Author's response to reviews

Title: Association of the smoking status with parameters of vascular structure and function in adults. Results from the EVIDENT study.

Authors:

Jose I Recio-Rodriguez (donrecio@gmail.com)
Manuel A Gomez-Marcos (magomez@usal.es)
Maria C Patino-Alonso (carpatino@usal.es)
Carlos Martin-Cantera (Carlos.Martin@uab.es)
Elisa Ibañes-Jalon (eibanesj@saludcastillayleon.es)
Amor Melguizo-Bejar (amormelguizo@gmail.com)
Luis Garcia-Ortiz (Lgarciao@usal.es)
on behalf of the EVIDENT group (ensayosalamedilla@gmail.com)

Version: 3 Date: 27 August 2013

Author's response to reviews: see over
Dear Editor of the BMC Cardiovascular Disorders:

Thank you for your help in reviewing this manuscript for consideration of publication in the BMC Cardiovascular Disorders.

Following the suggestions of the editor, we enclose a new version of our manuscript entitled: “Association of the smoking status with parameters of vascular structure and function in adults. Results from the EVIDENT study.” MS: 1985126110103178, together with replies to all the issues raised.

GENERAL COMMENTS:

1. All the changes made in the manuscript (text, tables and figures) are underlined.

2. Because Peripheral augmentation index is affected by heart rate, its values were standardized to a heart rate of 75 bpm. (page 6, line 3)

3. We have extended the discussion section including new references and comparisons between our findings and similar studies.

4. Following the suggestions of the reviewers, we think that the manuscript has improved in terms of understanding and clarity. We therefore think that its interest has increased considerably.
We look forward to hearing from you. If you have any additional request or need any information, please contact us.

Sincerely:

José Ignacio Recio Rodríguez,

Primary Care Research Unit, La Alamedilla Health Center

Avda. Comuneros 27, 37003 - Salamanca, Spain.

Tel:+34 923 290900 ext 53550; fax +34 923 123644; e-mail: donrecio@gmail.com
1. The authors adjusted their analysis for age, sex, systolic BP, HR, BMI, diabetes and drug treatment. I would like to see how these parameters affect vascular structure. Therefore please provide appropriate descriptive data and a univariate analysis of the effects of these parameters on vascular structure parameters. For categorical variables this will be a simple t-test or an appropriate non-parametric test, e.g. PWV in people with vs people without diabetes. For continuous variables this will be the calculation of a correlation coefficient (Pearson or Spearman as appropriate). For example, PWV vs age.

As suggested by the editor, we have included two new tables in the text. In the first table (table 2) we show the values of the vascular structure and functional parameters according to the categorical variables. In the second table (table 3) we have shown the bivariate correlations between vascular structure and functional parameters with continuous variables.

### Table 2: Values of vascular structure and functional parameters according to sex and presence of diabetes, antihypertensive, antidiabetic and lipid lowering drugs.

<table>
<thead>
<tr>
<th></th>
<th>PWV</th>
<th>IMT</th>
<th>PAIx75</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7.6 (6.7-9.5)</td>
<td>0.71±0.12</td>
<td>83 (94-71)</td>
<td>1.18±0.14</td>
</tr>
<tr>
<td>Female</td>
<td>6.8 (6.0-7.9)</td>
<td>0.66±0.09</td>
<td>91 (105-81)</td>
<td>1.17±0.13</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.6 (8.3-10.9)</td>
<td>0.74±0.07</td>
<td>93 (104-92)</td>
<td>1.15±0.16</td>
</tr>
<tr>
<td>No</td>
<td>7.0 (6.1-8.2)</td>
<td>0.67±0.11</td>
<td>87 (100-77)</td>
<td>1.18±0.13</td>
</tr>
<tr>
<td><strong>Antihypertensive Drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.3 (7.3-9.8)</td>
<td>0.74±0.10</td>
<td>89 (102-79)</td>
<td>1.18±0.14</td>
</tr>
<tr>
<td>No</td>
<td>6.8 (5.9-7.8)</td>
<td>0.66±0.10</td>
<td>87 (100-76)</td>
<td>1.17±0.13</td>
</tr>
<tr>
<td><strong>Antidiabetic Drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.5 (10.6-8.5)</td>
<td>0.74±0.08</td>
<td>93 (102-83)</td>
<td>1.14±0.16</td>
</tr>
<tr>
<td>No</td>
<td>7.0 (8.2-6.2)</td>
<td>0.68±0.10</td>
<td>88 (100-77)</td>
<td>1.18±0.13</td>
</tr>
<tr>
<td><strong>Lipid lowering Drugs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.1 (6.9-10.8)</td>
<td>0.74±0.09</td>
<td>91 (103-80)</td>
<td>1.17±0.14</td>
</tr>
<tr>
<td>No</td>
<td>6.9 (6.1-8.2)</td>
<td>0.67±0.10</td>
<td>87 (100-77)</td>
<td>1.17±0.13</td>
</tr>
</tbody>
</table>

IMT: Intima Media Thickness; PWV: pulse wave velocity; PAIx75: Peripheral or radial augmentation index adjusted for heart rate at 75 bpm, ABI: ankle brachial index.

