## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Polypharmacy among Patients with Diabetes: A Cross-Sectional Retrospective Study in a Tertiary Hospital in Saudi Arabia |
| **AUTHORS** | Alwhaibi, Monira; Balkhi, Bander; Alhawassi, Tariq; Alkofide, Hadeel; Alduhaim, Nouf; Alabdulaali, Rawan; drweesh, hadeel; Sambamoorthi, Usha |

## VERSION 1 – REVIEW

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| **REVIEWER** | Bik-Wai Bilvick Tai<br>Caritas Institute of Higher Education, Hong Kong |
| **REVIEW RETURNED** | 03-Jan-2018 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review this manuscript. This manuscript describes a cross-sectional study that examined the phenomenon of polypharmacy in diabetic patients conducted in Saudi Arabia. In general, this manuscript is well-structured with specific subheadings. The transition of thoughts runs smoothly that is easy to read and review. The background section provides a quick overview of what is known in the literature, and the study rationale that corresponds to the existing knowledge gap. However, providing more specifics and expanding in different sections with clarifications are opportunities for this manuscript before it can be considered for publication.<br><br>Each section and subheading in the manuscript has been reviewed with my comments and suggestions listed below:<br><br>Title:<br>1. “Polypharmacy” describes a phenomenon in which multiples medications are used. Therefore the word “use” is considered redundant after the word “polypharmacy”. This concern also appears throughout the manuscript.<br><br>Abstract:<br>1. P.2 Line 5-6: “Polypharmacy” is most often defined based on the number of medications regardless of the medication class. Therefore when the authors mentioned “use of multiple classes of medications”, it can be confusing to the readers. Please clarify. (Ref: Masnoon N et al. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017; 17: 230.)<br>2. P.2 Line 50: The use of word “tablet-counts” may not be the most suitable since medications are available in different dosage forms. Please revise.<br><br>Introduction:<br>1. P.4 Line 19: The authors mentioned “renal disease” is a chronic |

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| | health condition that often exists in diabetic patients and requires multiple medications for treatment. This study however only examined cardiovascular, musculoskeletal, respiratory, and mental health conditions, but not “renal disease”. Please also refer to P.7 “Independent variable” subheading in the “methods” section, and provide justification.<br>2. P.4 Line 35: Any reference(s) for “adverse drug events” and “drug-drug interactions”?<br>3. P.4 Line 56: Any reference(s) for “diabetes complications”?<br>4. Authors are advised to name several countries in which studies were also conducted to examine the 1) prevalence of and 2) factors associated with polypharmacy in diabetic patients.<br><br>Methods:<br>1. P.5: under “study design”, authors are recommended to briefly provide more information about the hospital, e.g. the name, number of beds, and the geographical location in Saudi Arabia.<br>2. P.5 Line 41: authors please mention the institution(s) that provided the IRB approval to conduct the study.<br>3. P.6 Line 5-8: “Polypharmacy” generally refers to all medications in the prescription and non-prescription/OTC medications categories in the literature. In this study, however, only the prescription drug file of the patient was examined. Please justify.<br>4. P.6 Line 50-51, in addition to the numerical definition of polypharmacy, please also include the categories of medications in the definition.<br>5. P.6 Line 41: please refer to the comment for “title”.<br>6. P.6 Line 55 and P.7 Line 5: please refer to the first comment for “abstract”.<br>7. P.7 Line 26: “stroke” is mentioned in the text but not included in Appendix I. Was it included in data analysis?<br>8. Please specify how each independent and dependent variable was treated (e.g. as continuous or categorical variable) in data analysis.<br><br>Results:<br>1. Perhaps the most surprising thing to note in this manuscript is that the authors did not report the number of medications as continuous variable (i.e. average, SD, range) in the study population. This information is considered the most important in study of this kind, yet it is missing in this manuscript. Authors are advised to report the number of medications used in the 1) overall sample, 2) polypharmacy patients, and 3) non-polypharmacy patients.<br>2. In addition, reporting of the therapeutic classes of the medications is also important in study of this kind, yet this manuscript does not mention anything about it. Authors are advised to report the most prevalent therapeutic classes used by the patients in this study. Common classification systems used for this purpose include the ATC classification system (http://apps.who.int/medicinedocs/en/d/Js4876e/6.2.html#Js4876e.6.2), or authors can use other appropriate classification system of medications at their discretion.<br>3. P.8 Line 4: please clarify there were 8,932 or 8,832 patients in this study.<br>4. P.8 Line 11: authors only listed 2 health conditions (hypertension and dyslipidemia). Several more examples should be provided.<br>5. P.8 Line 22: would age over 60 years be considered elderly? What is the cut-off in Saudi Arabia? Please clarify.<br>6. P.8 Line 33-40: please report the p-values. |

