Author's response to reviews

Title: Implications for treatment burden of comorbidity and polypharmacy in people with stroke: cross-sectional population-based study

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Version: 2 Date: 8 July 2014

Author's response to reviews:

Responses to Reviewer 1: (Will Whiteley)

We were glad this reviewer found the paper well written and worth publishing and thank him for his constructive comments. We provide our responses to his comments below.

1. The difference between multimorbidity and co-morbidity seems to me rather slight, and more a question of semantics than any meaningful difference. From a patient's and a clinician's perspective they are the same.

Author Response: Thank you for this comment and in response we have now tried to make it clearer that our emphasis is on multimorbidity and have made changes throughout the manuscript (title, abstract, introduction and discussion in particular) to ensure this is clearer.

2. The introduction is too long, and I would suggest paring it to a description of the key question.

Author Response: Thank you we have looked at this carefully and have had to add additional material to the introduction in response to reviewer 2 but have tried to trim this a little, in particular by losing the text defining comorbidity vs multimorbidity as described in response to comment 1.

3. Worth mentioning the particular characteristics of the Scottish population registered with GP, so other can compare.

Author Response: Thank you for this comment. We have provided the age, sex and deprivation distribution of the population in supplementary file 1 so that
comparisons can be made.

4. There is a qualitative difference between long term conditions, between those that might give daily symptoms (e.g. depression, heart failure) and those that are asymptomatic (e.g. blood pressure, diabetes)

Author Response: Thank you we would agree with this and have added a comment in the discussion in relation to this. “The measure of comorbidity was unweighted, as the aim was to be descriptive rather than to assess outcomes. This was deemed to be the most appropriate method and is similar to that used by others investigating the prevalence of multimorbidity [1] but could be viewed as a limitation especially as there may be a qualitative difference between the effects on perceived treatment burden of long term conditions that give regular symptoms (e.g. heart failure) and those that are asymptomatic (e.g. hypertension).”

It is worth noting that reviewer 2 had asked us to prune the discussion but this is instead an addition.

5. It is not necessary to describe the calculation of odds ratios

Author Response: Thank you we have deleted this description from the methods section.

7. The analysis has a very high power. Is such a high p-value appropriate?

Author Response: Thank you for this comment, We think this is a very fair point. However, we have reported p values > 0.001 in all our tables to make interpretation of results clearer for the reader. It is also the case that some of the smaller differences for the individual may be statistically significant but not clinically significant so we have added the following to the strengths limitations section of the discussion (page 14, para 3):

“As such the large numbers of cases and controls assessed in this study may have identified some associations which were statistically significant but not necessarily clinically significant, for example, for conditions such as cancer, glaucoma, asthma prostrate disorders and multiple sclerosis which had odds ratios between 1.08-1.12 but were statistically significant a t p<0.001”

8. Is 'painful condition' a construct you have made, or is it a Reed code?

Author Response: Thank you there is not a general Read code for “painful condition” so we used the definition previously used by another study using this same dataset (Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380: 37-43. DOI 10.1016/S0140-6736(12)60240-2.) which defined painful condition as any patient with #4 specified analgesic prescriptions in the preceding year (opioids/>8mg co-codamol/NSAIDS) OR #4 specified anti-epileptics in the absence of an
epilepsy Read code in the preceding year (gabapentin, pregabalin and carbamazepine). We have not added any text relating to this query into the paper as yet but can do so if the editors prefer.

9. I am not sure it necessarily follows from the analysis that patients are on too many drugs (though I agree that this is most likely, particularly in those on 11+ medications). The counter argument that some are on too few medications might also be made. At the very least, one would expect patients with an ICH to be on an antihypertensive; most of those with an ischaemic stroke might be prescribed 4 medications (an antiplatelet, 2 anti-hypertensives, and a statin). One co-morbidity, present in ~ half would add at least 1, so a median of 5-6 might be too few.

Author Response: Thank you we have modified the discussion as outlined below in response to comment 10, and we hope this makes it clear that polypharmacy is not necessarily a bad thing.

10. It is really unknown whether polypharmacy is causal for poor outcomes, so it is difficult to make firm recommendations without experimental evidence, though I agree a very important question (though my gut feeling is to agree with the authors). However, one might very reasonably ask if people with stroke have made their own decisions whether or not to take so many medications, given their modest benefits: treatment burden is necessarily subjective (some patients are terrified to stop medication, however small the benefit).

