PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Psychotropic drug use and alcohol consumption among older adults in Germany. Results of the German Health Interview and Examination Survey for Adults 2008-2011
AUTHORS	Du, Yong; Wolf, Ingrid-Katharina; Knopf, Hildtraud

VERSION 1 - REVIEW

REVIEWER	Mitchell Karno, PhD University of California, Los Angeles USA
REVIEW RETURNED	26-Apr-2016

GENERAL COMMENTS	This manuscript examines the co-occurrence of psychotropic medication use and alcohol use among older adults (aged 60-79) in Germany. Co-occurring alcohol and psychotropic medications can result in increased sedation and subsequent risk of injury and falls in older adults. Therefore the topic has significant public health implications. The study finds that worse health status and polypharmacy are each associated with combined use of psychotropics and daily use of alcohol. The study also finds there is a high prevalence of alcohol use among older adults, particularly for individuals who have higher socioeconomic status, better health and who live with another person. Thus while alcohol use itself appears to be associated with older adults who are generally functioning better, the higher-risk combination of alcohol and psychotropics is seen among those with poorer health who presumably are coping through the use of multiple substances. These findings have direct clinical implications. There are numerous strengths of the study. The sample (n=2,508) is based on a well-designed general population survey that used probability cluster sampling and was stratified by age and gender. The assessment of psychotropic medications was validated by in-person checks of medication packaging. The data analysis plan was appropriate. The paper is well-written, results are presented clearly, and the conclusions follow from the results. Overall the paper was very thoughtful and well done. I note a few potential areas for improvement in the paper that I describe below: (1) On p.6, the classification of participants into categories for frequency of alcohol use is unclear. It appears that the categories overlap in that the low frequency category seems to include daily use. This may be an oversight in the writing, but it should be clarified that the categories are mutually exclusive. The categories could be re-labeled as daily use and less-than-daily use to clearly convey these are distinct groups. (2) Please clarify in the methods if polypharmacy is operationalized to mean all non-psychotropic medications or if psychotropics are

	included in the polypharmacy count. Or is polypharmacy limited to the count of only psychotropics? At issue here is the extent to which polypharmacy (as a predictor variable) is independent of psychotropic use. If they are measuring the same behaviors then it becomes less meaningful to analyze their relationship. (3) Following from the above question, can the authors address in the discussion what they understand polypharmacy to mean in their sample? Is it related to poor health status? Or perhaps a style of coping with health issues? Because the constructs of polypharmacy and health status were the main predictors of combined alcohol and psychtropic use, it would be useful to provide further consideration of how those constructs intersect and diverge. This discussion could follow from their data or from the extant literature. (4) I have a question as to whether non-drinkers were removed from the analyses at some point (after Table 1). This question is particularly pertinent for the logistic regression analyses (reported in Table 5). For the alcohol consumption variables what is the comparison group? (e.g., is risky drinking compared to non-drinkers, or to non-risky drinkers, or to everyone in the 2,508 sample who are not risky drinkers?). It is important to be clear about those contrasts because interpretation of the results depends on them. If non-drinkers were removed from the analyses at any point then the functional sample size should be stated and the tables and figure should state the sample size for the analyses shown. (5) Because the authors are handling 2 different time scales for the alcohol use measure (past 12 months) and the psychotropic drug assessment (past week), they have chosen to examine daily drinking in combination with psychotropic drugs because presumably daily drinking will have happened in the past week (thereby temporally overlapping the alcohol and medication variables). This is a thoughtful decision. A negative side effect is that the findings (as reported in Table 5) lack symmetry. As reported now, the alcohol consumption variables address likelihood of drinking and likelihood of risky drinking. But then the combination variable (alcohol and psychotropics) examines likelihood of daily drinking. This shift renders it difficult to look across the analyses at shifts in the pattern of results. To wit, I wonder if the changes in significant predictors in that final analysis are a function of the combination of psychotropics and alcohol or a function of changing the alcohol variable? One suggestion is that the alcohol variables (when they are treated as individual outcomes) include daily drinking. This could substitute for the 'at least once a week' outcome. And the 'risky alcohol drinking' outcome could be looked at also in combination with psychotropics. This would allow for more symmetry in the analyses and still preserve efforts to maintain some overlap in temporality between the alcohol and psychotropics variables. If it is the case that the proportion of daily drinkers who are risky drinkers is very high then running those as separate analyses may not be appropriate, but it would be useful then to report on how those group comprise roughly the same individuals. (6) In Figure 1 the subgroup sample sizes do not sum to 2,508. There appear to be a large number of participants excluded from this figure. Is this so and why?

