PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: The prospective study on Chinese elderly with multimorbidity in primary care in Hong Kong
AUTHORS	ZHANG, Dexing; Sit, Regina Wing Shan; Wong, Carmen; Zou, Dan; Mercer, Stewart; Johnston, Marjorie; Wong, Samuel

VERSION 1 – REVIEW

REVIEWER	Cornelia Straßner University Hospital Heidelberg Department of General Practice and Health Services Research Germany
REVIEW RETURNED	19-Nov-2018

GENERAL COMMENTS	**Review of the manuscript**
	
	Cohort profile: Chinese elderly with multimorbidity in primary care in Hong Kong
	
	The authors present – to their own information – the first longitudinal cohort study in the Chinese population. Thus the data deriving from this study is likely to be relevant for researchers and policy makers in the field. Yet the manuscript needs some more elaboration:
	
	General comments:
	• I am not an English native speaker but I feel that especially in the introduction and discussion section there are various grammar and language mistakes. I recommend that the paper should be revised by an English native speaker. Some examples:
	  - *We found that those who suffered from multimorbidity had the psychological problems are common*
	  - *Sleep disturbance appears to be common with almost half being assessed reported significant sleep related symptoms*
	  - The authors very often use terms like "the cohort examines". It should be "cohort study".
	
	Abstract and Title
	• The exact design (longitudinal cohort study) should be mentioned in abstract and title

- The headlines of the abstract are uncommon. Usually abstracts are devided into Background, Objective, Methods (including study design, participants, measures), Results and Conclusions. As this is not a study protocol but a research report of a specific analysis, future plans are not relevant in the abstract in my opinion.

Introduction
- Generally the introduction section appears a bit superficial. In the first paragraph the authors report on the prevalence or multimorbidity without stating any numbers.
- Generally the introduction section should provide more background information on why this study is necessary (e.g. a better overview of which cohorts studies on multimorbidity are available in which countries, which research questions do they answer and which not and what are the differences of the settings compared to HongKong)
- Page 4, line 11: I don't understand what is meant by sedentary lifestyle and how it is connected with multimorbidity?
- Page 4, line 43: The abbreviation NICE has to be explained

Cohort description
- I recommend to name this section METHODS and structure it according to the headlines suggested by the STROBE checklist (especially the headlines "study design", "data sources/measurement" and "statistical analysis" should appear).
- Page 5, line 32-36: In my opinion this information belongs to the introduction section
- Page 5, line 40: I don't understand the phrase "which were available as indicated by administrative staffs for patient recruitment"
- Page 6, line 38: how were the 15 categories and 43 chronic conditions defined? Based on previous research?
- Page 7, line 36: Was the measurement of blood pressure standardized?

Findings to date

- I recommend to name this section "Results"
- The methods used for the comparison with other population-based surveys should be part of the method section not of the result section
- It should be stated where these 2 population-based surveys were conducted
- In my opinion the sections "follow-up" and "analysis plan" should not be part of the result section as they refer to future research. Some of the information could be moved to the discussion section.

	Discussion - The discussion section is very brief. The authors should elaborate on the meaning of the findings for health care providers, policy makers and researchers - Page 11, line 50: what is meant by stable cohort? References: - There is a large German cohort study on multi-morbidity called "MultiCare" which might be interesting for the authors: http://www.allgemeinmedizin.uni-frankfurt.de/forschung1/multicare01.html The website is in German, but if you scroll down all publications related to the study are listed in English.

REVIEWER	Prof. Hendrik van den Bussche Institute of Primary Medical Care University Medical Center Hamburg-Eppendorf Germany
REVIEW RETURNED	25-Nov-2018

GENERAL COMMENTS	This paper is to my humble opinion in fact a research protocol rather than a report on results of a completed study. As you describe yourself (p. 2) the potential value would result of a longitudinal follow-up of your cohort. The presentation of the baseline results and the rather simple item-per-item comparison with two other surveys do not present a value worthwhile to be published in an international journal. I would therefore suggest to overdo the paper in the sense of a research protocol and to present it a journal which is especially oriented towards research concepts. Apart from this general statement, I hope to support you by pointing to the more important deficiencies of the manuscript. The recruitment procedure lacks important details. Such as: • Why the 4 clinics out of 10; how do you exclude bias comparing to the elderly population of Hong Kong (e.g. 70% women and 61 % obese, or 4 diseases and 2 drugs typical for the elderly of HK?)? • How come that 70% of the eligible were excluded?: Quality problem of the recruitment process? Consequences for the specifics of the cohort? • How did you select the chronic diseases? How do you defined and selected 15 groups on the one hand and 43 single conditions on the other? The objectives of the study are very ambitious (p. 5), especially the "provision of information for policymakers in providing suitable health services". However, you will find associations between variables not allowing for the conclusion based on hard evidence. Please explain how your design will lead to which type of conclusions. The number of variables (22 complexes is too large to handle (in the sense of producing too many associations). Especially, I had the impression that the selection of variables and instruments was

| | not led by specific research questions and/or hypotheses. I would not support you to measure all one can do, but to find a narrower focus based on open questions derived from the literature.

Please consult also a statistician as a part of your specification of research questions describe above. For example, it is not appropriate to use Chi-square for testing differences in independent datasets. |
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REVIEWER	François Béland École de santé publique Université de Montréal Canada
REVIEW RETURNED	12-Feb-2019

| **GENERAL COMMENTS** | This paper covers the research objectives, design, descriptive results and several comparisons of two samples from the same population used in the study. A cohort of 4,381 elderly persons with two or more chronic diseases was recruited from four general outpatient clinics located in Hong Kong. 3,062 persons met the inclusion criteria. 1,617 declined or refused to participate, while 365 did not attend the baseline interview. Are characteristics (age and sex for example) of those 1,982 persons available? They should be reported. Interviews were conducted at a university affiliated clinic, not at the outpatient clinics where patients were recruited. Might this explain some of the missing respondents? Finally, a subset of measures is not available for 287 respondents.

Results from a systematic review (page 4, first paragraph) report that ten characteristics of elderly persons are associated with multimorbidity. These same characteristics are tested in the planned research. This raises the question of the expected contribution of this research to the topic at hand in addition to what is already known. However, hints as to the problems raised by multimorbidity in the context of primary care (page 4, paragraph 2) are mentioned: 1. fragmentation of care; 2. poor coordination; 3. increased healthcare expenditures; 4. search for cost-effective ways to manage patients; 5. treatment of disease in isolation; 6. duplication of care. However, the focus of the paper is not on development of theoretical models, study designs, measurements, or analytical procedures to approach these problems. The study focus is on the epidemiology and profiles of patients with multimorbidity…"to advance our understanding of potential causality" raising the expectation that this manuscript is focused on how patient profiles will be obtained, how causal links will be identified, and on how they will be estimated. None of these expectations are addressed in the paper.

Four out of ten general outpatient clinics in the New Territory East Cluster (NTEC) agreed to participate in the recruitment of patients, thus six clinics refused. Why? Is there evidence that they differ from the four participating clinics?

Descriptive results are provided, complemented by a comparison of some indicators with two studies presumably located in Hong Kong. The number of comparative tests is rather large (see Table 2). Adjustment for the number of tests should have been made. However, as most of the p-values were on the high side, results would probably not have differed much. On page ten, the authors list the significant differences between samples. They skip over the |
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difference of the most significant variable in their study: multimorbidity. In the NTEC sample only 19.5% had two chronic diseases, compared to 64.5% in the ETS and 47.4% in the THS samples. This result does not fit with the expected distribution of multimorbidity in a younger population (55% in NTEC vs 35% in ETS and THS aged 60 to 69), with higher educational levels (49% in NTEC vs 31% in ETS and THS with over six years of schooling), and with a lower proportion of social security recipients (59% in NTEC vs 76% in ETS). However, the lower proportion of respondents with two chronic diseases is in line with the lower proportion of respondents with poor self-rated health in the NTEC sample. There is no analysis, or suggestion, as to why the differences in the proportion of respondents with two chronic diseases are so dramatic between samples. Also, the authors do not comment on the consequences of the differences in their study.