Author Response: Thank you for this very thoughtful comment. We would wholeheartedly agree and have now added this as a recommendation in the discussion section of our manuscript. This of course is also again lengthening the discussion in contrast with Reviewer 2’s suggestion.

“While many pharmacological therapies may be beneficial for those with stroke, a key question is whether people with stroke have made informed decisions regarding whether or not to take so many medications, given their modest benefits. While perceived treatment burden and capacity to cope with any given treatment burden will vary we would recommend that patients with stroke are made aware of the relative benefits of their drugs - and are empowered to make their own decision whether to take them”.

Responses to Reviewer 2 - Danijela Gnjidic

We would like to thank this reviewer for her helpful comments which we have done our best to address.

1.Introduction - I suggest authors provide some data on polypharmacy/multimorbidity prevalence in the introduction section.

Author Response: Thank you for this suggestion. In response we have added the following to the introduction (page 6 para 2):
"with a study using routine Scottish health records finding that of those with two clinical conditions, 20.8% were receiving four to nine medications, and 1.1% were receiving ten or more medications; in those patients with six or more comorbidities, these values were 47.7 and 41.7%, respectively [19]. A systematic literature review investigating the relationship between number of chronic conditions and health care utilization outcomes found that about 60% of elderly respondents with zero or one condition reported taking prescription medications. This percentage went up to more than 90% for those with two or three conditions, and approached 100% for those with more than five [20]."

It is important to note that reviewer two asked us to shorten the introduction, so the addition of this information, rather goes against his suggestion. We are happy for the editorial team to decide whether they do or do not wish to use this additional material in the final manuscript.

2. Aims should be more specific/clear. i.e. comparing polypharmacy/multimorbidity in people with and without stroke.

Author Response: Thank you for pointing out that there was a perceived lack of clarity. In response we have edited the last sentence of the introduction on Page7 so that it now reads:

"Using a large, nationally representative cross-sectional primary care data set, we examined the prevalence of multimorbidity and polypharmacy in people with and without stroke."

3. While authors point out that there is no specific cut off to define polypharmacy I believe this is commonly defined as 5 or more medications - in particular in studies of older people.

Author Response: Thank you for this comment. We would agree that 5 or more medications is a figure often used by clinicians but as we have tried to point out there are also many references to other definitions of polypharmacy. If the reviewer can point us to a definitive reference on this subject which contradicts our statement of the literature being mixed in relation to this definition we will be happy to incorporate it. However, at present we would prefer to use our currently referenced definition of:

"Polypharmacy is most commonly defined as the use of multiple (usually five or ten) prescribed medications [14–16]."

4. Considering the large sample size in this study, I suggest authors conduct subgroup analysis across age groups (younger and older adults). Do authors anticipate to observe similar treatment burden prevalences across all age groups?

Author Response: Thank you for this suggestion, but we believe that subgroup analyses can be potentially dangerous with spurious results appearing by chance alone and this increases the more analyses one conducts (Brooks S et l"
Subgroup analyses in randomized trials: risks of subgroup-specific analyses; Journal of Clinical Epidemiology. J Clin Epidemiol. 2004 Mar;57(3):229-36.) One should only do this when convinced there is good reason to anticipate interaction with age and be confident of the results. Given the skewed distribution of stroke to those over age 75 years then any comparison between younger and older is difficult due to the small numbers in the younger age groups particularly for those with a high number of conditions or those on a high number of medications. To illustrate this we have added a table (supplementary file 4) showing analysis for age groups 35-44 and 75+ for number of condition and medications. We have also added the following to the main paper (page 10, para 1).

“In terms of assessing whether these differences exist across different age groups, a sub analysis for age groups 35-44 and 75 plus is presented in supplementary file 4. This indicates that differences were larger for the younger age group and increased with the number of conditions (a similar picture was found for number of repeat prescriptions). However, the skewed distribution of stroke prevalence towards the oldest age groups make any assessment of differences by age problematic, due to the small sample size in the youngest age groups.”

5. Methods. I feel methods section could be improved to include better description of datasets and data linkage process (especially for an international audience). A flow chart deriving study population would be helpful.