REVIEWER	Paul Sacco University of Maryland-Baltimore, United States
REVIEW RETURNED	02-May-2016

GENERAL COMMENTS	Thank you for the opportunity to review the manuscript, "Psychotropic drug use and alcohol consumption among older adults in Germany. Results from the German health Interview and Examination Survey for Adults 2008-2011". This manuscript has a number of strengths including the collection of detailed data on medication and other drug use combined with survey data on alcohol consumption. As a representative sample of older adults in Germany, it is informative to the German older adult population, and provides the opportunity to compare German older adults to older adult populations in different countries. Substantively speaking, the unanswered question in this study is the extent to which co-use of alcohol and these drugs leads to documented risk in this population, even as it is identified as a risk factor for falls and other bad outcomes. From the standpoint of methods, the small cell sizes could be problematic in terms of reliable estimates. Perhaps this requires collapsing of categories and not disaggregating classes/types of meds to the extent that has done in the analysis. Comments are provided below by section: Abstract & Summary: The use of the word "determinants" is a bit clunky in the abstract. Rather, I would suggest the term "correlates". The use of the word "conjunctive" is also problematic. Perhaps the word "concurrent" would be better here. Introduction: In lines 11-13, the authors report that older adults "…may suffer from emotional and mental disorders more frequently than younger people". Data from the United States at least, suggest just the opposite. Older adults show lower rates of most major mental health conditions with the exception of the dementias. The authors use the term "elderly" in the second paragraph, but I would suggest only using the term "older adult" Please change the term "pharmacodynamical" to "pharmacodynamic". In lines 30-31, the authors note that alcohol and psychotropic drugs even in small amounts are "extremely harmful". In my view that would depend on the substance and on the amount of alcohol. Methods: The authors focus on the older adults ages 60-79. Was that the oldest age in the survey, or were those over 79 excluded for the current study? Please provide more detail. Please change "physicians-administered" to "physician-administered". In the methods section, would it be possible to the authors to provide

	some data to readers about how the German alcohol risk limits compare with the United States and/or other countries, specifically the use of the older adult limits. The definition of “psychotropic” seems very broad; is there a citation or list of citations that can support the inclusion of so many different drugs. Also, the risk profile with alcohol may also be different depending on the drug, so grouping them may be problematic. For missing data, could the authors provide some information on the percentage of data that is missing in these analyses? I recognize that actual n sizes are provided but it would help for the reader to get a sense of much is missing at a glance “(e.g. between xx% and xx%) of data on x and y were missing”. Also, some information about how missing data were handled in analyses would be helpful. In a general sense, could the authors check on the small cell problem for some of the estimates. To what extent are these reliable? When n sizes get down to 17, are the estimates reliable? Results: On page 8, the authors remark on the “significantly high prevalence rate of psychotropic use”. The use of “significant” could be changed as it suggests the statistical term here and that is not what the authors are focused on if I am reading this correctly. In table 2, I don’t think that including individual agents adds much and the cell sizes get pretty small. Also, certain drug classes are mentioned twice over the table. I would suggest either grouping this information into larger bins by class of drug and report that. Then report the most common drug for each class in the text. In Table 3, the column organization is a bit confusing. There is a column for benzodiazepines and another column for sedative/hypnotics. How are these different? What is included in each group? The figure, although a nice way of visualizing the data is a bit hard to read. I think that if it is possible. Put the labels directly on the circles. Do no color code, but instead put the percentages inside the fields with the n sizes. Discussion: In the discussion, I think it would be helpful to make some general pronouncement about the findings, in relation to other studies. The authors do a great job of talking about other studies, but it would help to get a general sense if these estimates are lower or higher. Then when talking about the comparisons, the authors would benefit from discussing specific methodological factors that explain specific differences in the data. On page 19, the authors use the word “Finish”; Since it is the country, it is “Finnish”. In the discussion, it would be helpful to address the question of whether so-called “risk” of negative effects of alcohol and psychotropic use actually translates to negative outcomes. Recently, I have seen a number of studies focused on alcohol and medication concomitant use, but it remains unclear as to whether this is

	clinically, and from the standpoint of public health, truly high risk. This is also quite variable when one considers a broadest range of CNS medications and herbal drugs (e.g. St. John's Wort) versus benzodiazepines.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Mitchell Karno, PhD

