

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

### ARTICLE DETAILS

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| <b>TITLE (PROVISIONAL)</b> | Relative risk values of age, acrolein, IL-6, and CRP as markers of periventricular hyperintensities: a cross-sectional study |
| <b>AUTHORS</b>             | Abe, Arata; Nishiyama, Y; Abe-Harada, Mina; Okubo, Seiji; Ueda, Masayuki; Mishina, Masahiro; Katayama, Yasuo                 |

### VERSION 1 - REVIEW

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| <b>REVIEWER</b>        | Kazuei Igarashi<br>Graduate School of Pharmaceutical Sciences, Chiba University,<br>Japan |
| <b>REVIEW RETURNED</b> | 23-May-2014   |

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| <b>GENERAL COMMENTS</b> | <p>The manuscript entitled "Relative risk values of age, acrolein, IL-6, and CRP as markers of periventricular hyperintensities (PVH)" indicates that elevated RRV levels were significantly associated with increased predicted PVH. However, descriptions are confusing.</p> <ol style="list-style-type: none"><li>1. Tables 1 and 2. It should be clearly mentioned that age, BP, eGFR, and PVH are correlated with RRV. Thus, multiple linear regression analysis should be performed with three items (BP, eGFR, and PVH).</li><li>2. Table 3. Adjust* OR should be estimated for BP and eGFR only. Adjust** OR should be removed.</li><li>3. All subjects: 228; PVH: 103; DSWMH: 157. How many subjects have both PVH and DSEMH? How many subjects have silent brain infarction? Please explain the situation of subjects in more detail.</li></ol> <p>Minor points</p> <ol style="list-style-type: none"><li>1. First page; epartment → Department.</li><li>2. P. 5, l. 65; Ref. 12 → 15.</li><li>3. P. 7, l. 108; what is [Fazekas, 16]?</li></ol> |
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| <b>REVIEWER</b>        | Michael Firbank<br>Graduate School of Pharmaceutical Sciences, Chiba University,<br>Japan |
| <b>REVIEW RETURNED</b> | 26-Jun-2014   |

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| <b>GENERAL COMMENTS</b> | <p>The study aims to look at the relationship between RRV calculated from blood samples, and presence of WMH.</p> <p>My main concern is that no account is taken of the severity of WMH. WMH are present to some degree in most older people, but the extent varies greatly. There are a number of easy to perform visual rating scales of WMH eg<br/>Wahlund L-O, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke 2001; 32: 1318-1322.</p> <p>and some assessment of the WMH should be done to see whether the RRV predicts severity, rather than just presence of WMH.</p> <p>Since WMH are known to increase in frequency with age, I would be interested to see if the analysis in table 3 (tertiles RRV vs WMH) is still significant after controlling for age.</p> <p>The suggestion that PVH but not DSWMH are associated with cognition is not a universal finding - see eg:<br/>Deep versus Periventricular White Matter Lesions and Cognitive Function in a Community Sample of Middle-Aged Participants<br/>By: Jose Soriano-Raya, Juan; Miralbell, Julia; Lopez-Cancio, Elena; et al.<br/>JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY Volume: 18 Issue: 5 Pages: 874-885 Published: SEP 2012</p> <p>There are some oddities in the text - page 5 gives the age range as 31-83. Surely 31 is a bit young for an elderly volunteer?</p> <p>The values quoted for RRV in table 1 seem to have the wrong range (ie 0.51-0.07)</p> |
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### VERSION 1 – AUTHOR RESPONSE

To reviewers (s)

Thank you for your important suggestion. Accordingly, we revised the original ms as follows.

1. Multiple linear regression analysis was performed with BP, eGFR, and PVH, and the result was obtained as in renewed Table 2.
2. Table 2 was improved.
3. As you suggested, more details were incorporated in line 111. "In more detail, 76 among all the subjects had both PVH and DSWMH, the other 23 having silent brain infarction. Also, 22 subjects had a complication of PVH and silent brain infarction, while in 20 subjects there was complication of DSWMH and silent brain infarction."

As for the three minor points, "epartment" was corrected "Department", Ref 12 to Ref 15, and

“Fazekas” to Ref18.

To reviewer 2

1. We used the Fazekas classification instead of the new rating scale (Stroke 2001;32,1318-1322).
2. The references “J. Intern. Neurophysiol.Soc. 2012;18,874-885” was noted.
3. The year 31 was included in adult volunteer
4. In tertiles 1, 2, and 3, silent brain infarction risk values were corrected as  $0.51\pm 0.07$ 、 $0.69\pm 0.05$ ,  $0.86\pm 0.03$  (revised Table 1). Also, Table 3 was revised.

#### VERSION 2 – REVIEW

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| <b>REVIEWER</b>        | Kazuei Igarashi<br>Graduate School of Pharmaceutical Sciences, Chiba University,<br>Japan |
| <b>REVIEW RETURNED</b> | 11-Jul-2014   |

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| <b>GENERAL COMMENTS</b> | This manuscript was well revised according to the reviewer's comments. |
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