Author’s response to reviews

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

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Author’s response to reviews:

Re: “Increased C-reactive protein levels in participants with frequent headache. The HUNT Study 2006-2008”

Thank you for giving us the possibility to resubmit a revised manuscript. We have carefully considered all comments from the two reviewers and changed the manuscript accordingly. A point-by-point response to each of the reviewers’ comments is following below, and all changes in the manuscript are highlighted using red fonts.

Referee: 1 (Catello Vollono)

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.

Reply 1: We appreciate that you like our manuscript.

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.

Reply 2: We agree, and in the revised manuscript we present results of more detailed headache frequency categories and trend analyses. As suggested, we have avoided the term “frequent headache” in the revised manuscript. Consequently, the title of the manuscript is changed into: “The impact of C-reactive protein levels on headache frequency. The HUNT Study 2006-2008.”

Methods section

The statistical design should be modified.

Reply 3: As mentioned above, we present results of more detailed headache frequency categories. Thus, in the method section on page 5, we have included the following sentence: “Furthermore, based on the answer to the question about headache frequency, subjects were subdivided into five groups; no headache, headache < 1 days/month, headache 1-6 days/month, headache 7-14 days/month, or headache ≥15 days/month.” We have also added trend analyses in the statistic section on page 7; “To evaluate the probability of a linear relationship between elevated hs-CRP and headache frequency, the five categories were treated as a single variable and was incorporated in a two-sided test for trend.”

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.

Reply 4: The present study included only adults aged ≥20 years. Consequently, a sentence in the discussion was deleted regarding a study of children and adolescents with headache (reference 9). In the methods on page 4 regarding the study population, the following is added in brackets: (mean age 54.1 years, range 20-97 years).
It is important specify the timing of collection of the blood sample respect the last attack or the following one.

Reply 5: To clarify the relationship between headache attack and timing of collection of the blood sample, we have added the following sentence on page 4; “Blood samples for hs-CRP analyzes were drawn without any knowledge about last headache attack.”

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.

Reply 6: According to the current ICHD-3 criteria for migraine and tension-type headache, headache <1 days/month is defined as infrequent headache, 1-14 days/month as episodic headache, and ≥15 days/month as chronic headache. As stated in the Reply 3, the response option for the question about headache frequency in HUNT3 was <1 days/month, 1-6 days/month, 7-14 days month, and ≥15 days/month, and we have included these categories in the present manuscript (methods, results and discussion).

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

Reply 7: In the results section, the following sentence is added: In supplementary analyses, using individuals with “other headache” as reference category, elevated hs-CRP was more likely among those with MA (OR 1.17, 95% CI 1.05-1.31), but not MO (OR 1.04, 95% CI 0.92-1.19).

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.'

Reply 8: This sentence is changed into: “In this large (n=38,813) population-based study with presumably high statistical power, the association between elevated hs-CRP and headache was evident for those with headache 7-14 days/month and headache more than 14 days/month.”
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.

Reply 9: See Replies 3 and 6.

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.

Reply 10: See Reply 3.

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.

Reply 11: The following sentence is added on page 11: “The vast majority (93%) of the participants did not have insomnia, and in accordance with our main results, we found a relationship between elevated hs-CRP and headache also in this group.”

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).

Reply 12: To clarify the consistence of the results regarding impact of insomnia, we have added the following sentence in the end of results section: “Supplementary analyses considering only those with headache 7-14 days/month and ≥15 days/month did not change the results (data not shown).“

Minor point: There are few spelling and punctuation errors.

Reply 13: Some misprints are corrected.

Referee: 2 (Marco Carotenuto)
The present manuscript sounds original and well written in each section.

Background has been well focused on topic as the Discussion on data interpretation.

Statistical analysis has well described and well conducted.

Results were correctly interpreted and References are updated and adequate in the filed.

English is acceptable and easy to read.

Reply: Thank you for your nice comments

On behalf of all authors

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