Institution and Country

University of California, Los Angeles
USA

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

Please leave your comments for the authors below This manuscript examines the co-occurrence of psychotropic medication use and alcohol use among older adults (aged 60-79) in Germany. Co-occurring alcohol and psychotropic medications can result in increased sedation and subsequent risk of injury and falls in older adults. Therefore the topic has significant public health implications. The study finds that worse health status and polypharmacy are each associated with combined use of psychotropics and daily use of alcohol. The study also finds there is a high prevalence of alcohol use among older adults, particularly for individuals who have higher socioeconomic status, better health and who live with another person. Thus while alcohol use itself appears to be associated with older adults who are generally functioning better, the higher-risk combination of alcohol and psychotropics is seen among those with poorer health who presumably are coping through the use of multiple substances. These findings have direct clinical implications. There are numerous strengths of the study. The sample (n=2,508) is based on a well-designed general population survey that used probability cluster sampling and was stratified by age and gender. The assessment of psychotropic medications was validated by in-person checks of medication packaging. The data analysis plan was appropriate. The paper is well-written, results are presented clearly, and the conclusions follow from the results. Overall the paper was very thoughtful and well done. I note a few potential areas for improvement in the paper that I describe below:

(1) On p.6, the classification of participants into categories for frequency of alcohol use is unclear. It appears that the categories overlap in that the low frequency category seems to include daily use. This may be an oversight in the writing, but it should be clarified that the categories are mutually exclusive. The categories could be re-labeled as daily use and less-than-daily use to clearly convey these are distinct groups.
RESPONSE: Our aim was to look at how many people use alcohol frequently (at least once a day) and less frequently (at least once a week) according to the 11 possible answer choices for the question concerning alcohol use. The two groups are not mutually exclusive. Literally, one can easily understand that the group 'at least once a week' is included in the group 'at least once a day'. In addition, we have given the ns for the two groups in the table. While the group 'less-than-daily' suggested by the reviewer is interesting, it tells another story, however.

(2) Please clarify in the methods if polypharmacy is operationalized to mean all non-psychotropic medications or if psychotropics are included in the polypharmacy count. Or is polypharmacy limited to the count of only psychotropics? At issue here is the extent to which polypharmacy (as a predictor variable) is independent of psychotropic use. If they are measuring the same behaviors then it becomes less meaningful to analyze their relationship.

RESPONSE: We defined polypharmacy in the 'methods' section 'Polypharmacy was assumed if five or more medicines (prescription and/or OTC) were used in the past 7 days', which means that psychotropic medicines are included. The reason for including psychotropic drugs in the definition is that we also check the association of polypharmacy with alcohol use.

We agree with the reviewer that possible correlations may exist between psychotropic drugs and polypharmacy. We therefore did multiple sensitivity analyses with the additionally defined 'polypharmacy' variables: 1) we defined polypharmacy by counting the number of prescription drugs only; 2) we defined polypharmacy by excluding psychotropic drugs. Sensitivity analyses involving polypharmacy defined by prescription drugs only showed no substantial changes and the statistical significances did not change either. Sensitivity analyses involving polypharmacy excluding psychotropic drugs showed that the association between polypharmacy and any psychotropic drug use was attenuated while statistical significance remains unchanged (odds ratio 1.88, 95% confidence intervals 1.42-2.48, p<.0001). Also, the associations of polypharmacy with daily or risky alcohol drinking remain nonsignificant. We added this information in the 'Methods' and 'Results' section.

(3) Following from the above question, can the authors address in the discussion what they understand polypharmacy to mean in their sample? Is it related to poor health status? Or perhaps a style of coping with health issues? Because the constructs of polypharmacy and health status were the main predictors of combined alcohol and psychtropic use, it would be useful to provide further consideration of how those constructs intersect and diverge. This discussion could follow from their data or from the extant literature.

