Author's response to reviews

Title: Beverage Specific Alcohol Intake in a Population-Based Study: Evidence for a Positive Association between Pulmonary Function and Wine Intake

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PDF covering letter
We thank Dr. Cassano for her comments and the fair review. Below find our responses to Dr. Cassano’s review.

Please note that reviewers text is in bold, our replies in normal font.

Reviewer’s report

Beverage Specific Alcohol Intake in a Population-Based Study: Evidence for a Positive Association between Pulmonary Function and Wine Intake

Dr Pat Cassano - Reviewer:

I find this paper to be a well-written and straight-forward consideration of the hypothesis that alcohol is associated with pulmonary function. The question is an interesting one, and the finding that there are differential associations by type of alcohol consumed is important to know, both in terms of understanding past conflicting findings and in planning further research. The specific comments below are divided into major and minor points, and numbered within each category.

Major Points:
1. About 60% of the adults studied consume(d) multiple beverage types, making it difficult to disentangle the associations with specific beverage types. Is it possible to identify a subgroup drinking predominantly one type or another? Among the n=933 drinking various beverage types, what proportion are drinking wine? It is difficult to assess whether the wine-only drinkers are the main contributors to the wine-pulmonary function association, or whether the combined beverage group also contribute to these associations.

Reply: We agree with Dr. Cassano’s comment. Due to the limited sample size, it is difficult to disentangle the association with specific beverage types. We acknowledge this shortcoming in the manuscript. As a result of other comments we have modified the presented information. We are presenting the information by beverage type for recent alcohol intake (Table 2). Although our study lacked power for subgroup analyses, there was a trend that among those drinking various beverages recently wine intake was positively associated with lung function. The regression coefficient on FEV1% for wine intake was 1.743 (95% CI, –1.197 – 4.682). For comparison, it was 2.362 (95% CI, -2.490 – 7.214) in those who drank only wine. We included this information in the manuscript. 25% of those drinking various beverages did not drink wine. In addition, the association was present in both those above the median total lifetime alcohol intake and those above the median, while the latter group comprised more beer and liquor drinker.

We included the following section in the results section of the manuscript:

When we performed regression analysis separately by type of recent alcohol intake, there was a trend that among those drinking various beverages recently wine intake was positively associated with lung function. The regression coefficient on FEV1% for wine intake was 1.743 (95% CI, –1.197 – 4.682). For comparison, it was 2.362 (95% CI, -2.490 – 7.214) in those who drank only wine. 25% of those drinking various beverages did not drink wine.

Also relevant is the following section:

Also relevant is the following section:

A second limitation is the limited power to perform more definite subgroup analysis by smoking status or in groups who consumed a single beverage type only. A third limitation is the moderate participation rate and, as a consequence, the restricted generalization of the results to the general public.

Also relevant is the following section:
Our results did not change significantly when we restricted the analysis to participants below the median of total alcohol consumption. In this restricted sample mean alcohol intake from specific beverages differed little and alcohol intake from wine remained the strongest correlate of lung function even after adjustment for other beverage specific alcohol intake. This finding indicates that if those with the heaviest alcohol intake were excluded, the pattern of association between beverage specific alcohol intake and lung function was similar and could support a true positive effect of wine on lung health.

2. The authors are examining total lifetime alcohol consumption, but current vs. past consumption has not been considered explicitly. Do the findings for lifetime consumption mainly reflect current consumption, or is an independent effect of total consumption after current consumption is accounted for?

Reply: We provide results for both the measure of current and the lifetime measure of beverage-specific alcohol intake. We did not find independent additional effects of lifetime alcohol consumption after we included current alcohol intake. Thus, the results indicate no independent effect of lifetime alcohol intake beyond current intake.

We modified the results section and the relevant part reads:
... There was no statistically significant association between lifetime wine intake and lung function after we included recent alcohol intake from wine in the regression models. ...