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| | 7. Please include the study finding on nationality in the result section since it is included in the method section.<br>8. Authors are advised to briefly compare and contrast the difference in study findings between polypharmacy and non-polypharmacy patients. In addition, it would be helpful to report any patients with “hyperpolypharmacy” (those taking 10 or more medications)? (Reference: Nishtala PS, Salahudeen MS. Temporal Trends in Polypharmacy and Hyperpolypharmacy in Older New Zealanders over a 9-Year Period: 2005–2013. Gerontology. 2015;61(3):195-202.)<br><br>Discussion:<br>1. P.10 Line 40-45: the authors used a term “cardiometabolic condition”, but this does not belong to the 4 types of chronic conditions (cardiovascular, musculoskeletal, respiratory, and mental health) mentioned by the authors earlier in the methods and results sections. Please clarify.<br>2. P.11 Line 24-26: “People with the end of life care were included and this may have overestimated the rate of polypharmacy.” Please provide reference in the literature to support this statement.<br>3. Please comment on the generalizability of the study results in other practice settings, if applicable (e.g. clinics).<br>4. Please include any future research study direction.<br>5. Please revise based on the revisions made in the previous sections.<br><br>Ethics and data confidentiality:<br>1. Please write out the full name of “MRN”.<br><br>Appendix I:<br>1. Please clarify if “Diabetes” is categorized under “Cardiovascular conditions”.<br>2. Please check throughout the manuscript if the term “hyperlipidemia” or “dyslipidemia” should be used with reference to ICD and SNOMED. |

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| **REVIEWER** | Jesús Díez-Manglano<br>Hospital Universitario Miguel Servet<br>Zaragoza, Spain |
| **REVIEW RETURNED** | 14-Jan-2018 |

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| **GENERAL COMMENTS** | Manuscript ID: bmjopen-2017-020852<br>Title: Poypharmacy use among patients with diabetes: a cross-sectional retrospective study<br><br>GENERAL COMMENTS:<br>Alwhaibi et al have performed an interesting study. The objectives of the study are clearly defined. The main concerns are the design of the study and the clinical relevancy of results. I think the paper should better be submitted to a local journal in Arabia.<br><br>SPECIFIC COMMENTS<br><br>Methods<br>• Study population<br>All patients were included from the outpatient clinic of a tertiary teaching hospital. This was a selection bias ¿or perhaps severity |

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| | bias? Patients with diabetes who visit a hospital, and not a primary care office, presumably suffer a more severe diabetes and need more drugs. Authors do not comment anything about it.<br><br>• Dependent variable<br>The most accepted definition of polypharmacy is the concurrent use of five or more drugs. The authors define polypharmacy as the cumulative use of five or more medication classes during a one year period. This definition explains the results and the high prevalence of polypharmacy. A young diabetic woman, who uses contraceptive pills and/or anti-inflammatory drugs during her menstruation, will be surely a patient with polypharmacy. Is this relevant?<br><br>Results<br>• The final number of patients included was 8,932 (abstract) or 8,832 (first line of results)?<br>• Second paragraph: 77.9% of adults with diabetes were using (concurrent) or have used (cumulative) five or more drugs?<br>• I´m curious about the medication classes that used the patients. The authors must give data about<br>• Logistic regression. I recommend re-write the paragraph. I prefer "Cardiovascular disease, or mental condition was associated with polypharmacy".<br>• There is no data about Charlson index<br>• Table 1 is unnecessary. Data can be included in table 2<br>• P value <0.001 is better than 0.000<br>• Please explain the disbalance men-women<br>• What was the mean age of patients?<br>• Appendix I. The peripheral arterial disease was forgotten<br><br>Discussion<br>• It is brief and poor<br><br>Conclusion<br>The second and third sentences are not justified by results<br><br>References<br>• Reference 1 is incomplete. |

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| **REVIEWER** | Pedro Marques-Vidal<br>Lausanne university hospital<br>Switzerland |
| **REVIEW RETURNED** | 22-Jan-2018 |

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| **GENERAL COMMENTS** | The authors assessed the prevalence of polypharmacy (5+ drugs) in a sample of patients with diabetes. They conclude that polypharmacy is common among patients with diabetes, and that polypharmacy increases with age and presence of several comorbidities.<br><br>The paper is important from a public health perspective, at it shows the growing importance of adequately managing polypharmacy among patients with diabetes.<br><br>**Major issues**<br><br>1. Abstract: the methods could be reduced to provide more |