RESPONSE: Polypharmacy is common among older adults. Generally we assume that polypharmacy defined by the number of prescription drugs is related to health status based on the fact that polypharmacy is closely associated with multi-morbidities (and thus probably poor health status). Yet, polypharmacy defined by the number of any drugs used may be related to the style of coping with health issues, as phyto-medicine, vitamin and mineral preparations can be included in the definition of polypharmacy. Most of these preparations are self-medication, which is associated with a higher socioeconomic status (DuY and Knopf H. Self-medication among children and adolescents in Germany: results of the National Health Survey for Children and Adolescents (KiGGS). Br J Clin Pharmacol 2009; 68:599-608) and may imply the style of coping with health issues. However, sensitivity analyses suggest there is no substantial difference between the two different definitions of polypharmacy in our study (see above). Further addressing the association of polypharmacy with health status and other health issue is beyond the scope of the study.

(4) I have a question as to whether non-drinkers were removed from the analyses at some point (after Table 1). This question is particularly pertinent for the logistic regression analyses (reported in Table 5). For the alcohol consumption variables what is the comparison group? (e.g., is risky drinking compared to non-drinkers, or to non-risky drinkers, or to everyone in the 2,508 sample who are not risky drinkers?). It is important to be clear about those contrasts because interpretation of the results depends on them. If non-drinkers were removed from the analyses at any point then the functional sample size should be stated and the tables and figure should state the sample size for the analyses shown.

RESPONSE: Non-drinkers were not removed from the analyses. In logistic regression analyses, the dependent variable is dichotomized as 1 versus 0. In the present study, dependent variables were dichotomized as risky drinkers versus not risky drinkers, and daily drinkers versus not daily drinkers. In both cases, non-drinkers are included.

(5) Because the authors are handling 2 different time scales for the alcohol use measure (past 12 months) and the psychotropic drug assessment (past week), they have chosen to examine daily drinking in combination with psychotropic drugs because presumably daily drinking will have happened in the past week (thereby temporally overlapping the alcohol and medication variables). This is a thoughtful decision. A negative side effect is that the findings (as reported in Table 5) lack symmetry. As reported now, the alcohol consumption variables address likelihood of drinking and likelihood of risky drinking. But then the combination variable (alcohol and psychotropics) examines likelihood of daily drinking. This shift renders it difficult to look across the analyses at shifts in the pattern of results. To wit, I wonder if the changes in significant predictors in that final analysis are a function of the combination of psychotropics and alcohol or a function of changing the alcohol variable? One suggestion is that the alcohol variables (when they are treated as individual outcomes) include daily drinking. This could substitute for the 'at least once a week' outcome. And the 'risky alcohol drinking' outcome could be looked at also in combination with psychotropics. This would allow for more symmetry in the analyses and still preserve efforts to maintain some overlap in temporality between the alcohol and psychotropics variables. If it is the case that the proportion of daily drinkers who are risky drinkers is very high then running those as separate analyses may not be appropriate, but it would be useful then to report on how those group comprise roughly the same individuals.

RESPONSE: We agree with the reviewer and thank the reviewer for this helpful suggestion. We chose to add a column of 'daily drinking' in table 5.

In our study, approximately two thirds of daily drinkers are also risky drinkers (figure 1), the results of combined use of psychotropic drugs with daily drinking/risky drinking are similar. In addition, it is daily drinking, instead of risky drinking, that increases the likelihood of current exposure of the two substances. Therefore we chose to present results of combined use of psychotropic drugs and daily alcohol drinking.

(6) In Figure 1 the subgroup sample sizes do not sum to 2,508. There appear to be a large number of participants excluded from this figure. Is this so and why?

RESPONSE: This figure shows data of psychotropic drug use and alcohol drinking only. Data on persons who used neither psychotropic drugs nor alcohol are not shown in the figure. We added the number of nonusers of psychotropic drugs and alcohol into the figure.

Reviewer: 2

Reviewer Name

Paul Sacco

Institution and Country

University of Maryland-Baltimore, United States

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below Dear Authors:

Thank you for the opportunity to review the manuscript, “Psychotropic drug use and alcohol consumption among older adults in Germany. Results from the German health Interview and Examination Survey for Adults 2008-2011”. This manuscript has a number of strengths including the collection of detailed data on medication and other drug use combined with survey data on alcohol consumption. As a representative sample of older adults in Germany, it is informative to the German older adult population, and provides the opportunity to compare German older adults to older adult populations in different countries. Substantively speaking, the unanswered question in this study is the extent to which co-use of alcohol and these drugs leads to documented risk in this population, even as it is identified as a risk factor for falls and other bad outcomes. From the standpoint of methods, the small cell sizes could be problematic in terms of reliable estimates. Perhaps this requires collapsing of categories and not disaggregating classes/types of meds to the extent that has done in the analysis. Comments are provided below by section:

Abstract & Summary:

The use of the word “determinants” is a bit clunky in the abstract. Rather, I would suggest the term “correlates”.

