## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Factors associated with polypharmacy in primary care: A cross-sectional analysis of data from The English Longitudinal Study of Ageing (ELSA) |
| **AUTHORS** | Slater, Natasha; White, Simon; Venables, Rebecca; Frisher, Martin |

## VERSION 1 – REVIEW

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| **REVIEWER** | Maire O'Dwyer<br>School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin |
| **REVIEW RETURNED** | 11-Nov-2017 |

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| **GENERAL COMMENTS** | Thank for for the opportunity to review this interesting paper examining factors associated with polpharmacy and hyperpolypharmacy among older adults from the English Longitudinal Study on Ageing.<br><br>Specific comments are as follows:<br>Title: As this is a cross-sectional study in the title and throughout the paper I would recommend "Factors associated with polypharmacy" as opposed to "factors driving polypharmacy"<br>Introduction: In the definition of hyperpolypharmacy it would be useful to also include that this is also sometimes termed as "excessive polypharmacy"<br>The aim of the study is in the first paragraph of the introduction – this should be moved down to the end of the introduction.<br>Use of the terms chronic health conditions would be more appropriate than long-standing conditions.<br>In the second paragraph of the introduction I would recommend changing "independently associated with an increase in polypharmacy prevalence" to "significantly associated" as these old age and chronic health conditions are inter-related. This comment applies throughout.<br>Ethics: Please provide details of Ethical Approvals granted for the ELSA study and details as to how the authors accessed the data, including data protection.<br>Methods: Defining Polypharmacy: Please provide details as to how the medicines data was coded<br>Data Analysis: Please provide a sample size calculation for the multivariate models.<br>Results: Please provide details on missing data here and in the methods and the proportion of participants for whom medicines data was available for from Wave 6 of the study.<br>Table 1: Can the authors provide details of which long-standing conditions were more common and how many participants had multimorbidity? This would be a very important contributor to polypharmacy. |

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| | Page 6; Weak and positive correlations need to be defined in the methods.<br>Table 2 and 3: In the labelling for the tables the authors should state the sample size for each table.<br>Discussion: Please see my comments above about use of the words "driving polypharmacy" and "independently associated"<br>Can the authors provide more of an explanation as to why wealth in the UK would be significantly contributing to polypharmacy? |

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| **REVIEWER** | Nazanin Abolhassani<br>CHUV<br>Switzerland |
| **REVIEW RETURNED** | 17-Nov-2017 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review this manuscript.<br>1. When refering to defenition of polypharmacy and hyper polypharmacy by numbers, it is as 5-9 for polypharmacy and >10 for hyper polypharmacy (eg.P 2 line 8; p 4 line 4...) , it means that taking 10 medicines is not covered in these two categories! Please add equal or more than 10 medicines for hyper polypharmacy.<br>2. For long-standing illness, the duaration of "over a period of time" is not clear for me!<br>3. Duration of taking prescribed medicines was not mentioned, i.e if one prescribed medicines were taken only once , was included or not.<br>4. In the limitation , it is worth to mention the issue of underestimation of polypharmacy not only for OTC medicines, but also for those medicines which are combinations of active substances. And also, data of medicines were self reported and still at risk of recall bias.<br>4. Regarding the increase in polypharmacy and hyper polypharmacy at the oldest age group, it is worth that authors include the below article into the discussion. As in some studies reate of increase in polypharmacy and hyper polypharmacy decreased at the oldest age group (although these studies were mainly conducted among frail oldest people).<br>Tjia J, Velten SJ, Parsons C, et al. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging 2013;30(5):285-307 |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

We would like to take this opportunity to thank you for reviewing our manuscript. Our responses to your specific comments are detailed below.

-Title: As this is a cross-sectional study in the title and throughout the paper I would recommend "Factors associated with polypharmacy" as opposed to "factors driving polypharmacy"

Our response:The title of our manuscript has been changed to "Factors associated with polypharmacy in primary care: A cross-sectional analysis of data from The English Longitudinal Study of Ageing (ELSA)".

-Introduction: In the definition of hyperpolypharmacy it would be useful to also include that this is also sometimes termed as "excessive polypharmacy"

Our response: Our definition of hyper-polypharmacy has been amended to "At present, polypharmacy is commonly defined as "the use of five or more regular medications", whilst hyper-polypharmacy, which is sometimes termed as "excessive polypharmacy", is defined as "the use of ten or more regular medications".

