PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The journey to multimorbidity: a longitudinal analysis exploring cardiovascular risk factors and socio-demographic determinants in an urban setting.
AUTHORS	Ashworth, Mark; Durbaba, Stevo; Whitney, David; Crompton, James; Wright, Michael; Dodhia, Hiten

VERSION 1 - REVIEW

REVIEWER	Violán Fors, Concepción Institut universitari d'investigació en atenció primària (IDIAPJGol). Barcelona, Spain
REVIEW RETURNED	11-Jun-2019

GENERAL COMMENTS	It is an article that proposes a new an approach to study longitudinal multimorbidity based on anonymised primary care data to study the social determinants and risk factors for multimorbidity and the acquisition sequence of multimorbidity. The aim of the paper has interested, is an idea about which little research has been done. However, the study is carried out in a population of more than 300,000 inhabitants, of which only 5597 (1.7%) were included in the study. Patients had a record of three or more of the selected LTCs, the 'multimorbidity cohort'. This low proportion of patients with multimorbidity can produce selection biases that must be analyzed to see if they can influence the results. The authors could be added the flow chart study population. On the other hand, the article's methodology must be written again, there is a lack of relevant information regarding : the design of the study, the creation of the cohort, the variables included, the method of analysis, etcetera. Without this information is impossible to generalize the results and the study can not be replicated. The tables of results should be improved, the figures are excessive, two examples should be left and the rest of the information should be presented in supplementary files. For these reasons, I consider that the study is not suitable to be published in BMJOpen, Also, I did some comments included in the PDF of the main document The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

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REVIEWER	Leo Singer Department of Geography and Planning School of Environemntal Sciences University of Liverpool United Kingdom
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	This study responds to some of the acute health trends and demands on health care system in the UK. As such, it adopts a definition of multimorbidity driven by practitioners. On the one hand, it makes your prevalence estimates hard to compare with other studies, on the other hand it makes your results interesting and probably more directly useful to efforts in tackling the multimorbidity burden, especially in conjunction with the follow-up study as announced in this paper. The style and the visual display of results are very clear. My comments relate to possible implementation of the study, the under-analyzation of your sample and to the interpretation of results. 1. What type of intervention? On page 16, the authors claim that “the study of acquisition sequence may suggest potential interventions to prevent, minimise or delay progression towards multimorbidity”. Even without the information on the timing of these sequences, which will hopefully follow in the next paper, I would encourage the authors to outline a potential intervention or to mention an existing real-life example. This could be interesting for other practitioners reading your paper and possibly motivate them to conduct similar analyses. 2. What about the younger cohorts? This preventative aspect is related to my second challenge. The fact that you have got a rather large sample of patients younger than 65 years of age could be better utilized. Aren’t the younger cohorts those who could benefit most from these interventions? Some studies which analyzed a wider range of conditions than 12, found that there were more multimorbid patients among people younger than 65 years of age than among the older ones (Barnett et al. 2012 for Scotland, Taylor et al. 2010 for Australia). I understand that you may prefer to focus on this aspect in your second article. Still, I think it would be interesting and easy to do to add a simple breakdown of multimorbidity prevalence for 10-year age groups between the age of 18 and 65, as well as to show the rising ORs compared to the youngest reference group. 3. Risk factors are not replaceable for social determinants Among the results that you have reported, you found stronger association between multimorbidity and the risk factors than with social determinants. I think this claim is rather unwarranted as risk factors and social determinants refer to different levels of social exposure on individuals. I am sure you are aware of this but the distinction got somehow lost in the process of the analysis. Risk

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	factors are commonly understood as 'downstream' or proximate factors which are modifiable by individual action of the patient, while social determinants refer to the 'upstream', structural factors which can be changed 'from above' or politically. Seen from this perspective, the fact that you identified stronger ORs for the risk factors than social determinants does not minimize the role of the latter. If you measured the water throughput downstream you encounter much higher quantities than upstream, by the source, yet if you need to stop the stream you would need to act near to the source. Lifecourse studies of chronic disease accumulation have shown the causal paths leading from socio-economic determinants to risky behaviours with cumulative effects of the latter (Pavela and Latham 2015, Ferraro, Schaffer and Wilkinson 2016). So I'd advise to differentiate between these levels of exposure. For example, in the final section "What this study adds", I think it is a reduction of absolute and relative poverty and of gender and racial differences, what can reduce the prevalence of multimorbidity, while action on the risk factors can affect its onset and rate of accumulation. Acting on health behaviours without addressing the causal factors actually tends to increase health inequalities rather than reducing them, as Link and Phelan showed in their article 'Social conditions as fundamental causes of disease' (1995), later confirmed empirically by others. This is related to the fact that your statement is comparing data from different levels: your social deprivation is an aggregate, area-based variable but risk factors are measured at an individual level. Adding a sensitivity analysis with individually measured SES (e.g. income, occupation if available) would help to make the association clearer. Finally, a minor comment on the structure of the paper. It is a common practice to describe the data in a Data or Variables section. Your data is included under the heading "Study population" which might be confusing if someone wants to have a first quick look at your data information.

REVIEWER	Amaia Calderón Larrañaga Aging Research Center, Karolinska Institutet
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	This study explores longitudinal trajectories of multimorbidity development according to sociodemographic characteristics of an urban population in London. The paper is methodological sound, original and nicely written. I have only some minor comments: 1. I miss the rationale of the study objectives in the background section. 2. Regarding the studied factors, I would recommend the authors to change "demographic" by "socio-demographic" and "risk factors" by "cardiovascular risk factors" throughout the paper, for the sake of precision. 3. I suggest the authors use terms such as "correlates" instead of "determinants" in the paper, given that cross-sectional studies (as the one being reviewed) depart importantly from the causality assumptions. 4. A brief explanation as to why the authors decided to include two additional conditions beyond those included in QOF would be appreciated.

