Author's response to reviews

Title: Alcohol consumption and risk of gastric cancer: a cohort study of men in Kaunas, Lithuania, with up to 30 years follow-up

Authors:

Ruta Everatt (ruta.everatt@vuoi.lt)
Abdonas Tamosiunas (abdonas.tamosiunas@lsmuni.lt)
Irena Kuzmickiene (irena.kuzmickiene@vuoi.lt)
Dalia Virviciute (dalivirv@itc.kmu.lt)
Ricardas Radisauskas (ricardas.radisauskas@lsmuni.lt)
Regina Reklaitiene (regina@lsmuni.lt)
Egle Milinaviciene (egle.milinavicienegle.milinaviciene@kaunoklinikos.lt)

Version: 2 Date: 6 September 2012

Author's response to reviews: see over
Dear Danrolf de Jesus

Thank you for the opportunity to respond to the valuable and helpful reviewers’ comments, and resubmit the paper entitled “Alcohol consumption and risk of gastric cancer: a cohort study of men in Kaunas, Lithuania, with up to 30 years follow-up”. We revised the paper according to the reviewers’ comments.

Below are our point by point responses to the editorial point and reviewer’ comments. The changes are indicated in the manuscript as Bold text.

We hope that you will find our revisions satisfactory.

Thank you again for your kind consideration of this paper.

Yours sincerely,
Ruta Everatt
Editorial points

Consent - Please state in the Methods section whether written informed consent for participation in the study was obtained from participants or, where participants are children, a parent or guardian.

Response:
We now state in the Methods section: “Participants (volunteers) gave no written informed consent prior to the baseline examination as this was not required in the former Soviet Union” (p. 6, paragraph 2).

Different methods were used to invite the subjects to participate in the Kaunas Rotterdam intervention Study and Multifactorial Ischemic Heart Disease Prevention Study: personal invitations, telephone calls and standard letters of invitations [Glasunov IS, Dowd JE, Baubiniene A, Grabauskas V, Sturmans F, Schuurman JH: The Kaunas Rotterdam Intervention Study. Amsterdam, Elsevier/North-Holland Biomedical Press 1981]. No written informed consent to participate in the baseline interview and screening examination of Health Intervention Programmes was required in the former Soviet Union.

Referee 1: Francesco Gianfagna

Discretionary Revisions
1. The incidence of gastric cancer for each beverage type and, among these categories, for each amount should be reported (preferably adjusted for covariates). Computing raw incidence from number of cases and person-years reported in the table, a j-shaped curve among wine intake categories could be observed, suggesting a favorable effect of moderate wine consumption, which could be suggested also by observing the slightly higher incidence in the other categories. At the same time, the incidence in subgroup of heavy drinkers appears to be very high, which becomes more evident observing the apparent lower incidence in heavy drinkers of other beverage types. Then, once these data are confirmed by the Authors, when we observe incidence in categories, we should be more convinced that the significant association between different amounts of wine consumption, even if explained at least in part by minor incidence in reference group, is mainly driven by a true major effect observed in heavy drinkers.

Response: In assessing relationship between the factor and the disease in our cohort with multiple levels of exposure and multiple covariates, we believe that multivariate Hazard Ratio estimates obtained from Cox regression analysis are more useful than incidence rates. However, we agree with the reviewer that it is interesting and important to see incidence rates for comparison of disease risk across different types of alcoholic beverages. Very high incidence among heavy drinkers of wine compared with heavy drinkers of other beverage types support the observation of an increased risk among greater consumers of wine, already observed using HR estimates. To provide the reader with the most comprehensive information, we report now incidence rates and HRs in Tables 2 and 3, as suggested, while recognising that unadjusted incidence rates require cautious interpretation. We have modified Methods, Results and Discussion accordingly (p. 10 paragraph 1, p. 12 paragraph 3, p. 14 paragraph 3).
We are reluctant to conclude that our data suggest a favorable effect of moderate wine consumption, because: 1) the incidence rate among moderate drinkers of wine is very similar to
incidence of moderate consumers of vodka, 2) it is likely that group of moderate drinkers of wine has the lowest risk of gastric cancer because wine non-drinkers group might include participants who may have stopped drinking wine due to health problems related to gastric cancer.