RESPONSE: This has been corrected in the ‘Abstract & Summary’, and also elsewhere in the manuscript.

The use of the word “conjunctive” is also problematic. Perhaps the word “concurrent” would be better here.

RESPONSE: This has also been corrected.

Introduction:

In lines 11-13, the authors report that older adults “…may suffer from emotional and mental disorders more frequently than younger people”. Data from the United States at least, suggest just the opposite. Older adults show lower rates of most major mental health conditions with the exception of the dementias.

RESPONSE: We modified this sentence accordingly.

The authors use the term “elderly” in the second paragraph, but I would suggest only using the term “older adult”

RESPONSE: This has been corrected in the ‘Introduction’ and also elsewhere in the manuscript.

Please change the term “pharmacodynamical” to “pharmacodynamic”.

RESPONSE: This has been corrected in the ‘Introduction’ and also elsewhere in the manuscript.

In lines 30-31, the authors note that alcohol and psychotropic drugs even in small amounts are “extremely harmful”. In my view that would depend on the substance and on the amount of alcohol.

RESPONSE: We reworded this sentence accordingly.

Methods:

The authors focus on the older adults ages 60-79. Was that the oldest age in the survey, or were those over 79 excluded for the current study? Please provide more detail.

RESPONSE: DEGS1 was designed with the aim to provide representative data on the health of adults aged 18–79 years living in Germany (see the 'Methods' section). Drug use data were collected among persons who took part in the medical examination part only. Although DEGS covers a small part of participants aged 80 years and over, they did not take part in the medical examination part and did not provide data on drug use (see the 'Methods' section).

Please change "physicians-administered" to "physician-administered".

RESPONSE: This has been corrected.

In the methods section, would it be possible to the authors to provide some data to readers about how the German alcohol risk limits compare with the United States and/or other countries, specifically the use of the older adult limits.

RESPONSE: In the manuscript we had mentioned that there are no internationally agreed limits for the definition of risky alcohol consumption. We added a sentence saying that established limits do not differentiate according to age. There are studies specifically comparing international limits for risky drinking (see ref. 19, Dawson et al, for example). In the discussion we mentioned different limits used in comparison of findings of our study with studies in other countries including the United States.

The definition of "psychotropic" seems very broad; is there a citation or list of citations that can support the inclusion of so many different drugs. Also, the risk profile with alcohol may also be different depending on the drug, so grouping them may be problematic.

RESPONSE: As far as we know, there is no internationally agreed definition for 'psychotropic drugs'. Depending on study purpose and study design, more or less subgroups can be included under the umbrella term "psychotropic drugs" (for example: Moncrieff J, et al. The psychoactive effects of psychiatric medication: the elephant in the room. J Psychoactive Drugs 2013; 45:409-15. Quintana MI, et al: Psychotropic Drug Use in Sao Paulo, Brazil--An Epidemiological Survey. PLoS One 2015; 10(8):e0135059. Grinshpoon A, et al. Psychotropic drug use in Israel: results from the national health survey. Prim Care Companion J Clin Psychiatry 2007; 9:356-63). In our study, psychotropic drugs include not only 'classical' subgroups of psychotropic drugs, but also some other groups of drugs acting on the CNS. We believe this should have no substantial influence on our results given the fact that the major groups of psychotropic drugs account for the vast majority of all psychotropic drugs. Furthermore, we presented not only overall results but also results of major subgroups. Readers can easily find the groups of interest. Depending on the type of drugs used, the dose, co-medication, morbidity-profile, age, etc., as well as the amount of alcohol consumed, people might be exposed to different risks. To assess individual risk profiles is beyond the scope of this study but constitutes a very important issue.

For missing data, could the authors provide some information on the percentage of data that is missing in these analyses? I recognize that actual n sizes are provided but it would help for the reader to get a sense of much is missing at a glance "(e.g. between xx% and xx%) of data on x and y were missing". Also, some information about how missing data were handled in analyses would be helpful.

