PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Urinary albumin excretion as a marker of endothelial dysfunction in migraine sufferers; the HUNT study, Norway
AUTHORS	Jacobsen, Line; Winsvold, Bendik; Romunstad, Solfrid; Pripp, Are; Holmen, Jostein; Zwart, John-Anker

VERSION 1 - REVIEW

REVIEWER	Stefan Evers, MD PhD Professor of Neurology Department of Neurology University of Münster Germany There are no competing interests.
REVIEW RETURNED	22-May-2013

GENERAL COMMENTS	A clear and precise study. Although the main result is negative, it is worth being published. Minor comments: - Pleas use the term "migraine patient" and not "migraineur" - Table 1: Were the differences in age between the three groups significant? - Could the authors speculate whether it might be a difference when urine was sampled during and outside a migraine attack? Could it be possible to have endothelial dysfunction in the state of a migraine attack?

REVIEWER	Paola Sarchielli Neurologic Clinic, Department of Medical and Surgical Specialties and Public Health, University of Perugia, Ospedale Santa Maria della Misericordia, Perugia, Italy
REVIEW RETURNED	20-Jun-2013

THE STUDY	Are the methods adequately described? No, reference or data on the validity of questionnaire used should be provided
GENERAL COMMENTS	The authors investigated the urine albumin leakage as a marker of endothelial dysfunction in migraineurs. They did not found evidence of increased urine albumin leakage in migraineurs when compared to headache free controls. This study denies the involvement of a global endothelial dysfunction in migraineurs. The study has been well conducted. Statistical analysis has been correctly performed. Discussion and conclusions are exhaustive. We have a few concerns which need to be addressed The authors should provide data or reference on the validity of the

	questionnaire used for collecting headache characteristics and comorbid conditions. The authors should give a better explanation for the use of urinary albumin excretion (UAE) as a marker of endothelial dysfunction. Data on literature on evidence of a global endothelial dysfunction in migraineurs should be presented in more details.

VERSION 1 – AUTHOR RESPONSE

Reviewer Dr. Stefan Evers:
General: A clear and precise study. Although the main result is negative, it is worth being published

Minor comments:
1) Please use the term “migraine patients” and not “migraineur”.

Reply: The term “migraineur” has now been changed to “migraine patients”, “migraine subjects”, “subjects having migraine” or “migraine sufferers”.

2) Table 1. Were the differences in age between the three groups significant?

Reply: Using one-way independent ANOVA there was a significant effect of headache status (three levels: no headache, non-migraine headache, migraine) on age in both the random and morbid samples (both p-values <0.001). Using contrasts, each of non-migraine headache and migraine were characterized by significantly lower age when compared to headache free controls, in both random and morbid samples (all p-values <0.001). As described in the manuscript each of the listed variables were tested for confounding effect on the association between headache status and ACR, and variables with confounding effect >5% were included in the final model (age, sex, self-reported diabetes and self-reported use of antihypertensive medication).
In the revised manuscript we have left Table 1 unchanged, i.e. not included p-values for each variable, as this would make the table more extensive, and since these tests are not part of the study hypothesis. We will, however, change Table 1 to include p-values if the reviewer disagrees on this.

3) Could the authors speculate whether it might be a difference when urine was sampled during and outside a migraine attack? Could it be possible to have endothelial dysfunction in the state of a migraine attack?

Reply: This is a very interesting question and we agree that one cannot exclude that there may be a difference in endothelial dysfunction during and outside a migraine attack. We did unfortunately not have data stating whether the migraine subjects performed urine sampling during their ictal or interictal period. This limitation is now addressed in the manuscript in the Discussion section, paragraph 2, page 12.

Reviewer Dr. Paola Sarchielli:
General: The authors investigated the urine albumin leakage as a marker of endothelial dysfunction in migraineurs. They did not find evidence of increased urine albumin leakage in migraineurs when compared to headache free controls. This study denies the involvement of a global endothelial dysfunction in migraineurs. The study has been well conducted. Statistical analysis has been correctly

performed. Discussion and conclusions are exhaustive.

Minor comments:
1) The authors should provide data or reference on the validity of the questionnaire used for collecting headache characteristics and comorbid conditions.

Reply: The validity of the questionnaire was shortly addressed in the Method section with the reference: Hagen et al 2000; Head-HUNT: validity and reliability of a headache questionnaire in a large population-based study in Norway. To further specify the classification and validation, we have now re-written this section with more extensive information in the Methods section, paragraph 1, page 6.

2) The authors should give a better explanation for the use of urinary albumin excretion (UAE) as a marker of endothelial dysfunction.

Reply: This is a good suggestion and according to the reviewers comment this has now been addressed more extensively in the Introduction section, paragraph 4, page 5, and the Discussion section, paragraph 3, page 12, with additional references.

3) Data on literature on evidence of a global endothelial dysfunction in migraineurs should be presented in more details.

Reply: We realize that the term “global endothelial dysfunction” may not be addressed with enough literature evidence. With the term “global” we meant systemic endothelial dysfunction, and we have now changed the word “global” to “systemic” in the Discussion section, paragraph 6, page 14. In the manuscript it is now made clear where evidence of systemic endothelial dysfunction is discussed, in both the Introduction section, paragraph 3, page 4, and Discussion section, paragraph 5, page 14.