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	5. It is not clear to me what was the difference between the main analysis and the sensitivity analysis. A mixed-effect logistic regression seems to be used in both cases with the patient as the 1st level factor and the general practice (GP) as the 2nd level factor. Thus, a random effect for the GP was assumed in both cases. Please clarify. 6. Also, the authors state that a pseudo-R2 and ROC curves were derived from the sensitivity analysis, but could these not be derived from the main analysis too? 7. Please spell-out the abbreviations used for diseases in Figures 1-6 in footnotes. 8. Why didn't the authors provide any alluvial plots for South Asians (the 3rd ethnic group included in the study)? 9. The authors should add a limitation related to the low number of chronic conditions included in their study, which has a direct impact on the prevalence of multimorbidity (much lower compared to other studies), and largely impoverishes the analyses related to the acquisition sequence.

REVIEWER	Stergiani Tsoli University College London, UK
REVIEW RETURNED	01-Aug-2019

GENERAL COMMENTS	Thank you for giving me the opportunity to revise this paper. The paper sets out to describe the demographic characteristics and some risk factors for multimorbidity and the acquisition of multimorbidity in a multi-ethnic borough in London, UK. In general, it addresses a topic with serious public health implications that merit further investigation. I have the following points for each section: Introduction The aim of the paper is "to study the characteristics of this multimorbiity cohort, defining both the demographic determinants and risk factors associated with multimorbidity acquisition". Nevertheless the introduction is focusing on the effects of multimorbidity on healthcare utilization. This is a useful point covered but authors should consider having an introductory paragraph with the (issue) of definition of multimorbidity (now briefly covered in the second paragraph), relevant consequenses in the UK (like healthcare utlisation) and quite importantly theprevious literature in the topic. In other words, how the current literature in the topic necessitates the present study? The rationale stated at the STROBE statement at the "Background/rationale" section should be, also, included in the draft with relevant support by the literature. Methods • Please state the initial sample size at this section. • "We conducted a cross-sectional analysis and longitudinal study". This appears confusing without the essential time range covered by the extracted data, both on the risk factors and demographic characteristics and the outcome data so the longitudinal nature of the data is better understood. Also, would allow for examining the suitability of the current risk factors in the adjusted models.

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	• Multimorbitiy cohort risk factor determinants: 3 risk factors, namely hypertension, moderate obesity and smoking have been added as adjustments in this model. What is the rationale for this selection? • Data analysis: I think this section could be revised to avoid redundancies. Results Missing data: "Patients were included in the final sample even though some demographic data were missing": Could authors elaborate on how they treated these missing data in the analysis? eg Have they completed a complete case analysis etc. Discussion The authors acknowledge the lack of access to more data but the current models are missing important demographics that could attenuate the current findings.This is mentioned in the discussion section but the implications on the current findings need to be explored, as well.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 response:

1) Thank you for the first comment: 'It is an article that proposes a new an approach to study longitudinal multimorbidity based on anonymised primary care data to study the social determinants and risk factors for multimorbidity and the acquisition sequence of multimorbidity. The aim of the paper has interested, is an idea about which little research has been done'

We agree – this is a novel approach to the study of multimorbidity, in which we have tried to identify and define the acquisition sequence of multimorbidity.

2) The Reviewer then comments: 'However, the study is carried out in a population of more than 300,000 inhabitants, of which only 5597 (1.7%) were included in the study.'

We agree that this study only focusses on the more severe end of the definition of multimorbidity (i.e. 3 or more conditions and up to 12 specified LTCs). We have not used the broader definition of multimorbidity included in many studies. This was insufficiently clear in the Introduction. In response to this comment, we have added the following text to the Introduction (penultimate para.):

'A focus on this narrowly defined category of multimorbidity would inevitably mean that the proportion of patients defined as 'multimorbid' would be lower than in studies based on broader definitions of multimorbidity (2,3).'

3) The Reviewer suggests adding a flowchart of the study population. We would be very happy to include a Flow Chart if this clarified. However, since we already list the number and % of patients with 3 LTCs, 4 LTCs, and 5 or more LTCs (Results, para 1), we have simply added the following sentence which we trust will be sufficient:

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‘Of the remaining population, 45,241 (13.6%) had one LTC and 10,992 (3.3%) had two LTCs.’

4) The Reviewer states: ‘On the other hand, the article's methodology must be written again, there is a lack of relevant information regarding : the design of the study, the creation of the cohort, the variables included, the method of analysis, etcetera. Without this information is impossible to generalize the results and the study can not be replicated.’

