

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	An investigation of social, demographic and health variations in the usage of prescribed and over-the-counter medicines within a large cohort (South Yorkshire, UK)
AUTHORS	Green, Mark; Little, Emma; Cooper, Richard; Relton, Clare; Strong, Mark

VERSION 1 - REVIEW

REVIEWER	Sabine Vogler WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Gesundheit Österreich GmbH (GÖG/Austrian Public Health Institute), Austria
REVIEW RETURNED	17-Apr-2016

GENERAL COMMENTS	<p>Thank you very much for giving me the opportunity to review this paper. It is a nice analysis, and it provides a valuable contribution to this field of research for which few pieces of research are available. The results are interesting and informative, and they tend to confirm previous research.</p> <p>However, I would be reluctant calling this work novel since there are similar results for other European countries available. The non-consideration of further research in this field and the missing discussion of the policy context are major flaws of the current version of the manuscript that should definitively be addressed in a revision. In addition, I have a few questions related to the methodology.</p> <p>Methodological concerns:</p> <p>I understand that you used data from the Yorkshire Health Study, and indicators surveyed are thus pre-defined. I highly welcome that this survey also has indicators such as walking, physical exercise, tobacco and alcohol use which is interesting. However, key socio-economic indicators such as income or employment status that are usually surveyed in such studies are missing – pls. include them in the analysis, if possible, or discuss the missing indicators under limitations.</p> <p>I would require some information about the age of the respondents – did only adults and/or youth above a certain age respond? If not, the authors should consider excluding data for people below the age of 16 (or 18) due to its confounding character.</p> <p>On page 7 the authors state that the cohort is not representative for the population of England. However, as a reader I would be interested in learning why they are not representative, and not only have the reference to another study. I do not understand why a weighting of the number of medicines by age, gender, deprivation (how exactly did you do the latter? which factors were included?) was necessary. Do you want to claim a representativeness for the results for England? In any case, it was a survey for South</p>
-------------------------	--

	<p>Yorkshire, so it would be of interest to see the results unweighted for this region. I strongly advise running a sensitivity analysis with unweighted data.</p> <p>Consideration of further literature: The discussion (and introduction) need(s) to be rewritten in order to take into consideration the policy context (see below) and to discuss the results in the light of similar research. Major references are missing, such as: Mayer S, Österle A. Socioeconomic determinants of prescribed and non-prescribed medicine consumption in Austria. <i>The European Journal of Public Health</i>. 2014;cku179. Vogler S, Österle A, Mayer S. Inequalities in medicine use in Central Eastern Europe: an empirical investigation of socioeconomic determinants in eight countries. <i>International Journal for Equity in Health</i>. 2015;14(1):124. Geckova AM, van Dijk JP, Zezula I, Tunistra J, Groothoff JW, Post D. Socio-economic differences in health among Slovak adolescents. <i>Sozial- und Präventivmedizin</i>. 2004;49(1):26–35. Gorecka K, Linhartova A, Vlcek J, Tilser I. Cardiovascular drug utilisation and socio-economic inequalities in 20 districts of the Czech Republic. <i>Eur J Clin Pharmacol</i>. 2005;61(5-6):417–23.</p> <p>In this respect, I would also challenge the statement made in lines 3ff at page 10 about the missing information outside the US. There are few, but the EHIS (European Health Information Surveys) do allow for such analyses.</p> <p>Policy context: While the statistical analysis is nicely done, the manuscript lacks a consideration of the health policy context. A description of health policy context would be necessary (→ pls. rewrite the introduction), and the discussion of the results should also address them (→ rewriting of the discussion section is strongly suggested).</p> <p>Two major features of the English health care and pharmaceutical system are relevant for this paper: (1) England has a policy to enhance patients' empowerment and to promote self-medication, in contrast to several other (European) countries. There are NHS policy papers, as well as pieces of research (e.g. by LSE) on this issue for England, and there are pieces of comparative health system research, pls. consider them. (2) The use of medicines has to be seen in connection with funding issues. In European countries, including England (pls. confirm), non-prescribed medicines are not funded by public payers, thus their costs are fully borne by the patients. Thus, it might be assumed (and was confirmed in other studies) that people of higher socio-economic status tend to consume more non-prescribed medicines. When revising the introduction, these two elements should be considered.</p> <p>In this context, the distinction between over-the-counter medicines and non-prescribed medicines should be made clear. In many European countries, over-the-counter medicines are excluded from reimbursement, thus they offer an opportunity for savings in public funding. However, if prescribed, their costs are covered by the public payer. Pls. specify for England in the introduction how the situation related to funding, and explain in the methods section what 'non-prescribed medicines' means, i.e. those OTC medicines not funded by the state. As a result, I suggest rephrasing the sentence on page 4, line 26: into 'non-prescribed over-the counter medicine use has been argued to represent a potential savings ...'.</p> <p>Further comments: Pls. consider extending the title by including the geographic coverage ('in South Yorkshire').</p> <p>Abstract: As stated above, I would not call the results 'novel' (they</p>
--	--

	<p>are, of course, novel for South Yorkshire)</p> <p>Pls. be careful with the use of abbreviations (e.g. GCSE, CNS) and explain them the first time you used.</p> <p>Pls. consider that the readership of BMJ is international and might not be familiar with England-specific characteristics (e.g. GCSE level, A-level).</p> <p>Introduction, first sentence: pls. note that there is an updated WHO World Medicines Situation report as of 2011. The issue is not the production and consumption of medicines, but the affordable access to essential medicines in a rational way (not only avoiding underuse, but also preventing overuse or misuse)</p> <p>Introduction, page 4, line 15: why paradoxically – this is not surprising</p> <p>Introduction, page 4, line 30: ‘the medical applications of the use and growth of medicines’ – I am sorry but I do not understand the sentence</p> <p>Introduction, page 4, line 38 ff.: I would challenge this statement. What is right, is that demographic factors including age, and also gender, were more considered in research than pure socio-economic factors. With regard to gender-related analysis of medicine use, pls. also consider the work of the group of Anita Wagner at Harvard Medical School.</p> <p>Introduction, page 4, line 48: pls. focus on the research about (demographic and) socio-economic factor related to medicine use, not to health service use in general</p> <p>Introduction, page 5, line 25: I strongly recommend rephrasing the objective and deleting the part ‘and health-related behaviours’ since this was not addressed in the study (also neither mentioned in the title nor the abstract)</p> <p>Table 1: pls. check the data point ‘100’ related to contraception indicating the percentage of medicines prescribed for prescribed – should it read ‘0’?</p> <p>Walking: Though explained in the text, it is not clear in Tables 2-4 which denominators (per day, week, month) were used.</p>
--	--

REVIEWER	Amy Heshmati Centre for Health Equity Studies (CHES) Stockholm University/Karolinska Institutet Sweden
REVIEW RETURNED	22-Apr-2016