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| | space for the results. The sentence on statistical methods could be deleted and more information on the factors associated with polypharmacy could be provided in the results.<br>2. Methods: are the three classifications of diseases (ICD-9, ICD-10 and SNOMED) used in the same hospital? How were non-matching codes handled?<br>3. Methods: the authors indicate that 91% of the patients had complete data and 85% had complete medication-related information. How were the 9% of patients with incomplete data (and the 15% with incomplete medication-related information) managed? Were they excluded (but seems not as the authors state page 6 line 32 that no exclusion criteria were applied) or did the authors perform some multiple imputation to complete the missing data?<br>4. Methods: a large fraction (43.3%) of the patients were aged over 60. The authors could stratify this large age group into smaller categories to check if polypharmacy continues to increase after 60 or tends to lever.<br>5. Results: the odds ratios for each selected comorbidity (i.e. cardiovascular, musculoskeletal, respiratory and mental diseases) considerably overlap, suggesting that it is the number of comorbidities present that is associated with polypharmacy rather than the type of comorbidity. The authors could run a model including the total number of comorbidities plus each comorbidity type to check this assumption.<br>6. Results, tables 2 and 3: there is no need to provide the p-values and the asterisks simultaneously; only the p-value is enough. Please note that p-values of zero are impossible, as they correspond to an infinite value of the test. P-values of 0.000 should be replaced by "<0.001".<br><br>**Minor issues**<br><br>1. Results, page, 8, second line from the end: the value 54.7% relates to NO cardiovascular comorbidity. Overall, it would be better that the authors do not replicate the results of the tables in the text.<br>2. Results, table 1: the authors can reduce size by providing the values/percentages only for the "yes" rows, as the "no" can be derived by simple subtraction.<br>3. Results, table 3: please delete rows "No (ref)" and indicate in the table that the odds ratios are for the presence of the condition, i.e. "Female vs. male", "Non-Saudi vs. Saudi", "Cardiovascular yes vs. no".<br>4. Discussion: the authors could use some subtitles (at least the "strengths and limitations" one) to structure the discussion.<br>5. References: reference 1 seems incomplete. Is reference 1 a book, a report… Would it be possible for the authors to provide a doi or an URL?<br>6. References: reference 10 is rather old (20 years). If possible, provide a more recent one. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author
Reviewer# 1

Thank you for the opportunity to review this manuscript. This manuscript describes a cross-sectional study that examined the phenomenon of polypharmacy in diabetic patients conducted in Saudi Arabia. In general, this manuscript is well-structured with specific subheadings. The transition of thoughts runs smoothly that is easy to read and review. The background section provides a quick overview of what is known in the literature, and the study rationale that corresponds to the existing knowledge gap. However, providing more specifics and expanding in different sections with clarifications are opportunities for this manuscript before it can be considered for publication.

Each section and subheading in the manuscript has been reviewed with my comments and suggestions listed below:

Title
Comment # 1: "Polypharmacy" describes a phenomenon in which multiples medications are used. Therefore the word "use" is considered redundant after the word "polypharmacy". This concern also appears throughout the manuscript.

Response: Thank you for this suggestion. Now, we have removed the word "use" that comes after the word "polypharmacy" from the manuscript.

Abstract
Comment # 1: P.2 Line 5-6: "Polypharmacy" is most often defined based on the number of medications regardless of the medication class. Therefore when the authors mentioned "use of multiple classes of medications", it can be confusing to the readers. Please clarify. (Ref: Masnoon N et al. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017; 17: 230.)
Response: Thank you for pointing this out, we totally agree with the reviewer. Now, we have removed the word "class" from polypharmacy definition and throughout the manuscript.

Comment # 2: P.2 Line 50: The use of word "tablet-counts" may not be the most suitable since medications are available in different dosage forms. Please revise.

Response: The word "tablet-counts" is now replaced by "medications"

Introduction
Comment # 1: P.4 Line 19: The authors mentioned "renal disease" is a chronic health condition that often exists in diabetic patients and requires multiple medications for treatment. This study however only examined cardiovascular, musculoskeletal, respiratory, and mental health conditions, but not "renal disease". Please also refer to P.7 "Independent variable" subheading in the "methods" section, and provide justification.
Response: Thank you for this comment. In fact, we have identified the rate of chronic kidney disease and now we have added this variable to the text in the "results" section and table # 1.

Comment # 2: P.4 Line 35: Any reference(s) for "adverse drug events" and "drug-drug interactions"?
Response: Now we have added the corresponding references (Reference # 12,13,14).

Comment # 3: P.4 Line 56: Any reference(s) for “diabetes complications”?
Response: Now we have added the corresponding reference (Reference # 10).

Comment # 4: Authors are advised to name several countries in which studies were also conducted to examine the 1) prevalence of and 2) factors associated with polypharmacy in diabetic patients.

Response: Now we have named several counties that examine the prevalence of polypharmacy with diabetes (page #4, paragraph #1)

Methods
Comment # 1: P.5: under “study design”, authors are recommended to briefly provide more information about the hospital, e.g. the name, number of beds, and the geographical location in Saudi Arabia.
Response: Change has been made (Page#5, under “study design”)

Comment # 2: P.5 Line 41: authors please mention the institution(s) that provided the IRB approval to conduct the study.
Response: Now, we have added the institute that provided the IRB approval

Comment # 3: P.6 Line 5-8: “Polypharmacy” generally refers to all medications in the prescription and non-prescription/OTC medications categories in the literature. In this study, however, only the prescription drug file of the patient was examined. Please justify.
Response: The polypharmacy in our definition included both the prescription and the OTC medications, for example, pain-relieving medications such as Ibuprofen is an OTC and was included in our definition. Now, we have added the following sentence to clarify the medications included in the definition “We have included all the prescription and the non-prescription/OTC medications categories in our definition” (Page # 7).