The research setting, the study design, and the measurements used in the reported study raise an opportunity to examine some fundamental issues and search for solutions. Missed opportunities in this paper include:

1. Only the data from questionnaires seems to have been reported. However, diseases, medications used, and health services utilization were recorded on administrative files and were available. Why wasn't this data reported in the paper? Also, self-reported data and data from administrative files on the same indicators should have been compared;
2. Two steps are used to measure some respondent characteristics: depression; anxiety; insomnia; pain; physical activity; alcohol use. Implied in this strategy is a distribution of scores with an inflated zero. How will inflated zeros be considered in this study? Will all variables end up as dichotomies? In which case, why use a two-step strategy, estimating variations over ordered categories in the second step? Will procedures for count indicators be used? This will introduce problems in the analysis of longitudinal models (for example in growth models);
3. The sample size is not justified. It is not sufficient to mention that "the sample size is relatively large…" (page 11). It may possibly be considered rather small. For example, with the high number of variables introduced in the analyses, plus asymmetrical distributions, measured longitudinally, and with loss to follow up with time (no estimate provided), what is the expected number of useful time periods in this study? What is the power to detect expected associations and causal model parameters?
4. The baseline sample size is further reduced, from 995 to 712, when variables measured "at later stages" are included. How will this be dealt with in analysis? How about sample size and statistical power? Selecting respondents with full response sets? Are there differences between the 712 with full response sets and the 283 respondents with partial sets?
5. Hypertension appears in all of the chronic disease combinations listed on page eight. Also, 27% of patients have a combination of hypertension and arthritis. This suggests that analysis of multimorbidity including and excluding hypertension is needed, as well as excluding the combination of hypertension and arthritis;
6. The analysis plan is not informative. Longitudinal analysis introduces numerous problems, such as autocorrelation of errors, stability of measurement reliability though time, modelling mediators and moderators, causality vs growth models, etc. None

	of the general issues associated with longitudinal data analysis have been considered.

REVIEWER	Clemens Wittenbecher German Institute of Human Nutrition Potsdam-Rehbruecke Germany
REVIEW RETURNED	14-Feb-2019

GENERAL COMMENTS	Zhang et al. provide an informative and well-written description of a new cohort that was recruited among elderly Chinese speaking primary care patients in Hong Kong. The study includes individuals of sixty years and above with two or more chronic health conditions (i.e. multimorbidity). Apart from the information on diseases and treatments retrieved from electronic health records, the primary focus of the cohort is a comprehensive mainly questionnaire-based assessment of psychological and social characteristics of the study participants. Although by nature not novel in terms the presented findings, this cohort description provides a useful basis for future publications and may facilitate potential external collaborations. In the following I give a couple of suggestions to extend and specify the provided information. (Page and line numbers refer to the PDF version.) Abstract Please include a brief summary of assessment methods Please include a brief definition of "chronic condition" (which disease categories were considered) Probably the frequencies of broad categories of chronic conditions is also of high enough interest to be reported in the Abstract p.2, Line 22: "The study sample comprised 70% women with a mean age of 70.0 years (SD=6.8)" reads as if the mean age only referred to women – in that case, report mean age for men as well. Otherwise, please rephrase. Compared to the description of other relevant study characteristics, the information on frequency of psychosocial factors seems very detailed. Information in the sections "Purpose" and "Future Plans" is partly redundant. Strengths and limitations of this study p.3, Line 16: Please specify "long-term outcomes" p.3, Line 19/20: Why is this limitation? – reflect in relation to the overall study aims. INTRODUCTION The overarching aims of the cohort could be stated even more clearly: Etiological research into health-related determinants of psychological integrity and social integration or rather health service research, i.e. efficient resource-allocation in a specific primary care setting - … They are stated implicitly at the end of the Introduction section but may be separated more clearly from operational plans such as description of specific cohort subgroups and longitudinal modeling. Also consider a short separate section for the cohort aims. COHORT DESCRIPTION Study setting and participants p.5, Line 52: "2) with two or more chronic diseases confirmed by physicians" – it remains unclear how exactly this criterion was assessed in the recruitment procedure; please specify Please provide more information on the informed consent. How were participants informed and what did they agree on? Measures

	Please include some more details on the electronic health records, i.e. included information, coverage and data quality
	p.6, Line 52: "7) physical activity (measured by Physical Activity Scale for the Elderly (PASE)29 among those who were screened positive in pain)" - physical activity only assessed among those who were positively screened for pain? Why?
	Patient and Public Involvement
	No comments
	Findings to date
	No comments
	Comparison of participant characteristics with two other population-based surveys
	The objective for including the cohort comparison with ETS and THS surveys is not entirely clear. The inclusion criteria differed between the studies and the surveys seem not to reflect the same source population (different inclusion criteria, different time). Especially I do not see a reason for statistical comparison (Chi-square tests). Please explain why these comparisons are important for evaluating cohort that was recruited in public primary care clinics.
	Follow-up
	Please state the contact procedures.
	Does the follow-up include repeated assessment of all measures with exactly the same tools? Please be explicit.
	Analysis plan
	p.10, Line 33: "psychosocial factors such as pain, sarcopenia" – According to my understanding, pain and sarcopenia are generally not considered as psychosocial factors.
	Discussion
	p.11, Line 10-16: "In the present study, we found that those who suffered from multimorbidity had the psychological problems are common, including more than 10% suffering from mild cognitive impairment, more than half suffering from chronic physical pain involving two body parts and with almost 20% with either depressive or anxiety symptoms." Please review the structure of the sentence.
	You may consider a concluding sentence or paragraph on how you expect that findings from this cohort might inform the future "holistic approach that addresses general physical and functional domain of health".
	Strengths and Limitations
	p.11, Line 50-53: "Fourth, as this is relatively stable cohort, it will allow us to follow-up them in the very long term with the support from doctors and nurses, as well as the use of clinical management system information." While this is certainly a strength it is not easy to conceive where this assumption comes from. Please explain.
	For the limitations, please reflect on their relevance in relation to specific aims. Representativeness is mostly an issue for health service planning in the specific primary care setting. Sample size may predominantly limit the etiological question, particularly potential interaction and subgroup analyses that could be of interest…

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Cornelia Straßner

Institution and Country: University Hospital Heidelberg - Department of General Practice and Health Services Research - Germany
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
Please find my comments in the file attached.
Review of the manuscript
Cohort profile: Chinese elderly with multimorbidity in primary care in Hong Kong

The authors present – to their own information – the first longitudinal cohort study in the Chinese population. Thus the data deriving from this study is likely to be relevant for researchers and policy makers in the field. Yet the manuscript needs some more elaboration.
Our response:
Thank you very much for your valuable comments and advice. We have revised the manuscript accordingly. The responses are shown below one by one.

General comments:
• I am not an English native speaker but I feel that especially in the introduction and discussion section there are various grammar and language mistakes. I recommend that the paper should be revised by an English native speaker. Some examples:
☐ We found that those who suffered from multimorbidity had the psychological problems are common
☐ Sleep disturbance appears to be common with almost half being assessed reported significant sleep related symptoms
☐ The authors very often use terms like "the cohort examines". It should be "cohort study".
Our response:
We have updated the manuscript by a native English speaker for the grammar and language. The sentences above have been revised and the indicated terms have now been omitted.

Abstract and Title
• The exact design (longitudinal cohort study) should be mentioned in abstract and title
• The headlines of the abstract are uncommon. Usually abstracts are divided into Background, Objective, Methods (including study design, participants, measures), Results and Conclusions. As this is not a study protocol but a research report of a specific analysis, future plans are not relevant in the abstract in my opinion.
Our response:
As mentioned above, we have revised and reformatted the manuscript and now reported the baseline data of the study, i.e. biopsychosocial health profile of Chinese elderly with multimorbidity in Hong Kong. We have updated the title and abstract according to the comment and the guideline of BMJ Open. Since our sample was collected in primary care, but our results were weighted according to the census data of the general population (as a representative sample in primary care is not available), we now have omitted the term "primary care" in our title, and stated in the abstract about our sample, the weighting, and that "The weighted results might have underestimated the situation in elder primary care patients and be close to the situation of the general elderly."