3. What is the postulated mechanism through which wine may be associated with FVC? If the proposed biological mechanism is via contributions to antioxidant levels, would we expect an effect on FVC? The authors mention that the Cohen paper (ref 18) uses the ratio of FEV1/ FVC: the issue might be informed by a discussion of which outcome indicator(s) should be informative and why, based on the proposed biological mechanism.

Reply: We hypothesize that antioxidant effects in the lung are likely to be cumulative and long-term through defense against oxidative stress (Schünemann, Freudenheim and Grant; Epidemiologic Reviews, 23; 248-267, 2001), but can occur at any stage of early lung development throughout later in life during physiologic lung function decline. Because alcohol intake usually starts later in life, effects of alcoholic beverages are likely to relate to pulmonary function decline. FEV1 and FVC are highly correlated in populations without significant degree of airway obstruction. Thus, results of the analysis of the association between antioxidants and FEV1 or FVC will be similar, unless in a population, free of reported lung disease, very strong effects on airway narrowing or airflow limitation are present. In our analyses we are showing that both FEV1 and FVC are associated with wine intake. A differential effect would have prompted us to investigate, in secondary analyses, effects on airway obstruction (such as the in the report by Cohen et al.). However, the latter was not aim of our investigation.

We modified the discussion and it reads in the revised manuscript:
FEV1 and FVC are highly correlated in populations without significant degree of airway obstruction. Thus, results of the analysis between antioxidants and FEV1 or FVC will be similar unless in a population free of reported lung disease very strong effects on airway narrowing or airflow limitation are present. This study shows that both FEV1 and FVC are associated with wine intake and this leaves us with little evidence for a strong effect of alcohol intake on airway narrowing.

4. Measurement of alcohol intake--The accurate and precise measurement of recent and lifetime alcohol consumption is central to the manuscript. The test-retest reliability of the lifetime measure has been mentioned, but is there any information on the validity of the measures? In the abstract it is stated that a validated questionnaire has been used, but it is not clear if this refers to the measurement of recent, lifetime or both, and it is also not clear which reference (is it reference 32?) provides information on validity (also not clear what type of validity has been demonstrated, eg, concurrent?)
Reply: Although we have not established criterion validity for the questionnaires we have found a high degree of construct validity. In a study involving 147 subjects (reference 32), we compared the average daily volume of alcohol consumed during the 12-24 months prior to the interview as estimated from the alcohol questionnaire with those estimated from two different food frequency questionnaires (FFQ), the Health Habits and History Questionnaire and the Harvard Semiquantitative Food Frequency Questionnaire. FFQs have been shown to produce valid estimates of alcohol intake, with correlations of about 0.5-0.9. In this study, the CLDH compared favorably to the FFQs with correlations between 0.7 and 0.8, and therefore we can infer reasonable validity. Because the FFQs query intake over a one year period, we did not estimate 30 day intake in that study. It is unlikely, however, that the accuracy of 30 day recall would be poorer than over the past year, as there would be less reliance on memory and little need to estimate average intake over the time period. Furthermore, the repeatability of the CLDH over an average two week period was excellent (r=0.84) indicating that this questionnaire performs well in measurement of short term alcohol intake. Although we do have evidence for validity of current alcohol intake, in view of the debate about criterion validity for lifelong alcohol intake measurement we rephrased the section of the manuscript referring to validity (the abstract) and it reads now:

Methods: We expressed pulmonary function as percent of predicted normal FEV$_1$ (FEV$_1$/% and FVC (FVC%) after adjustment for height, age, gender and race. To obtain information on alcohol intake we used a questionnaire that reliably queries total alcohol and beverage specific recent (past 30 days) and lifetime alcohol consumption.