Comment # 4: P.6 Line 50-51, in addition to the numerical definition of polypharmacy, please also include the categories of medications in the definition.
Response: All the medication categories have been considered when we defined the polypharmacy. As there is not enough space to mention all of them in the text, now we have included Table 2 of the most prevalent medication category used.

Comment # 5: P.6 Line 41: please refer to the comment for “title”.
Response: Change has been made.

Comment # 6: P.6 Line 55 and P.7 Line 5: please refer to the first comment for “abstract”.
Response: Change has been made.

Comment # 7: P.7 Line 26: “stroke” is mentioned in the text but not included in Appendix I. Was it included in data analysis?
Response: Thanks. Now, we have included it in Appendix I.

Comment # 8: Please specify how each independent and dependent variable was treated (e.g. as continuous or categorical variable) in data analysis.

Response: We have added the following sentence to the statistical analysis to clarify this point: “Frequency and percentage were used to describe the categorical variables (age, sex, marital status, nationality, co-existing chronic conditions, and polypharmacy) Mean and Standard deviation were used to describe continuous variables.” (Page # 8)

Results

Comment # 1: Perhaps the most surprising thing to note in this manuscript is that the authors did not report the number of medications as continuous variable (i.e. average, SD, range) in the study population. This information is considered the most important in study of this kind, yet it is missing in this manuscript. Authors are advised to report the number of medications used in the 1) overall sample, 2) polypharmacy patients, and 3) non-polypharmacy patients.

Response: Thank you for raising this point. Now we have included the mean (SD) of polypharmacy in overall sample and polypharmacy groups in Table # 1

Comment # 2: In addition, reporting of the therapeutic classes of the medications is also important in study of this kind, yet this manuscript does not mention anything about it. Authors are advised to report the most prevalent therapeutic classes used by the patients in this study. Common classification systems used for this purpose include the ATC classification system (http://apps.who.int/medicinedocs/en/d/Js4876e/6.2.html#Js4876e.6.2), or authors can use other appropriate classification system of medications at their discretion.

Response: Thank you for this important suggestion. Now we have mentioned the prevalent therapeutic classes used by the patients in this study in Table 2.

Comment # 3: P.8 Line 4: please clarify there were 8,932 or 8,832 patients in this study.

Response: This was a typo error; the study population was 8,932 diabetic patients.

Comment # 4: P.8 Line 11: authors only listed 2 health conditions (hypertension and dyslipidemia). Several more examples should be provided.

Response: Thank you for this suggestion; now we have added asthma, osteoarthritis, and anxiety to the list of the common coexisting chronic conditions.

Comment # 5: P.8 Line 22: would age over 60 years be considered elderly? What is the cut-off in Saudi Arabia? Please clarify.

Response: There is no consensus on the cut-off point to define elderly, some studies consider elderly those with 65 years and above and other consider 60 years and above as elderly. We have used the World Health Organization and the Saudi Census cut-off point to define elderly (60 years and above).

Reference: 1. Khoja AT, Aljawadi MH, Al-Shammari SA, et al. The health of Saudi older adults; results from the Saudi National Survey for Elderly Health (SNSEH) 2006–2015. Saudi Pharmaceutical Journal. 2017.

2. World Health Organization, http://apps.who.int/iris/bitstream/10665/170250/1/9789240694439_eng.pdf?ua=1&

Comment # 6: P.8 Line 33-40: please report the p-values.

Response: Now, we have reported the p-values

Comment # 7: Please include the study finding on nationality in the result section since it is included in the method section.

Response: Now, we have included the study finding on the nationality (Page # 8, Paragraph # 3).

Comment # 8: Authors are advised to briefly compare and contrast the difference in study findings between polypharmacy and non-polypharmacy patients. In addition, it would be helpful to report any patients with “hyperpolypharmacy” (those taking 10 or more medications)? (Reference: Nishtala PS, Salahudeen MS. Temporal Trends in Polypharmacy and Hyperpolypharmacy in Older New Zealanders over a 9-Year Period: 2005–2013. Gerontology. 2015;61(3):195-202.)

Response: We thank the reviewer for this suggestion. The rate of hyperpolypharmacy reported below is now included in the manuscript (Page # 8, Paragraph # 2)

| | | N | % |
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| Hyperpolypharmacy | >=10 Medications | 1501 | 17.2 |
| Polypharmacy | 5-9 Medications | 4680 | 53.6 |
| No Polypharmacy | 0-4 Medications | 2551 | 29.2 |

Discussion

Comment # 1: P.10 Line 40-45: the authors used a term “cardiometabolic condition”, but this does not belong to the 4 types of chronic conditions (cardiovascular, musculoskeletal, respiratory, and mental health) mentioned by the authors earlier in the methods and results sections. Please clarify.
Response: Thank you for pointing this out. Now, we have removed it and called it cluster of diseases rather than cardiometabolic conditions”. Now, the paragraph read as :” we found a high rate of polypharmacy among adults with diabetes with disease cluster (diabetes and cardiovascular disease) as compared to adults without cluster of diseases which is consistent with the published literature among the elderly with disease cluster”

Comment # 2: P.11 Line 24-26: “People with the end of life care were included and this may have overestimated the rate of polypharmacy.” Please provide reference in the literature to support this statement.
Response: As per the reviewer suggestion, we have included the following reference from the literature to support this statement in the manuscript (Reference # 41: Maddison AR, Fisher J, Johnston G. Preventive medication use among persons with limited life expectancy. Progress in palliative care. 2011;19(1):15-21.).