2. Mean age at diagnosis in different categories of estimated ethanol amount or kind of beverages could be added, to have an estimate of the public health impact of heavy drinking, along with the number of gastric cancer cases expected to be attributable to heavy drinking at population level.

Response: We calculated mean age at diagnosis in categories of estimated ethanol amount (g/week) and in categories of alcohol consumption frequency. Both calculations produced similar results. We added a line in Table 1 to provide the mean age at diagnosis in categories of alcohol consumption frequency. The estimates for categories of ethanol amount (non-drinkers, 0.1–9.9, 10.0–24.9, 25.0–99.9 and ≥100.0 g/week of ethanol) were 67.6, 66.4, 66.3, 67.3 and 66.7 years respectively.

We present now the population attributable fraction for this cohort according to suggestion (p. 11 paragraph 2). We have supplemented Methods and Discussion section accordingly (p. 10 paragraph 1, p. 13 paragraph 2).

3. Since acetaldehyde content was estimated by kind of beverage, confounding factors as non-alcoholic components of beverages cannot be considered in analyses comparing ethanol and acetaldehyde content in the same statistical model. In fact, wine has the highest acetaldehyde content, but it contains also substances thought to be protective. Then, considering both acetaldehyde and ethanol in covariates, the reduced HR (towards apparently protective values) could be due to this confounding. Perhaps this comment could be added in discussion.

Response: We agree with the suggestion, this has been added in the Discussion (p. 16 paragraph 2).

Minor Essential Revisions

4. In abstract, sentence on analysis using all kind of beverages as covariates is not clear, perhaps it requires a more detailed explanation; furthermore it seems not to be shown and explained in full-text; similarly, in abstract conclusions, 'equivocal' evidence of acetaldehyde effect could be explained more in details.

Response: We provide more detailed explanation in the abstract as suggested. Although the sentence „In the analysis of beer, wine and vodka consumption, all beverages were included simultaneously in the model“ is in the Methods (p. 9 paragraph 2), we also provide more detailed explanation in the full-text (p. 12 paragraph 3). We have modified abstract conclusion according to suggestion.

5. In methods, the Authors should indicate a reference if the questionnaire was used also for other publications.

Response: The reference where the questionnaire was published as well as a study where the questionnaire was used, has been specified in Methods (p. 6 paragraph 3). There were a number of other publications, however due to lack of space we could not include them.
6. Results could be structured in population description, effect of ethanol amount and of kind of beverages; perhaps result section requires to be smaller, some results shown in tables could not be shown also in full-text.

Response: Results section was structured in population description (no specific subtitle), ‘effect of drinking frequency and ethanol amount’, ‘type of alcoholic beverage’ and ‘acetaldehyde intake’. We deleted some sentences or parts of them where results are reported in the text and in the table (p. 11 paragraph 2 and p. 12 paragraph 1).

7. It is not clear if a statistical test was performed to compare values in categories shown in table 1.

Response: Statistical tests were not performed to compare values in categories shown in Table 1 as we believe that they are not very useful for data description. In the text (Results) we describe only factors, which obviously change with alcohol consumption (education and smoking), we took out comment on BMI (p. 11 paragraph 1).

8. In table 3 decimals of person-years could be deleted; the note ‘a’ appears at the bottom of the table; the Authors should specify if ‘stratified by study’ means that ‘study’ was used as class variable in covariates.

Response: Decimals of person-years were deleted as suggested (Tables 1, 2 and 3). ‘a’ at the bottom of the table 3 indicates that Cox models were stratified (in STATA using strata(STUDY)), ‘study’ as a stratification variable (not as covariate), to control for possible differences across two cohorts. We revised the Methods section according to suggestion (Statistical analysis, p. 8 paragraph 1).