We also included the following in the method section:

We have previously demonstrated construct validity of the questionnaires. In a study involving 147 subjects (32), we compared the average daily volume of alcohol consumed during the 12-24 months prior to the interview as estimated from the alcohol questionnaire with those estimated from two different food frequency questionnaires (FFQ), the Health Habits and History Questionnaire and the Harvard Semiquantitative Food Frequency Questionnaire. FFQs have been shown to produce valid estimates of alcohol intake, with correlations of about 0.5-0.9. In this study, the CLDH compared favorably to the FFQs with correlations between 0.7 and 0.8, and therefore we can infer reasonable validity. Because the FFQs query intake over a one year period, we did not estimate 30 day intake in that study. Furthermore, the repeatability of the CLDH over an average two week period was excellent (r=0.84) indicating that this questionnaire performs well in measurement of short term alcohol intake.

5. If wine is postulated to contribute to antioxidant status, is there any possibility of over-control in adjusting the analysis for antioxidants measured in serum (and by the way seems to be in serum, not in diet as stated in paper on page 19, line 7). If so, given other publications by the same authors, we know that there are more complete data on antioxidants. If all the antioxidants are adjusted (rather than just the few that have statistically significant associations), is the effect size diminished?

Reply: Adjusting for dietary antioxidants is one way to adjust for a healthy diet and possible control for confounding by healthy diet. As suggested by the reviewer, in the revised manuscript we have adjusted for other possibly important antioxidants in the regression model. We recalculated regression coefficients. Therefore, the coefficients are slightly changed. (We also included 95% confidence intervals for the coefficients as the reviewer suggests in the last comment.) Overall, there is little change in the results for alcohol intake after including these other antioxidant vitamin variables the reviewer refers to.

In regards to the word *dietary* in the sentence Dr. Cassano refers to: The way that we interpret dietary antioxidant intake data is, that there is often only little correlation between what we obtain from dietary questionnaires and what we measure in serum. However, if there is any influence of antioxidant vitamins on lung function, it will be largely attributable to dietary intake even though effects of metabolism may also play a role. Thus, the use of the word *dietary* in the conclusions (but not in the methods or results).

The relevant section now reads:
… In addition, we previously reported that several serum and dietary antioxidant vitamins levels were correlated with pulmonary function (11,34). Therefore, we included these serum antioxidant vitamins in the regression models for FEV1% (vitamin E, vitamin C, lutein/zeaxanthin, β-cryptoxanthin and retinol) and FVC% (vitamin E, vitamin C, β-cryptoxanthin and lutein/zeaxanthin)…

6. How was the internal prediction equation developed (maximum R-squared?) and how does it compare to external standards that are in common use (eg., Hankinson et al 1999).

Reply: The choice of the internal prediction equation was based on the largest fraction of variability ($R^2$) in FEV$_1$ and FVC explained. In this and in previous analyses, we have observed that the choice of internal or external prediction equation has almost no bearing on the results observed. Pearson’s correlation coefficients for the predicted FEV$_1$ and FVC using NHANES III and our prediction equation for the different subgroups of the population were as follows:

**MEN**
- Caucasian
  - FEV$_1$ = 0.99
  - FVC = 0.99
- African-American
  - FEV$_1$ = 0.99
  - FVC = 0.99

**WOMEN**
- Caucasian
  - FEV$_1$ = 0.99
  - FVC = 0.99
- African-American
  - FEV$_1$ = 0.97
  - FVC = 0.94

We modified the text and it reads now:

… We chose the model that explained the greatest fraction of variability ($R^2$) in lung function….

7. Did the Cohen paper (ref 18) find any trend in the same direction?

Reply: After adjusting for other variables there is no trend across the classes of light moderate and heavy drinkers in the paper by Cohen et al. However, as we describe in the manuscript Cohen et al. focus on airways obstruction as an outcome measure. Thus, their results are not comparable to our results.

8. Ultimately, it would be helpful to put the results back into units that are more easily interpreted. Perhaps you could express the association of wine (from the best model) with FEV1 in terms of drinks per day of wine and %predicted FEV1?

Reply: We don’t agree that expressing the results in FEV$_1$% per drink per day is useful for the analysis of alcohol data, because this measure leaves uncertainty due to variation in drink size across populations. Unless a drink is defined by amount of alcohol or in volume of beverage it is not useful for comparison. This data can be derived from the tables.