Comment # 3: Please comment on the generalizability of the study results in other practice settings, if applicable (e.g. clinics).
Response: Thank you for pointing this out. Now we have included the following sentence with the study limitations “the study was conducted in a tertiary hospital in Riyadh; therefore the findings from this study cannot be generalized to primary care settings or to other regions in Saudi Arabia” (Page # 12, Paragraph # 1)

Comment # 4: Please include any future research study direction.
Response: We thank the reviewer for this suggestion. The future research study direction is now included in the manuscript (Page # 12, Paragraph # 2)
Comment # 5: Please revise based on the revisions made in the previous sections.

Ethics and data confidentiality

Comment # 1: Please write out the full name of “MRN”.
Response: suggestion has been made.

Appendix I

Comment # 1: Please clarify if “Diabetes” is categorized under “Cardiovascular conditions”.
Response: Diabetes was not categorized under cardiovascular conditions, now we have corrected the Appendix.

Comment # 2: Please check throughout the manuscript if the term “hyperlipidemia” or “dyslipidemia” should be used with reference to ICD and SNOMED.

Response: This was a typo mistake; hyperlipidemia term is now replaced by dyslipidemia.

Reviewer#2

GENERAL COMMENTS

Alwhaibi et al have performed an interesting study. The objectives of the study are clearly defined. The main concerns are the design of the study and the clinical relevancy of results. I think the paper should better be submitted to a local journal in Arabia.

SPECIFIC COMMENTS

Methods

Comment # 1: Study population
All patients were included from the outpatient clinic of a tertiary teaching hospital. This was a selection bias ¿or perhaps severity bias? Patients with diabetes who visit a hospital, and not a primary care office, presumably suffer a more severe diabetes and need more drugs. Authors do not comment anything about it.

Response: We thank the reviewer for this suggestion. Now we have included this as one of the limitations of this study (Page # 12, Paragraph # 1)

Comment # 2: Dependent variable
The most accepted definition of polypharmacy is the concurrent use of five or more drugs. The authors define polypharmacy as the cumulative use of five or more medication classes during a one year period. This definition explains the results and the high prevalence of polypharmacy. A young diabetic woman, who uses contraceptive pills and/or anti-inflammatory drugs during her menstruation, will be surely a patient with polypharmacy. Is this relevant?
Response: Thank you for pointing this out. Although the most common definition for polypharmacy is the concurrent use of five or more medications, the cumulative use has been widely used in the literature to identify polypharmacy use during a time interval. It has to be noticed that defining polypharmacy depends on the nature of data collection; we have used secondary data (EHR), if we have used primary data collection, then we will use the concurrent use of medications to define polypharmacy use. The following reference has been used to define the polypharmacy use:
Reference: Monégat M, Sermet C, Perronnin M, Rococo E. Polypharmacy: definitions, measurement and stakes involved: review of the literature and measurement tests. Quest d’économie la santé. 2014;204:1-8.
Results

Comment # 1: The final number of patients included was 8,932 (abstract) or 8,832 (first line of results)?
Response: This was a typo error; the study population was 8,932 diabetic patients.

Comment # 2: Second paragraph: 77.9% of adults with diabetes were using (concurrent) or have used (cumulative) five or more drugs?
Response: We have corrected this; 77.9% of adults with diabetes have used (cumulative) five or more drugs

Comment # 3: I´m curious about the medication classes that used the patients. The authors must give data about
Response: Thank you for this suggestion, now we have included Table 2 with the most common therapeutic classes

Comment # 4: Logistic regression. I recommend re-write the paragraph. I prefer “Cardiovascular disease, or mental condition was associated with polypharmacy”.
Response: We totally agree, it sounds better. Change has been made as per the reviewer suggestion

Comment # 5: There is no data about Charlson index
Response: We have not used Charlson comorbidity index to assess the comorbidities, although is index is the most commonly cited index in the literature, the index was developed from a cohort of patients in the inpatient setting to predict one year mortality. However, our study population includes patients from outpatient setting. Also, we have not used Charlson comorbidity index because of limited number of diseases are included in the calculation the index and the prognosis for some health conditions has improved since index developed. Rather, we have also used broad disease categories to identify the coexisting chronic conditions, because they are easily understood by healthcare providers.

Comment # 6: Table 1 is unnecessary. Data can be included in table 2
Response: Now we have merged Table 1 and 2.

Comment # 7: P value <0.001 is better than 0.000
Response: Changes have been made

Comment # 8: Please explain the disbalance men-women
Response: Thank you for pointing this out. Looking at the literature, we found that there are more women with diabetes than men, This may explain the higher percentage of women in our study population
References:
1. World Health Organization, ed. Global tuberculosis report 2013. World Health Organization, 2013.