Introduction
• Generally the introduction section appears a bit superficial. In the first paragraph the authors report on the prevalence of multimorbidity without stating any numbers.
• Generally the introduction section should provide more background information on why this study is necessary (e.g. a better overview of which cohorts studies on multimorbidity are available in which countries, which research questions do they answer and which not and what are the differences of the settings compared to Hong Kong)
• Page 4, line 11: I don't understand what is meant by sedentary lifestyle and how it is

connected with multimorbidity?
• Page 4, line 43: The abbreviation NICE has to be explained
Our response:
Thank you for your comments and suggestions.
• For prevalence, we have added that: "A recent systematic review suggests that the prevalence of multimorbidity is high among the elderly ranging from 12.9% to 95.1% in different studies.1" (Line 7-8, Page 5)
• We included and summarized the study information in the introduction by indicating countries and the research gaps: that most studies were conducted in the Western countries and did not study physical, mental and social health at the same time. Please see the highlighted parts: "Most studies on primary care patients with multimorbidity are conducted in western countries such as UK, USA, Australia, Spain and Belgium,2-10 and limited research has been conducted on psychological and social problems accompanying with multimorbidity.1,11-14 Several longitudinal studies of multimorbidity have been conducted in Asian populations,15-17 but none of these are of primary care patients. Important knowledge gaps still exist regarding the biopsychosocial health profiles of elderly people with multimorbidity in primary care in Asian Chinese elderly.18" (Line 23-30, Page 5)
• Sedentary lifestyles increase the risk of obesity which then increases the risk of common chronic conditions such as hypertension and diabetes etc. This information has been added to the introduction : "The prevalence has increased in recent decades as a result of an aging population and changes in lifestyle e.g. more sedentary lifestyles have increased the risk of obesity, resulting in a higher risk of developing chronic conditions.19,20" (Line 4-6, Page 5)
• The full spelling (The National Institute for Health and Care Excellence) has been added to NICE in the manuscript. (Line 20-21, Page 5)

Cohort description
• I recommend to name this section METHODS and structure it according to the headlines suggested by the STROBE checklist (especially the headlines "study design", "data sources/measurement" and "statistical analysis" should appear).
• Page 5, line 32-36: In my opinion this information belongs to the introduction section
• Page 5, line 40: I don't understand the phrase "which were available as indicated by administrative staffs for patient recruitment"
• Page 6, line 38: how were the 15 categories and 43 chronic conditions defined? Based on previous research?
• Page 7, line 36: Was the measurement of blood pressure standardized?
Our response:
• Thank you for your suggestion on the format and the STROBE checklist. We have updated the manuscript accordingly.
• The sentence "Hong Kong has a population of 7.34 million according to the 2016 census data,21 with 23.7% aged 60 years or above, which was higher than the rates of 16.5% and 19.5% in 2006 and 2011, respectively" has been moved to the last paragraph of the Introduction section. (Line 1-3, Page 6)
• Each time researchers want to do research in public clinics in Hong Kong, official approval should be granted first by the Hospital Authority. We have revised the sentence to be: "as permission to recruit from these four was given by the local regulator (the Hospital Authority). (Line 22, Page 6)
• Yes, the 15 categories and 43 chronic conditions were adapted by a group of family physicians and researchers based on two previously frequently cited epidemiological study on multimorbidity22,23 and the International Statistical Classification of Diseases 11 (ICD-11). The detailed information of these conditions can be seen in Table 1 (chronic conditions). (Line 24-27, Page 7)
• Yes, the measurement of blood pressure was standardized according to the hypertension framework by the primary care office in Hong Kong. Two assessments were taken by nurses. Patients sat for at least 5 minutes before the first assessment, and they were assessed again 15 minutes later. This information was added to the manuscript: "For blood pressure, two assessments were taken by the

nurses. Patients sat for at least 5 minutes before the first assessment, and they were assessed again 15 minutes later" and we also added that "Handgrip strength was also assessed twice for each hand." (Line 27-30, Page 8)

Findings to date
• I recommend to name this section "Results"
• The methods used for the comparison with other population-based surveys should be part of the method section not of the result section -It should be stated where these 2 population-based surveys were conducted
• In my opinion the sections "follow-up" and "analysis plan" should not be part of the result section as they refer to future research. Some of the information could be moved to the discussion section.
Our response:
Thank you for the suggestion.
• We have revised our manuscript and renamed the section as Results..
• The two surveys were conducted in Hong Kong as well. Considering comments from other reviewers together, we have now moved the information of comparison with the other two surveys to the Supplementary File. (Please see the supplementary file for information)
• The sections "follow-up" and "analysis plan" are now deleted from Results section. Relevant information has been simplified and moved to the Discussion section to show that follow-up assessments and future analysis would be conducted as suggested: "Based on these findings, we have been designing and testing a model for tackling biopsychosocial health problems in Hong Kong. In addition, the patients in this study will be followed-up regularly to monitor changes in health status and outcomes by both questionnaire and physical assessments. The first follow-up started in early 2018. The longitudinal biopsychosocial health profiles of these primary care patients will be evaluated, as well as the longitudinal associations of psychosocial factors and multimorbidity, and the impact of biopsychosocial health status on different health outcomes, healthcare use, quality of life and mortality." (Line 2-9, Page 13)

Discussion
• The discussion section is very brief. The authors should elaborate on the meaning of the findings for health care providers, policy makers and researchers
• Page 11, line 50: what is meant by stable cohort?
Our response:
Thank you for the suggestion.
• The meaning of the findings for healthcare providers, policy makers and researchers were further elaborated in Discussion by including the key data of biopsychosocial health problems, and suggesting that "The results suggested that a holistic approach that addresses general physical and functional domain of health, at the same time assessing and managing psychological and social problems may be needed to look after older adults with multimorbidity." (Line 22-24, Page 12)
• We have deleted the term stable to reduce misunderstanding, but rather, we stated that "Third, because it contains linked electronic medical records, it will allow us to follow them up for mortality and public medical service use." (Line 16-17, Page 13)

References:
• There is a large German cohort study on multi-morbidity called "MultiCare" which might be interesting for the authors: http://www.allgemeinmedizin.unifrankfurt.de/forschung1/multicare01.html The website is in German, but if you scroll down all publications related to the study are listed in English.
Our response:

Thank you very much for the information of MultiCare, we have noticed it and further added some of the representative publications, along with some other studies, in the background and discussion sections to better link our current study with other studies on multimorbidity worldwide.

Reviewer: 2
Reviewer Name: Prof. Hendrik van den Bussche
Institution and Country: Institute of Primary Medical Care - University Medical Center Hamburg-Eppendorf - Germany
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
Prof. Hendrik van den Bussche
Comments to D. Zhang et al.: Cohort profile protocol

This paper is to my humble opinion in fact a research protocol rather than a report on results of a completed study. As you describe yourself (p. 2) the potential value would result of a longitudinal follow-up of your cohort. The presentation of the baseline results and the rather simple item-per-item comparison with two other surveys do not present a value worthwhile to be published in an international journal. I would therefore suggest to overdo the paper in the sense of a research protocol and to present it a journal which is especially oriented towards research concepts.
Apart from this general statement, I hope to support you by pointing to the more important deficiencies of the manuscript.
Our response:
Thank you very much for your valuable comments and suggestions. In BMJ Open, there are a number of studies which are cohort profiles, and we followed the journal guidelines in preparing our manuscript previously. We agree that as our study is at the beginning stage, different from others who already had published results, we only had the baseline results (although there is an overall plan for follow-up assessments but the plan is not concrete in details at this moment). After further consideration, as well as taking into account the overall editor and reviewer comments, we have reshaped our study by cross-sectionally reporting the baseline results of this study, and tried to make the results more representative through weighting according to age, gender and marital status from the most recent census data. But in the future, we will report further findings based on this study by referring to this paper as the main paper at baseline. These will include subgroup analysis and also longitudinal analyses. This current study was not perfectly designed due to time and manpower constraints, but we do hope the findings can inform future healthcare practices and policy making by providing biopsychosocial health information of elder patients in primary care, as often psychosocial health problems are neglected during the patient-centred healthcare services. Along with global population ageing, disease burden from multimorbidity has increased. The findings suggested that psychosocial problems are prominent among elder primary care patients in Hong Kong, and a holistic way in tackling physical, mental and social problems is warranted.

