Author's response to reviews

Title: Alcohol consumption and carotid artery structure: a population-based cross-sectional study of Korean adults aged 50 years and older

Authors:

Young-Hoon Lee (lyh8275@hanmail.net)
Min-Ho Shin (mhshinx@paran.com)
Sun-Seog Kweon (uijingogo@paran.com)
Sung-Woo Choi (jcsqw74@hanmail.net)
Hye-Yeon Kim (dainghi@naver.com)
So-Yeon Ryu (canssy@chosun.com)
Bok-Hee Kim (kimbh@chosun.ac.kr)
Jung-Ae Rhee (jarhee@healthis.org)
Jin-Su Choi (jschoix@chonnam.ac.kr)

Version: 3 Date: 4 August 2009

Author's response to reviews: see over
Author's response to reviews

Title: Alcohol consumption and carotid artery structure: a population-based cross-sectional study of Korean adults aged 50 years and older

Authors:

Young-Hoon Lee (lyh8275@hanmail.net)
Min-Ho Shin (mhshinx@paran.com)
Sun-Seog Kweon (ujingogo@paran.com)
Sung-Woo Choi (jcsw74@hanmail.net)
Hye-Yeon Kim (dainghi@naver.com)
So-Yeon Ryu (canrsy@chosun.com)
Bok-Hee Kim (kimbh@chosun.ac.kr)
Jung-Ae Rhee (jarhee@healthis.org)
Jin-Su Choi (jschoix@chonnam.ac.kr)

Version: 2 Date: 7 August 2009

Author's response to reviews: see over
Dear BioMed Central Editorial Team

Thank you for the opportunity to revise our manuscript, and also thank the reviewers for the useful and insightful comments. In accordance with reviewers’ suggestions, we have highlighted changes in the revision manuscript by using bold font. Enclosed with this letter please find a point-by-point response to concerns. We hope that all the suggestions and corrections have been incorporated appropriately, and hope that it is suitable to be reviewed and considered for publication please. Thank you for your consideration. We look forward to hearing from you.

Sincerely yours,

Young-Hoon Lee,
Min-Ho Shin,
Sun-Seog Kweon,
Sung-Woo Choi,
Hye-Yeon Kim,
So-Yeon Ryu,
Bok-Hee Kim,
Jung-Ae Rhee,
Jin-Su Choi
Reviewer: Ulf Schminke
Reviewer's report:
This study aims to investigate the association between subclinical carotid atherosclerosis and alcohol consumption in a population based study in South Korea. Carotid ultrasonography was performed in 4302 subjects at age 50 or older to assess common carotid artery (CCA) intima media thickness (IMT), carotid bifurcation (CB) IMT, carotid artery plaques and the diameter of the CCA. Their main findings were that alcohol consumption was inversely associated with CCA-IMT and CB-IMT in men but not in women. In contrast, carotid plaques were positively associated with alcohol consumption of more than 40g/d. Alcohol consumption was further associate with carotid artery enlargement.
Although this is a well-written manuscript, there are some critical issues:

Major compulsory revisions
1. A major limitation of the study is the low response-rate of the residents of the study area to the invitation to take part in the study. The response rate was 27.9% in women and 19.9% in men, respectively. This is considerably lower than response rate reported in other studies, which is higher than 60% in the some major studies. This limitation needs to be discussed, specifically, since a response rate of less than 30% does not mirror the entire population, anymore. Therefore, the authors should not use the term ‘population-based’ in the introduction and in the discussion (Paragraph on strengths and limitations).

Authors’ comments: We have replaced the title with “Alcohol consumption and carotid artery structure in Korean adults aged 50 years and older” to address the reviewer’s comment. As suggested, we have removed the term ‘population-based’ from the Introduction and Discussion. We have added a comment to our discussion of the study’s limitations:

First, an important limitation of our study is the low response rate (24.3%) of the residents of the study area, despite numerous contacts by telephone requesting participation. It is possible that many potential respondents overlooked the telephone invitations. The response rate of this study was considerably lower than that reported in other studies; it has been higher than 60% in some major studies. It is possible that a response rate of less than 30% does not reflect the status of the entire population.
2. Methods: The authors should describe in more detail, how they have defined never-drinker and former-drinkers, and more importantly, which methods they have used (interview, which questions were asked?; biomarker?) to separate both groups from each other.