GENERAL COMMENTS	<p>This manuscript on “Understanding the socio-economic factors that influence usage of prescribed and non-prescribed medicine using a large population cohort” is an interesting paper with a lot of promise. The paper would benefit considerably from polishing of the text before it is suitable for publication. At times the paper feels rushed and there have been many simple oversights.</p> <p>I have some comments below:</p> <p>A) Title 1. The title of the manuscript does not match the study. The title suggests many socio-economic factors influence the use of medicines, when in fact only one socio-economic variable is used in the study i.e. education.</p> <p>B) Abstract 1. Page 2, Line 13: The aim is not clearly defined. The reader gets a</p>
-------------------------	--

	<p>general overview of what the paper is about, but not what the authors' intentions are. Although it is just semantics, I would rewrite the aim to something along the lines of, "Our study objectives are to describe the social, demographic and health factors that influence the individual behaviour regarding medicine usage". That is of course, if this is your intended objective of the study.</p> <p>2. Page 2, Line 18: Move 'Negative binomial regression models were used to analyse the count of medicine usage' from Design to Measures.</p> <p>3. Page 2, Line 31: State some of the 14 categories that the medicines were grouped into. Perhaps just the most common categories, such as cardiovascular disease, CNS pain, gastrointestinal, dietary supplements.</p> <p>4. Page 2, Line 31: It states that you 'controlled for age, gender...' I did not see evidence that you controlled for these variables in your analyses, but these were exposure variables. Please amend the text to ensure it is in line with your analyses.</p> <p>5. Page 2, Line 33: It would be useful to state which exposure variables fall under your social, demographic and health factors. Health factors could be split into health-related behaviours and chronic health conditions. Again, it would be useful to list the more common chronic health conditions.</p> <p>6. Page 2, Line 44: Not all health conditions were negative associated with non-prescribed medicines. From Table 2, only four health conditions were negatively associated with non-prescribed medicines. Please review this sentence.</p> <p>7. Page 2, Line 47: 'suggesting the importance of social factors in understanding behaviours' is not suitable for the results section. On a side note, education is a predicator of occupation status and income, but it also captures human capital which influences health-related behaviours.</p> <p>8. Page 2, Line 52: The authors state that 'this study has provided a new understanding of multiple socio-economic factors that influence medicine usage'. This is a strongly worded and perhaps misleading statement considering only one socio-economic variable is used in the study.</p> <p>C) MeSH Keywords</p> <p>1. Page 3, Line 6: Consider replacing 'socioeconomic factors' or adding 'education' to key words</p> <p>D) Introduction</p> <p>1. Page 4, Line 51: The authors' state that 'ethnicity, health and weight status have also shown to be important'. In what way? Please elaborate.</p> <p>2. Page 5, Line 23: The aims are not clearly defined to the reader. I can understand what you are trying to convey, but suggest the aim is rewritten to avoid ambiguity. Your aims in the main text should be the same as that in the Abstract. At the moment they somewhat differ.</p> <p>E) Methods</p> <p>1. In the Introduction the authors use the term 'over-the-counter' medicine rather than 'non-prescribed' medicine. However throughout the rest of the manuscript including the title and Abstract, the term 'non-prescribed' medicine is used. Please be consistent in your terminology. I would suggest using 'over-the-counter' medicine rather than 'non-prescribed' as this is what non-prescribed medicines are called in clinical practice.</p> <p>2. In general it would be helpful for the reader if the explanatory</p>
--	--

variables were organised better. For example, the social factor is education...., The demographic factors were age, gender and ethnicity, etc. As mentioned above, I would split health related behaviours and chronic health conditions, and then list/explain the variable.

3. Page 6, Line 23: describe your ethnicity variable.

4. Page 6, Line 44: Was smoking status just yes or no?

5. Page 7, Line 32: 95% confidence intervals were also reported in tables. Suggest adding in text.

6. Page 7, Line 40: Unsure if it is mandatory to cite what statistical package you used for your analyses. Consider adding this information to the Statistical Analysis section.

F) Results

1. For Tables 1-4, please state N in the table headings.

2. For Tables 2-4, organise your variables into groups with subheadings. E.g. demographic factors, health related behaviour etc. This will enable the reader to read your results more easily.

3. For Tables 2-4, replace 'gender' with 'men'. At the moment you cannot ascertain which direction is for men or women when just looking at the tables.

4. Tables 2-4, replace 'smoke' with 'smoking'.

5. Page 7, Lines 49: what was the p-value for the difference in gender found to be taking any category of medicine? Was there a statistically significant difference in the mean number of medicines split by category or gender? State the p-values in Table 1 and where appropriate in text.

6. Page 7, Line 51: what was the proportion for prescribed medicines? State in text.

7. Page 8, Line 31: replace 'greater' with 'stronger'.

8. Page 8, Lines 49-56: What are your p-values for heterogeneity for walking, physical exercise and education? State in table.

9. Do you adjust for education when analysing any of the demographic or health related behaviour variables?

10. Page 8, Line 56: The authors' state that education is negatively associated with total prescribed medicine, but no p-value for linear trend nor p-value for heterogeneity have been given. Please provide in the table and text if you are going to mention the direct of the associations.

11. Page 9, Lines 8-13: Description of the analysis should be in the methods under statistical analysis not in the results section.

12. Page 9, Lines 17-28: Paragraph is vague and uninformative. Direct the reader to the most interesting findings. Please rewrite.

G) Discussion

1. Page 9, Line 37: I think your wording is too strong with regards to the study showing important social and demographic variations in medicine usage at the population level. Gender appears to matter more for purchasing over the counter medicines than for prescribed medicines, likewise for education. The reader does not know enough about the ethnicity variable. The UK is now very multicultural, splitting this variable into just white and non-white is uninformative.

2. Page 10, Line 39: I do not think you can necessarily deduce that those with high level of educational attainment are of high socio-economic position. As mentioned earlier, while it is true that education is a predictor of occupation status and income, education attainment captures human capital which influences health-related behaviours. I would focus on education as an explanatory variable rather than using it as a proxy for socio-economic position. In doing so you could discuss educational attainment and health related

	<p>behaviours (bmi, physical exercise, walking, smoking and alcohol consumption). It would be worthwhile to see if the associations with the health related behaviour variables were diminished after adjustment for education.</p> <p>3. Page 11, Line 24: Consider using the term 'minorities' instead of non-White. The authors' state that the finding with non-White was independent of socio-economic status. Did you stratify or adjust your results by education? I do not see these results. What was the evidence from the US which your research supports? Were these people healthier? Was it poorer access to health care? Please specify.</p> <p>4. Suggest a concluding paragraph/summary at the end of the manuscript.</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Sabine Vogler

Institution and Country

WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Gesundheit Österreich GmbH (GÖG/Austrian Public Health Institute), Austria

Please state any competing interests or state 'None declared':

None declared

Please leave your comments for the authors below

Thank you very much for giving me the opportunity to review this paper. It is a nice analysis, and it provides a valuable contribution to this field of research for which few pieces of research are available. The results are interesting and informative, and they tend to confirm previous research.

