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)	Prevalence of potentially serious alcohol-medication interactions in older adults in community pharmacy setting: A cross-sectional study
AUTHORS	Holton, Alice; Keeney, Cora; Ryan, Benedict; Cousins, Gráinne

VERSION 1 – REVIEW

REVIEWER	faika zanjani VCU, USA
REVIEW RETURNED	02-Dec-2019

GENERAL COMMENTS	Manuscript number BMJopen-2019-035212 • General: Valuable topic, and well written paper, but sample sizes need to be clarified. • Abstract: 1. Define POSAMINO in initial mention in Abstract. • Results 1. "Decline, increasing, decreasing, etc" terms cannot be used in cross-sectional work, since change cannot be detected. 2. Unclear why alcohol use is missing from Table 1. 3. Total sample Ns needed for Tables 2 and 3 to clarify alcohol consuming vs. total sample. 4. Table 2 needs a note, or more descriptive titles for the columns, with n-values. • Discussion 1. It is EXTREMELY important to ensure that numbers presented for POSAMINO risk are among those older adults reported alcohol consumption, sample n=1065. It is unclear right now if the POSAMINO rate is for the alcohol consumers or the total sample.

REVIEWER	Stephen Bright Edith Cowan University I have published in this area, though have made this clear to the authors in my review
REVIEW RETURNED	26-Jan-2020

GENERAL COMMENTS	Thank you for the opportunity to review this well-written paper that addresses the increasing prevalence of hazardous and harmful drinking among older adults, which is an under-reported issue in the medical literature. More specifically, this study examines the role of older adults' use of medications that could lead to adverse drug events when used concurrently with alcohol. The methodology is sound so my primary feedback aims to improve the paper by increasing clarity of expression, breath literature cited and transparency of limitations.

Page 2: POSAMINO needs to be defined in the first sentence of the abstract.

Page 3: The authors state "we estimated that 18% of older adults are at risk, with 8% at risk of one potentially serious alcohol-medication interaction". Could the authors clarify what the 18% of older adults were at risk of and how this risk is different from those at risk of one potentially serious alcohol-medication?

Page 6: The use of flash cards was a good way of increasing the self-reported estimation of a standard drink containing 10 grams of ethanol, though given most servings of wine at pubs or restaurants are 150mls and free pouring of wine and spirits can vary considerably, it is likely that participants underestimated how much they consumed of these beverages compared to beer and alcopops. For example, Wilkinson et al. (2011) found that older "men poured drinks that were on 32% larger than a standard drink (10 g of ethanol).The comparable figure for older women was 16%". Perhaps future studies using POSAMINO could get participants to pour a simulated drink to increase estimations of consumption such as has been used in the methodology of brief interventions for older adults (Bright & Williams 2017; Bright & Williams, 2018).
Bright, S. J., & Williams, C. M. (2017). Development of Australia's first older adult-specific early intervention for alcohol-related harm: Feasibility and proof of concept. Australasian Journal on Ageing, 36(1), 52-55.
Bright, S. J., & Williams, C. M. (2018). Evaluation of Australia's first older adult-specific early intervention for reducing alcohol-related harm. Australian Health Review, 42(6), 676-679.
Wilkinson, C. T., Allsop, S., & Chikritzhs, T. (2011). Alcohol pouring practices among 65 to 74 year olds in Western Australia. Drug and Alcohol Review, 30(2), 200-206.

Page 7: The rationale for threshold for "heavy drinking" needs further explanation as these amounts are significantly greater than the most recent guidelines for older adults. For example, the draft National Health and Medical Research Council guidelines classifies heavy drinking among health adults as >40 grams (cf. > 60 grams on any occasion) and >70grams/week (cf. >170 grams/week), recommending that older adults drink less than this given the increased risk of alcohol-related harms from ageing related changes in alcohol metabolisation, medical co-morbidities, etc. Perhaps theses high values used to define "heavy drinking" could lead to an underestimation of participants who were at risk and should be noted in the discussion?