Authors’ comments: As suggested, we have now provided this information in the Methods section:

Alcohol intake was assessed using a structured interview, including four questions. The following two questions were used to determine the current drinking status of the study population: "Prior to the date of this study, have you ever drunk alcoholic beverages?" and "Do you presently drink alcoholic beverages (in the 12 months prior to this interview)?" Participants who answered "no" to both questions were classified as never-drinkers (lifetime abstainers). Participants who answered "yes" to the first question and "no" to the second question were classified as former drinkers. Current drinkers were defined as participants who answered "yes" to both questions. Current drinkers additionally answered two related questions: “On a day when you do drink alcohol, how many drinks do you usually have?” and “How often do you have a drink containing alcohol, per month?” The amount of ethanol consumed per day was calculated from the average number of alcoholic beverages consumed.

No biomarker was used to separate never drinkers from former drinkers.

3. Methods. IMT measurement: Which methods were used to measure IMT? Did the authors measure IMT manually or with the use of an automated edge tracking software? If IMT was measured manually, how many measurements were performed in a single arterial segment, e.g., on the CCA far wall? Did the authors perform only a single measurement on each CCA at a point 10mm proximally to the carotid bifurcation or did the authors perform multiple (e.g. 10) measurement in an arterial segment of 10mm in length? If the latter was true, did the authors calculate a mean value out of 10 measurements on each CCA or did they use the maximum value out of 10 measurements per arterial segment and calculate the mean of the maximum values of both CCA to obtain the mean IMT? Reading the present version of the measurement, it seems that only a single point measurement at each arterial segment was performed. If this
true, the single point measurement of the CCA-IMT of each segment is more prone to measurement error compared with an average value out of 10 measurements. Is it possible to re-read the ultrasonography images to perform either manual IMT measurement of at least 10 measurement points per arterial segment or an automatic IMT reading using an edge tracking software? This would improve reproducibility considerably. Otherwise the limitations of a single point measurement have to be discussed. Moreover, only the measurement point of the CCA IMT measurement was explained in the methods section: Where did the authors measure carotid bulb IMT?

Authors’ comments: We measured carotid IMT and diameter manually, using the SigmaScan software. We did not calculate a mean value of two to five measurements in each arterial segment. We also now explain the measurement point of the carotid bulb IMT in the Methods:

\textit{Between the carotid bulb origin and a point 10 mm proximal to the common carotid artery on the longitudinal view (10 mm in length), we performed multiple (two to five) measurements to determine the maximal IMT of the CCA. The maximal value of two to five measurements was determined as ‘the maximal IMT value of the left/right CCA.’ We also performed multiple (two to five) IMT measurements between the origin of the carotid bulb and the origin of the internal carotid artery to determine the maximal IMT of the carotid bulb. The maximal value of two to five measurements was determined as ‘the maximal IMT value of the left/right carotid bulb.’ Finally, ‘CCA-IMT,’ defined as the average of the maximal values of both CCA and ‘CB-IMT,’ defined as the average of the maximal values of the four arterial segments, including the CCA and bulb of the left and right carotid artery, was used for analysis.}

Unfortunately, it was not possible to re-examine the ultrasonography images to perform manual IMT measurements. As suggested, we have added a statement to our discussion of study limitations:

\textit{Fourth, we determined the maximal IMT value at each arterial segment by a single maximal point selection, rather than the mean of multiple measurements. Single-point measurement of the IMT of each segment is more prone to measurement error than an average value of multiple measurements. Moreover, because we measured the IMT value manually, the reproducibility of our study was lower than that of other\ldots}
studies using automated edge-tracking software.

4. Methods. ultrasonography: The authors provide information on the reproducibility of the ultrasonography measurement only for the procedure of IMT measurement. What was the interreader and intrareader variability for the detection of carotid plaques and of the diameter measurement of the CCA? How many technicians were involved in the study? Was the measurement procedure performed by the same technician who performed the scanning procedure?

Authors’ comments: Two technicians evaluated the carotid artery structure in all participants. Of the two ultrasonography technicians, only one performed the scanning procedure. We have addressed the inter-reader and intra-reader variability for the detection of carotid plaques (using the kappa coefficients) and of the diameter measurement of the CCA (using the correlation coefficients) in the Methods section: The correlation coefficients for between and within examiner variability were 0.86 and 0.90, respectively for CCA-IMT and 0.87 and 0.95, respectively, for CCA-diameter. The kappa coefficients were 0.76 for between-examiner agreement and 0.85 for within-examiner agreement.

5. Methods. ultrasonography: The CCA is a pulsatile vessel. Did the authors perform the diameter measurement ECG-triggered?

Authors’ comments: The high-resolution B-mode ultrasound used in our study did not provide ECG on carotid measurements. Instead, we evaluated consecutive images of the carotid artery during a 10-s phase (video clip) and stored images of the minimum common carotid artery diameter, representing end-diastolic phase.