However, I would be reluctant calling this work novel since there are similar results for other European countries available. The non-consideration of further research in this field and the missing discussion of the policy context are major flaws of the current version of the manuscript that should definitively be addressed in a revision. In addition, I have a few questions related to the methodology.

Methodological concerns:

I understand that you used data from the Yorkshire Health Study, and indicators surveyed are thus pre-defined. I highly welcome that this survey also has indicators such as walking, physical exercise, tobacco and alcohol use which is interesting. However, key socio-economic indicators such as income or employment status that are usually surveyed in such studies are missing – pls. include them in the analysis, if possible, or discuss the missing indicators under limitations.

- The first wave of the YHS does not collect data on income (although this is asked in the second wave thus representing the possibility for future work to explore patterns in greater depth). There is some information on occupation, but it would require a more detailed analysis than can be offered in this article alone to pick apart differences (and the variable has greater missing data compared to the education variable).
- We have mentioned these socio-economic factors in the limitations section in the discussion to make this clear ("Finally, we only use one measure of socio-economic status (education) and

extending our analyses to additional measures such as income or occupation will help to improve our understanding socio-economic behaviours in medicine usage.” Pages 19-20).

- Alongside other changes, the title of the work and text have been changed throughout to focus on exploring education differences to keep the paper focused in line with this comment also.

I would require some information about the age of the respondents – did only adults and/or youth above a certain age respond? If not, the authors should consider excluding data for people below the age of 16 (or 18) due to its confounding character.

- The survey were collected for adults only (individuals aged over 16). We have made a note of this in the methods section (“This contained information on 27,806 individuals aged 16 and over that consisted of the South Yorkshire region of England.” Page 6).
- Re-running the analyses for individuals aged 18 and over did not alter the findings.

On page 7 the authors state that the cohort is not representative for the population of England. However, as a reader I would be interested in learning why they are not representative, and not only have the reference to another study. I do not understand why a weighting of the number of medicines by age, gender, deprivation (how exactly did you do the latter? which factors were included?) was necessary. Do you want to claim a representativeness for the results for England? In any case, it was a survey for South Yorkshire, so it would be of interest to see the results unweighted for this region. I strongly advise running a sensitivity analysis with unweighted data.

- We have made the section clearer in what we did and our justification for this: “Prevalence of each medicine category was reported and weighted using sample weights. Weighting was necessary because the Yorkshire Health Study contains some bias since it is over-representative of the elderly, females, and individuals from affluent areas (26). Weighting allowed us to correct for known bias (sample weights were not applied subsequent analyses)” (page 9). We have also removed any reference to being representative of any region as this is not what is important for our study (nor within our remit).
- We feel that it is important to correct for these biases to have a more truthful and reflective set of results in this Table (which is less problematic in the regression analyses).

Consideration of further literature:

The discussion (and introduction) need(s) to be rewritten in order to take into consideration the policy context (see below) and to discuss the results in the light of similar research. Major references are missing, such as:

Mayer S, Österle A. Socioeconomic determinants of prescribed and non-prescribed medicine consumption in Austria. *The European Journal of Public Health*. 2014;cku179.

Vogler S, Österle A, Mayer S. Inequalities in medicine use in Central Eastern Europe: an empirical investigation of socioeconomic determinants in eight countries. *International Journal for Equity in Health*. 2015;14(1):124.

Geckova AM, van Dijk JP, Zezula I, Tunistra J, Groothoff JW, Post D. Socio-economic differences in health among Slovak adolescents. *Sozial- und Präventivmedizin*. 2004;49(1):26–35.

Gorecka K, Linhartova A, Vlcek J, Tilser I. Cardiovascular drug utilisation and socio-economic inequalities in 20 districts of the Czech Republic. *Eur J Clin Pharmacol*. 2005;61(5-6):417–23.

- Thank you for the references on socio-economic patterns in medicine usage that we missed. We have included them throughout our introduction and discussion, and they have contributed to improving the content of our manuscript. The changes made in light of them are discussed in the following responses.

In this respect, I would also challenge the statement made in lines 3ff at page 10 about the missing

information outside the US. There are few, but the EHIS (European Health Information Surveys) do allow for such analyses.

- We have also removed the comment from the strengths section of the discussion (page 19), as well as from the introduction (page 5).

Policy context:

While the statistical analysis is nicely done, the manuscript lacks a consideration of the health policy context. A description of health policy context would be necessary (→ pls. rewrite the introduction), and the discussion of the results should also address them (→ rewriting of the discussion section is strongly suggested).

Two major features of the English health care and pharmaceutical system are relevant for this paper: (1) England has a policy to enhance patients' empowerment and to promote self-medication, in contrast to several other (European) countries. There are NHS policy papers, as well as pieces of research (e.g. by LSE) on this issue for England, and there are pieces of comparative health system research, pls. consider them. (2) The use of medicines has to be seen in connection with funding issues. In European countries, including England (pls. confirm), non-prescribed medicines are not funded by public payers, thus their costs are fully borne by the patients. Thus, it might be assumed (and was confirmed in other studies) that people of higher socio-economic status tend to consume more non-prescribed medicines. When revising the introduction, these two elements should be considered.

- We would like to point out that given the word limit, and that the focus of our paper is not policy orientated, we have limited the detail of our responses here. However, we still feel these are important areas for us to engage with hence our inclusion in line with your comments.
- We have now rewritten part of the introduction to incorporate your point, including new references. It now reads: "Over-the-counter medicine use has been argued to represent a potential saving by reducing NHS spending by shifting the financial burden to individuals (4). However, the approach also follows a wider NHS strategy to enhance patient's empowerment through promoting self-medication contrary to other European nations (5–7)." (page 4)
- For the second point here, we have decided to shift the discussion of financial burdens as possibly influencing behaviours (which now makes our discussion fit better) to avoid repetition. The discussion point now reads: "Individuals of high education are associated with better employment prospects and higher incomes, and hence they will be in a better position to absorb the financial burden associated with purchasing additional medicines (9,11,21)." (page 20).
- We then further touch on the above point in the policy sphere in our summary: "With the NHS moving towards greater self-medication (both to empower patients and reduce costs), such an approach may have important implications for social inequalities in health and health-related behaviours." (page 21)

In this context, the distinction between over-the-counter medicines and non-prescribed medicines should be made clear. In many European countries, over-the-counter medicines are excluded from reimbursement, thus they offer an opportunity for savings in public funding. However, if prescribed, their costs are covered by the public payer. Pls. specify for England in the introduction how the situation related to funding, and explain in the methods section what 'non-prescribed medicines' means, i.e. those OTC medicines not funded by the state. As a result, I suggest rephrasing the sentence on page 4, line 26: into 'non-prescribed over-the counter medicine use has been argued to represent a potential savings ...'.