Page 8: It would be helpful for the reader to include the alcohol risk categorisation to Table 1 (e.g., nil alcohol, low risk drinker, heavy drinker). Or would no consumption of alcohol mean by default that there was no POSAMINO? My understanding is that they still could have >1 POSAMINO, though not be at current risk. If it is the latter then the prevalence of POSAMINO among the different categories of drinking status

Page 11: The term "heterogeneity" of medications included in previous studies seems confusing. Can the authors state what they are alluding to about the limitation of medication inclusion more directly? For example, would methodologies such as that

recently used by Bright et al. (2019) that demarcate between medications that could lead to adverse drug events vs reduced treatment efficacy from concurrent alcohol consumption be considered too heterogeneous or does this methodology address the issue of heterogeneity? Disambiguation would mean I would already know the answer to this question.

Bright, S., Milroy, J., Walsh, K., & Blatchford, E. (2019). Medication use among older Australians seeking alcohol and other drug treatment. Australasian Journal on Ageing. [Early Online]

Page 11: Second para, third sentence, place comma before rather than after thus.

Page 12: Integrating POSAMINO criteria into pharmacy dispensing, as suggested by the authors would be a great public health initiative. Doing so in the context of a Screening, Brief Intervention and Referral to Treatment (SBIRT) intervention would be ideal. As such, the POSAMINO criteria might be used to improve within pre-existing computerised screening tools for older adults that already use algorithms take into account alcohol consumption in the context of medical use, medical co-morbidities and activities of daily living such as the Alcohol-Related Problems Survey, developed by Fink et al. (2002) at UCLA. A 10 gram recalibrated version of this tool was used in the aforementioned brief intervention by Bright and Williams.

Fink, A., Tsai, M. C., Hays, R. D., Moore, A. A., Morton, S. C., Spritzer, K., & Beck, J. C. (2002). Comparing the alcohol-related problems survey (ARPS) to traditional alcohol screening measures in elderly outpatients. Archives of gerontology and geriatrics, 34(1), 55-78.

Page 12: Insert "since" after "concurrent use of alcohol and medications.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

Thank you for your comments in relation to the value of this study. In response to specific issues you raised in your review:

1. ***General: Valuable topic, and well written paper, but sample sizes need to be clarified.***

Response:

The purpose of this paper was to estimate the prevalence of potentially serious alcohol-medication

interactions in community dwelling older adults in a community pharmacy setting (as set out in our

study aims see abstract (objectives); Introduction (last line page 5). We also make clear in the

methods that our statistical analysis relates to the total sample : "The overall prevalence of

POSAMINO and the prevalence per individual POSAMINO criterion were calculated as a proportion

3

of all eligible participants." The focus of this paper was not on current drinkers. *We feel that the sample size as presented in the methods and the flow diagram is clear. We included those fitting the inclusion criteria who had complete data on both alcohol consumption and medication dispensing records (n=1599). Non-drinkers were included in our sample, as we are interested in the total sample- we are seeking to estimate the prevalence of POSAMINO in older community dwelling adults.*

We also report our sample size in the results:

In total, 2704 consecutive patients were invited to participate, 1780 (65.8%) consented to complete the interview and have it linked to their pharmacy dispensing records. Subsequently, we excluded participants attending other pharmacies as their pharmacy records were incomplete (n=125), and those with incomplete alcohol data (n=47) and missing data on age (n=9), **leaving a final sample of 1599 participants.**

2. ***Abstract: Define POSAMINO in initial mention in Abstract.***

Response:
We updated the abstract to include the definition of POSAMINO in line 1 of the abstract:

"Previous prevalence estimates of POtentially Serious Alcohol-Medication INteractions in Older adults (POSAMINO) are based on in-home inventories of medications, however this method has…"

Results
3. ***"Decline, increasing, decreasing, etc." terms cannot be used in cross-sectional work, since change cannot be detected.***

Response:
We have revised the manuscript throughout to avoid the use of terms such as decline, increasing, decreasing etc.

Results: The regression analyses (Table 3) showed that older age (AOR: 0.95; 95% CI: 0.93-0.97) and female gender (AOR: 0.42; 95% CI: 0.33-0.53) were associated with lower odds of any POSAMINO; whilst urban dwellers (AOR: 1.40; 95% CI: 1.05-1.86) and higher number of co-morbidities (AOR: 1.09; 95% CI: 1.03-1.14) were associated with a higher odds of any POSAMINO exposure. A similar pattern was observed from the negative binomial regression analysis which also showed that older age (AIRR: 0.97; 95% CI: 0.95-0.98) and female gender (IRR: 0.55; 95% CI: 0.45-0.67) were associated with a lower number of POSAMINO criteria. While, a higher number of co-

4

morbidities (AIRR: 1.05; 95% CI: 1.01-1.13) were associated with a greater number of POSAMINO criteria.