Comment # 9: What was the mean age of patients?
Response: The mean age was 57.7 (SD = 12.12). We have added this information to Table # 1. We have also added the mean age for polypharmacy and non-polypharmacy groups.

Comment # 10: Appendix I. The peripheral arterial disease was forgotten
Response: The peripheral arterial disease was one of the vascular heart diseases and it does not have its own diagnosis code in the hospital EMR.

Discussion

Comment # 1: It is brief and poor
Response: Thank you for pointing this out. We have made a lot of modification for the content and the organization to the discussion to make it more clear and interesting to the reader.

Conclusion
Comment # 1: The second and third sentences are not justified by results
Response: As per the reviewer suggestion, we have replaced these sentences with sentences justified by the results.

References

Comment # 1: Reference 1 is incomplete.
Response: Change has been made

Reviewer#3

The authors assessed the prevalence of polypharmacy (5+ drugs) in a sample of patients with diabetes.
They conclude that polypharmacy is common among patients with diabetes, and that polypharmacy increases with age and presence of several comorbidities. The paper is important from a public health perspective, at it shows the growing importance of adequately managing polypharmacy among patients with diabetes.

Major issues

Abstract

Comment # 1: the methods could be reduced to provide more space for the results. The sentence on statistical methods could be deleted and more information on the factors associated with polypharmacy could be provided in the results.

Response: Thanks for the suggestion. Changes have been made in the abstract.

Methods

Comment # 1: are the three classifications of diseases (ICD-9, ICD-10 and SNOMED) used in the same hospital? How were non-matching codes handled?

Response: Thank you for pointing this out. The physicians are not required to report all the codes for a single diagnosis; rather some physicians prefer one coding system over the other. The mapping was conducted by a data scientists using SAS software, for example, all the following codes were used to identify hypertension (IC-D-9 code: 401.9, ICD-10 codes: I10, 10, SNOMED codes: 64176011, 2164904016)

Comment # 2: the authors indicate that 91% of the patients had complete data and 85% had complete medication-related information. How were the 9% of patients with incomplete data (and the 15% with incomplete medication-related information) managed? Were they excluded (but seems not as the authors state page 6 line 32 that no exclusion criteria were applied) or did the authors perform some multiple imputation to complete the missing data?

Response: This rate is among adults in general, however, among diabetes, the medication-related information was complete. We have no patients with missing data, and the demographics and clinical conditions data add up to 100% in our study population.

Comment # 3: A large fraction (43.3%) of the patients were aged over 60. The authors could stratify this large age group into smaller categories to check if polypharmacy continues to increase after 60 or tends to lever.

Response: Thank you for the suggestion, we have stratified patients >60 years old into smaller categories (60-69, 70-79, >80). We found that the rate of polypharmacy is higher among older individuals (Table 1)

Results

Comment # 1: the odds ratios for each selected comorbidity (i.e. cardiovascular, musculoskeletal, respiratory and mental diseases) considerably overlap, suggesting that it is the number of comorbidities present that is associated with polypharmacy rather than the type of comorbidity. The authors could run a model including the total number of comorbidities plus each comorbidity type to check this assumption.

Response: Thank you for pointing this out. We have initially added the number of comorbidities to the model, but because the # of comorbidities was highly correlated to the comorbidities type, we have removed the # of comorbidities variable to avoid multicollinearity that can affect the estimates of our regression model.

Comment # 2: Results, tables 2 and 3: there is no need to provide the p-values and the asterisks simultaneously; only the p-value is enough. Please note that p-values of zero are impossible, as they correspond to an infinite value of the test. P-values of 0.000 should be replaced by "<0.001".

Response: Change has been made

Minor issues

Results
Comment # 1: page, 8, second line from the end: the value 54.7% relates to NO cardiovascular comorbidity. Overall, it would be better that the authors do not replicate the results of the tables in the text.

Response: Now, we have corrected the rate for polypharmacy use among individuals with cardiovascular comorbidity

Comment # 2: table 1: the authors can reduce size by providing the values/percentages only for the "yes" rows, as the "no" can be derived by simple subtraction.

Response: Thank you for the suggestion, we have provided the "No" row as it might be useful for the reader to recognize that the data was not missing for some variables.

Comment # 3: table 3: please delete rows "No (ref)" and indicate in the table that the odds ratios are for the presence of the condition, i.e. "Female vs. male", "Non-Saudi vs. Saudi", "Cardiovascular

yes vs. no".

Response: Change has been made

Discussion
Comment # 1: the authors could use some subtitles (at least the "strengths and limitations" one) to structure the discussion.

Response: Change has been made (Page #11)

References

Comment # 1: reference 1 seems incomplete. Is reference 1 a book, a report… Would it be possible for the authors to provide a doi or an URL?

Response: Change has been made

Comment # 2: reference 10 is rather old (20 years). If possible, provide a more recent one.
Response: Thank you for pointing this out. Now, we have replaced it with a recent reference (Golchin N, Frank SH, Vince A, Isham L, Meropol SB. Polypharmacy in the elderly. Journal of research in pharmacy practice. 2015;4(2):85.)