We agree that the Methods section should be clarified regarding study design, cohort, included variables and method of analysis. We have therefore added the following to the Methods:

a) Under the heading, ‘Study Design’, we agree that reference to both a longitudinal and cross-sectional study design was confusing. Since the analysis included a cohort of patients with multimorbidity, followed over a period of time from the onset of the first, second and third LTCs, we have described the study as a ‘longitudinal analysis (study)’. This is more in keeping with the title which refers to the ‘The journey to multimorbidity’. We have therefore removed the additional reference to a ‘cross-sectional study’

b) Included variables: the Reviewer asked us to clarify the included variables. They are already summarised in the Results section with details in Table 3 and Table 4. However, given that the Method was described as requiring clarification, we have amended the opening sentence of the section entitled, ‘Data Analysis’, to read:

‘We analysed demographic (age, gender, ethnicity), social (area level deprivation) and cardiovascular risk factor (hypertension, moderate obesity, smoking status) data for the multimorbidity cohort and general population’.

c) Under the heading ‘Data Analysis’, our method of analysis was not sufficiently clear in defining the random and fixed effects of the ‘mixed effects multilevel logistic regression model’. We have therefore clarified which variables were included as random effects and which as fixed effects with the amended sentence:

‘Demographic and risk factor determinants of multimorbidity were analysed at patient level using mixed effects multilevel logistic regression models, adding fixed effects to describe patient characteristics and random effects to describe general practice level, based on the registered general practice of each patient in the study sample.’

5) The Reviewer states: ‘The tables of results should be improved, the figures are excessive, two examples should be left and the rest of the information should be presented in supplementary files.’

We agree that the Figures could be viewed as excessive. The unique Figures are the edited alluvial plots which display the dominant pathways from single LTCs to the acquisition of multimorbidity. These have been retained in the main body of the paper as Figures 1-4b. We would request that all are retained since each edited plot shows a different perspective on the acquisition sequences of multimorbidity. The un-edited alluvial plots have been removed, and appear in the Supplementary file as Figures 5 - 9.

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6) Reviewer (1) also made 32 Comments added directly into the PDF file version. We are grateful for the benefit of this level of scrutiny. Most of the comments are covered by the broader points discussed above. However, some specific comments need to be addressed:

a. Pg1. The Reviewer is correct that our Abstract has not defined the size of the multimorbidity cohort. This has now been added to the Results section of the Abstract:

'5597 (1.7%) patients had ≥3 selected LTCs, the 'multimorbidity cohort'.

b. Pg2. The Reviewer has suggested inclusion of 'selection bias' in the section, 'Strengths and Limitations'. This has now been added (in the 4th bullet point)

c. Pg4. The Reviewer asks for a reference to the 'Care Coordination' cohort referred to in the Introduction. This has already been cited, Reference 8: 'From one to many. Exploring people's progression to multiple long-term conditions in an urban environment. Guy's and St Thomas' Charity. London, 2018'. We have therefore not amended.

d. Pg4. Methods. The Reviewer has asked us to add the term 'UK' to the description of the setting ('Our study was set in Lambeth, one of the two inner London boroughs'). We have now added that.

e. Pg5: Study Population. The Reviewer has asked for clarification of 'deprivation quintiles'. We have not amended our description since in the previous sentence, we described the use of Index of Multiple Deprivation to define deprivation, to derive quintiles, and referenced this (reference 8).

f. Pg5: The Reviewer asks us to change the heading from 'Data Variables' to 'Data Source'. However, most of the paragraph refers to 'Data Variables' so we have not amended.

g. Pg5: The Reviewer asks us to clarify 'the period of study'. This is an important point to clarify since the study has a longitudinal component. We have therefore added a statement to the section describing the included LTCs (pg 5):

'For each LTC, the date of onset was obtained from the EHR and used in the longitudinal analysis'

h. Pg6: several questions from the Reviewer relate to whether the included variables were continuous or categorical. Rather than describing each variable in these terms, the Results Tables should make it clear which are categorical and which are continuous. Table 2 displays the variables and it can be seen that 'age' was considered as a categorical variable (4 age groups) and deprivation was also categorical (5 quintiles). We have therefore not amended.

i. Pg8: we have summarised in the text the ages of various demographic groups within our study (multimorbid, not multimorbid, Black, White, South Asian, most and least deprived, and so on). We had only included mean values for the age in years to simplify the presentation of Results. The Reviewer asked us to include Standard Deviations (SDs) for each mean value presented. We have amended, adding 5 separate SDs.

j. Pg14: the Reviewer states that we have 'not properly justified' our lack of access to a wider data source. The relevant sentence currently reads: 'Data access was a limitation to this analysis. We were only able to obtain data from one of the two boroughs adopting this approach to multimorbidity, the other lacked a data extraction system preventing us from analysing large datasets of patient-level data'. We consider that this does sufficiently explain our lack of access to additional data. We would be happy to amend if further clarification needed.

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Reviewer 2 response:

1) We thank the Reviewer for their comment, 'The style and the visual display of results are very clear'

2) The Reviewer states: 'What type of intervention' and, 'On page 16, the authors claim that "the study of acquisition sequence may suggest potential interventions to prevent, minimise or delay progression towards multimorbidity". Even without the information on the timing of these sequences, which will hopefully follow in the next paper, I would encourage the authors to outline a potential intervention or to mention an existing real-life example. This could be interesting for other practitioners reading your paper and possibly motivate them to conduct similar analyses.'

Although the main focus of this paper was not on implementation or intervention, we agree that the Results do imply that control of Risk Factors (of which we included three in our study) might delay the onset of LTCs and multimorbidity. We have therefore added a final sentence to section headed, 'Comparison with the literature' to state:

'The control of hypertension, smoking and obesity are often perceived in terms of primary cardiovascular disease prevention or of secondary prevention of single LTCs but may also be conceptualised in terms of multimorbidity prevention'

3) The Reviewer states: 'What about the younger cohorts?'