Discussion: Risk of exposure to multiple POSAMINO criteria was associated with younger age, male sex and a higher number of co-morbidities.

4. Unclear why alcohol use is missing from Table 1.

Response:

Apologies for this oversight, we had discussed alcohol use in our description of the study population but we had not included in Table 1. We have now revised Table 1 to include information on alcohol consumption as recommended by Reviewer 1.

5. Total sample Ns needed for Tables 2 and 3 to clarify alcohol consuming vs. total sample.

Response:

We have revised table 2 to demonstrate the prevalence of POSAMINO in the total sample (the primary aim of our study), and the prevalence among current drinkers and those using medications within the specific drug classes. As suggested by Reviewer 1 we have included the Ns for total sample and current drinkers in the table. Please note the number of people taking medications within the specific drug classes varies. Therefore we recorded the n for each drug class separately at the end of the table. We have also removed any individual POSAMINO criteria which include less than 5 people to ensure anonymity of respondents.

*We have also clarified the legend for **Table 3.Logistic regression and negative binomial regression models for any and number of POSAMINO among total sample (N=1599)***

6. Table 2 needs a note, or more descriptive titles for the columns, with n-values.
Response:

As described above we have amended table 2, and it includes descriptive titles for the columns with their respective n-values.

7. .Discussion It is EXTREMELY important to ensure that numbers presented for POSAMINO risk are among those older adults reported alcohol consumption, sample n=1065. It is unclear right now if the POSAMINO rate is for the alcohol consumers or the total sample.

Response:

We respectfully disagree. The purpose of this study was to estimate the prevalence of POSAMINO among community dwelling older adult, using pharmacy dispensing records to obtain a more objective measure of medications. The aim was not to focus on those who consumed alcohol alone. This would be a biased estimate, as we are seeking to determine the prevalence of POSAMINO in the total sample. We have added the following clarification to the results section describing the prevalence of POSAMINO, to include information prevalence of POSAMINO among drinkers (of course all non-drinkers have zero POSAMINO as if you do not drink it is not possible to have a potentially serious alcohol-medication interaction):

Prevalence of potentially serious alcohol medication interactions

The overall prevalence of POSAMINO among the total sample was 28%, with 10% of participants at risk of one potentially serious alcohol-medication interaction and 18% at risk of two or more serious interactions. Among current drinkers, 42% were at risk of any POSAMINO, with 15% at risk of one POSAMINO and 27% at risk of 2 or more.

*However, for the discussion section, after much consideration the authors have decided to describe the prevalence among **the total sample**, as this was set out as our primary study aim a priori. Furthermore, this enables direct comparisons with prevalence estimates from previous research reporting on the prevalence of POSAMINO among community dwelling older adults:*

"When we compare our estimates from this study to our previous study of older adults in TILDA, using an in-home inventory for ascertainment of medications, we note a higher risk of exposure to any potentially serious alcohol-mediation interactions using POSAMINO (28% v's 18% in TILDA) and to number of POSAMINO criteria (18% with ≥ 2 POSAMINO criteria v's 8% in TILDA). [10]"

Response to Reviewer 2

Reviewer: #2

Thank you for the opportunity to review this well-written paper that addresses the increasing prevalence of hazardous and harmful drinking among older adults, which is an under-reported issue in the medical literature. More specifically, this study examines the role of older adults' use of medications that could lead to adverse drug events when used concurrently with alcohol. The methodology is sound so my primary feedback aims to improve the paper by increasing clarity of expression, breath literature cited and transparency of limitations.