- In accordance with a comment from the other reviewer, we have removed all reference to 'non-prescribed' medicines in favour of using 'over-the-counter' medicines throughout the text. We have

also included you description in the introduction: “Over-the-counter (i.e. non-prescribed and not funded by the state) medicines” (page 4). Due to including this line earlier in the introduction, we no longer feel that we need to add the additional comment you have suggested as this is will now be repetitious.

Further comments:

Pls. consider extending the title by including the geographic coverage (‘in South Yorkshire’).

- We have changed our title in accordance to your suggestions and the other reviewer to “An investigation of social, demographic and health variations in the usage of prescribed and over-the-counter medicines within a large cohort (South Yorkshire, UK)” (page 1).

Abstract: As stated above, I would not call the results ‘novel’ (they are, of course, novel for South Yorkshire) Pls. be careful with the use of abbreviations (e.g. GCSE, CNS) and explain them the first time you used.

- Agreed. We have removed the term ‘novel’. We have explained CNS in both the text and the Tables. The same has been completed for GCSE in the text.

Pls. consider that the readership of BMJ is international and might not be familiar with England-specific characteristics (e.g. GCSE level, A-level).

- We have described the education categories so that they are comparable internationally (i.e. secondary level, degree level) – the England specific qualifications are for greater detail. To help readers, we have now included the equivalent level based on the European Qualifications Framework (page 7).

Introduction, first sentence: pls. note that there is an updated WHO World Medicines Situation report as of 2011. The issue is not the production and consumption of medicines, but the affordable access to essential medicines in a rational way (not only avoiding underuse, but also preventing overuse or misuse)

- We have now replaced the reference (reference 1) with the one suggested and made a note of affordability in the sentence (page 4).

Introduction, page 4, line 15: why paradoxically – this is not surprising

- We have removed ‘paradoxically’ from the sentence (page 4).

Introduction, page 4, line 30: ‘the medical applications of the use and growth of medicines’ – I am sorry but I do not understand the sentence

- We have removed this part of the sentence to avoid confusion and moved the rest of the sentence to the start of the next paragraph where it makes more sense (page 4).

Introduction, page 4, line 38 ff.: I would challenge this statement. What is right, is that demographic factors including age, and also gender, were more considered in research than pure socio-economic factors. With regard to gender-related analysis of medicine use, pls. also consider the work of the group of Anita Wagner at Harvard Medical School.

- We have removed the sentence in question, and now replaced it with two separate paragraphs first starting with more detail about demographic factors before moving onto social ones. The paragraphs

now read:

- “Previous research into predictors of medicine usage have focused on demographic factors particularly age and gender. Prescribed medication usage has been shown to increase with age due to the association between ill health and age (8–11), although childhood and adolescence also represent important focal points of research (12,13). In contrast, over-the-counter medicine usage decreases with age (9,11,14). Differences in terms of gender have also been explored extensively, with females consistently found to use greater prescribed and over-the-counter medicines (9–11,14–16). Women are more health conscious than men, and have greater interactions with health care systems, which might explain these differences (17). There has also been some investigation of gender inequity in medication usage in low- and medium-income countries (17,18).” (pages 4-5)
- “There have been fewer studies that have explored the influence of social determinants on medicine usage, particularly for over-the-counter medicines. This is despite a more extensive literature on social inequalities in health, health-related behaviours and health service usage (19). Inconsistent findings have been reported for patterns by prescribed medicines usage although this appears dependent on the policy context (9–12,15,20,21). The association for non-prescribed medicine utilisation appears clearer, with greater usage among individuals of higher social standing (9,11,14,21). However, there has been less investigation of the social determinants of over-the-counter medicine due to a lack of available data. Understanding differences in medicine utilisation is important in explaining the existence of social inequalities in health.” (page 5)
- We have also made reference to some of the work undertaken by Anita Wagner here: “There has also been some investigation of gender inequity in medication usage in low- and medium-income countries (17,18)” (page 5).

Introduction, page 4, line 48: pls. focus on the research about (demographic and) socio-economic factor related to medicine use, not to health service use in general

- We have reworded the entire paragraph in line with your suggestions so hopefully this is less an issue now (pages 4-5 – also see response to above comment).

Introduction, page 5, line 25: I strongly recommend rephrasing the objective and deleting the part ‘and health-related behaviours’ since this was not addressed in the study (also neither mentioned in the title nor the abstract)

- Given the recommendation from the other reviewer, and since health-related behaviours are part of our results (e.g. smoking, physical activity), we have made this clearer throughout the text and have added it to our title and abstract. So it should be less of an issue now (especially as we have no moved away from socio-economic status as the primary focus like you suggest).

Table 1: pls. check the data point ‘100’ related to contraception indicating the percentage of medicines prescribed for prescribed – should it read ‘0’?

- We have changed it to NA as this makes more sense than putting a 0 – good spot!

Walking: Though explained in the text, it is not clear in Tables 2-4 which denominators (per day, week, month) were used.

- We have included this in the Table now.

Reviewer: 2

Reviewer Name

Amy Heshmati

Institution and Country

Centre for Health Equity Studies (CHES)
Stockholm University/Karolinska Institutet
Sweden

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below

This manuscript on "Understanding the socio-economic factors that influence usage of prescribed and non-prescribed medicine using a large population cohort" is an interesting paper with a lot of promise. The paper would benefit considerably from polishing of the text before it is suitable for publication. At times the paper feels rushed and there have been many simple oversights.

I have some comments below:

A) Title

1. The title of the manuscript does not match the study. The title suggests many socio-economic factors influence the use of medicines, when in fact only one socio-economic variable is used in the study i.e. education.

- We have altered the title accordingly to reflect this point. It now reads "An investigation of social, demographic and health variations in the usage of prescribed and over-the-counter medicines within a large cohort (South Yorkshire, UK)" (page 1).

B) Abstract

1. Page 2, Line 13: The aim is not clearly defined. The reader gets a general overview of what the paper is about, but not what the authors' intentions are. Although it is just semantics, I would rewrite the aim to something along the lines of, "Our study objectives are to describe the social, demographic and health factors that influence the individual behaviour regarding medicine usage". That is of course, if this is your intended objective of the study.

- We have changed our stated aim in the abstract to read "Our study aims to understand how prescribed and over-the-counter medicine patterns vary by demographic, social and health characteristics within a large population cohort" (page 2) in line with your comment.

2. Page 2, Line 18: Move 'Negative binomial regression models were used to analyse the count of medicine usage' from Design to Measures.