This preventative aspect is related to my second challenge. The fact that you have got a rather large sample of patients younger than 65 years of age could be better utilized. Aren't the younger cohorts those who could benefit most from these interventions? Some studies which analyzed a wider range of conditions than 12, found that there were more multimorbid patients among people younger than 65 years of age than among the older ones (Barnett et al. 2012 for Scotland, Taylor et al. 2010 for Australia). I understand that you may prefer to focus on this aspect in your second article. Still, I think it would be interesting and easy to do to add a simple breakdown of multimorbidity prevalence for 10-year age groups between the age of 18 and 65, as well as to show the rising ORs compared to the youngest reference group.'

We agree with the Reviewer and this raises the challenging issue that the LTC components of multimorbidity are not evenly distributed according to age. Mental illnesses are more common in younger cohorts; cardiovascular disease and dementia are more common in older cohorts. We considered expanding our Results section to include Odds Ratios for different age cohorts. However, this would increase an already complex presentation of findings. We would be happy to include more detail if required. However, the opening paragraph under 'Comparison with the Literature' already discusses age effects in some detail. To further acknowledge this point, we have added this sentence to the paragraph:

'The known influence of population age profiles on the demography of multimorbidity (19) is illustrated by our finding of markedly differing alluvial plot profiles describing multimorbidity acquisition in a younger cohort dominated by mental health related conditions (Figure 6) and an older cohort dominated by CHD and DM (Figure 7).'

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4) The Reviewer states: ‘Risk factors are not replaceable for social determinants’. The point is expanded in a further paragraph from the Reviewer.

We agree with the Reviewer that this is a substantial challenge. As stated by the Reviewer, ‘risk factors and social determinants refer to different levels of social exposure on individuals’. In response, we need to modify our statement in the Discussion which in the light of this comment, gives undue prominence to Risk Factors, underplays the role of social deprivation, and fails sufficiently to demonstrate understanding of the interaction between the two. The Reviewer has suggested inclusion of two highly relevant articles, ‘Social conditions as fundamental causes of disease’ (1995) and Ferraro, Schaffer and Wilkinson (2016). We have therefore added these references in support and revised our final paragraph of ‘Comparison with the Literature’ to state:

‘However, a focus on risk factors should not detract from ‘the causes of the causes’, since social conditions themselves generate causal pathways leading from socio-economic determinants to risk behaviours (27) and interventions which address health behaviours while failing to engage in social determinants may paradoxically result in increased health inequalities (28).’

Reviewer 3 response:

1) We thank the Reviewer for their opening comment, ‘The paper is methodological sound, original and nicely written. I have only some minor comments’

2) The Reviewer states: ‘I miss the rationale of the study objectives in the background section’.

We already describe the Aim of the study in the background section; we have now added the study Objectives:

‘The aim was to study the characteristics of the multimorbidity cohort. The main objectives were to define both the socio-demographic determinants and cardiovascular risk factors associated with multimorbidity acquisition; also to determine the acquisition sequence of multimorbidity and the influence of demographic factors on this sequence.’

3) The Reviewer states: ‘Regarding the studied factors, I would recommend the authors to change “demographic” by “socio-demographic” and “risk factors” by “cardiovascular risk factors” throughout the paper, for the sake of precision’

We agree and have made the changes as suggested to both terms (which are displayed in the Track Changes revised version).

4) The Reviewer states: ‘I suggest the authors use terms such as “correlates” instead of “determinants” in the paper, given that cross-sectional studies (as the one being reviewed) depart importantly from the causality assumptions’

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Whilst we acknowledge this point from the Reviewer, it is common practice in the reporting of cross-sectional studies to refer to 'predictor' variables in multivariable analysis as 'determinants'. Nevertheless, we do need to clarify that associations between predictor variables/determinants and outcomes in a regression model do not confirm causality. We have therefore added these two sentences to the Discussion, Strengths and Limitations:

'In common with other observational studies, significant associations between multimorbidity and socio-demographic or risk factor determinants may imply, but cannot prove, causality. Whilst interventional studies are required to obtain stronger evidence of causality, causal inference may be derived by time series analyses and further study of potential confounding and residual variance.'

5) The Reviewer states: 'A brief explanation as to why the authors decided to include two additional conditions beyond those included in QOF would be appreciated.'

We agree and have added the sentence (Study Population, para 1):

'Two of the conditions selected for inclusion within the definition of multimorbidity were not included within the QOF:….'.

We trust that this clarification will be sufficient, combined with the existing statement at the opening of the section on 'Study Population': 'Our study was set in Lambeth, one of the two inner London boroughs adopting the 'care coordination' definition of multimorbidity (8)'

6) The Reviewer states: 'It is not clear to me what was the difference between the main analysis and the sensitivity analysis. A mixed-effect logistic regression seems to be used in both cases with the patient as the 1st level factor and the general practice (GP) as the 2nd level factor. Thus, a random effect for the GP was assumed in both cases. Please clarify'.

We have therefore clarified as our description of the mixed effects model was insufficiently clear in terms of which variables were included as 'random effects' and which as 'fixed effects'. See response to Reviewer 1, point 4c:

'Demographic and risk factor determinants of multimorbidity were analysed at patient level using mixed effects multilevel logistic regression models, adding fixed effects to describe patient characteristics and random effects to describe general practice level, based on the registered general practice of each patient in the study sample.'

7) The Reviewer states: 'the authors state that a pseudo-R2 and ROC curves were derived from the sensitivity analysis, but could these not be derived from the main analysis too'

This is an anomaly and a feature of STATA analyses using mixed effects multilevel logistic regression models. The pseudo-R2 values and ROC curves cannot readily be produced using this more sophisticated modelling. Hence the use of a sensitivity analysis which involved the simpler process of

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constructing a mixed effects logistic regression model, adjusted for clustering at practice level. By using both approaches, the two analyses complement each other. The suggestion from the Reviewer could be developed, but only by using a more sophisticated Stats package.