6. Methods. Covariates: Physical exercise was categorized as none, irregular and regular according to which criteria?

Authors’ comments: We have added the below sentences to the Methods section. Physical exercise was assessed by asking the frequency of recreational activity and exercise over 30 min during a week. Physical exercise was categorized as none (0-1 time per week), irregular exercise (2-4 times per week), and regular exercise (5 or more times per week).
7. Discussion: While carotid IMT and carotid plaques are well-established so-called intermediate risk factors, which have been shown being associated with prevalent vascular risk factors and also prevalent and incident cardiovascular and cerebrovascular diseases, the role of carotid diameter enlargement as a surrogate marker for subclinical atherosclerosis is rather unknown. The authors should provide some information, either in the introduction or in the discussion, on studies, which have investigated associations of carotid diameter enlargement with vascular risk factors and also with prevalent or incident vascular disease such as stroke or myocardial infarction. Specifically, they should elucidate the question why they think that carotid diameter enlargement could play a role as a predictor of future cardiovascular or cerebrovascular events. Are there any reports about this topic in the literature?

Authors’ comments: Most previous studies have focused on the role of arterial luminal enlargement in compensating for thickening of the arterial wall. In fact, without this compensatory mechanism, the arterial wall would cause the lumen of the artery to narrow, thereby subjecting the endothelium to an increase in shear stress, caused by blood flow. The artery appears to compensate for the presence of thickened walls by dilating, thereby stabilizing the shear stress caused at the interface between the blood and endothelium. Although atherosclerosis often leads to lumen narrowing and symptomatic cardiovascular disease, it is now recognized that arteries have the potential to compensate by enlarging in response to atherosclerosis. Many studies have reported that arterial diameter is correlated with cardiovascular risk factors, such as systolic blood pressure, body mass index, smoking, alcohol consumption, blood lipids, and carotid artery IMT. Furthermore, carotid enlargement has been considered as a surrogate end point of cardiovascular events. The Rotterdam Study reported a positive association of carotid lumen diameter with acute myocardial infarctions [32]. A larger lumen in diastole might reflect a lesser intrinsic vessel elasticity and thus a stiffer vessel, which might explain the positive association. The Three-City Study found that the increase in carotid distension was significantly predictive of CHD occurrence independently of age, sex, brachial and carotid PPs, heart rate, antihypertensive drugs, CCA-IMT, carotid plaques, and other major cardiovascular risk factors [33].
8. Discussion: It is difficult to read if the amount of daily alcohol intake because it is given in some studies as drinks per week, in others as ml per week, and in the present study as g per day. Alcohol consumption should be uniformly expressed in g per day.

Authors’ comments: As suggested, we now state alcohol content in grams. We have revised the unit of alcohol consumed in grams per day (g/d) accordingly. However, in reference 12, we cannot convert the alcohol unit (mL/wk) to grams per day, because there is information missing about beverage types and ethanol content.

9. Discussion: The present study categorized daily alcohol consumption in categories of 0, 1-10g/d, 11-20g/d, 20-40g/d, and >40g/d. These categories are different from categories used in other studies. Reference 13 classified alcohol consumption in groups of 0, 1-20g/d, 20-40g/d, 40-60g/d, 60-80g/d and >80g/d. The authors of reference 13 reported a linear decrease of IMT with increasing alcohol consumption up to 60-80g/d. An increase of IMT was reported in the group with an alcohol intake >80g/d. Furthermore, reference 2 reported a protective effect of alcohol against coronary heart disease up to 72g/d, while the harmful effect started at >89g/d. Compared to these studies, the overall daily alcohol consumption in the population from South Korea was lower. The choice of categories with the highest categories of >40g/d made it impossible to find a J-shaped relationship. On the other hand, the linear decrease in IMT across categories as shown in the present study is still in line with references 2 and 13, because both showed a linear trend towards lower IMT up to an alcohol intake of 40g/d. This problem should be discussed.