Author Response: Thank you for this comment. The dataset that we used comprised data that were extracted directly from medical records, as described in our methods section under ‘study design and participants’. Data obtained are described in the methods sections under ‘data collected and disease definition’. All the information in the study was taken from one dataset and as such there is no data linkage process. Therefore we do not believe a flow chart would be helpful or is necessary. The characteristics of the study population are outlined in Supplementary File 1.

6. What was the time frame used to define regular prescriptions? Studies suggest 90 days and more is most sensitive (Fincke B et al PDS 2004).

Author Response: Thank you for pointing out that there was still some apparent lack of clarity on this point. The time frame to define regular prescriptions was 84 days as this was the maximum length of a repeat prescription in Scotland at the time of data collection. This is described in the methods section (page 8 para 4) but we have added some explanatory text to ensure the rationale for this is clearer:

“For the purposes of this analysis, any regular prescription that was still active (i.e. available for issue on request) on the date of extraction and had been prescribed in the last 84 days was counted as current and was selected as this was the maximum length of a repeat prescription in Scotland at the time of data collection.”
7. There were two related comments that we have addressed in one response: Methods a) Should have a paragraph on covariates included in the analysis; Results b) Should table 1 include data on covariates?

Author Response: Thank you for raising these issues. The final paragraph of the methods section outlines which variables were adjusted for. In order to make this clearer we have added the following sentences (page 9):

“Age and deprivation were used as continuous variables. Deprivation was measured using the Carstairs score which is widely used in health research. The Carstairs score is based on four census indicators: low social class, lack of car ownership, overcrowding and male unemployment. The scores have been described as a measure which reflects access to those material resources which provide access to "those goods and services, resources and amenities and of a physical environment which are customary in society" [26]. The scores therefore cannot be described as a measure of the extent of an individuals material wellbeing but are rather a summary measure applied to populations contained within small geographic localities.”

All tables report unadjusted odds as well as adjusted to show the effect of the controls. As the purpose of the paper is not to show the individual effect of age, sex, deprivation we believe that reporting of individual effects may confuse the general readers as well as potentially producing spurious results.

9. Regular prescriptions, spearman correlation analysis - this should be mentioned in methods too.

Author Response : Thank you for pointing this out. We have added the following to the last paragraph of the methods section (page 9) in order to address this omission.

“Associations between numbers of morbidities and prescriptions were assessed using Spearman correlation coefficients”

10. Discussion: Overall I thought this section is too long and somewhat repetitive.

Author Response: Thank you we have tried to abbreviate certain portions of this discussion to make it more concise but reviewer 1 has asked for certain additions, so overall there is little change in overall length. So it was impossible to fully meet expectations of both reviewers in relation to this.

11. How can you compare the results with studies conducted in older populations when you haven't done the analysis in this subgroup?

Author Response: Thank you we believe our response to comment number 4 above now addresses this issue but we have also removed this comment from the discussion.
12. Confounding due to disease severity should be mentioned in the study limitations.

Author Response: Thank you we have now added this limitation to the Discussion section

13. Why not look at clinical consequences of treatment burden when can routinely link datasets?

Author Response: Thank you, we agree this would have been an excellent idea. Unfortunately, the dataset we possessed was a free standing dataset that was not linked to other datasets and we did not have ethical permission to undertake such linkage. We are investigating the potential to undertake such studies in the future.

Minor essential comments

14. Suggest to combine Table 1 and 2

Author Response: Thank you for this suggestion. At this time we would prefer to keep these tables separate but are happy to take advice from the editors on this.

15. Figures - please define what OR stands for?

Author Response: Thank you for this comment we have amended this figure to ensure this is clearer.

16. Fig 2 - it is stated that you are looking at medical conditions but have a bar for 'drug-related problems'. Please clarify this.

Author Response: Thank you for pointing out that this was not clear. Drug related problems is any Read code which records psychoactive substance abuse which includes both drug misuse which is what is implied by the name, and prescription drug problems of multiple sources. We have added a legend to figure 2 to ensure this is clear to the reader.

We have tried to address all the reviewer comments and hope you find our responses satisfactory and wish to proceed to publication in your journal. We look forward to hearing your final decision in the near future.

Yours sincerely

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