8) The Reviewer states: 'Please spell-out the abbreviations used for diseases in Figures 1-6 in footnotes'

We agree – the Footnote abbreviations have been amended.

9) The Reviewer states: 'Why didn't the authors provide any alluvial plots for South Asians (the 3rd ethnic group included in the study)?'

We agree – we should have commented on this point in the text. The alluvial plot was produced but relatively small numbers compared to the other ethnic groups resulted in poor definition. We have therefore added this sentence to the Results:

'Relatively small numbers resulted in poor definition of the alluvial plot in the South Asian group and this figure is not presented.'

10) The Reviewer states: 'The authors should add a limitation related to the low number of chronic conditions included in their study, which has a direct impact on the prevalence of multimorbidity (much lower compared to other studies), and largely impoverishes the analyses related to the acquisition sequence'

We agree that low number of included LTCs within our own definition of multimorbidity will have resulted in lower reported prevalence of multimorbidity. We already make this point in the revision to the Introduction in response to Reviewer 1, point 2. where we write:

'A focus on this category of multimorbidity would inevitably mean that the proportion of patients defined as 'multimorbid' would be lower than reported in studies based on broader definitions of multimorbidity (2,3)'.

We had already noted this limitation in the Discussion, Comparison with the Literature, para 1: 'Comparison with other multimorbidity studies is difficult because of the highly restricted definition of multimorbidity used in the current study.' Please let us know if we should add to this sentence.

Reviewer 4 response:

1) The Reviewer states: 'The aim of the paper is "to study the characteristics of this multimorbiity cohort, defining both the demographic determinants and risk factors associated with multimorbidity acquisition". Nevertheless the introduction is focusing on the effects of multimorbidity on healthcare

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utilization. This is a useful point covered but authors should consider having an introductory paragraph with the (issue) of definition of multimorbidity (now briefly covered in the second paragraph), relevant consequenses in the UK (like healthcare utlisation) and quite importantly theprevious literature in the topic. In other words, how the current literature in the topic necessitates the present study? The rationale stated at the STROBE statement at the "Background/rationale" section should be, also, included in the draft with relevant support by the literature.

We consider that the 7 references mentioned in the Introduction give a balanced view of the context of multimorbidity research and the reason why this research is unique – the multimorbidity cohort in our study was derived through a process of local consultation and the formation of an 'expert panel' resulting in a definition aligned to the needs of an urban, deprived, multi-ethnic community. However, this is not sufficient reflected in the STROBE statement which we have now modified with the addition of this sentence to the Background/rationals:

For the purposes of this study, a locally derived definition of 'multimorbidity' has been used based on predicted high healthcare and social care demand. In contrast, most previously reported studies of multimorbidity have more inclusive definitions of multimorbidity.

2) The Reviewer states: 'Methods: Please state the initial sample size at this section'

Although the Reviewer requested the 'initial sample size' be included in the Methods, we have carefully separated the description of the sample in the Methods ('We included data on all patients aged 18 years and over registered with a general practice') and the description of the sample numbers which appear in the Results. We would prefer to keep to convention and retain this distinction. However, if considered important, we could readily add the total sample size ('n = 345,722') into the Methods.

3) The Reviewer states: ''We conducted a cross-sectional analysis and longitudinal study". This appears confusing without the essential time range covered by the extracted data, both on the risk factors and demographic characteristics and the outcome data so the longitudinal nature of the data is better understood. Also, would allow for examining the suitability of the current risk factors in the adjusted models.'

We agree – this description was unclear and has now been modified. See Response 4a to Reviewer 1:

Under the heading, 'Study Design', we agree that reference to both a longitudinal and cross-sectional study design was confusing. Since the analysis included a cohort of patients with multimorbidity, followed over a period of time from the onset of the first, second and third LTCs, we have described the study as a 'longitudinal analysis (study)'. This is more in keeping with the title which refers to the 'The journey to multimorbidity'. We have therefore removed the additional reference to a 'cross-sectional study'

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4) The Reviewer states: 'Multimorbitiy cohort risk factor determinants: 3 risk factors, namely hypertension, moderate obesity and smoking have been added as adjustments in this model. What is the rationale for this selection?'

We agree – the selection of Risk Factors needed to be further justified. As per our Response 3 to Reviewer 3, we have now referred throughout to the selected Risk Factors as 'cardiovascular risk factors'.

5) The Reviewer states: 'Data analysis: I think this section could be revised to avoid redundancies'

We have amended the Data Analysis section. Rather than avoiding 'redundancies', our response to Point 6 and Point 7, Reviewer 3, required additional detail to the Data Analysis section. We have added detail about each of the variables entered into the regression model and which were entered as random effects and which as fixed effects. We trust that this has clarified the section.

6) The Reviewer states: 'Results: Missing data: "Patients were included in the final sample even though some demographic data were missing": Could authors elaborate on how they treated these missing data in the analysis? eg Have they completed a complete case analysis etc.'

The Reviewer is referring to the sentence in the Results stating: "Patients were included in the final sample even though some socio-demographic data were missing: 3289 (0.99%) patients could not be linked to a LSOA and therefore had missing IMD-2015 score data; ≤10 patients had missing coded gender data….". The Reviewer is absolutely correct. All patients were included in the univariable analysis, even though this resulted in slightly different denominator values (i.e. the 3289 patients missing from the summary of LSOA quintiles), as already described in the Results. However, the description of the multivariable analysis has been amended in the light of the Reviewer comment, to state: 'Patients with any category of missing data (n = 3301) were excluded from the multivariable analysis'.