The recruitment procedure lacks important details. Such as:
• Why the 4 clinics out of 10; how do you exclude bias comparing to the elderly population of Hong Kong (e.g. 70% women and 61 % obese, or 4 diseases and 2 drugs typical for the elderly of HK?)?
Our response:
Thank you for your comment. Planned research in public clinics in Hong Kong must be first approved by the Hospital Authority. The Hospital Authority do not allow recruitment in all ten clinics for research projects in order to minimize extra workload for the staff in the clinics.
To reduce sample bias, we have weighted our sample according to the most recent census data. We believe the weighted results might be an underestimation of the situation in elder primary care patients and be close to the situation of the general elderly. We also compared our study sample to

the elderly population in two other populations-based surveys in Hong Kong . We did not compare it with a representative sample in primary care as this kind of sample is not available in Hong Kong currently. The information for comparison with the two population-based surveys is now moved to the supplementary file after considering all the comments. From comparison, we may know better of the characteristics of our samples, while making generalization to the general population. But it might be unlikely to completely reduce bias, what we can do can be adjusting for the baseline characteristics during data analysis in the future. We added this in our discussion that: "Future analysis will need to consider this in the interpretation of findings." (Line 18-19, Page 14)

• How come that 70% of the eligible were excluded?: Quality problem of the recruitment process? Consequences for the specifics of the cohort?
Our response:
In our study, 1196 eligible cases refused or did not show up in the baseline assessment after screening. So the recruitment rate was 47% (1077/(1196+1077)): almost half of the eligible cases joined in the study. The recruitment rate was comparable or slightly higher than other studies in Hong Kong. Our study might have included a relatively healthier and higher-functioning sample due to voluntary participation and only those who could walk were included, and the real situation might be worse in primary care than what was rates reported in our study even after weighting, as it was according to the census not the primary care patients. We have added in our limitation in the discussion section that: "First, self-selection bias might still exist which was consistent with other similar studies,24 although we used weighting for adjustment, as not all variables were available for weighting such as education. Since only ambulatory adults who agreed to join were recruited and these usually are more likely to be female and those with higher educational level and higher self-motivation, and those who were house-bound or institutionalized are less likely to have been included, we might have resulted in a relatively healthier and higher-functioning patients in primary care, and the real health status might be worse than what are reported in our study. Future studies may need to take measures to increase participation from male and vulnerable patients." (Line 20-28, Page 13)

• How did you select the chronic diseases? How do you defined and selected 15 groups on the one hand and 43 single conditions on the other?
Our response:
These 43 common chronic conditions in Hong Kong were slightly adapted by a group of family physicians and researchers based the chronic conditions in two previously frequently cited epidemiological studies on multimorbidity22,23 and they were further grouped according to the International Statistical Classification of Diseases 11 (ICD-11) (Line 24-27, Page 7). Detailed information of these categories and conditions can now be seen in Table 1.

• The objectives of the study are very ambitious (p. 5), especially the "provision of information for policymakers in providing suitable health services". However, you will find associations between variables not allowing for the conclusion based on hard evidence. Please explain how your design will lead to which type of conclusions.
Our response:
Thank you for your comments. As mentioned above, we have reshaped our study by showing the baseline biopsychosocial health profile of the patients. The aim was also updated as: "To inform healthcare providers and policymakers in providing suitable health services for people with multimorbidity in primary care, the present study aimed to study the biopsychosocial health profiles of Chinese patients with multimorbidity who present to public primary care in Hong Kong." (Line 8-11, Page 6) The rates and results reported in this paper may be helpful for people to understand the health situations among the elderly with multimorbidity from biopsychosocial aspects. As we plan to conduct further follow-up assessments and also link the data with the routine clinical management system (CMS) data, this would allow us to observe and analyse the results longitudinally so that inform researchers, policy makers and healthcare providers more information at a later stage.

The number of variables (22 complexes is too large to handle (in the sense of producing too many associations). Especially, I had the impression that the selection of variables and instruments was not led by specific research questions and/or hypotheses. I would not support you to measure all one can do, but to find a narrower focus based on open questions derived from the literature.
Our response:
Thank you very much for the comment and suggestions. As mentioned above, after discussions, we have now reframed our study and narrowed it to be a cross-sectional study describing the baseline biopsychosocial health profile of the elder patients with multimorbidity in primary care. But in future subgroup analysis and longitudinal analysis after follow-up assessments, we would look into specific research questions among the study population based on hypotheses.

Please consult also a statistician as a part of your specification of research questions describe above. For example, it is not appropriate to use Chi-square for testing differences in independent datasets.
Our response:
Thank you for your comment. We are sorry for the misunderstanding. We have updated our manuscript overall. For the statistical part, chi square tests were used for categorical data analysis.

Reviewer: 3
Reviewer Name: François Béland
Institution and Country: École de santé publique - Université de Montréal - Canada
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This paper covers the research objectives, design, descriptive results and several comparisons of two samples from the same population used in the study. A cohort of 4,381 elderly persons with two or more chronic diseases was recruited from four general outpatient clinics located in Hong Kong. 3,062 persons met the inclusion criteria. 1,617 declined or refused to participate, while 365 did not attend the baseline interview. Are characteristics (age and sex for example) of those 1,982 persons available? They should be reported. Interviews were conducted at a university affiliated clinic, not at the outpatient clinics where patients were recruited. Might this explain some of the missing respondents? Finally, a subset of measures is not available for 287 respondents.
Our response:
Thank you very much for your comments and suggestions. Unfortunately, the information of the 1982 patients were not available. The university affiliated clinic is nested in the one of the GOPCs in the study. Whilst location may explain some non-attendance, particularly for more frail individuals, the clinic is close to an MTR train station and bus stations which are popular and convenient mode of transport for residents of any age in Hong Kong. As we needed to conduct a comprehensive biopsychosocial assessment (such as body weight, height, handgrip strength, cognition), participants needed to come to our clinic where equipment and space were available. It was also not possible to conduct the assessments on the same day of recruitment, as we allowed time between signing the consent form and attending for assessment for ethical reasons (so that participants had the opportunity to change their mind about participation).
We agree that it is a limitation that some measures are not available for about one fourth of the patients. This was because we decided to add some additional questions based on the existing questionnaire to enrich the study findings at a later stage. However, this was only applied to the additional data, such as sarcopenia, oral health and meaning. We believe it would be still helpful in reporting these further data to inform healthcare providers, policy makers and researchers while the key indicators are collected from all patients. At the same time, this study would serve as the basis for future subgroup analyses and longitudinal analyses to look into some specific research questions based on hypotheses. We had included in the limitations in Discussion that "Furthermore, some

additional assessments such as meaning, sarcopenia, oral health were added at a later stage. So only subgroup data could be reported in this paper or analyzed in the future when using these data. " (Line 8-10, Page 14)

Results from a systematic review (page 4, first paragraph) report that ten characteristics of elderly persons are associated with multimorbidity. These same characteristics are tested in the planned research. This raises the question of the expected contribution of this research to the topic at hand in addition to what is already known. However, hints as to the problems raised by multimorbidity in the context of primary care (page 4, paragraph 2) are mentioned: 1. fragmentation of care; 2. poor coordination; 3. increased healthcare expenditures; 4. search for cost-effective ways to manage patients; 5. treatment of disease in isolation; 6. duplication of care. However, the focus of the paper is not on development of theoretical models, study designs, measurements, or analytical procedures to approach these problems. The study focus is on the epidemiology and profiles of patients with multimorbidity…"to advance our understanding of potential causality" raising the expectation that this manuscript is focused on how patient profiles will be obtained, how causal links will be identified, and on how they will be estimated. None of these expectations are addressed in the paper.
Our response:
Thank you for your comments. We have now narrowed our manuscript by focusing on the biopsychosocial profile of the elder patients with multimorbidity in primary care, with the findings suggesting that: "A holistic approach that addresses general physical and functional domain of health, at the same time assessing and managing psychological and social problems may be needed to look after older adults with multimorbidity." Treatment programmes may be developed based on the findings of this study to improve the outcomes through a more holistic care approach targeting at the identified problems. At the same time, the causal links would be explored based on hypotheses in future studies based on the baseline and follow-up data of participants in this study. The Introduction section has been modified and information of "1. fragmentation of care; 2. poor coordination; 3. increased healthcare expenditures; 4. search for cost-effective ways to manage patients; 5. treatment of disease in isolation; 6. duplication of care" has now been omitted to make the study more focused on the current theme.

