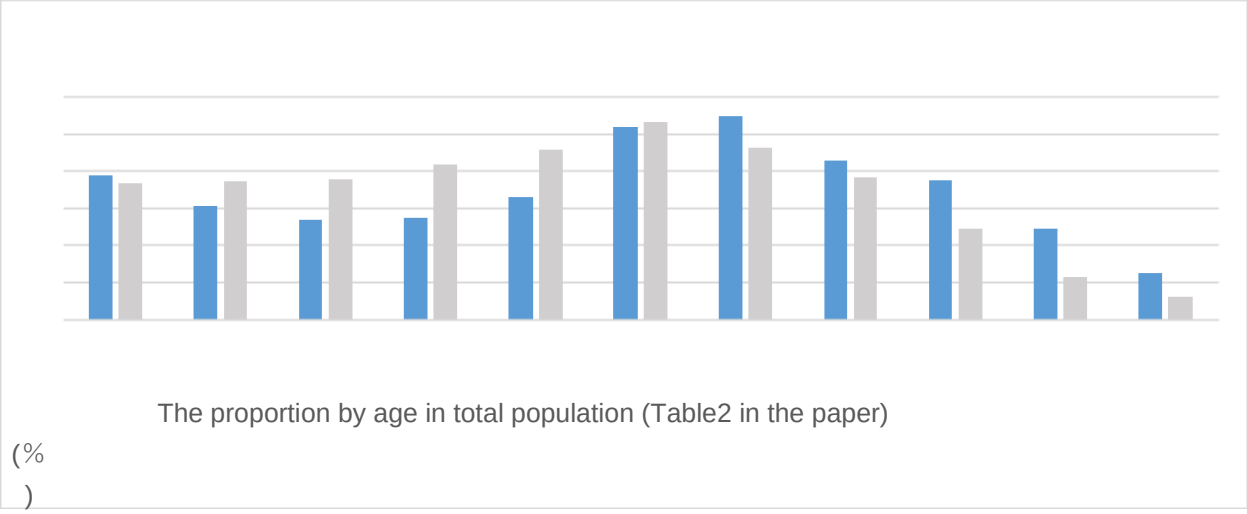
http://dokenpo.or.jp/union/pdf/toukei/iryou_r02h.pdf

I found some helpful information to clarify our answer.

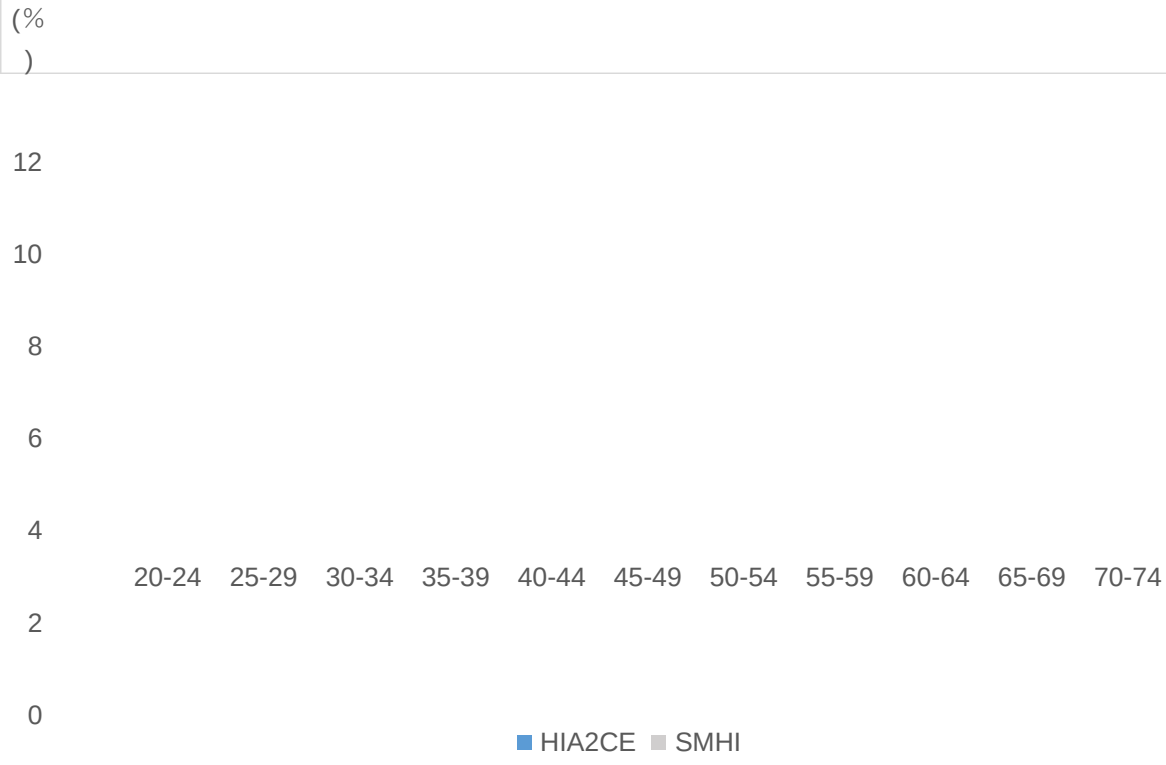
Medical expenditure (Table 8 in the paper)