-The aim of the study is in the first paragraph of the introduction – this should be moved down to the end of the introduction.
Our response:The aim of the study has now been moved to the last paragraph of the introduction

-Use of the terms chronic health conditions would be more appropriate than long-standing conditions.
Our response: Throughout the manuscript, the term "long-standing conditions" has been replaced with "chronic health conditions." Please see tracked changes in the manuscript.

-In the second paragraph of the introduction I would recommend changing "independently associated with an increase in polypharmacy prevalence" to "significantly associated" as these old age and chronic health conditions are inter-related. This comment applies throughout.
Our response: Throughout the manuscript, the term "independently associated" has been changed to "significantly associated". Please see tracked changes in the manuscript.

-Ethics: Please provide details of Ethical Approvals granted for the ELSA study and details as to how the authors accessed the data, including data protection.
Our response: Our ethics statement has been modified to "Ethical approval for ELSA Wave 6 was granted from the National Research Ethics Committee under the National Research and Ethics Service (NRES). Participants gave informed written consent to participate in the study. [12] All ELSA data is anonymous and freely accessible from the UK Data Service Discover. [13] Only data contained within the ELSA database was included in the analyses. No patients were involved in the development of the research question, study design or interpretation of the data in this study; therefore, ethical approval was not required for this study."

-Methods: Defining Polypharmacy: Please provide details as to how the medicines data was coded
Our response: The following sentence has been added to the methods section: "A maximum of 27 prescribed medications could be recorded for each participant. Medication information was coded by the nurse, according to the British National Formulary (Edition 61) chapter and subsection." Further information about drug coding in ELSA appears in the discussion section.

-Data Analysis: Please provide a sample size calculation for the multivariate models.
Our response: Using the following formula N=10k/p (Peduzzi et al), where k is the number of covariates and p is the smallest proportion of positive or negative cases. "the minimum sample size required for the first multivariate model (polypharmacy) was 333; whilst the minimum sample size required for the second multivariate model (hyper-polypharmacy) was 1250". This information has been added to the data analysis section.

-Results: Please provide details on missing data here and in the methods and the proportion of participants for whom medicines data was available for from Wave 6 of the study.
Our response: A statement regarding missing data has been included in the data analysis section of the methods and missing data figures have been presented as a separate category in the multivariate analysis models.
The following statement has been added into the sample and participants section "In Wave 6, information from 10,601 participants was collected, which included 9,169 'core' participants. Members were considered 'core' if they were aged over 50 years old at the time of study enrollment and living at private residential addresses in England.

[11] 8,054 nurse visits were completed at Wave 6, of whom 7,730 were carried out with core members. This latter group are the focus of the current study. [11]

-Table 1: Can the authors provide details of which long-standing conditions were more common and how many participants had multimorbidity? This would be a very important contributor to polypharmacy.
Our response: In this study, we controlled for self-rated health and the presence of chronic conditions. To determine the latter, the following question from ELSA was analysed "[^Do you / Does [^name]] have any long-standing illness, disability or infirmity? By long-standing I mean anything that has troubled [^you / [^name]] over a period of time, or that is likely to affect [^you / [^name]] over a period of time." Participants could respond with either yes or no. This study examined categories of polypharmacy predictors, rather than examining specific chronic conditions. Our findings show that chronic conditions are associated with polypharmacy and hyper-polypharmacy in primary care. The research team intend to explore this finding in more detail. Future work will aim to identify which types of chronic conditions are most commonly associated with polypharmacy, whilst also identifying the combinations of chronic conditions (multi-morbidities) which are most commonly associated with polypharmacy, using ELSA data.

-Page 6; Weak and positive correlations need to be defined in the methods.
Our response: Our Pearson correlation coefficient values have now been defined in the methods section "Findings were presented as Pearson correlation coefficients (r). The strength of each correlation was considered and described as either strong (1.00 – 0.50), moderate (0.49-0.30) or weak (0.29-0.10).[20]"

-Table 2 and 3: In the labelling for the tables the authors should state the sample size for each table.
Our response: N values have been added to both tables

-Discussion: Please see my comments above about use of the words "driving polypharmacy" and "independently associated"
Our response: We have removed the term "driving" throughout the manuscript and replaced it with "associated with" Please see tracked changes in the manuscript.