9. In Table 3, since white wine is so much more strongly associated than red wine, why not try the simultaneous model with white and red wine as separate variables? Is multicollinearity a problem?
Reply: The reviewer is correct. Multicollinearity is a problem. Red and white wine intake are highly correlated.

The relevant section in the manuscript reads:
…The correlation between red and white wine intake were high for both recent ($r = 0.8$) and lifetime ($r = 0.5$) intake...

10. It might be helpful to provide some additional discussion of the lack of association of total alcohol with FEV1, which is brought about by associations in opposite directions for the subtypes of alcohol (at least in Table 4 for total alcohol intake).

Reply: Please note the coefficients changed after adjusting for other antioxidant vitamins as suggested above. However, we did extend the discussion and the relevant section reads:

Evidence suggests that alcohol may increase oxidative burden (12, 13, 14, 15). However, while alcohol could potentially act as an oxidant, there is a large body of evidence that wine has antioxidant properties (12, 13, 16, 17). Our data indicate that these antioxidant properties might exist and could have positive influence on lung function.

11. The authors suggest that the stronger association of white wine is due to residual confounding by smoking. If the analysis is limited to the subgroup of nonsmokers (hence no residual confounding possible), is the effect of white wine still greater?

Reply: The effect is slightly weaker in never-smokers (possibly because we remove the residual confounding by smoking), but because of the large proportion of participants who did not consume wine among the never smokers we lose power rapidly. We see this as evidence that residual confounding may play a role.

12. Given the proposed biological model, effect modification of the wine-pulmonary function association by cigarette smoking was considered. Small numbers of current smokers yields low power for such an analysis. Have the authors considered the subgroup of ex-smokers (as 43% are former smokers)? Are there data on time since quitting?

Reply: We have not noted effect modification by smoking, including the group of ex-smokers. We have added the information and the fact that we adjust for smoking status to the relevant section and tables 3 and 4.

The relevant section reads:

However, we determined that interaction terms would be important if the level of significance was $p < 0.1$. We investigated interaction by including interaction terms of beverage specific alcohol intake, smoking status (never, former, current), gender and other covariates and stratification, but we did not observe statistically significant interactions.

13. Page 15, line 16/17: Sentence reading "Alcohol from beer and liquor is significantly related to pulmonary function" doesn't fit with findings. Is this an error?

Reply: The reviewer is correct. The text should have read “Alcohol from beer and liquor is not significantly related to pulmonary function.” We corrected this error.

14. In looking at the various beverage types, are there consumers of all types across all ages, or is there a cohort effect such that heavy lifetime consumers of hard liquor are all older?

Reply: We did not identify important trends of age by type of alcohol consumption (Table 2).
Minor Points:
1. pg 9, line 13: does "related to alcohol" mean the alcohol variables themselves? Are these log base10 or natural log? Please provide some information for assessing the magnitude of the association as it is presented only for a unit change in the log-transformed variable (tables 3 and 4).

Reply: We referred to the alcohol variables themselves. We agree that information on log transformation is missing frequently in publications on nutrients and lung function. Transformation was based on lg10 (alcohol intake + 1), where alcohol intake resembles current or lifetime beverage specific or total alcohol intake, respectively. We included this information in the methods section and Tables 3 and 4. The relevant section reads:

...The total and beverage specific alcohol intake variables were not normally distributed and, therefore, we performed a logarithmic transformation. Transformation was based on lg10 (alcohol intake + 1), where alcohol intake resembles current or lifetime beverage specific or total alcohol intake, respectively...

2. What are the numbers of subjects in the various regression models presented? Are all subjects in the regressions (n=1555?) regardless of single or multiple beverage type?

Reply: All subjects are included. We added to the methods section and the relevant sentence reads now:

...The principal analysis we used was multiple linear regression analysis including all 1555 subjects...

3. page 13, first paragraph: sentence beginning "There was some indication that hard liquor consumption was negatively associated...." Does this sentence refer to the finding in the simultaneous model in Table 3? If so, please clarify.