Four out of ten general outpatient clinics in the New Territory East Cluster (NTEC) agreed to participate in the recruitment of patients, thus six clinics refused. Why? Is there evidence that they differ from the four participating clinics?
Our response:
Thank you for your comment. As responded in the above comments, planned research in public clinics in Hong Kong must be first approved by the Hospital Authority. The Hospital Authority do not allow recruitment in all ten clinics for research projects in order to minimize extra workload for the staff in the clinics. At the time for recruitment, only four clinics were available for us to do recruitment. Although we have no data to confirm this, the characteristics of the patients in the other six clinics were less likely to be greatly different from patients in the four clinics in the study as the demographic and social economic data are similar within this area. In addition, as mentioned above, we have now showed the weighted data according to age, gender and marital status of the general population based on the most recent census data in Hong Kong. The unweighted and weighted rates were in general similar, however, as it was weighted based on representative primary care data (as it is not available currently), the weighted results might be an underestimation of the situation in elder primary care patients and be close to the situation of the general elderly.

Descriptive results are provided, complemented by a comparison of some indicators with two studies presumably located in Hong Kong. The number of comparative tests is rather large (see Table 2). Adjustment for the number of tests should have been made. However, as most of the p-values were on the high side, results would probably not have differed much. On page ten, the authors list the significant differences between samples. They skip over the difference of the most significant variable

in their study: multimorbidity. In the NTEC sample only 19.5% had two chronic diseases, compared to 64.5% in the ETS and 47.4% in the THS samples. This result does not fit with the expected distribution of multimorbidity in a younger population (55% in NTEC vs 35% in ETS and THS aged 60 to 69), with higher educational levels (49% in NTEC vs 31% in ETS and THS with over six years of schooling), and with a lower proportion of social security recipients (59% in NTEC vs 76% in ETS). However, the lower proportion of respondents with two chronic diseases is in line with the lower proportion of respondents with poor self-rated health in the NTEC sample. There is no analysis, or suggestion, as to why the differences in the proportion of respondents with two chronic diseases are so dramatic between samples. Also, the authors do not comment on the consequences of the differences in their study.

Our response:

Thank you for your comments and suggestions. We believe that the discrepancy in the percentage of two chronic conditions in the three samples was due to several reasons. First, chronic conditions might have been under-reported in THS and ETS as both surveys relied on participants' self-report, and the current study had extracted information from both patient self-report and clinical medical records. Second, sample difference, as one was in primary care settings, and the other two were among the general populations, and primary care patients usually have more problems than those who are from the general population. Third, more female in our study as women usually reported more number of chronic conditions comparing to men.25,26 Due to the use of different data collection methods on multimorbidity, to be conservative, we have deleted the information. Instead, we have weighted our sample according to the age, gender and marital status based on the most recent census data. The weighted and unweighted results are similar in general. However, we believe the weighted results might be an underestimation of the situation in elder primary care patients and be close to the situation of the general elderly. We had added this message in our Abstract, discussion and highlight for readers' information.

The research setting, the study design, and the measurements used in the reported study raise an opportunity to examine some fundamental issues and search for solutions. Missed opportunities in this paper include:

1. Only the data from questionnaires seems to have been reported. However, diseases, medications used, and health services utilization were recorded on administrative files and were available. Why wasn't this data reported in the paper? Also, self-reported data and data from administrative files on the same indicators should have been compared;

Our response:

Thank you for your comments. The information of diseases, medications used, and health services utilization was included in the paper. After reformatting the paper, the information can be more clearly seen in the Results sections under the subheadings "Chronic conditions" and "Health service utilization". For more information, readers can also refer to Table 2. We did not compare these data but integrated them into one during data collection and data entry in the e-database, making it is unavailable for comparison. As the data in the public health records do not include information from private practice, as well as that patients sometimes do not self-report all existing chronic conditions, from our experiences, this could supplement the disease information as much as possible.

2. Two steps are used to measure some respondent characteristics: depression; anxiety; insomnia; pain; physical activity; alcohol use. Implied in this strategy is a distribution of scores with an inflated zero. How will inflated zeros be considered in this study? Will all variables end up as dichotomies? In which case, why use a two-step strategy, estimating variations over ordered categories in the second step? Will procedures for count indicators be used? This will introduce problems in the analysis of longitudinal models (for example in growth models);

Our response:

For these variables, the results were case by case. For depression and anxiety, they were screened by the widely used screening tools PHQ-2 and GAD-2 respectively, the rates reported in PHQ-9 or GAD-7 were then the number of patients in each subgroup dividing by the total number of patients (N=1077). There could be false negative cases using this method, but the chance could be low since the specificity and sensitivity were reported to be high and this method was suggested by the recent meta-analytic reviews.27,28 For insomnia, pain and alcohol use, if the patients reported no to the screening questions, it is unlikely that they would answer the subsequent questions in the relevant scales. So it is unlikely this under-reports the rates of these problems. For physical activity, only those with pain were measured. This was because that this was a sub-research question within the study, and the scale was long, so not all the components were measured. It was a limitation that only subgroup analyses could be conducted among these patients regarding physical activity. We also agree that it would cause problem if we use longitudinal analysis such as growth models. We have included in the limitations in our Discussion section that: "Third, we used a two-step assessment for some health indicators. While false negative reported rates of pain, insomnia and alcohol use were unlikely, there might be false negative rates for depression and anxiety as the specificity and sensitivity of PHQ-2 and GAD-2 were not 100% (although results from meta-analytic reviews suggest they are reasonable to use in initial screening).27,28 In addition, as PHQ-2 and GAD-2 are often used for screening with results in dichotomies (negative/positive), this might limit application of some statistical analysis such as using growth models in future longitudinal data." (Line 30, Page 13 – Line 6, Page 13) and "Fourth, for a few assessments, we only conducted them among a subgroup of participants, e.g. PASE for physical activity among those patients with pain. Furthermore, some additional assessments such as meaning, sarcopenia, oral health were added at a later stage. So only subgroup data could be reported in this paper or analyzed in the future when using these data." (Line 6-10, Page 14)

3. The sample size is not justified. It is not sufficient to mention that "the sample size is relatively large…" (page 11). It may possibly be considered rather small. For example, with the high number of variables introduced in the analyses, plus asymmetrical distributions, measured longitudinally, and with loss to follow up with time (no estimate provided), what is the expected number of useful time periods in this study? What is the power to detect expected associations and causal model parameters?
Our response:
Thank you for your comment and advice. We agree with the comment. As mentioned above, we have now revised our paper and narrowed our focus to the biopsychosocial health profile of the patients. We have added in the method section that the study sample size would allow for a margin of error of 3% for the rates reported in the study. (Line 7-8, Page 7) In future follow-up studies, we would take distributions of specific variables, as well follow-up rates, into account when conducting the specific analyses driven by hypotheses.

4. The baseline sample size is further reduced, from 995 to 712, when variables measured "at later stages" are included. How will this be dealt with in analysis? How about sample size and statistical power? Selecting respondents with full response sets? Are there differences between the 712 with full response sets and the 283 respondents with partial sets?
Our response:
For those variables which were not measured in all patients, we would do subgroup analysis in the future. The statistical power would be lower among these subgroup analyses. However, key indicators, such as depression, anxiety, chronic conditions, quality of life, were included for all participants, so we did not conduct subgroup analyses for comparison for these few subscales (such as meaning of existence, oral health, incontinence and sarcopenia). We agree that in future subgroup analysis, comparisons could be made to see if there were any differences, as well as with the general population for these subgroups.

5. Hypertension appears in all of the chronic disease combinations listed on page eight. Also, 27% of patients have a combination of hypertension and arthritis. This suggests that analysis of multimorbidity including and excluding hypertension is needed, as well as excluding the combination of hypertension and arthritis

Our response:

Thank you for the comment and suggestion. We agree that it could be more informative if we excluded these two conditions. However, readers can still refer to the figures in Figure 3 in looking into combinations of other chronic conditions, and the rates of comorbidities were already as low as 0.4% for other common combinations in the figure. We therefore tend to show the existing % in Figure 3 by including hypertension and Skeletal &connective tissue inflammation (e.g. arthritis), and indicate to readers in the text that they may also check % of other comorbidities in the figure.

6. The analysis plan is not informative. Longitudinal analysis introduces numerous problems, such as autocorrelation of errors, stability of measurement reliability though time, modelling mediators and moderators, causality vs growth models, etc. None of the general issues associated with longitudinal data analysis have been considered.