-Can the authors provide more of an explanation as to why wealth in the UK would be significantly contributing to polypharmacy?
Our response: We briefly discussed the issue of UK wealth inequalities in the original manuscript; however, this discussion has been supplemented with information regarding chronic health conditions and their association with lower wealth. Please refer to paragraph 2 in the discussion to see tracked changes.

Reviewer: 2
We would like to take this opportunity to thank you for reviewing our manuscript. Our responses to your specific comments are detailed below.

- When refering to defenition of polypharmacy and hyper polypharmacy by numbers, it is as 5-9 for polypharmacy and >10 for hyper polypharmacy (eg.P 2 line 8; p 4 line 4...) , it means that taking 10 medicines is not covered in these two categories! Please add equal or more than 10 medicines for hyper polypharmacy.
Our response: Thank you for identifying this issue. We have removed ">10 medicines" throughout the manuscript and replaced it with "≥10 medicines" Please see tracked changes in the manuscript.

-For long-standing illness, the duaration of "over a period of time" is not clear for me!

Our response:This statement was taken directly from the ELSA Wave 6 nurse questionnaire; however, to avoid any ambiguity, the description of a long-standing illness has been removed from our manuscript.

-Duration of taking prescribed medicines was not mentioned, i.e if one prescribed medicines were taken only once , was included or not.
Our response: Details about medication duration, from the ELSA nurse questionnaire have been added to the manuscript ". The nurse determined current medication usage by asking the participant to confirm whether they had taken or used each reported medicine within the last seven days."

-In the limitation , it is worth to mention the issue of underestimation of polypharmacy not only for OTC medicines, but also for those medicines which are combinations of active substances. And also, data of medicines were self reported and still at risk of recall bias.
Our response:Our limitation paragraph in the discussion has been modified to include the important points that you raised. Please see tracked changes in the manuscript.

-Regarding the increase in polypharmacy and hyper polypharmacy at the oldest age group, it is worth that authors include the below article into the discussion. As in some studies reate of increase in polypharmacy and hyper polypharmacy decreased at the oldest age group (although these studies were mainly conducted among frail oldest people).
Tjia J, Velten SJ, Parsons C, et al. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging 2013;30(5):285-307
Our response:Thank you for bringing this article to our attention. Several studies, included in the systematic review, reported polypharmacy in older individuals; therefore, we have included this article within our discussion.

All changes made to the manuscript are shown as tracked changes.
We hope the revised manuscript is now suitable for publication in the BMJ Open and look forward to hearing from you in due course.

Yours sincerely
Natasha Slater, Martin Frisher, Rebecca Venables, Simon White

**VERSION 2 – REVIEW**

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| **REVIEWER** | Maire O'Dwyer<br>School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin |
| **REVIEW RETURNED** | 15-Jan-2018 |

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| **GENERAL COMMENTS** | Thank you for these revisions. Most of the comments outlined in the previous review have been addressed sufficiently by the authors. I have two remaining comments.<br>1. Can the authors confirm if all 7730 "core participants" had available medicines data, and was there any missing medicines data here among these core participants?<br>2. The limitations should include an acknowledgment that associations with multi morbidity and specific chronic health conditions were not examined in this study. |

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| **REVIEWER** | Nazanin Abolhassani<br>Lausanne university hospital (CHUV), Switzerland |

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| **REVIEW RETURNED** | 03-Jan-2018 |

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| **GENERAL COMMENTS** | Thank you for accurate revision |

## VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1:
Thank you for reviewing our manuscript. We have addressed your two additional comments. Please see our responses below.

1. Can the authors confirm if all 7730 "core participants" had available medicines data, and was there any missing medicines data here among these core participants?

Our response: We can confirm that all "core" participants (n=7730) provided a response to the following question: “Are they taking or using any medicines, pills, syrups, ointments, puffers or injections prescribed for them by a doctor or a nurse?”. The nurse interviewer coded each participant’s response; however, there were 5 cases where the nurse couldn't code the data, because the name of the drug was not available in the coding system. Table 1 has been amended to reflect the 5 missing cases.

2. The limitations should include an acknowledgment that associations with multi morbidity and specific chronic health conditions were not examined in this study.

Our response: The final paragraph of the discussion has been altered to incorporate this acknowledgement. Please see the tracked changes in the manuscript.