7) The Reviewer states: 'Discussion: The authors acknowledge the lack of access to more data but the current models are missing important demographics that could attenuate the current findings. This is mentioned in the discussion section but the implications on the current findings need to be explored, as well.'

We agree that our focus on three cardiovascular Risk Factors may have detracted from the importance of social deprivation as a determinant of multimorbidity. This was also mentioned by Reviewer 2 (Point 4). In response, we have modified our statement in the Discussion which gives undue prominence to Risk Factors, underplays the role of social deprivation, and fails sufficiently to demonstrate understanding of the interaction between the two. We have added further references on the theory of social conditions as fundamental causes of diseases and revised our final paragraph of 'Comparison with the Literature' to state:

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‘However, a focus on risk factors should not detract from ‘the causes of the causes’, since social conditions themselves generate causal pathways leading from socio-economic determinants to risk behaviours (27) and interventions which address health behaviours while failing to engage in social determinants may paradoxically result in increased health inequalities (28).’

VERSION 2 – REVIEW

REVIEWER	Concepción Violán Institut universitari d’investigació en atenció primària (IDIAP J Gol) Barcelona, Spain
REVIEW RETURNED	13-Sep-2019

GENERAL COMMENTS	The article “The journey to multimorbidity: a longitudinal analysis exploring cardiovascular risk factors and determinants in an urban setting” is a resubmission of the previous paper titled “The journey to multimorbidity: a longitudinal study in an urban setting”. The new paper , proposes a new an approach to study longitudinal multimorbidity based on anonymised primary care data to study the social determinants and risk factors for multimorbidity and the acquisition sequence of multimorbidity. In the resubmission , the authors included some suggestions previously commented in the first revision, but there are still information gaps in the part of methods that must be improved (see comments in the PDF) The tables of results should be improved, the tables and figures are excessive (5 tables and 7 figures) , two examples should be left and the rest of the information should be presented in supplementary files. Regarding these changes, the STROBE- Chek list will be modified. For these reasons, I consider that the study is not suitable to be published in BMJOpen Also, I did some comments included in the PDF of the main document. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Amaia Calderón-Larrañaga Aging Research Center, Karolinska Institutet, Sweden
REVIEW RETURNED	03-Sep-2019

GENERAL COMMENTS	- My main concern is related to the statistical analysis section. The authors state that, as part of the sensitivity analysis, they run "mixed effects logistic regression models to allow for random effects, adjusted for clustering at the practice level". Did the authors actually mean normal (not mixed effects) logistic regression with robust standard errors to account for clustering at the practice level? If not, I still don't understand how a mixed effects logistic regression is different from a mixed effects multilevel logistic regression with a random intercept at the GP level (which is what they seem to use in the main analysis). - I would write "socio-demographic determinants" instead of just "determinants" in the title.

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	- In the abstract “Main outcome measures” section, change the following sentence as indicated: "Multilevel logistic regression was used to model the socio-demographic characteristics and cardiovascular risk factors for multimorbidity". - Check the last paragraph of the introduction as there are some repetitions (I guess the authors forgot to delete the first part of the paragraph). - In the "Data analysis" section, change the following sentence as indicated (if it is actually true): "...adding fixed effects to describe patient characteristics and a random intercept at the general practice level...". - "Risk factor" needs to be changed by “cardiovascular risk factor” in many places still.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 response:
Reviewer 1 states:

1) The new paper, proposes a new an approach to study longitudinal multimorbidity based on anonymised primary care data to study the social determinants and risk factors for multimorbidity and the acquisition sequence of multimorbidity. In the resubmission, the authors included some suggestions previously commented in the first revision, but there are still information gaps in the part of methods that must be improved (see comments in the PDF)

Response: We thank you for your further suggestions. Our response is itemised to each of the 13 comments made in the PDF and appears under (4), below.

2) The tables of results should be improved, the tables and figures are excessive (5 tables and 7 figures), two examples should be left and the rest of the information should be presented in supplementary files.

Response: We agree that the inclusion of five Tables and four Figures is a large number. We had already removed FIVE Figures after the first review, placing them into the Supplementary File.

In response, we have additionally removed a further two Tables (Table 3 and Table 5), placing them in the Supplementary File. If required, we would consider removing Table 2 (describing health inequalities) and placing that too in the Supplementary file. However, we would like to argue for the retention of Figures 1-4 (7 colour plots in all) since these all form a unique body of work. Alluvial plots to the best of our knowledge have never previously been used before to display the acquisition sequence of multimorbidity. Each plot displays a health inequality related to deprivation (Fig 2), ethnicity (Fig 3) or age (Fig 4). If at all possible, we would like to retain these Figures intact?

3) Regarding these changes, the STROBE- Chek list will be modified.

Response: We have amended STROBE, as required and re-submitted with ‘track changes’.

4) Reviewer 1 also includes 13 comments in the text:
Also, I did some comments included in the PDF of the main document

Pg 2: Comment: ‘selection bias’.
Response: The Reviewer correctly comments that in our summary of ‘Strengths and Limitations’, there will be selection bias. We have already acknowledged this in the same section of ‘Strengths and Limitations’, stating ‘Difficulties gaining access to anonymised primary care data limited the sample size and may have contributed to selection bias’. In the Discussion, we have also addressed the issue about selection bias, stating: “the richness of locally based data…..has to be offset against possible loss of generalisability to other areas with very different social deprivation and ethnicity characteristics.” We have therefore not amended the text, but we do acknowledge this issue.