- We have moved this line from Design to Measures as suggested (page 2).

3. Page 2, Line 31: State some of the 14 categories that the medicines were grouped into. Perhaps just the most common categories, such as cardiovascular disease, CNS pain, gastrointestinal, dietary supplements.

- We have added some examples of the categories to the abstract (page 2).

4. Page 2, Line 31: It states that you 'controlled for age, gender...' I did not see evidence that you

controlled for these variables in your analyses, but these were exposure variables. Please amend the text to ensure it is in line with your analyses.

- We have changed the text to “We included demographic (age, gender, ethnicity), social (education), health-related (body mass index, smoking, alcohol consumption, physical activity) factors and chronic health conditions (e.g. stroke, anxiety and heart disease) in our analyses.” (page 2).

5. Page 2, Line 33: It would be useful to state which exposure variables fall under your social, demographic and health factors. Health factors could be split into health-related behaviours and chronic health conditions. Again, it would be useful to list the more common chronic health conditions.

- We have altered the abstract in line with your comment. It now reads “We included demographic (age, gender, ethnicity), social (education), health-related (body mass index, smoking, alcohol consumption, physical activity) factors and chronic health conditions (e.g. stroke, anxiety and heart disease) in our analyses.” (page 2).

6. Page 2, Line 44: Not all health conditions were negative associated with non-prescribed medicines. From Table 2, only four health conditions were negatively associated with non-prescribed medicines. Please review this sentence.

- We have changed this sentence to read “Health conditions were found to be positively associated with prescribed medicine usage, but mixed in their associated to non-prescribed medicines.” (page 2)

7. Page 2, Line 47: ‘suggesting the importance of social factors in understanding behaviours’ is not suitable for the results section. On a side note, education is a predictor of occupation status and income, but it also captures human capital which influences health-related behaviours.

- We have removed this line from the abstract (page 3).
- We have also added your second comment about the role of education to the methods section (“Education also captures human capital which may influence health-related behaviours through greater cognitive ability to engage with health promotion resources.” page 7).

8. Page 2, Line 52: The authors state that ‘this study has provided a new understanding of multiple socio-economic factors that influence medicine usage’. This is a strongly worded and perhaps misleading statement considering only one socio-economic variable is used in the study.

- Agreed. We have changed this sentence and the entire part of the conclusions to “Our study addresses a dearth of evidence to provide new insights into how behaviours in medicine usage vary by demographic, social and health-related factors. Differences in over-the-counter medicine usage by educational attainment may help our understanding of the determinants of health inequalities.” (page 3) which better reflects the paper.

C) MeSH Keywords

1. Page 3, Line 6: Consider replacing ‘socioeconomic factors’ or adding ‘education’ to key words

- We have replaced ‘Socioeconomic Factors’ with ‘Education’ (page 3).

D) Introduction

1. Page 4, Line 51: The authors’ state that ‘ethnicity, health and weight status have also shown to be important’. In what way? Please elaborate.

- We have removed this line from the introduction (page 5)

2. Page 5, Line 23: The aims are not clearly defined to the reader. I can understand what you are trying to convey, but suggest the aim is rewritten to avoid ambiguity. Your aims in the main text should be the same as that in the Abstract. At the moment they somewhat differ.

- As described previously, we have changed our stated aim in the text to read “Our study aims to understand how prescribed and over-the-counter medicine patterns vary by demographic, social and health characteristics within a large population cohort” (page 6) in line with your comment. This now matches the aim in the abstract.

E) Methods

1. In the Introduction the authors use the term ‘over-the-counter’ medicine rather than ‘non-prescribed’ medicine. However throughout the rest of the manuscript including the title and Abstract, the term ‘non-prescribed’ medicine is used. Please be consistent in your terminology. I would suggest using ‘over-the-counter’ medicine rather than ‘non-prescribed’ as this is what non-prescribed medicines are called in clinical practice.

- We have changed all occurrences of ‘non-prescribed’ to ‘over-the-counter’ throughout the text (apart from the first mention in the abstract (page 2), strengths and limitations of the this study points (page 3), Tables 1-4, and manuscript (page 4) to make the link between the two terms clear.

2. In general it would be helpful for the reader if the explanatory variables were organised better. For example, the social factor is education...., The demographic factors were age, gender and ethnicity, etc. As mentioned above, I would split health related behaviours and chronic health conditions, and then list/explain the variable.

- We have reorganised the structure of the variables into the order that you suggest (pages 7 and 8).

3. Page 6, Line 23: describe your ethnicity variable.

- We have described this in our methods section (“Ethnicity was dichotomised into White or Non-White. We did not disaggregate the Non-White category further due to the lack of heterogeneity in the sample (i.e. 5.9% of the sample were Non-White).” Page 7)

4. Page 6, Line 44: Was smoking status just yes or no?

- We have described this variable in the methods section now (“Smoking status refers to whether an individual currently smokes or not.” Page 8)

5. Page 7, Line 32: 95% confidence intervals were also reported in tables. Suggest adding in text.

- We have added this in the text (“Incidence rate ratios (IRR) and their 95% Confidence Intervals (CIs) were reported.” Page 9).

6. Page 7, Line 40: Unsure if it is mandatory to cite what statistical package you used for your analyses. Consider adding this information to the Statistical Analysis section.

- We have now added this information (“All analyses were undertaken using STATA/SE 13.0.” page 9).

F) Results

1. For Tables 1-4, please state N in the table headings.

- These have all been added to the Tables.

2. For Tables 2-4, organise your variables into groups with subheadings. E.g. demographic factors, health related behaviour etc. This will enable the reader to read your results more easily.

- We have reorganised all the Tables as you have suggested.

3. For Tables 2-4, replace 'gender' with 'men'. At the moment you cannot ascertain which direction is for men or women when just looking at the tables.

- We have changed 'gender' to 'male' in all the Tables.

4. Tables 2-4, replace 'smoke' with 'smoking'.

- We have changed 'smoke' to 'smoker' in all the Tables since we feel this easier to read than 'smoking status' to be able to understand the direction of the results.

5. Page 7, Lines 49: what was the p-value for the difference in gender found to be taking any category of medicine? Was there a statistically significant difference in the mean number of medicines split by category or gender? State the p-values in Table 1 and where appropriate in text.

- Table 1 presents descriptive results and we do not perform any formal statistical testing here since we are just presenting summary statistics. Given that the recent debates over the (mis-) usage of p-values, we chose to avoid this here particularly given that they are supplied in the more formal models in Tables 2-4.

6. Page 7, Line 51: what was the proportion for prescribed medicines? State in text.

- We have stated the percentage for both males (49.3%) and females (62.2%) in the text as suggested (page 9).

7. Page 8, Line 31: replace 'greater' with 'stronger'.

- This has been changed as suggested (page 12).