6

Response:

Thank you for your helpful comments and suggestions. We feel the various clarifications which you have requested, have improved the reporting and discussion of our findings. In response to particular issues you raised in your review:

1. **Comment: Page 2: POSAMINO needs to be defined in the first sentence of the abstract.**

Response:

We updated the abstract to include the definition of POSAMINO in line 1 of the abstract:

"Previous prevalence estimates of POtentially Serious Alcohol-Medication Interactions in Older adults (POSAMINO) are based on in-home inventories of medications, however this method has…"

2. **Page 3: The authors state "we estimated that 18% of older adults are at risk, with 8% at risk of one potentially serious alcohol-medication interaction". Could the authors clarify what the 18% of older adults were at risk of and how this risk is different from those at risk of one potentially serious alcohol-medication?**

Response:

Apologies for this lack of clarity, we identified that 18% of the sample in TILDA were at risk of any potentially serious alcohol-medication interactions, with 8% at risk of one potentially serious alcohol-medication interaction and 10% at risk of two or more. We have clarified this in the text:

"In our initial validation of the POSAMINO criteria using the first three waves of the Irish Longitudinal Study of Ageing (TILDA), we estimated that 18% of older adults are at risk of any potentially serious alcohol medication interactions, with 8% at risk of one potentially serious alcohol-medication interaction and 10% at risk of two or more."

3. **Page 6: The use of flash cards was a good way of increasing the self-reported estimation of a standard drink containing 10 grams of ethanol, though given most servings of wine at pubs or restaurants are 150mls and free pouring of wine and spirits can vary considerably, it is likely that participants underestimated how much they consumed of these beverages compared to beer and alcopops. For example, Wilkinson et al. (2011) found that older "men poured drinks that were on 32% larger than a standard drink (10 g of ethanol).The comparable figure for older women was 16%". Perhaps future studies using POSAMINO could get participants to pour a simulated**

7

drink to increase estimations of consumption such as has been used in the methodology of brief interventions for older adults (Bright & Williams 2017; Bright & Williams, 2018).

Bright, S. J., & Williams, C. M. (2017). Development of Australia's first older adult-specific early intervention for alcohol-related harm: Feasibility and proof of concept. Australasian Journal on Ageing, 36(1), 52-55.

Bright, S. J., & Williams, C. M. (2018). Evaluation of Australia's first older adult-specific early intervention for reducing alcohol-related harm. Australian Health Review, 42(6), 676-679. Wilkinson, C. T., Allsop, S., & Chikritzhs, T. (2011). Alcohol pouring practices among 65 to 74 year olds in Western Australia. Drug and Alcohol Review, 30(2), 200-206.

Response:
Thank you for this additional information and relevant references. We have reviewed these papers and have now included this information in our discussion – highlighting how future studies could further reduce potential under-reporting of alcohol consumption among older adults. The additional text is reported below:

"Future studies of POSAMINO could further reduce the potential risk of under-reporting of alcohol consumption by asking participants to pour a simulated drink, particularly for beverages which often involve free pouring such as wine and spirits.[34 35] A study of 844 current drinkers aged 65-74 years in Australia found that older men poured drinks that were 32% larger than a standard drink of 10 grams alcohol, with older women pouring drinks that were 16% larger.[36]"

4. **Page 7: The rationale for threshold for "heavy drinking" needs further explanation as these amounts are significantly greater than the most recent guidelines for older adults. For example, the draft National Health and Medical Research Council guidelines classifies heavy drinking among health adults as >40 grams (cf. > 60 grams on any occasion) and >70grams/week (cf. >170 grams/week), recommending that older adults drink less than this given the increased risk of alcohol-related harms from ageing related changes in alcohol metabolisation, medical co-morbidities, etc. Perhaps theses high values used to define "heavy drinking" could lead to an underestimation of participants who were at risk and should be noted in the discussion?**

Response:
We acknowledge this limitation to our study. However in the absence of age-specific guidelines we applied national limits. We have addressed this limitation in our discussion:

8

"Furthermore, in the absence of internationally agreed age-specific drinking guidelines, we used national Irish recommendations to define heavy alcohol consumption in the development of the POSAMINO criteria[9] and in this study to classify participants as heavy drinkers. Given that older adults are more vulnerable to harm even at low levels of alcohol consumption, our estimates of POSAMINO may reflect an underestimate of the true prevalence among older adults particularly for those criteria involving heavy alcohol consumption."

8. **Page 8: It would be helpful for the reader to include the alcohol risk categorization to Table 1 (e.g., nil alcohol, low risk drinker, heavy drinker). Or would no consumption of alcohol mean by default that there was no POSAMINO? My understanding is that they still could have >1 POSAMINO, though not be at current risk. If it is the latter then the prevalence of POSAMINO among the different categories of drinking status**

Response:
The POSAMINO criteria specify "any alcohol consumption" or "heavy alcohol consumption" depending on the medication, therefore no consumption of alcohol would by default mean there was no POSAMINO. If a person does not drink they cannot be at risk of a potentially serious alcohol-medication interaction.