PWV and PAIx75 are showed in median and interquartile range and IMT and ABI as mean ± Standard deviation.

p-values are for comparison of subgroups by T-Student independent groups and U Mann Whitney test.
Table 3: Bivariate correlations between vascular structure and functional parameters and systolic blood pressure, heart ratio and body mass index

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>SBP</th>
<th>HR</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV</td>
<td>0.558**</td>
<td>0.623**</td>
<td>0.169**</td>
<td>0.353**</td>
</tr>
<tr>
<td>IMT</td>
<td>0.687**</td>
<td>0.441**</td>
<td>-0.054</td>
<td>0.250**</td>
</tr>
<tr>
<td>PAIx75</td>
<td>0.222**</td>
<td>0.134**</td>
<td>0.361**</td>
<td>0.103**</td>
</tr>
<tr>
<td>ABI</td>
<td>0.045</td>
<td>-0.063*</td>
<td>-0.038</td>
<td>0.033</td>
</tr>
</tbody>
</table>

SBP: Systolic blood pressure; HR: heart rate; BMI: body mass index; IMT: Intima Media Thickness; PWV: pulse wave velocity; PAIx75: Peripheral or radial augmentation index adjusted for heart rate at 75 bpm, ABI: ankle brachial index.

We added the following paragraph in the introduction section related to the determinants of the arterial stiffness and vascular function parameters used in the regression model (page 4, line 8):

Several authors have proposed the age, sex, blood pressure, heart rate and the presence of obesity, diabetes and vascular drugs as the main determinants of the parameters that assess arterial stiffness and vascular function [1-4].

We added the next sentence in the statistical analysis section (page 6, line 18):

Age, sex, blood pressure, heart rate, and the presence of obesity, diabetes and vascular drugs have shown effect on the values of PWV, IMT or augmentation index. Therefore it is necessary to control the effect of these variables in the relationship between smoking status and parameters of vascular structure and function.

We added the next paragraphs in the results section (page 7, line 10):

Table 2 shows the values of IMT, PWV, PAIx75 and ABI according to the sex and the presence of diabetes, antihypertensive, antidiabetic and lipid-lowering drugs. IMT and PWV are higher in males and individuals with diabetes and in those on vascular treatment. The PAIx 75 shows the highest values in females and in those with diabetes and on vascular treatment. While ABI shows differences in individuals with and without diabetes.

Table 3 shows the bivariate correlation between systolic blood pressure, heart rate and body mass index with each vascular structure and functional parameter (PWV, IMT, PAIx75 and ABI) analyzed. Age shows a linear relationship with PWV, IMT and PAIx75 (Figure 1).
2. The continuous relationships (i.e. age, SBP, BMI vs vascular parameters) should be shown as scatterplots so that the reader can get a better impression of the data.

Age is the major factor affects the vascular structure and function. Due to this, we have included a new figure (scatterplots) that represents the relation between age with each vascular structure and functional parameter (PWV, IMT, PAIx75 and ABI).

We added the next sentence in the results section (page 7, line 18):

Age shows a linear relationship with PWV, IMT and PAIx75 (Figure 1).
3. The current figure should be replaced by something more meaningful. It is not appropriate to connect the categories with lines (this should only be done for longitudinal studies indicating progression from one to another category, e.g. when data on 1, 2, 3-year follow-up are shown). There is also no indicator of spread of the data. Box plots with medians, IQR and range or at least bar graphs with SDs or SEMs would be appreciated. The current figure is rather hiding data than adding any value.

We have deleted the old figure (lines). Instead of this figure, we added a new figure that represents the same relationship adjusted for confounders (without lines).
We have extended the discussion section including new references and comparisons between our findings and similar studies.

The following paragraph has been added related to the findings between smoking status and IMT (page 8, line 10): Some authors have reported the presence of smoking with increased inflammatory markers [5, 6]. Other authors have shown that the polymorphism -930A/G may modify the association between smoking and IMT values, especially among healthy young adults [7].

The following has been added in relation to the findings between smoking status and PWV (page 8, line 14): After controlling for confounders, we found no association between the presence of smoking and increased arterial stiffness, although the trend is similar to that found in relation to IMT. In a systematic literature review, Doonan RJ et al.[8] found that some studies found no statistical difference in arterial stiffness between nonsmokers and long-term smokers and concluded that the effect of smoking on arterial stiffness remains to be established by prospective smoking cessation trials. Rhee et al found an association between PWV and cigarette smoking in male smokers with hypertension. The study of Rhee et al explored the acute effects of smoking in a sample of men with and without hypertension, while our work examined the chronic effects of smoking on a larger sample of the Spanish general population. Other differences between the study of Rhee and Kubozono [9, 10] and our work are the different variables used in the multiple regression models.

The following paragraph was added in relation to the findings between smoking status and ABI (page 9, line 5): Present smokers have lower values of ABI, similarly to the results of other authors [11, 12]. However, our results did not remain significant after adjustment for confounders. The study population of Lee YH et al. [12] was general population with a mean age of 65 and 70 years in subjects with and without peripheral arterial disease, respectively. The peripheral arterial disease is one of the major manifestations of generalized atherosclerotic disease, as a result of progressive atherosclerosis [13], so it is expected that individuals with a greater history of smoking will have lower ABI values. The population studied in our work has a lower median age (52.9 ± 13 years), being the smokers the youngest.
REFERENCES

1. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: ‘establishing normal and reference values’. 

   BMC Cardiovasc Disord 2012, 12:3.


4. Lee HY, Oh BH: Aging and arterial stiffness. 


    Cardiovascular Heart Study (CHS) Collaborative Research Group. 