8. Page 8, Lines 49-56: What are your p-values for heterogeneity for walking, physical exercise and education? State in table.

- We do not feel this is standard practice undertaken in similar analyses using this approach within the field. We state the p-values for each effect (in comparison to the reference category - referred to in the text as the significance level, but also now stated as p-value next to this), however the 95% confidence intervals are just as useful for understanding differences between groups as you suggest since you can observed the existence of overlap in effect sizes between categories. We feel this is more useful than additional analysis, and easier to interpret.

9. Do you adjust for education when analysing any of the demographic or health related behaviour variables?

- Our analyses are multivariate – so all of the variables were included in each model. We have made this clearer in the statistical analysis part of the methods section (“All explanatory variables were included in each multivariate model.” Page 9).

10. Page 8, Line 56: The authors’ state that education is negatively associated with total prescribed medicine, but no p-value for linear trend nor p-value for heterogeneity have been given. Please provide in the table and text if you are going to mention the direct of the associations.

- We have re-written the text to avoid any confusion in the interpretation of the results: “Higher education levels were each negatively associated with total prescribed medicine (in comparison to the ‘no qualification’ category), although the strength of each association was weak.” (Page 13).

11. Page 9, Lines 8-13: Description of the analysis should be in the methods under statistical analysis not in the results section.

- We have moved this to the methods section (“Only the most prevalent medicine types (a sample size greater than 10%; Table 1) were selected to avoid small sample size issues.” (page 9).

12. Page 9, Lines 17-28: Paragraph is vague and uninformative. Direct the reader to the most interesting findings. Please rewrite.

- We have rewritten this paragraph to emphasise more specific associations which build on the other results. The paragraph now reads “Tables 3 and 4 present the results from these analyses. There were fewer significant associations, however the results mostly followed the findings from Table 2 particularly for age, gender and education. We observed some large effect sizes for some chronic health conditions to medicines associated with treating the condition (e.g. cardiovascular medicine and individuals reporting high blood pressure (IRR = 4.205, 95% CIs = 3.995-4.425). These associations were not always immediately obvious, with depression strongly associated with CNS medicine (IRR = 5.088, 95% CIs = 4.695-5.514) and fatigue associated with dietary supplements (IRR = 2.273, 95% CIs = 1.877-2.752). Similar associations were not observed for chronic health conditions and over-the-counter medicines, although chronic pain was significantly positively associated with each medicine type apart from cardiovascular medicine. Some chronic health conditions were also negatively associated with medicine usage (e.g. diabetes and gastrointestinal medicine; IRR = 0.327, 95% CIs = 0.142-0.752).” (page 13).

G) Discussion

1. Page 9, Line 37: I think your wording is too strong with regards to the study showing important social and demographic variations in medicine usage at the population level. Gender appears to matter more for purchasing over the counter medicines than for prescribed medicines, likewise for education. The reader does not know enough about the ethnicity variable. The UK is now very multicultural, splitting this variable into just white and non-white is uninformative.

- We have toned down the wording of the paragraph, included your point about gender differences and tidied up the result of the paragraph to better reflect our findings. It now reads: “This study has demonstrated variations by demographic, social and health factors in prescribed and over-the-counter medicine usage within a large cohort.” (page 19).

- Information about the ethnicity variable (and our reason for splitting it as ‘White’ or ‘Non-White’) has been provided previously (“Ethnicity was dichotomised into White or Non-White. We did not disaggregate the Non-White category further due to the lack of heterogeneity in the sample (i.e. 5.9% of the sample were Non-White).” page 7). Splitting the variable further would not be useful due to the small sample size.

2. Page 10, Line 39: I do not think you can necessarily deduce that those with high level of educational attainment are of high socio-economic position. As mentioned earlier, while it is true that education is a predictor of occupation status and income, education attainment captures human capital which influences health-related behaviours. I would focus on education as an explanatory variable rather than using it as a proxy for socio-economic position. In doing so you could discuss educational attainment and health related behaviours (bmi, physical exercise, walking, smoking and alcohol consumption). It would be worthwhile to see if the associations with the health related behaviour variables were diminished after adjustment for education.

- We have rewritten the paragraph explaining the role of education in line with your suggestions: “While individuals of high education took fewer medications compared to individuals with no qualifications (Table 2), the effect size was only small and medicine usage was influenced more strongly by health status and age. In contrast, a distinct social gradient in over-the-counter medicine usage was observed. These findings support similar results found in other countries (11,21). At first instance this may appear unintuitive, since individuals of high education tend to have better health. Individuals of high education are associated with better employment prospects and higher incomes, and hence they will be in a better position to absorb the financial burden associated with purchasing additional medicines (9,11,21). Education also incorporates an individual's ability to cognitively understand the potential benefits of over-the-counter medicines, as well as effectively communicate health information to clinicians (38). Alternative explanations for the role of education may include: differences in compliance to treatment, inequalities in access to pharmacies, and variations in self-treatment behaviours (10,11). Evaluating the contribution of these potential pathways is important for future research to be able to address social inequalities in health behaviours.” (page 20).

- We have also rewritten the following paragraph about behaviours as well in line with your comment and to match the paragraph above: “The relationships for physical exercise, walking and smoking may also be explained similarly to that of the cognitive role of education. Individuals who exercise regularly or do not smoke have been shown to have greater health consciousness (39,40). Health consciousness may be captured through these variables in our analysis and it may be that these types of individuals also try to maximise their health using over-the-counter medicines. Given the association between high education and positive health-related behaviours throughout the literature (19), the role played by cognition appears important. This is contrary to the relationships with prescribed medicine where physical exercise is protective to health (35–37) and smoking damaging (31,33,34), independently influencing the need for prescribed medicine. However, the results for alcohol consumption only followed this pattern for prescribed medicine.” (page 21).

3. Page 11, Line 24: Consider using the term ‘minorities’ instead of non-White. The authors’ state that the finding with non-White was independent of socio-economic status. Did you stratify or adjust your results by education? I do not see these results. What was the evidence from the US which your research supports? Were these people healthier? Was it poorer access to health care? Please specify.

- We have decided to keep ‘non-White’ as opposed to ‘minorities’ as ‘non-White’ is clearer about what the variable is measuring (‘minorities’ could represent White minorities and this may introduce some confusion to the interpretation of our results).

- We did not stratify our results as you suggest, rather this was a wording issue as we meant that an association was observed even with education in our model. We have removed this sentence now as it is not required.

- We have also included a clearer description of how the results are similar to the US evidence (“Our results support evidence from the US which has found similar associations of lower medicine usage amongst non-White individuals (14,41).” Page 21).

- We (and the literature) are unsure why this association may exist in the context of our study, but I have expanded on the text to make suggestions for future research to follow (“However, there is little

understanding of why this this association exists and therefore further research should explore possible explanations including social factors, access to health care or cultural factors.” Page 21).