Our response:

Thank you for your advice. We believe these are important statistical issues for longitudinal studies. Since our paper has now been narrowed down to describing the baseline biopsychosocial health profile, as suggested by other reviewers, we have now omitted the analysis plan in detail, but simplified and elaborated it in the discussion sections that longitudinal analysis would be conducted later. At this stage, we are still exploring possible analyses driven by hypotheses with our collected data and ongoing follow-up assessments.

Reviewer: 4
Reviewer Name: Clemens Wittenbecher
Institution and Country: German Institute of Human Nutrition Potsdam-Rehbruecke - Germany
Please state any competing interests or state 'None declared': "None declared"

Please leave your comments for the authors below

Zhang et al. provide an informative and well-written description of a new cohort that was recruited among elderly Chinese speaking primary care patients in Hong Kong. The study includes individuals of sixty years and above with two or more chronic health conditions (i.e. multimorbidity). Apart from the information on diseases and treatments retrieved from electronic health records, the primary focus of the cohort is a comprehensive mainly questionnaire-based assessment of psychological and social characteristics of the study participants. Although by nature not novel in terms the presented findings, this cohort description provides a useful basis for future publications and may facilitate potential external collaborations. In the following I give a couple of suggestions to extend and specify the provided information. (Page and line numbers refer to the PDF version.)

Our response:

Thank you for your overall positive comments and valuable suggestions for revisions. We have responded one by one below and revised accordingly.

Abstract
Please include a brief summary of assessment methods
Please include a brief definition of "chronic condition" (which disease categories were considered)
Probably the frequencies of broad categories of chronic conditions is also of high enough interest to be reported in the Abstract
p.2, Line 22: "The study sample comprised 70% women with a mean age of 70.0 years (SD=6.8)" reads as if the mean age only referred to women – in that case, report mean age for men as well. Otherwise, please rephrase.

Compared to the description of other relevant study characteristics, the information on frequency of psychosocial factors seems very detailed. Information in the sections "Purpose" and "Future Plans" is partly redundant.

Strengths and limitations of this study

p.3, Line 16: Please specify "long-term outcomes"

p.3, Line 19/20: Why is this limitation? – reflect in relation to the overall study aims.

Our response:

Thank you for your comments and suggestions.

• Since it would be too long to include all the measurements, we have briefly included the summarized information in Abstract: "Primary and secondary outcome measures: Biopsychosocial health indicators (primary), health service utilization and quality of life (secondary)."

• As there is no consistent definition of chronic conditions currently, we referred to the previously popularly used chronic conditions22,23 and slightly modified by a group of family physicians and researchers based on the Hong Kong situation, and grouped them into 15 groups according to ICD-11.(Line 24-27, Page 7) The detailed information of these conditions can now be seen in Table 1.

• Since we have now conducted weighting of the results, the sentence has been rephrased to be: "The weighted data are shown in the bracket beside the unweighted data. The mean age of the study patients was 70 (SD=6.8) (70.5, SD=7.9) years, 70% (52.8%) were female, 67% (68%) were married, 14% (15%) lived alone, 92% (87%) were retired or housewives, 49% (52%) had 6 years of education or above…"

• Due to the word count limit, we only described key health indicators in our study. But readers can also find other health indicators in Table 2. Information of Purse and Future Plans are omitted now as suggested. Instead, in Discussion section, we simplified and mentioned a bit about it: "In addition, the patients in this study will be followed-up regularly to monitor changes in health status and outcomes by both questionnaire and physical assessments. The first follow-up started in early 2018. The longitudinal biopsychosocial health profiles of these primary care patients will be evaluated, as well as the longitudinal associations of psychosocial factors and multimorbidity, and the impact of biopsychosocial health status on different health outcomes, healthcare use, quality of life and mortality. ." (Line 3-9, Page 13)

• Also based on other reviewers' comments above, we have revised the Strengths section to reduce confusion: "Second, this is one of the very few studies based on Chinese primary care patients with multimorbidity . Third, because it contains linked electronic medical records, it will allow us to follow them up for mortality and public medical service use." (Line 15-16, Page 13)

• Because those patients who were house-bounded or institutionalized were not included. We included in the limitation section that: "First, self-selection bias might still exist which was consistent with other similar studies,24 although we used weighting for adjustment, as not all variables were available for weighting such as education. Since only ambulatory adults who agreed to join were recruited and these usually are more likely to be female and those with higher educational level and higher self-motivation, and those who were house-bound or institutionalized are less likely to have been included, we might have resulted in a relatively healthier and higher-functioning patients in primary care, and the real health status might be worse than what are reported in our study. Future studies may need to take measures to increase participation from male and vulnerable patients. " (Line 20-28, Page 13)

INTRODUCTION

The overarching aims of the cohort could be stated even more clearly: Etiological research into health-related determinants of psychological integrity and social integration or rather health service research, i.e. efficient resource-allocation in a specific primary care setting - … They are stated implicitly at the end of the Introduction section but may be separated more clearly from operational plans such as description of specific cohort subgroups and longitudinal modeling. Also consider a short separate section for the cohort aims.

Our response:

Thank you for the suggestion. To reduce confusion and also based on suggestions from other reviewers, we have reshaped our study, and we have now included it at the end of the last paragraph in Introduction section to show the aim: The aim was also updated as: "To inform healthcare providers and policymakers in providing suitable health services for people with multimorbidity in primary care, the present study aimed to study the biopsychosocial health profiles of Chinese patients with multimorbidity who present to public primary care in Hong Kong." (Line 8-11, Page 6)

COHORT DESCRIPTION
Study setting and participants
p.5, Line 52: "2) with two or more chronic diseases confirmed by physicians" – it remains unclear how exactly this criterion was assessed in the recruitment procedure; please specify
Please provide more information on the informed consent. How were participants informed and what did they agree on?
Our response:
The chronic diseases were recorded in the electronic medical system by clinical doctors in their routine practices. The information of medical records was supplemented by patients' self-report. To make it clearer, we have included this in the methods: "2) with two or more chronic diseases confirmed by the medical information in the public health record system and patients' self-report" (Line 28-30, Page 6) The consent included assessment of the patients at baseline and follow-up, as well as reviewing their medical records. Patients would be asked to sign an updated consent form after the amendment consent form was approved by the ethics committee. So patients were informed of any research activities before their participation.

Measures
Please include some more details on the electronic health records, i.e. included information, coverage and data quality
p.6, Line 52: "7) physical activity (measured by Physical Activity Scale for the Elderly (PASE)29 among those who were screened positive in pain)" - physical activity only assessed among those who were positively screened for pain? Why?
Our response:
Thank you for your comment. The electronic health records include all routine clinical activities and patient information and diagnosis, health examinations, medication prescriptions, and health visits in public health system. It covers all patients who seek medical services in the public health system. It is a medical record system of routine clinical practice with quality ensured by all healthcare professionals including trained doctors, nurses and allied health professionals under Hospital Authority in Hong Kong. This information has now been added to the manuscript: "The electronic medical records include patient information and diagnosis, health examinations, medication prescription, and health visits to the public health system. The records cover all patients who seek medical services in public health system. It is a medical record system of routine clinical practices with quality ensured by all healthcare professionals including trained doctors, nurses and allied health professionals under Hospital Authority in Hong Kong." (Line 19-23, Page 7) We only included PASE among those with pain as there was a sub-research question to see the physical activity of the elderly with pain. We agree this could be a limitation if we would like to study those patients without pain, though more than two thirds had pain and were assessed by the PASE in this study. We have added this in the limitations section: "Fourth, for a few assessments, we only conducted them among a subgroup of participants, e.g. PASE for physical activity among those patients with pain. Furthermore, some additional assessments such as meaning, sarcopenia, oral health were added at a later stage. So only subgroup data could be reported in this paper or analyzed in the future when using these data." (Line 6-10, Page 14)

Patient and Public Involvement
No comments

Our response:
No action is needed.

Findings to date
No comments
Our response:
No action is needed.