Reply: We have removed this sentence after including other antioxidant vitamin variables in the model, because the coefficients became smaller (see above).

4. page 13, final sentence: Would it be simpler to say that beer had little or no association with pulmonary function?

Reply: We agree and modified this sentence. In the revised manuscript it reads:

.. Alcohol intake from beer and liquor showed little or no association with lung function...

5. page 13, lines 13-15: These data do not appear in table 4 which is being discussed here. It would be helpful to clarify that the data are not shown or to amend the table to show these findings.

Reply: We clarified that the data are not included in Table 4.

The relevant section reads:

The association of alcohol intake from white wine persisted even after inclusion of other alcohol variables in the regression model, but red wine was not significantly related to lung function (data not shown).

6. page 14, paragraph: It would be helpful to have some idea of how the effect sizes compared when the top portion of the alcohol distribution was omitted.

Reply: The regression coefficients (95% CI) on FEV1% for wine intake were 2.024 (0.075 - 3.973) in those below the median and 1.967 (0.628 – 3.306) for those above the median.

We included this information in the manuscript. The relevant section reads:
The regression coefficients (95% confidence intervals, CI) on FEV₁% for wine intake were 2.024 (0.075 - 3.973) in those below the median and 1.967 (0.628 – 3.306) for those above the median.

7. page 15, line 3: Suggested wording change, as follows: "lifetime alcohol intake from wine" to "lifetime intake of wine (grams alcohol)"

Reply: We do not believe that this wording suggestion improves readability or accuracy of the conveyed information and have not changed the phrase.

8. page 15, line 6/7: Please clarify how residual confounding may explain the difference between the regression coefficient for red wine compared to the regression coefficient for white wine.

Reply: This summary statement is explained in the following section in the discussion:

Alternatively, it is conceivable that the stronger association of white wine with pulmonary function compared with red wine may also be due to confounding by other, healthy lifestyle factors. Approximately 74% of the participants reported both red and white wine intake during their lifetime. Compared with those who did drank red wine but not white wine, total pack years of smoke exposure was higher in participants who reported white and red wine intake together (15.7 versus 10.9 pack years, p < 0.05) and, thus, residual confounding by smoking and/or other lifestyle factors could again explain our findings. Because of the limited sample size in the subgroups of wine drinkers we were unable to provide strong data in groups who only consumed either red or white wine.

9. page 17, line 7: delete the word "did" from "did drank"

Reply: We made this change.

10. page 17, first sentence: Do the properties of flavonoids and other compounds refer to red wine specifically, or to both red and white wine?

Reply: We clarified this section. It reads now:

There is strong evidence that the antioxidant properties of wine are, at least in part, due to activity of different flavonoids and other compounds (reference). In addition, white wine contains several phenols with antioxidant activity (references).

11. page 18, last line: Suggest rewording to read, "this study is important in that it suggests the importance of beverage type in assessing the relation of alcohol to pulmonary outcomes."

Reply: We agree with the suggestion and made this change.

12. Tables: as 3% are never drinkers, where do the n=219 come from in Table 2 (they are called no alcohol, and apparently classified by lifelong alcohol intake, but the numbers are not would be expected based on how I read Table 1)

Reply: We had previously provided information using different classifications of never drinker and non-current drinkers using the lifetime and recent intake. We have corrected this error in table 1 and 2 and provide the information using the classification described in the methods section. In Table 2 we present only the information for recent alcohol intake by beverage type.

13. Table 3. The asterisk indicates that 1.933 is statistically significant at p=0.05, but my calculation of the 95% confidence interval includes 0 (-0.08, 3.95) suggesting that this p value may be in error. The confidence intervals would be useful here, rather than the SE, although one can derive each from the other.
Reply: The regression coefficient was in error. However, we are presenting information according to the suggestion below and there are slight changes to all regression coefficients. As the reviewer suggested we have included 95% confidence intervals for all coefficients in table 3 and 4.

14. Table 3. What base is the log transformation?

Reply: We included this information (see above).