4. Suggest a concluding paragraph/summary at the end of the manuscript.

• We have added a final summary paragraph at the end of the discussion (“In summary, we find differences in prescribed and over-the-counter medicine usage by demographic, social and health characteristics. Education was an important factor in explaining variations in over-the-counter utilisation. With the NHS moving towards greater self-medication (both to empower patients and reduce costs), such an approach may have important implications for social inequalities in health and health-related behaviours.” Page 21).

VERSION 2 – REVIEW

REVIEWER	Sabine Vogler WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies, Health Economics Department, Gesundheit Österreich GmbH (GÖG / Austrian Public Health Institute) Asutria
REVIEW RETURNED	02-Jul-2016

GENERAL COMMENTS	<p>The authors took the comments and suggestions of the previous review on board. The article has thus improved, well-done. In principle, the paper can be published as it is. However, I suggest considering a few minor comments:</p> <p>1) Editorial comments</p> <p>Page 6, Line 3 in track change version: a bracket too much</p> <p>Page 6, Line 322 in track change version: last sentence of the Introduction needs to be repaired</p> <p>Page 9, Line 16 in track change version: 'were not applied .. subsequent analyses'</p> <p>Page 13, Line 23 in track change version: '... from these analyses' - this requires more clarity</p> <p>Page 13, Line 28 in track change version: not fully clear - do you mean prescribed medicines?</p> <p>Content:</p> <p>Page 20, Line 17 in track change version: ad the sentence ' -At first instance, this may appear unintuitive ...' why was this a surprise? We know from research that patients with a higher socio-economic status might even use OTC medicines instead of state-funded POM - in order to avoid waiting times at doctors. Please consider revisign - deleted the sentence and start the next one by stating 'Though individuals of hight education'</p>
-------------------------	--

REVIEWER	Amy Heshmati Centre for Health Equity Studies (CHESS) Stockholm University/Karolinska Institutet Sweden
REVIEW RETURNED	05-Jul-2016

GENERAL COMMENTS	Thank you to the authors for your response. The manuscript has improved considerably – the paper is now more focused and structured.
-------------------------	--

	<p>I do have a few minor comments:</p> <p>Abstract Page 2, Line 31: Thank you for putting some examples of medicine categories into the abstract, however I do question the term 'anti-infection' as a category. As noted in your methods you base your medicine categories on the BNF. In the BNF they use the term 'Infection'.</p> <p>Page 2, Line 49: grammatical note 'mixed in their associated to...' should be 'mixed in their association with...'</p> <p>Introduction Page 5, Lines 20 and 35: You have mentioned 'non-prescribed' medicine(s) twice. I am not sure if this is intentional as your comment started that "we have changed all occurrences of 'non-prescribed' to 'over-the-counter' throughout the text (apart from... manuscript (page 4)). Please review this.</p> <p>Methods Page 6, Lines 31-44: Diabetes is an endocrine disorder which also has its own category like oral contraceptives. Please state the rationale for doing so.</p> <p>Table 1 Page 9, Line 19: Similar to my first comment above, please review the medicine category names so that it is consistent with the BNF, though there may be instances where it's not applicable. Although this is a small detail, I think it would benefit the paper. EG. Gastro-intestinal system vs Gastrointestinal Cardiovascular system vs Cardiovascular Respiratory system vs Respiratory Infection vs Anti-infection Endocrine system Genito-urinary system Malignant disease vs Chemotherapy/immunosuppressant Musculoskeletal system</p> <p>Not in the BNF as a major category, but consider 'allergy' vs 'anti-allergy' – this would be consistent with the above categorisation.</p> <p>Results Page 11, Line 42: Stroke could also be included with diabetes, high blood pressure and heart disease.</p> <p>Page 12, Line 13: This sentence 'Tables 3 and 4 present the results from these analyses' is unclear. Please change to something like 'Tables 3 and 4 present the results of the negative binomial regression for prescribed and OTC medicines, respectively.'</p> <p>Page 12, Line 19: I would add 'prescribed' before medicines. Otherwise it is difficult to ascertain whether you are taking about prescribed or OTC medicines in this section.</p> <p>Page 12, Line 26: With regards to the IRR for the effect of depression with CNS, the IRR is 4.210 not 5.088 as written in text – that is the IRR for pain with CNS Pain medicine. Please review.</p> <p>Discussion</p>
--	--

	In your response to the reviewers you mentioned that you had 'included [my] point about gender differences...' I do not see where in the discussion you have mentioned gender. Did you intend to include something on gender in the discussion?
--	---

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1 (Sabine Vogler)

The authors took the comments and suggestions of the previous review on board. The article has thus improved, well-done.

In principle, the paper can be published as it is.

However, I suggest considering a few minor comments:

1) Editorial comments

Page 6, Line 3 in track change version: a bracket too much

- The second bracket is correct since it is a reference (which must be placed in brackets) within a bracketed part of the sentence. We have not changed this.

Page 6, Line 322 in track change version: last sentence of the Introduction needs to be repaired

- We have tidied up the sentence by removing the unnecessary detail from it to be clear on what we will do in the study. "We also disaggregate our analyses by medicine type" (page 6)

Page 9, Line 16 in track change version: 'were not applied .. subsequent analyses'

- We have made the sentence clearer "sample weights were not used in the regression models" (page 8).

Page 13, Line 23 in track change version: '... from these analyses' - this requires more clarity

- We have changed the sentence to "Tables 3 and 4 present the results of the negative binomial regression for prescribed and OTC medicines, respectively." (page 10).

Page 13, Line 28 in track change version: not fully clear - do you mean prescribed medicines?

- We have made it clear we were referring to prescribed medicines here "We observed some large effect sizes for some chronic health conditions to prescribed medicines associated with treating the condition (e.g. cardiovascular system medicine and individuals reporting high blood pressure (IRR = 4.205, 95% CIs = 3.995-4.425)." (page 12)

Content:

Page 20, Line 17 in track change version: ad the sentence ' -At first instance, this may appear unintuitive ...' why was this a surprise? We know from research that patients with a higher socio-economic status might even use OTC medicines instead of state-funded POM - in order to avoid waiting times at doctors. Please consider revising - deleted the sentence and start the next one by stating 'Though individuals of high education'

- We have removed the sentence as suggested and revised the following sentence to incorporate your comment about waiting times to flesh out the point "Individuals of high education are associated with better employment prospects and higher incomes, and hence they will be in a better position to

absorb the financial burden associated with purchasing additional medicines particularly if it allows them to avoid long waiting times to see their GP (9,11,21).” (page 19).

Reviewer: 2 (Amy Heshmati)

Thank you to the authors for your response. The manuscript has improved considerably – the paper is now more focused and structured.