	HIA2CE		SMHI	
	cost	proportion%	cost	proportion%
inpatient	188	26.56	10,886	24.93
out patient	287	40.62	18,032	41.29
dental	84	11.96	5,706	13.07
pharmacy	147	20.86	9,043	20.71
total	706	100	43,668	100

unit: 100million yen



The proportion by age in total population (Table2 in the paper)



6. How did you define the prevalent condition? Was one single claim sufficient for a patient to be included? What if that was an initial diagnosis that was not confirmed later? Did you account for prescription data as well? Sometimes people have multiple conditions but the claim (outpatient claims mostly) picks up only one or two. You did not account for the data from 2013 or 2012 to identify people who don't visit physicians too often, did you? Please describe the inclusion and exclusion in more detail and explain how they might have impacted the validity of the results (underestimation, overestimation). Sensitivity analysis using 2-year data or at least 2-3 claims per year might help.

We appreciate your important and insightful comments. We collected diseases which were occurred during the year (FY2014). Therefore, patients who were untreated, undiagnosed, or discontinued treatment cannot be picked up, which may result in an underestimation of the prevalence rate.

As you pointed out, extending the period for defining comorbidity from one year to two to three years may prevent the underestimation of diseases with long intervals between visits. On the other hand, the observation period of the outcomes would be lost.

To clarify this point, we add these limitations in the Discussion (noted around line 285).

"The presence of mental or psychosomatic disorders, which have been shown to be increasing, particularly in individuals already suffering from other chronic diseases,27 younger people,28 and people with a low socio-economic status. 29 Such diseases often remain undiagnosed or underreported in health records. 30 Also, we collected diseases which were occurred during the year (FY2014). Therefore, patients who were

untreated, undiagnosed, or discontinued treatment cannot be picked up. These limitations likely contributed to an underestimation of multimorbidity in our cohort."

7. Results. The primary outcomes are the prevalence of chronic diseases and MM but also hospitalizations and risk of death. In your analysis, the outcomes are clinical events. Please define what that is. Regardless, the primary outcomes need to be brought into the text as well.

Thank you for your important suggestion.

This study includes two analyses: first, to describe the prevalence of MM, in which the primary outcome is MM; and second, to examine the association between MM and the composite outcomes of hospitalization or death. In this case, the outcome is the composite outcomes of hospitalization for death.

To clarify this point, we add the following sentences in Method section.

"Primary and Secondary Outcomes

Primary outcome for descriptive analysis: The standardised prevalence of multimorbidity across age groups was evaluated using data from FY 2014 and extrapolated to the Japanese total population. Secondary Outcome for Cox regression model: Hospitalisation or death events were traced by month using medical claims data and insurer enrolment data. Associations between multimorbidity and 5-year hospitalisation and/or death events across age groups were analysed using a Cox regression model."

8. Along the same lines: In Figure 3 you just say Hazard ratios of no multimorbidity (0-1 disease) versus multimorbidity. Hazard ratios for what? Clinical events, hospitalizations, deaths, all of those combined? Please be correct in presenting the results.

Thank you for your careful comment.

Our hypothesis was aging and MM or these combination leads to worsen clinical events. Therefore, we defined 6 groups which were combination of 3 category of generation and MM, and we estimated HR in each group on reference of young (aged 20-39) without MM. Regarding this model, we interpreted both the independent impact of generation and MM on outcomes and the impact of MM in each generation.

We added this sentence in the Statistical analysis section.

"Statistical analysis

Cox regression was conducted for the association of multimorbidity with outcome by age group. Our hypothesis was aging and MM or these combination leads to worsen clinical events. Therefore, we defined 6 groups which were combination of 3 category of generation

and MM, and we estimated HR in each group on reference of young (aged 20-39) without MM. Regarding this model, we interpreted both the independent impact of generation and MM on outcomes and the impact of MM in each generation. Results were considered statistically significant at a two-sided P-value of less than 0.05. All analyses were conducted using Stata software version 15.1 (StataCorp LLC; College Station, TX, USA).”

*9. References. Please take a closer look at the references. Ref #19 Mikk, et al feature the first names and not the family names as should. The correct refere*nce is Jürisson, et al… Please correct this.

We deeply apologize for your comment. We revised this point according to your suggestion.