However in response to this comment and a comment from Reviewer 1 we have included Alcohol Consumption status in Table 1 – which shows what proportion of the sample are current drinkers, heavy drinkers and the proportions who are at risk of POSAMINO.

9. **Page 11: The term "heterogeneity" of medications included in previous studies seems confusing. Can the authors state what they are alluding to about the limitation of medication inclusion more directly? For example, would methodologies such as that recently used by Bright et al. (2019) that demarcate between medications that could lead to adverse drug events vs reduced treatment efficacy from concurrent alcohol consumption be considered too heterogeneous or does this methodology address the issue of heterogeneity? Disambiguation would mean I would already know the answer to this question.**

Bright, S., Milroy, J., Walsh, K., & Blatchford, E. (2019). Medication use among older Australians seeking alcohol and other drug treatment. Australasian Journal on Ageing. [Early Online]

Response:

As detailed in the introduction we carried out a systematic review which estimated that between one-in-five and one-in-three older adults are potentially susceptible to alcohol-medication interactions.[8] *However, these estimates may be biased as there was a lack of consensus regarding what constitutes an alcohol interactive medication across studies, and many of the proposed interactions were theoretical with trivial clinical significance. Furthermore, most studies failed to acknowledge that certain interactions may occur with any alcohol, whereas others may follow a dose response, with severity and risk of the interaction increasing with increasing levels of alcohol consumption.*

This review found that that among the twenty identified studies, nine studies reported on a wide range of prescription and/or over the counter (OTC) medicines with potential to interact with alcohol. Three studies investigated any medication use during the recall period and a further eight focused on psychotropic medications. Of the eight studies focusing on psychotropic medications, five investigated psychotropic medications alone and three studies also included analgesics. As a result, there was heterogeneity across studies in relation to classifying medications as alcohol interactive and methods used to quantify alcohol consumption (i.e. there was a lack of consensus regarding what constitutes an alcohol interactive medication). As outlined in our introduction, in light of the findings from our systematic review we developed an explicit list of potentially serious alcohol-medication interactions for use in older adults (POSAMINO) using a systematic review, review of multiple drug compendia (British National Formulary (BNF), Stockley's Drug Interactions and Martindale Complete Drug Reference), clinical guidance documents and a two-round Delphi consensus method (with a panel of 19 healthcare professionals). We hope this addresses your question.

10. **Page 11: Second para, third sentence, place comma before rather than after thus.**

Response
We have amended this statement as suggested.

11. **Page 12: Integrating POSAMINO criteria into pharmacy dispensing, as suggested by the authors would be a great public health initiative. Doing so in the context of a Screening, Brief Intervention and Referral to Treatment (SBIRT) intervention would be ideal. As such, the POSAMINO criteria might be used to improve within pre-existing computerised screening tools for older adults that already use algorithms take into account alcohol consumption in the context of medical use, medical co-morbidities and activities of daily living such as the Alcohol-Related Problems Survey, developed by Fink et al. (2002) at UCLA. A 10 gram recalibrated version of this tool was used in the aforementioned brief intervention by Bright and Williams.**

Fink, A., Tsai, M. C., Hays, R. D., Moore, A. A., Morton, S. C., Spritzer, K., & Beck, J. C. (2002). Comparing the alcohol-related problems survey (ARPS) to traditional alcohol screening measures in elderly outpatients. Archives of gerontology and geriatrics, 34(1), 55-78.

Response:

Thank you for this useful suggestion. We have revised this section to include:

"*POSAMINO criteria could also be integrated into pharmacy dispensing systems, as part of a Screening, Brief Intervention and Referral to Treatment (SBIRIT) intervention.*"

12. **Page 12: Insert "since" after "concurrent use of alcohol and medications.**

Response:

We have made this correction.

VERSION 2 – REVIEW

REVIEWER	Stephen Bright Edith Cowan University, Australia
REVIEW RETURNED	07-Mar-2020

GENERAL COMMENTS	The authors have adequately addressed the feedback that I provided for improving the quality of the paper and I believe that it is ready for publication.