Authors’ comments: Thank you very much for insightful comments. We agree that this is an important point. Many studies, including reference 13, have shown a J-shaped relationship between alcohol intake and carotid atherosclerosis. However, we did not find the J-shaped or U-shaped association between alcohol consumption and carotid atherosclerosis described in previous epidemiological studies. Instead, we observed a linear decrease in carotid IMT and a linear increase in carotid plaques with alcohol intake in men, but not women. In comparison with other studies, young adults, aged 20-49 years old, were not included in our study. In South Korea, the amount and frequency of alcohol consumption is generally lower for older than younger adults.
As suggested, we reclassified alcohol consumption into groups of 0, 1-20 g/d, 20-40 g/d, 40-60 g/d, 60-80 g/d and > 80 g/d. However, we found no increase of IMT in the group with an alcohol intake > 80 g/d. Moreover, we also observed a linear decrease in carotid IMT with the reclassification. One possible explanation for these findings is the influence of former drinkers. In Table 3, former drinkers had higher IMT values than current drinkers (0, 1-10 g/d, 11-20 g/d, 20-40 g/d, and > 40 g/d). Another possible explanation is the influence of measurement error. In particular, heavy drinkers tend to underreport their alcohol consumption. Recall bias among an older population might also have occurred. However, alcohol consumption was positively associated with biochemical parameters that are correlated with alcohol use, including AST and GGT, in men, suggesting that the alcohol consumption values in our study were reasonably valid.

Some studies have found a J-shaped relationship between alcohol consumption and carotid IMT, whereas others, including the ARIC study [14], the NHLBI Family Heart Study [15], and the Three-City Study [16], reported no relationship between alcohol intake and carotid atherosclerosis. Thus, we think that our finding of a linear inverse association between alcohol intake and carotid IMT is noteworthy.

10. References: Reference No. 13 and No. 30 are the same.

Authors’ comments: We have corrected this.

Minor essential revisions
1. Page 5. Methods, 5th sentence: ‘….who resides in five dong in the DONG-gu district of the Gwangju Metropolitan City of South Korea, …’ The word ‘dong’ should be translated into English.

Authors’ comments: We have corrected this.

2. Page 7, second paragraph, 4th sentence: ‘The presence of cardiac plaques was recorded, if…’ The word ‘cardiac’ should be replaced by ‘carotid’.

Authors’ comments: We have corrected this.
Reviewer: Daejung Kim
Reviewer's report:
I think this study is well designed, and composed of large sized data. The main finding that alcohol consumption might be protective role to carotid atherosclerosis is very interesting. However, if these finding would be acceptable, several explanation should be needed.

1. Why are different between CCA-IMT and carotid plaque as association with alcohol consumption?

Authors’ comments: To our knowledge, only one reported study [16] has evaluated the difference between carotid IMT and carotid plaque in association with alcohol consumption. A weak positive association between alcohol consumption and carotid plaque was observed in men, although no association between alcohol consumption and carotid IMT was observed. However, we have reported that high alcohol consumption is associated with a decrease in CCA-IMT and an increase in the occurrence of carotid plaques in men. We explained this discrepancy by differences in histological characteristics and the stage of carotid atherosclerosis in the study. Several epidemiological studies have shown that the natural history, pattern of risk factors, and the prediction of cardiovascular events are different for carotid IMT and carotid plaques. Atherosclerosis proceeds through a series of pathological stages: (a) intimal medial thickening; (b) fatty streaks; (c) intermediate lesions; (d) fibrous plaques; and (e) complex plaques. Although CCA-IMT and carotid plaque are commonly related with subclinical atherosclerosis, brain ischemia, and ischemic heart disease, they have different pathologic characteristics. It has been suggested that the intima-media layer of the arterial intima and media cells thickens at an early stage of atherosclerosis in response to lipid deposits and high blood pressure. Plaque is formed by inflammation, oxidation, and endothelial dysfunction as a late response. In our study, alcohol consumption was inversely related to CCA-IMT in men, suggesting that increased alcohol consumption has a beneficial effect early in the atherosclerotic process. In contrast, alcohol consumption was positively correlated with the occurrence of carotid plaques. A higher incidence of carotid plaques was observed in heavy drinkers, compared with non-drinkers, suggesting that increased alcohol consumption has a harmful effect on later stages of atherosclerosis. Recent studies have reported that carotid plaques are a better predictor of coronary artery
disease, including myocardial infarction, than IMT. As discussed, we could not
make causal inferences between alcohol consumption and carotid atherosclerosis
because of the limitations of the study’s cross-sectional design. Thus, the effects of
alcohol consumption on the progression of carotid IMT and carotid plaques should
be investigated in prospective epidemiological studies. We will investigate the
relationship between alcohol use and carotid atherosclerosis in a future prospective
study.