RESPONSE: For missing data we added the percentage data in the 'methods' section. And we have mentioned in the 'Methods' section that 'Persons with missing values were excluded from the analyses, with pairwise deletion for descriptive and listwise deletion for multivariable analyses', which shows how missing data were handled in analyses.

In a general sense, could the authors check on the small cell problem for some of the estimates. To what extent are these reliable? When n sizes get down to 17, are the estimates reliable?

RESPONSE: Considering the small sizes in some cells, we gave conservative 95% confidence intervals for each prevalence estimate. The smaller the cell size, the wider the 95% confidence intervals, which suggests generally unreliable estimates.

Results:
On page 8, the authors remark on the "significantly high prevalence rate of psychotropic use". The use of "significant" could be changed as it suggests the statistical term here and that is not what the authors are focused on if I am reading this correctly.

RESPONSE: We modified this sentence.

In table 2, I don't think that including individual agents adds much and the cell sizes get pretty small. Also, certain drug classes are mentioned twice over the table. I would suggest either grouping this information into larger bins by class of drug and report that. Then report the most common drug for each class in the text.

RESPONSE: We agree with the reviewer. We deleted some cells with small ns, but reported them in the text.

In Table 3, the column organization is a bit confusing. There is a column for benzodiazepines and another column for sedative/hypnotics. How are these different? What is included in each group?

RESPONSE: Although benzodiazepines are the major group of sedatives/hypnotics, they can be used for the treatment of other conditions such as epilepsy (anti-epileptics, in the ATC N03 group) and anxiety (in the ATC group N05BA).

The figure, although a nice way of visualizing the data is a bit hard to read. I think that if it is possible. Put the labels directly on the circles. Do no color code, but instead put the percentages inside the fields with the n sizes.

RESPONSE: Because of a large amount of texts for each label, we believe it may be better readable to use footnotes instead of placing the text directly on the circles.

Discussion:

In the discussion, I think it would be helpful to make some general pronouncement about the findings, in relation to other studies. The authors do a great job of talking about other studies, but it would help to get a general sense if these estimates are lower or higher. Then when talking about the comparisons, the authors would benefit from discussing specific methodological factors that explain specific differences in the data.

RESPONSE: In the first paragraph of 'discussion' section, we've summarized the major findings of this study. And we pointed out that comparison of our findings with findings of other studies is limited to study design, study population and methods used, particularly definitions for psychotropic drugs and alcohol consumption. We were reserved to draw a direct conclusion if these estimates are lower or higher than in our study due to the obvious differences mentioned above.

On page 19, the authors use the word "Finish"; Since it is the country, it is "Finnish".

RESPONSE: This has been corrected.

In the discussion, it would be helpful to address the question of whether so-called "risk" of negative effects of alcohol and psychotropic use actually translates to negative outcomes. Recently, I have seen a number of studies focused on alcohol and medication concomitant use, but it remains unclear as to whether this is clinically, and from the standpoint of public health, truly high risk. This is also quite variable when one considers a broadest range of CNS medications and herbal drugs (e.g. St. John's Wort) versus benzodiazepines.

RESPONSE: Identifying the "risks" of concomitant use of alcohol and psychotropic use in epidemiological studies is only the first step. Further well-designed studies are required in order to verify whether the risks found can translate to negative outcomes and are clinically relevant risks. Like most other observational studies, our study has a cross-sectional design, which makes it impossible to draw such conclusion lack of evidence-based outcome evaluations.

We hope that you will find the revised manuscript sufficiently improved and acceptable for publication and we thank you very much for your very valuable contributions

VERSION 2 – REVIEW

REVIEWER	Mitchell Karno, PhD University of California, Los Angeles USA
REVIEW RETURNED	17-Jun-2016

GENERAL COMMENTS	This revised manuscript offers a useful contribution to the literature on factors associated with the use of alcohol and psychotropic medications among older adults. The findings have direct public health implications by identifying poor health status and polypharmacy as risk factors for concurrent daily use of psychotropic medications and alcohol. The authors have been responsive to reviewer comments and the manuscript reads very well. The population based survey design is a strength. The results are presented clearly and the authors provide a thoughtful discussion of the findings.