**VERSION 2 – REVIEW**

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| **REVIEWER** | Pedro Marques-Vidal<br>Lausanne University Hospital<br>Lausanne<br>Switzerland |
| **REVIEW RETURNED** | 07-Mar-2018 |

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| **GENERAL COMMENTS** | The authors have performed the changes indicated and the manuscript has improved considerably. There are only two very minor points<br><br>Introduction, page 4, lines 40-48. It is stated "polypharmacy (…) decreases compliance to antidiabetic medications, and poor glycemic control". Please delete the word "poor" as it seems that polypharmacy decreases poor glycemic control (which is a good thing), while it actually decreases glycemic control (which is bad)<br><br>Results, page 9, lines 19-20: I believe it is "the rate of HYPERpolypharmacy (i.e. taking 10+ medication)" rather than the rate of polypharmacy. Please check<br><br>Tables: in my copy I have the title of table 1 that appears just before the table 3. Might be a formating issue<br><br>Table 3: the authors could use the 18-29 age group as a reference, so that the AORs increase with age, making the point of the authors (increase in polypharmacy with increasing age) easier to understand. It only requires a change in the reference group in the logistic model and it does not influence the AORs for the other variables |

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| **REVIEWER** | Jesús Díez-Manglano<br>Internal Medicine Department. Hospital Universitario Miguel Servet. Zaragoza. Spain. |
| **REVIEW RETURNED** | 14-Mar-2018 |

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| **GENERAL COMMENTS** | Manuscript ID: bmjopen-2017-020852.R1<br>Title: Poypharmacy among patients with diabetes: a cross-sectional retrospective study in a tertiary hospital in Saudi Arabia<br><br>GENERAL COMMENTS:<br>Alwhaibi et al have included a point-to-point response to my previous comments. However, the authors did not adequately address some of my concerns.<br><br>• Dependent variable<br>The most accepted definition of polypharmacy is the concurrent use of five or more drugs. The authors define polypharmacy as the cumulative use of five or more medication classes during a one year period. This definition explains the results and the high prevalence of polypharmacy. I recommend reading Masnoon N et al. What is polypharmacy? A systematic review of definitions BMC Geriatrics 2017; 17: 230, and including this issue in discussion.<br><br>Results<br>• Second paragraph: 77.9% of adults with diabetes were using (concurrent) or have used (cumulative) five or more drugs?<br>Authors have not corrected the text “Overall, 77.9% of adults with diabetes were using five or more…..”<br>• Logistic regression. I recommend re-write the paragraph. I prefer “Cardiovascular disease, or mental condition was associated with polypharmacy”.<br>Authors answered that change has been made but I cannot find this change.<br>• P value <0.001 is better than 0.000<br>Change was made. Please, what means ** in table 1? p<0.05, p<0.01? p< 0.005?<br>• Please explain the disbalance men-women in your results. I recommend the reference No 2: Alqurashi et al. Prevalence of diabetes mellitus in a Saudi community. Annals of Saudi medicine 2011; 31(1): 19-23.<br>• What was the mean age of patients? Please add in table 1 a comparison (t Student test or other) among patients with and without polypharmacy. |

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| **REVIEWER** | Bik-Wai Bilvick Tai<br>Caritas Institute of Higher Education<br>Hong Kong |
| **REVIEW RETURNED** | 15-Mar-2018 |

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| **GENERAL COMMENTS** | My previous comments were addressed to a satisfactory level. I have no further comments. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author

Reviewer# 1

Comment # 1: My previous comments were addressed to a satisfactory level. I have no further comments.

Response: We thank the reviewer for his valuable comments that have improved our manuscript substantially.

Reviewer# 2

GENERAL COMMENTS

Alwhaibi et al have included a point-to-point response to my previous comments. However, the authors did not adequately address some of my concerns.

Comment # 1: Dependent variable : The most accepted definition of polypharmacy is the concurrent use of five or more drugs. The authors define polypharmacy as the cumulative use of five or more medication classes during a one year period. This definition explains the results and the high prevalence of polypharmacy. I recommend reading Masnoon N et al. What is polypharmacy? A systematic review of definitions BMC Geriatrics 2017; 17: 230, and including this issue in discussion.

Response: Thanks for your valuable comments; we agree with the reviewer that the most accepted definition for polypharmacy is the concurrent use of five or more medications. In our study, we have used secondary data (EHR), and we have looked at the cumulative use of medications over one year period, using this definition may have overestimated the rate of polypharmacy. Fincke et al. have compared the cumulative versus the concurrent use of medications and found that using the cumulative definition provides a higher rate of polypharmacy as compared to the concurrent definition.1 Therefore, now we have acknowledged this limitation in the manuscript (Page # 12, paragraph #2).