2. Why are inconsistent between male and female?

Authors’ comments: First, the absence of an association between alcohol
consumption and carotid atherosclerosis in women may be explained by the fact
that women consume less alcohol than men. Within the study population, only
32.9% of women were current alcohol drinkers. Additionally, the average amount
of alcohol consumed was 1.3±4.8 g/d for women, but 12.9±23.1 g/d for men. Second,
we suggest that underreporting may be higher in women than men. A potential
weakness of epidemiological studies on alcohol consumption is that self-reporting
of alcohol use may not be accurate. A criticism of self-reporting is that it may lead
to an underestimation of alcohol consumption, particularly by heavy drinkers.
Furthermore, women drinking alcohol is not generally accepted in Korean culture,
as compared with men, especially heavy drinking habits. Third, alcohol
consumption was positively associated with GGT and HDL cholesterol in women,
and AST, GGT, HDL cholesterol, and current smoking status in men.
Measurement errors might have affected the relationship between alcohol
consumption and CCA-IMT and carotid plaques in women. Similar findings were
observed in the Study of Health in Pomerania [13].

3. In your data, higher alcohol consumption group is more prevalent than never
or smaller group in terms of hypertension, diabetes, and hypercholesterolemia,
and more obese, and proportion of current smoker in higher alcohol group is
much more than other groups. All the cardiovascular risk factors are bad. How
can you explain the finding that association between conventional
atherosclerotic risk factors and CIMT is not seen in your data?

Authors’ comments: As noted, Table 1 shows that the higher alcohol consumption
group had higher prevalences than the never or lower alcohol consumption groups
of hypertension, diabetes, hypercholesterolemia, obesity, and current smoking status in men. Additionally, Table 3 shows that CCA-IMT had a significant negative correlation with alcohol consumption. However, these findings cannot be interpreted as saying that the thinner CCA-IMT group had a higher prevalence than the thicker CCA-IMT group of hypertension, diabetes, hypercholesterolemia, obesity, and current smoking status. It is difficult to show that conventional atherosclerotic risk factors had a significant negative correlation with CCA-IMT. Table 1 shows the characteristics of subjects according to alcohol consumption, using only a univariate analysis method. The characteristics of subjects according to CCA-IMT are given in Table 1-1 (below). This shows that the thicker IMT group had higher prevalences than the thinner CCA-IMT group of hypertension, diabetes, hypercholesterolemia, and obesity, consistent with previous epidemiological studies.

### Table 1-1. Characteristics of Study Population According to CCA-IMT in Men (n=1492)

<table>
<thead>
<tr>
<th></th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Quartile (0.46-0.65 mm)</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Quartile (0.66-0.77 mm)</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Quartile (0.78-0.86 mm)</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; Quartile (0.87-1.64 mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.1 ± 7.1</td>
<td>66.1 ± 7.2</td>
<td>68.6 ± 7.2</td>
<td>69.8 ± 6.6</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>23.3 ± 2.7</td>
<td>23.6 ± 2.9</td>
<td>23.9 ± 2.7</td>
<td>24.1 ± 2.8</td>
</tr>
<tr>
<td>WC, cm</td>
<td>85.8 ± 7.7</td>
<td>86.6 ± 7.9</td>
<td>87.6 ± 7.4</td>
<td>88.5 ± 7.7</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>118.9 ± 14.5</td>
<td>122.5 ± 15.2</td>
<td>123.1 ± 15.5</td>
<td>127.0 ± 17.1</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>72.2 ± 9.7</td>
<td>73.3 ± 9.2</td>
<td>72.7 ± 10.1</td>
<td>73.4 ± 9.5</td>
</tr>
<tr>
<td>FBG, mg/dL</td>
<td>111.3 ± 28.4</td>
<td>108.7 ± 20.9</td>
<td>109.0 ± 24.1</td>
<td>113.4 ± 27.6</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>178.7 ± 36.7</td>
<td>180.2 ± 36.6</td>
<td>179.2 ± 35.7</td>
<td>186.6 ± 36.1</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>50.7 ± 13.8</td>
<td>49.5 ± 12.8</td>
<td>48.4 ± 11.7</td>
<td>48.2 ± 10.9</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>153.3 ± 177.8</td>
<td>139.8 ± 101.0</td>
<td>130.3 ± 89.5</td>
<td>138.4 ± 82.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>35.3</td>
<td>42.2</td>
<td>44.1</td>
<td>53.6</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>21.0</td>
<td>19.2</td>
<td>23.2</td>
<td>28.4</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>8.9</td>
<td>12.2</td>
<td>11.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>24.0</td>
<td>20.8</td>
<td>23.4</td>
<td>23.2</td>
</tr>
<tr>
<td>Regular exercise, %</td>
<td>29.9</td>
<td>32.7</td>
<td>36.4</td>
<td>32.8</td>
</tr>
</tbody>
</table>

Data are means ± standard deviations.

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein.
*p for difference was obtained by analysis of variance for continuous variables and chi-square test for categorical variables, respectively.