I do have a few minor comments:

Abstract

Page 2, Line 31: Thank you for putting some examples of medicine categories into the abstract, however I do question the term ‘anti-infection’ as a category. As noted in your methods you base your medicine categories on the BNF. In the BNF they use the term ‘Infection’.

- We have changed the term in the abstract (page 2) in accordance with this point and the later point about terminology.

Page 2, Line 49: grammatical note ‘mixed in their associated to...’ should be ‘mixed in their association with...’

- We have made the required change (page 2).

Introduction

Page 5, Lines 20 and 35: You have mentioned ‘non-prescribed’ medicine(s) twice. I am not sure if this is intentional as your comment started that “we have changed all occurrences of ‘non-prescribed’ to ‘over-the-counter’ throughout the text (apart from... manuscript (page 4)). Please review this.

- Apologies for this – we missed them. We have now changed them both to ‘over-the-counter’ (page 5).

Methods

Page 6, Lines 31-44: Diabetes is an endocrine disorder which also has its own category like oral contraceptives. Please state the rationale for doing so.

- We have added our explanation in the text “We separated both oral contraceptives and diabetes medicine from other endocrine agents. Oral contraceptives were considered separately to be able to explore gender variations in endocrine system medicine use (16). Diabetes medicines were also separated due to their high prevalence and relative importance in public health decision making.” (page 6).

Table 1

Page 9, Line 19: Similar to my first comment above, please review the medicine category names so that it is consistent with the BNF, though there may be instances where it’s not applicable. Although this is a small detail, I think it would benefit the paper.

EG.

Gastro-intestinal system vs Gastrointestinal

Cardiovascular system vs Cardiovascular

Respiratory system vs Respiratory

Infection vs Anti-infection

Endocrine system

Genito-urinary system
Malignant disease vs Chemotherapy/immunosuppressant
Musculoskeletal system

Not in the BNF as a major category, but consider 'allergy' vs 'anti-allergy' – this would be consistent with the above categorisation.

- We have revised the categories as you suggest throughout the paper. The only one we did not alter was 'Chemotherapy/immunosuppressant' since we feel this is more useful than 'Malignant disease' as a descriptor even (if this is used in the BNF). We make a note of this difference in the text: "Names of groups follow the BNF other than 'Malignant disease' medication which we refer to as 'chemotherapy/immunosuppressant' as it is a more useful descriptor." (page 6).

Results

Page 11, Line 42: Stroke could also be included with diabetes, high blood pressure and heart disease.

- We swapped the order of 'Stroke' and 'Osteoarthritis' in each table in accordance with your comment.

Page 12, Line 13: This sentence 'Tables 3 and 4 present the results from these analyses' is unclear. Please change to something like 'Tables 3 and 4 present the results of the negative binomial regression for prescribed and OTC medicines, respectively.'

- We have added the sentence you suggest: "Tables 3 and 4 present the results of the negative binomial regression for prescribed and OTC medicines, respectively." (page 12).

Page 12, Line 19: I would add 'prescribed' before medicines. Otherwise it is difficult to ascertain whether you are taking about prescribed or OTC medicines in this section.

- We have rewritten the sentence and the one previous to it additionally to avoid any of these issues "Table 2 presents the results from the regression models exploring the association of our variables to the number of prescribed and over-the-counter medicines taken. Age was positively associated with both greater prescribed and over-the-counter medicine usage." (page 10).

Page 12, Line 26: With regards to the IRR for the effect of depression with CNS, the IRR is 4.210 not 5.088 as written in text – that is the IRR for pain with CNS Pain medicine. Please review.

- Apologies – we have changed this as you suggest (page 12).

Discussion

In your response to the reviewers you mentioned that you had 'included [my] point about gender differences...' I do not see where in the discussion you have mentioned gender. Did you intend to include something on gender in the discussion?

- We apologise for forgetting to add this. We have added a sentence at the start of the discussion to make the point now. "Gender was also important for the purchasing of both medicine type, although the effect size was larger for over-the-counter medicines." (page 18).

VERSION 3 – REVIEW

REVIEWER	Amy Heshmati
----------	--------------

	Centre for Health Equity Studies Stockholm University/Karolinska Institutet Sweden
REVIEW RETURNED	25-Aug-2016

GENERAL COMMENTS	<p>Thank you to the authors for your response. The manuscript is looking good, congratulations, and in my opinion the manuscript is ready to be published. However, I do have a few minor comments from the last resubmission:</p> <p>I had previously written: “Page 2, Line 49: grammatical note ‘mixed in their associated to...’ should be ‘mixed in their association with...’” The authors stated that they had ‘made the required change’, but no change has been made.</p> <p>I had previously written: “Page 11, Line 42: Stroke could also be included with diabetes, high blood pressure and heart disease.” The authors stated they had swapped the order of stroke and osteoarthritis in accordance to my comment. However, what I meant was that negative associations were also shown between stroke and OTC medicines, like diabetes etc. Apologies if this was not clear previously.</p> <p>I had previously written “Page 12, Line 13: This sentence ‘Tables 3 and 4 present the results from these analyses’ is unclear. Please change to something like ‘Tables 3 and 4 present the results of the negative binomial regression for prescribed and OTC medicines, respectively.’” The authors added the sentence including the abbreviation for over-the-counter that I had used to give an example, but the rest of the manuscript does not use this abbreviation. Please review.</p>
-------------------------	--

VERSION 3 – AUTHOR RESPONSE

Amy Heshmati

Thank you to the authors for your response. The manuscript is looking good, congratulations, and in my opinion the manuscript is ready to be published. However, I do have a few minor comments from the last resubmission:

I had previously written: “Page 2, Line 49: grammatical note ‘mixed in their associated to...’ should be ‘mixed in their association with...’” The authors stated that they had ‘made the required change’, but no change has been made.

- We made the change in the results section of the abstract (page 2) to “...but mixed in their association with...” as you suggested in the previous round of comments, so we are not sure why you have said the change has not been made.

I had previously written: “Page 11, Line 42: Stroke could also be included with diabetes, high blood pressure and heart disease.” The authors stated they had swapped the order of stroke and osteoarthritis in accordance to my comment. However, what I meant was that negative associations were also shown between stroke and OTC medicines, like diabetes etc. Apologies if this was not clear previously.

- We apologise for misunderstanding your comment. We have now included Stroke in the list of

negative associations (page 11).

I had previously written “Page 12, Line 13: This sentence ‘Tables 3 and 4 present the results from these analyses’ is unclear. Please change to something like ‘Tables 3 and 4 present the results of the negative binomial regression for prescribed and OTC medicines, respectively.’” The authors added the sentence including the abbreviation for over-the-counter that I had used to give an example, but the rest of the manuscript does not use this abbreviation. Please review.

- We have now changed the abbreviation (sorry that was lazy of us) from ‘OTC’ to ‘over-the-counter’ (page 12).