“This study has some limitations; we defined polypharmacy as the cumulative use of five or more medications during a one year period rather than the concurrent use of medications, using this definition may have overestimated the rate of polypharmacy”

However, the main advantage of using cumulative polypharmacy is that it measures all medications that the patients used during the study period including continuously used medications. By doing so this measure can allow us to calculate the total number of medication that the patients used over specific period of time.

Although this definition is not the most accepted definition, it has been widely used in the literature to define polypharmacy.2-6 For example, Chao et all defined polypharmacy using the cumulative

concept, that is the sum of all types of different medications prescribed for treating cardiovascular disorders within a 3-month period before admission5.

References


1. Fincke BG, Snyder K, Cantillon C, et al. Three complementary definitions of polypharmacy: methods, application and comparison of findings in a large prescription database. Pharmacoepidemiology and drug safety. 2005;14(2):121-128.

2. Slabaugh SL, Maio V, Templin M, Abouzaid S. Prevalence and Risk of Polypharmacy among the Elderly in an Outpatient Setting. Drugs & aging. 2010;27(12):1019-1028.

3. Grimmsmann T, Himmel W. Polypharmacy in primary care practices: an analysis using a large health insurance database. Pharmacoepidemiology and drug safety. 2009;18(12):1206-1213.

4. Monégat M, Sermet C, Perronnin M, Rococo E. Polypharmacy: definitions, measurement and stakes involved: review of the literature and measurement tests. Quest d'économie la santé. 2014;204:1-8.

5. Chao C-T, Tsai H-B, Wu C-Y, et al. Cumulative cardiovascular polypharmacy is associated with the risk of acute kidney injury in elderly patients. Medicine. 2015;94(31).

6. Chang Y-P, Huang S-K, Tao P, Chien C-W. A population-based study on the association between acute renal failure (ARF) and the duration of polypharmacy. BMC nephrology. 2012;13(1):96.

7. Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Annals of Saudi medicine. 2011;31(1):19.


Comment # 2: Results: Second paragraph: 77.9% of adults with diabetes were using (concurrent) or have used (cumulative) five or more drugs? Authors have not corrected the text "Overall, 77.9% of adults with diabetes were using five or more….."

Response: Now we have corrected this sentence in the second paragraph of the results (Page # 8, paragraph #3)

Comment # 3: Logistic regression. I recommend re-write the paragraph. I prefer "Cardiovascular disease, or mental condition was associated with polypharmacy". Authors answered that change has been made but I cannot find this change.

Response: Thank you for the suggestion, we have made the suggested changes now (Page # 9, paragraph #2).

Comment # 4: P value <0.001 is better than 0.000. Change was made. Please, what means ** in table 1? p<0.05, p<0.01? p< 0.005?

Response: Thank you for pointing this out, now we have added what ** means in Table 1.

** 0.001< P< 0.01.

Comment # 5: Please explain the disbalance men-women in your results. I recommend the reference No 2: Alqurashi et al. Prevalence of diabetes mellitus in a Saudi community. Annals of Saudi medicine 2011; 31(1): 19-23.

Response: Thank you for pointing this out again. Now we have reported the reason for disbalance in men-women in the discussion section (Page # 12, paragraph #2)

“It has to be noted that the majority of patients with diabetes in our study were women, this is not surprising since the rate of diabetes is higher in women as compared to men in Saudi Arabia.7”

Comment # 6: What was the mean age of patients? Please add in table 1 a comparison (t Student test or other) among patients with and without polypharmacy.

Response: The mean age for the total and by polypharmacy has been added to Table 1 as per the reviewer suggestion.

Reviewer# 3

The authors have performed the changes indicated and the manuscript has improved considerably. There are only two very minor points

Comment # 1: Introduction, page 4, lines 40-48. It is stated “polypharmacy (…) decreases compliance to antidiabetic medications, and poor glycemic control”. Please delete the word “poor” as it seems that polypharmacy decreases poor glycemic control (which is a good thing), while it actually decreases glycemic control (which is bad)

Response: We thank the reviewer for this suggestion. Now we have removed the word “poor” from this sentence.

Comment # 2: Results, page 9, lines 19-20: I believe it is “the rate of HYPERpolypharmacy (i.e. taking 10+ medication)” rather than the rate of polypharmacy. Please check

Response: This was a typo error; thank you for this comment.

Comment # 3: Tables: in my copy I have the title of table 1 that appears just before the table 3. Might be a formatting issue

Response: We thank the reviewer for this comment. Change has been made

Comment # 4: Table 3: the authors could use the 18-29 age group as a reference, so that the AORs increase with age, making the point of the authors (increase in polypharmacy with increasing age) easier to understand. It only requires a change in the reference group in the logistic model and it does not influence the AORs for the other variables

Response: Thank you for this suggestion; we have changed the reference group to 18-29 and reported the AORs in Table 3 as well as in the text.

**VERSION 3 – REVIEW**

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| **REVIEWER** | Jesús Díez-Manglano<br>Internal Medicine Department. Hospital Universitario Miguel Servet. Zaragoza. Spain. |
| **REVIEW RETURNED** | 24-Apr-2018 |

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| **GENERAL COMMENTS** | The authors have answered properly all my previous concerns. |