Comparison of participant characteristics with two other population-based surveys
The objective for including the cohort comparison with ETS and THS surveys is not entirely clear. The inclusion criteria differed between the studies and the surveys seem not to reflect the same source population (different inclusion criteria, different time). Especially I do not see a reason for statistical comparison (Chi-square tests). Please explain why these comparisons are important for evaluating cohort that was recruited in public primary care clinics.
Our response:
Thank you for pointing out this. We agree that the sources of the populations are different. We previously included the comparison with two population-based surveys because we would like to see the representativeness of the population among the general Hong Kong elder adults so that we could provide more information for policy making, and we do not have a representative sample in primary care so far in Hong Kong. As mentioned above, to be conservative, we have deleted the comparison results in the paper. Instead, we have now added weighted results weighted by age, gender and marital status according to the most recent and available census data in 2016, which is the most representative data we can refer to. The weighted and unweighted results are in general similar, however, as we might have included a relatively healthier sample, and not all variables can be used for weighting such as education, we believe that: "The weighted results might have underestimated the situation in elder primary care patients and be close to the situation of the general elderly." And this information has been expressed in Abstract, highlight and discussion.

Follow-up
Please state the contact procedures.
Does the follow-up include repeated assessment of all measures with exactly the same tools? Please be explicit.
Our response:
Thank you. We have included the contact information of our principal investigator Prof. Samuel Wong. We would include key biopsychosocial assessments such as depression, anxiety, loneliness, pain, frailty, as well as quality of life in the follow-up assessments, but each follow-up may include some additional assessments. As this is an ongoing longitudinal study, we have not fixed all the follow-up assessments. We welcome collaborations but at this moment, a concrete procedure for collaboration has not been established. However, it would be similar to projects in other areas, e.g. a protocol for research question and potential collaboration would be needed. And if there is continuous funding support, the data would be shared for free (with personal identifiers of cohort participants removed) .

Analysis plan
p.10, Line 33: "psychosocial factors such as pain, sarcopenia" – According to my understanding, pain and sarcopenia are generally not considered as psychosocial factors.
Our response:
Thank you for pointing out this. We have deleted this in the sentence.

Discussion
p.11, Line 10-16: "In the present study, we found that those who suffered from multimorbidity had the psychological problems are common, including more than 10% suffering from mild cognitive

impairment, more than half suffering from chronic physical pain involving two body parts and with almost 20% with either depressive or anxiety symptoms." Please review the structure of the sentence. You may consider a concluding sentence or paragraph on how you expect that findings from this cohort might inform the future "holistic approach that addresses general physical and functional domain of health".

Our response:

Thank you for your comment and suggestion. We have revised the sentence to be "The study results were overall in consistency with results reported in the western populations, that biopsychosocial health problems are prominent among the elder adults with multimorbidity in primary care clinics in Hong Kong. Depression, anxiety, insomnia and loneliness were prevalent. Almost one fifth had either depressive or anxiety symptoms, and one quarter reported feeling lonely. Moreover, sleep disturbance appears to be common with almost half reporting significant sleep related symptoms. Some also showed cognition decline with more than one fifth suffered from mild cognitive impairment. In addition, we found that about one quarter of the patients were overweight and another one third were obese, about two thirds of the participants suffered from chronic physical pain involving two body parts, one quarter used 5 or more medications regularly and one third forgot using medications sometimes, one quarter had chewing difficulty, one fifth self-reported incontinence, more than one in ten reported being frail, and some had reduced handgrip strength and signs of sarcopenia. At least one in ten needed help in daily function." (Line 3-15, Page 12) We had included the suggested information on informing future holistic approach into the manuscript: "The results suggested that a holistic approach that addresses general physical and functional domain of health, at the same time assessing and managing psychological and social problems is therefore needed in the care of older adults with multimorbidity." (Line 22-24, Page 12)

Strengths and Limitations

p.11, Line 50-53: "Fourth, as this is relatively stable cohort, it will allow us to follow-up them in the very long term with the support from doctors and nurses, as well as the use of clinical management system information." While this is certainly a strength it is not easy to conceive where this assumption comes from. Please explain.

For the limitations, please reflect on their relevance in relation to specific aims. Representativeness is mostly an issue for health service planning in the specific primary care setting. Sample size may predominantly limit the etiological question, particularly potential interaction and subgroup analyses that could be of interest…

Our response:

Thank you for your comments. As mentioned above, we have revised the sentence to be "Third, because it contains linked electronic medical records, it will allow us to follow them up for mortality and public medical service use" (Line 16-17, Page 13) to reduce confusion. We have reframed our study aim by mainly focusing on the biopsychosocial health profiles of elder primary care patients with multimorbidity in Hong Kong. For representativeness, we believe that since we only included those ambulatory patients who were willing to join the programme, we were missing those who were house-bounded or institutionalized. Thus, as described previously, the real health situation among the primary care patients in Hong Kong could be worse than what is reported in this study after weighting. And the weighted results could be more likely to close to the situation of the elderly of the general population.: "First, self-selection bias might still exist which was consistent with other similar studies,24 although we used weighting for adjustment, as not all variables were available for weighting such as education. Since only ambulatory adults who agreed to join were recruited and these usually are more likely to be female and those with higher educational level and higher self-motivation, and those who were house-bound or institutionalized are less likely to have been included, we might have resulted in a relatively healthier and higher-functioning patients in primary care, and the real health status might be worse than what are reported in our study. Future studies may need to take measures to increase participation from male and vulnerable patients." (Line 20-28, Page 13); "Second, the sample size may limit examinations of potential interactions and factors associated with

multimorbidity in some subgroups such as older men and people with lower educational levels, or uncommon health problems among these patients." (Line 28-30, page 13); and in generalizability of the Discussion section that: "We might have resulted in a relatively healthier sample. After weighting according to age, gender and marital status based on the most recent census data in Hong Kong, the weighted results might be an underestimation of the real situation among elder primary care patients, but be more representative of the situation of the older adults of the general population. The rates of health problems reported in our study might be an underestimation of the real situation among the elder primary care patients with multimorbidity in Hong Kong. Future analysis will need to consider this in the interpretation of findings." (Line 13-19, page 13)

FORMATTING AMENDMENTS (if any)
Required amendments will be listed here; please include these changes in your revised version:
1. Please include Figure legends at the end of your main manuscript.
Our response:
Thank you. Figure legends are now added at the end of the main manuscript.

References:
1. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: A systematic review of observational studies: PLoS ONE. 9 (7) , 2014. Article Number: e102149. Date of Publication: 21 Jul 2014.; 2014.
2. Gunn JM, Ayton DR, Densley K, et al. The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort. Social psychiatry and psychiatric epidemiology 2012; 47(2): 175-84.
3. Mavaddat N, Valderas JM, van der Linde R, Khaw KT, Kinmonth AL. Association of self-rated health with multimorbidity, chronic disease and psychosocial factors in a large middle-aged and older cohort from general practice: a cross-sectional study. 2014.
4. Bock J-O, Luppa M, Brettschneider C, et al. Impact of depression on health care utilization and costs among multimorbid patients–results from the multicare cohort study. PloS one 2014; 9(3): e91973.
5. Calderon-Larranaga A, Hernandez-Olivan P, Gonzalez-Rubio F, Gimeno-Feliu LA, Poblador-Plou B, Prados-Torres A. Multimorbidity and weight loss in obese primary care patients: Longitudinal study based on electronic healthcare records. 2015.
6. France EF, Wyke S, Gunn JM, Mair FS, McLean G, Mercer SW. Multimorbidity in primary care: A systematic review of prospective cohort studies. 2012.
7. Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, et al. Multimorbidity patterns in the elderly: a prospective cohort study with cluster analysis. Bmc Geriatr 2018; 18(1): 16.
8. Boeckxstaens P, Vaes B, Legrand D, Dalleur O, De Sutter A, Degryse JM. The relationship of multimorbidity with disability and frailty in the oldest patients: A cross-sectional analysis of three measures of multimorbidity in the BELFRAIL cohort. 2015.
9. Brettschneider C, Leicht H, Bickel H, et al. Relative impact of multimorbid chronic conditions on health-related quality of life–results from the MultiCare Cohort Study. PloS one 2013; 8(6): e66742.
10. Ibarra-Castillo C, Guisado-Clavero M, Violan-Fors C, et al. Survival in relation to multimorbidity patterns in older adults in primary care in Barcelona, Spain (2010-2014): a longitudinal study based on electronic health records. Journal of Epidemiology & Community Health 2018; 72(3): 185-92.
11. Farmer C, Fenu E, O'flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of NICE guidance. BMJ: British Medical Journal (Online) 2016; 354.
12. Prados-Torres A, Poblador-Plou B, Gimeno-Miguel A, et al. Cohort Profile: The Epidemiology of Chronic Diseases and Multimorbidity. The EpiChron Cohort Study. International journal of epidemiology 2018; 47(2): 382-4f.
13. Mercer SW, Gunn J, Wyke S. Improving the health of people with multimorbidity: the need for prospective cohort studies. SAGE Publications Sage UK: London, England; 2011.

