Reviewer’s report

Title: The impact of C-reactive protein levels on headache frequency. The HUNT Study 2006-2008

Version: 0 Date: 17 Jul 2019

Reviewer: Catello Vollono

Reviewer's report:

Dear Editor, dear Authors,

This is an interesting large-scale population-based study assessing the levels of high sensitivity C-reactive protein (hs-CRP) in headache patients. The Authors conclude that elevated hs-CRP was associated with headache ≥ 7 days/month, especially frequent migraine with aura.

This is a stimulating paper and the aims of the study are important topics since many previous papers have evaluated the association between migraine and high sensitivity C-reactive protein, with conflicting results, and the influence of insomnia on the relationship between hs-CRP and migraine is complex and non-completely clear.

However, I suggest that the Authors rearrange the paper, modifying the statistical strategy, the definition of frequent headache and, consequently, the discussion prior to consider the paper suitable for publication.

Methods section

The statistical design should be modified.

No data about mean age and the age range, because, as admitted by the authors themselves, the children and adolescents with headache were more likely to be in the highest CRP quintile.

It is important specify the timing of collection of the blood sample respect the last attack or the following one.

In the present study the patients are divided into 2 arbitrary categories (<7 attacks/month and >7 attacks/month).
In my opinion the 7-attacks frequency cut-off used by the Authors does not correctly distinguish frequent forms from infrequent forms of headache. Normally, the cut-off for infrequent or episodic migraine and high frequent migraine is 4-attacks/month.

It might be interesting to compare statistically the 'weight' on the results of each category (MO, MA and other headache).

Discussion section

The results of the study do not allow to conclude with the following sentence 'in this large (n=38,813) population-based study with presumably high statistical power, the association between elevated hs-CRP and headache was strongly dependent on frequency of headache.'

In fact, in my opinion, the subjects with 6 attacks of headache/month have a frequent headache and are different from those that have 2 attacks/month but they are not completely different from those with 8 attacks.

In order to confirm this hypothesis, it would be better to use a different statistical model, as well as a correlation model (levels compared to headache frequency) rather than differentiating two populations with an arbitrary frequency cut-off.

The Authors also could explain and discuss the peculiar result of the relationship between elevated hs-CRP and headache founded among subjects without insomnia, whereas no such association was found among those with insomnia.

Probably even this 'negative' result obtained, in the part of the study that assessed the insomnia impact, could be caused by an inadequate statistical comparison (the use of the aforementioned 7-attacks/month cut-off).

Minor point: There are few spelling and punctuation errors.

Best regards

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I recommend additional statistical review

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