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Pg2: Comment: ‘selection bias solved with multiple imputation’.
Response: We agree that multiple imputation is a useful approach to the issue of missing data. However, in the Discussion, ‘Strengths and Limitations’, we provide more detail about the missing data: “Data access was a limitation to this analysis. We were only able to obtain data from one of the two boroughs adopting this approach to multimorbidity, the other lacked a data extraction system preventing us from analysing large datasets of patient-level data. Had we gained access to the data, this would have approximately doubled our sample size”. Multiple imputation would not have been valid as a tool to explore missing data from a neighbouring borough (potentially, 50% of the sample). We have therefore not amended the text, but we do acknowledge this issue.

Pg4: Comment: Those phrases started : " Then to determ" and " the aim was to study the characteristics" Are are redundant phrases. I suggest delete.
Response: the Reviewer has noted the repetition also noted by Reviewer 3, point (4). We apologise for retaining two sentences which were revised following the previous round of Reviewer comments. The additional sentence has now been deleted.

Pg4: Comment: ‘you could be modify the objective in order to obtain more information. Added source and study population “in the electronic records of a population xxx years’.
Response: On reflection, we have not amended the ‘Objectives’ as we consider that description of the data source and duration is more usefully included in the Methods section. The Methods section (pg5) does clarify the data source (‘electronic health records’). We have therefore not amended the text, but we do acknowledge this issue.

Pg4: Comment: ‘Please clarify the numbers. Add a Flow Chart. Define index dat a, baseline’.
Response: This comment refers to our sentence: “The population sample consisted of all patients registered at all general practices in Lambeth, with the exception of patients who had opted out of anonymised data sharing for research purposes”. The Reviewer asked us to ‘clarify the numbers’. In fact, we had already done this but placed the summary of the numbers in the Results section rather than in the Methods. In the Results, para 1, we stated: “Data from 13,369 (4.0%) patients had been excluded because a data sharing opt-out code was recorded in their EHR”. We consider that this response should be placed in the Results rather than in the Methods section. We have not added a Flow Chart as suggested since we have tried to reduce the overall number of Tables/Figures (see Reviewer 1 response, point (2)). We agree that we had not defined what the Reviewer meant by ‘index date’, i.e. when data was first recorded electronically. In response, we have therefore added this sentence to the Methods, Data Variables, section: “Routinely collected electronic data was available from all included practices from 2004”.

Pg5: Comment: ‘Missing the flow chart, target population, study period, etc. The data base is only one Health Center? Please specify the setting better’.
Response: This comment has arisen because we had omitted to mention the number of included practices. We had already described the target population in terms of patient numbers. We have therefore added this clarification to the Methods, Study Setting: “The population sample consisted of all patients registered at all general practices (n = 44) in Lambeth”.

Pg5: Comment: ‘The authors have to clarify the variables: Age, which date? At index date? The authors, have to clarify the age variable in tables there are groups ages, but previously you had not defined at the variables in, methods section.’
Response: We agree that the date from which age is measured should be stated more clearly. We have therefore added this phrase to the section on Methods, Study Population: “Demographic data consisted of gender, age in years (on the date of data extraction) and self-ascribed ethnicity obtained from the EHR”. In order to avoid repetition in the Methods section, we had not specified the age bands used in the analysis since these are clearly set out in Table 1. However, we would be happy to add this detail to the Methods section too, if required.

Pg5: Comment: ‘It is necessary to explain, inclusion and exclusion criteria. I suggest a sentence like this: In our study the inclusion criteria were individuals aged xxxx years on xx (month) xx (year) with at least xxxx one PHC visit since 2012. Only participants who survived until xxxx (exact date) (index date) were included in the analysis’.
Response: The Reviewer may have misunderstood our study design. In the Methods, Study Population section, we had already stated: “We included data on all patients aged 18 years and over

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registered with a general practice". Patients did not necessarily have to attend their general practice in any given year in order to have an electronic health record. However, we do agree that this may have left some ambiguity about the date when data was gathered and the fact that all patients had to be alive and registered with a study practice in order to have their electronic health record data extracted. In response, we have therefore clarified in the Methods, Data Variables, section, adding the following: "The data used in this study were extracted in May 2018 and related to all patients registered at each of the included practices on that date."

Pg6: Comment: 'It is not clear how many years patients are followed up. It is necessary to indicate the study period'.
Response: we agree that we had not previously specified the date when electronic health records (the EHR) were first developed. We trust that our addition of the sentence under Methods, Data Variables, has clarified: "Routinely collected electronic data was available from all included practices from 2004" (this additional sentence was also necessary because the Reviewer made a similar comment on pg4).

Pg6: Comment: 'The authors should have added : How many GP clusters have been cosidered in the study before data analysis'
Response: we agree that we had omitted the number of GP practices within the borough where all practices were selected. This has been corrected under Methods, Study Setting, where we have added, "(n = 44)", to indicate the number of practices.

Pg7: Comment: 'Tables 2-5 continue without separating the variables and putting all categories together'.
Response: We agree that we have categorised the demographic data in Tables 2-5. This was so that we could display % frequency results for each age category. Most demographic features are difficult to display without using categories. However, we agree that it would be helpful to include overall mean values for one of the variables, age. We have therefore added the mean age of the sample to the Results: "The mean age for the multimorbid cohort was 69.9 years (compared with a mean of 41.6 years in the sample population)". Other means (gender, ethnicity, deprivation) are already displayed in 'Results, Multimorbidity cohort characteristics', para 4.