14. France EF, Wyke S, Gunn JM, Mair FS, McLean G, Mercer SW. Multimorbidity in primary care: a systematic review of prospective cohort studies. Br J Gen Pract 2012; 62(597): e297-e307.

15. Kuo RN, Lai MS. The influence of socio-economic status and multimorbidity patterns on healthcare costs: a six-year follow-up under a universal healthcare system. International journal for equity in health 2013; 12: 69.

16. Gu J, Chao J, Chen W, et al. Multimorbidity and health-related quality of life among the community-dwelling elderly: A longitudinal study. 2018.

17. Tromp J, Tay WT, Ouwerkerk W, et al. Multimorbidity in patients with heart failure from 11 Asian regions: A prospective cohort study using the ASIAN-HF registry. 2018.

18. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age and ageing 2012; 42(1): 62-9.

19. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. The European journal of general practice 2008; 14 Suppl 1: 28-32.

20. Pefoyo AJ, Bronskill SE, Gruneir A, et al. The increasing burden and complexity of multimorbidity. BMC public health 2015; 15: 415.

21. The Government of Hong Kong Special Administrative Region. 2016 Population By-census. http://wwwbycensus2016govhk/en/bc-mthtml 2018; Accessed on July 31, 2018.

22. Wang HH, Wang JJ, Wong SY, et al. Epidemiology of multimorbidity in China and implications for the healthcare system: cross-sectional survey among 162,464 community household residents in southern China. BMC Med 2014; 12: 188.

23. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380(9836): 37-43.

24. Silva Junior SH, Santos SM, Coeli CM, Carvalho MS. Assessment of participation bias in cohort studies: systematic review and meta-regression analysis. Cad Saude Publica 2015; 31(11): 2259-74.

25. Abad-Diez JM, Calderon-Larranaga A, Poncel-Falco A, et al. Age and gender differences in the prevalence and patterns of multimorbidity in the older population. Bmc Geriatr 2014; 14: 75.

26. Alimohammadian M, Majidi A, Yaseri M, et al. Multimorbidity as an important issue among women: results of a gender difference investigation in a large population-based cross-sectional study in West Asia. Bmj Open 2017; 7(5): e013548.

27. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. General hospital psychiatry 2016; 39: 24-31.

28. Mitchell AJ, Yadegarfar M, Gill J, Stubbs B. Case finding and screening clinical utility of the Patient Health Questionnaire (PHQ-9 and PHQ-2) for depression in primary care: a diagnostic meta-analysis of 40 studies. BJPsych Open 2016; 2(2): 127-38.

VERSION 2 – REVIEW

| REVIEWER | François Béland
Université de Montréal
Canada |
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| REVIEW RETURNED | 18-Jun-2019 |

| GENERAL COMMENTS | Biopsychosocial health profile of Chinese elderly with multimorbidity in Hong Kong
2018-027279.R1

This revised version is much improved. Objectives of the study are focused on the biopsychosocial profile (note use of the singular) of patients aged 60+ with multi-morbidity from four primary care |
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clinics in Hong Kong. The design, data collection procedures, measurements, statistical analyses and reports of results are presented straightforwardly. The writing style is clear and the text is easy to read. Nonetheless, two issues remain. This first has to do with the editorial policy of BMJOpen; the other is to what extent the main objective of the study has been reached:

1. This paper is essentially a descriptive report of a list of social and psychosocial characteristics, and health status and health care utilization patterns of a specific sample of elderly persons. The editorial policy of BMJOpen is receptive to this type of paper, and it may, in its present form, be accepted for publication. Nonetheless, some minor revisions and improvements are needed. My concern is with the extended claims that go over and above a legitimate interpretation of results in the Discussion and Conclusion sections. Some of the claims are supported with references in the literature, but others go beyond the reach of the descriptive statistics reported by the authors;

2. The main problem in this paper is the alleged relevance of the results for the biopsychosocial profile of elderly patients with multi-morbidity: univocal interpretation of multi-morbidity problems; complexity of healthcare needs; need for information to plan and deliver appropriate care; holistic approach; and development of integrated models of care. These problems can be addressed easily in the Discussion and Conclusion sections. Here are some issues the authors should consider:

a. Epidemiology of multi-morbidity. The authors pretend that they have examined "physical, psychosocial and social problems accompanying multi-morbidity". However, comparative figures of the distribution of multiple chronic disease from other samples have been excluded from this version of the paper, restricting its contribution to the epidemiology of multi-morbidity in elderly persons in Hong Kong. For problems with this topic in the original paper, refer to my previous review. Also, without comparative figures on elderly persons with one or no chronic illness it is impossible to state that a biopsychosocial profile specific to elderly persons with multi-morbidity has been identified;

b. Biopsychosocial problems. It is not necessarily true that "biopsychosocial health problems are prominent among elderly adults with multi-morbidity in primary care clinics in Hong Kong". Without a gold standard, or "some" standards, on what is considered a "prominent problem", or again, lacking comparative figures from persons without multi-morbidity on frequencies of potential prominent problems, it is not legitimate to conclude on this topic;

c. Multi-morbidity profiles. However, with the data available, it is possible to identify biopsychosocial profiles (note the plural) associated with different multi-morbid patterns. Figures 2 and 3 provide information on the frequency of joint morbid conditions. These are "morbidity profiles". The most frequent "triplet" is arthritis, dyslipidemia and hypertension (38.2% for the last two and 26.9% for the first and the third). The frequency of diseases known for their severity and consequences for survival did not reach the 10% level. In line with the authors' preoccupations, the question is: are there different biopsychosocial profiles for different multi-morbidity profiles? If the answer is positive, then what is the contribution of this paper, whose objective is the identification of a biopsychosocial profile, to the epidemiology of multi-morbidity?

| | d. Complex health care needs and holistic approach. The authors conclude that a holistic approach is required to address complex health care needs. However, the analyses are not aimed at examining the extent of health care needs complexity, nor identifying components of a holistic approach. Some further analyses are needed to examine these issues. As noted above, the results shown in Figures 2 and 3 give some clues as to the extent and type of complexity. With this diversity in multi-morbidity profiles, the legitimacy of a global holistic approach is in jeopardy. Given the strictly descriptive analysis, the objective of the paper was to identify a single biopsychosocial profile. Suggestion of a holistic approach for complex health care needs seems to stem from the limited objective of the paper rather than from a careful analysis of the data; |
| | e. Integrated care. The extent to which multi-morbid profiles and biopsychosocial profiles are implicated is not unique, but claims for a unique integrated approach to chronic care are not well founded. Both types of profiles differ in terms of complexity and need for a holistic and integrated approach. The literature on the integration of models of care is vast. This diversity suggests that a careful approach is needed here, if only to address issues raised by one of the five of Leutz's laws of integration: "Your integration is my fragmentation". The care for persons with multi-morbidity is particularly sensitive to issues raised by this law. |

VERSION 2 – AUTHOR RESPONSE

Thank you for letting us know the comments from the Editor-in-Chief. According to the email communications with the Deputy Editor Ms. Clare Partridge dated on Oct 2, 17 and 22 2019, we do not need to respond to Reviewer 3's comments on our revised manuscript "Biopsychosocial health profile of Chinese elderly with multimorbidity in Hong Kong", and are advised to reverse our manuscript back to be a "Cohort Profile" paper based on the original comments from Reviewers 1, 2, 3 and 4.

We are now keeping our manuscript as a "Cohort Profile" paper, and updated our responses to the reviewers' original comments. Please kindly see our response letter with responses one by one and the updated manuscript.

We sincerely thank the editors in inviting reviewers in providing valuable comments to our paper, which has been improved greatly. Though it took some time for revision, we believe it would be good if our study can reach more readers as a cohort file paper. We hope the paper is acceptable upon revisions and resubmission. We believe the study would be of great interest to the wider readers of BMJ Open.