REVIEWER	Paul Sacco University of Maryland, Baltimore, MD, 21212
REVIEW RETURNED	26-Jun-2016

GENERAL COMMENTS	Thank you for the opportunity to review this paper again. I have a

	few comments regarding minor stylistic elements and suggestions regarding discussion points. Please see below: Abstract/Summary: • I would reword the term “intoxicant substances” to “intoxicating substances” or something else. The usage is not quite right. Measures: • In the USA, there are age specific drinking limits. For men, this number is two standard drinks or 28 grams of alcohol per day and for women it is one standard drink or 14 grams of alcohol. I would suggest some comparison between the values chosen for this study and the risk limits provided by other countries, e.g. USA, Australia, England or others. Essentially, I would suggest that the authors state that the threshold that they have used is lower than some other studies which may account for the prevalence differences. Discussion: • I would suggest some more specific discussion of sedative hypnotics and older adults as this has been an area of specific concern among older adults even in the absence of alcohol. For instance, in the United States, there is a push to improve prescribing practices related to these medications, called “Choose Wisely”. The current recommendation is that older adults should not be prescribed these medications for insomnia, agitation or delirium. The addition of alcohol can only be problematic.For more information on this, see: http://www.choosingwisely.org/clinician-lists/american-geriatrics-society-benzodiazepines-sedative-hypnotics-for-insomnia-in-older-adults/

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name

Mitchell Karno, PhD

Institution and Country

University of California, Los Angeles
USA

Please state any competing interests or state ‘None declared’:
None declared.

Please leave your comments for the authors below This revised manuscript offers a useful contribution to the literature on factors associated with the use of alcohol and psychotropic medications among older adults. The findings have direct public health implications by identifying poor health status and polypharmacy as risk factors for concurrent daily use of psychotropic medications and alcohol. The authors have been responsive to reviewer comments and the manuscript reads very well. The population based survey design is a strength. The results are presented clearly and the authors provide a thoughtful discussion of the findings.

Reviewer: 2

Reviewer Name

Paul Sacco

Institution and Country

University of Maryland, Baltimore, MD, 21212

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

Please leave your comments for the authors below Thank you for the opportunity to review this paper again. I have a few comments regarding minor stylistic elements and suggestions regarding discussion points. Please see below:

Abstract/Summary:

• I would reword the term "intoxicant substances" to "intoxicating substances" or something else. The usage is not quite right.

Response: This has been corrected as 'intoxicating substances'.

Measures:

• In the USA, there are age specific drinking limits. For men, this number is two standard drinks or 28 grams of alcohol per day and for women it is one standard drink or 14 grams of alcohol. I would suggest some comparison between the values chosen for this study and the risk limits provided by other countries, e.g. USA, Australia, England or others. Essentially, I would suggest that the authors state that the threshold that they have used is lower than some other studies which may account for the prevalence differences.

Response: In the discussion section (page 20), we added the comparison of studies from USA (ref. 37), Australia (Ref. 39), and England (Ref. 40). In addition, we added the definition of 'risky drinking', 'heavy drinking', or 'binge drinking', etc. used in the studies to help readers understand this issue. At the end of this paragraph, we wrote that 'The thresholds used in our study are lower than those in some other studies, which may partly account for the prevalence differences between studies'.

Discussion:

• I would suggest some more specific discussion of sedative hypnotics and older adults as this has been an area of specific concern among older adults even in the absence of alcohol. For instance, in the United States, there is a push to improve prescribing practices related to these medications, called "Choose Wisely". The current recommendation is that older adults should not be prescribed these medications for insomnia, agitation or delirium. The addition of alcohol can only be problematic.For more information on this, see: http://www.choosingwisely.org/clinician-lists/american-geriatrics-society-benzodiazepines-sedative-hypnotics-for-insomnia-in-older-adults/

Response: We added the suggestion of American Geriatrics Society at the beginning of the paragraph concerning concomitant use of alcohol and psychotropic drugs, particularly sedatives,

hypnotics and benzodiazepines (Page 21): ‘The American Geriatrics Society suggests that benzodiazepines or other sedative-hypnotics should not be used in older adults as first choice for insomnia, agitation or delirium because of the substantial risks associated with them’.

VERSION 3 – REVIEW

REVIEWER	Paul Sacco University of Maryland-Baltimore USA
REVIEW RETURNED	20-Aug-2016

GENERAL COMMENTS	Thank you for your thoughtful response to my suggestions. They were very thorough and nicely illustrated international differences in alcohol risk limits for older adults. Thank you for including the recommendations about benzodiazepines and older adults as well.