Pg9: Comment: 'The sequences continue without giving information about the time between conditions. After commenting on limitations: "We aimed to display the acquisition sequence of LTCs using alluvial plots. However, these plots do not readily display time data resulting in a lack of clarity in the rate of progression of multimorbidity."Then is a strong limitation in order to conclude which is the temporal sequence off disease adquisition.'
Response: We agree that the lack of time data in our display of Long Term Condition 'acquisition sequence' is a substantial limitation. As the Reviewer comments, we had already noted this in the section on Limitations. However, in the light of the Reviewer comments, we need to elaborate our comment. We therefore now state: "Although these plots clearly display the sequence in which patients develop LTCs, they do not readily display time data and thus fail to distinguish between rapidly and slowly progressing multimorbidity."

Pg9: Comment: '"identical dates of onset " You should extplain the methods that would be done a priori not a posteriori.'
Response: We agree that it would be helpful to state this in the Methods. We have therefore added this sentence to the Methods, Data Analysis: "Patients with identical dates of onset recorded for two or more LTCs were excluded from this analysis."

Reviewer 2 response: not applicable

Reviewer 3 response:
Reviewer 3 states:

1) My main concern is related to the statistical analysis section. The authors state that, as part of the sensitivity analysis, they run "mixed effects logistic regression models to allow for random effects, adjusted for clustering at the practice level". Did the authors actually mean normal (not mixed effects) logistic regression with robust standard errors to account for clustering at the practice level? If not, I still don't understand how a mixed effects logistic regression is

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different from a mixed effects multilevel logistic regression with a random intercept at the GP level (which is what they seem to use in the main analysis).

Response: Thank you for pointing out the potential ambiguity in how we have described our principal analysis and sensitivity analysis. In fact, the simplest way to summarise the two approaches is that the principal analysis was conducted using a multi-level logistic regression to model for practice level variation. The sensitivity analysis was conducted using a logistic regression adjusted for clustering at practice level and allowed us to construct RoC curves (which appear in the Supplementary File).

This distinction became somewhat blurred, as the Referee has stated, by use of the terms, random effects, mixed effects and fixed effects. To simplify, we have removed these terms.

To answer the specific question from the Referee, the adjustment for clustering (the sensitivity analysis) was conducted in STATA using cluster robust standard errors to account for practice level clustering.

We have therefore amended our text to state:
"Socio-demographic and risk factor determinants of multimorbidity were analysed ~~at patient level~~ using ~~mixed effects~~ multilevel logistic regression models to model practice level variation. ~~, adding fixed effects to describe patient characteristics and random effects to describe general practice level, based on the registered general practice of each patient in the study sample.~~ We also conducted a sensitivity analysis using ~~mixed effects~~ logistic regression ~~models to allow for random effects~~, adjusted for clustering at the practice level."

2) I would write "socio-demographic determinants" instead of just "determinants" in the title.

Response: We agree with this suggestion to improve the title. The title now reads:
"The journey to multimorbidity: a longitudinal analysis exploring cardiovascular risk factors and socio-demographic determinants in an urban setting"

3) In the abstract "Main outcome measures" section, change the following sentence as indicated: "Multilevel logistic regression was used to model the socio-demographic characteristics and cardiovascular risk factors for multimorbidity".

Response: We agree that the Abstract needs to reflect the revised description of the principal analysis (multilevel regression model). The Abstract had already simplified the description of the regression modelling, reading: "Multilevel logistic regression was used to model the social determinants and risk factors for multimorbidity". That remains an accurate description of the methodology so we have not needed to amend.

4) Check the last paragraph of the introduction as there are some repetitions (I guess the authors forgot to delete the first part of the paragraph).

Response: Thank you for noticing that we had inadvertently retained two sentences in the Introduction, final paragraph. This occurred during revision to the first round of Reviewer responses when we were asked to clarify Aims and Objectives. The revised sentence describing Aims and Objectives has been retained. The original sentence has been removed.

5) In the "Data analysis" section, change the following sentence as indicated (if it is actually true): "...adding fixed effects to describe patient characteristics and a random intercept at the general practice level...".

Response: We fully accept this suggestion, that our approach to regression modelling required clarification. We have amended the paragraph in the Data Analysis section, as stated in (1), above.

6) "Risk factor" needs to be changed by "cardiovascular risk factor" in many places still.

We have added the clarification, 'cardiovascular risk factors' to each mention of the term, 'risk factor' (14 replacements).

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VERSION 3 - REVIEW

REVIEWER	Violán Fors, Concepción Institut universitari d'investigació en atenció primària (IDIAP J Gol), Barcelona, Spain
REVIEW RETURNED	20-Nov-2019

GENERAL COMMENTS	The article "The journey to multimorbidity: a longitudinal analysis exploring cardiovascular risk factors and determinants in an urban setting" is a resubmission of the previous paper titled "The journey to multimorbidity: a longitudinal study in an urban setting". The new paper , proposes a new an approach to study longitudinal multimorbidity based on anonymised primary care data to study the social determinants and risk factors for multimorbidity and the acquisition sequence of multimorbidity. In the resubmission , the authors included suggestions previously commented in the second revision, For these reasons, I consider that the study is suitable to be published in BMJOpen

REVIEWER	Amaia Calderón-Larrañaga Aging Research Center, Karolinska Institutet, Sweden
REVIEW RETURNED	09-Nov-2019

GENERAL COMMENTS	The authors adequately addressed my comments and improved their manuscript.

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