**Author's response to reviews**

**Title:** Clinical features of headache associated with mobile phone use: A cross-sectional study in university students.

**Authors:**

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**Author's response to reviews:** see over
Re: Submission of manuscript entitled “Clinical features of headache associated with mobile phone use: a cross-sectional study in university students.”

Dear Sabina Alam,

Thank you for your comments regarding our manuscript, “Clinical features of headache associated with mobile phone use: A cross-sectional study in university students.” The reviewer’s comments are very much appreciated. We have made major revisions to our manuscript including Title, Abstract, Background, Results and Discussions. We believe that our paper has improved greatly. In addition, we submitted Korean and English versions of questionnaires for initial screening survey and subsequent telephone interview as additional files. This study is an observational study and was conducted in accordance with the guidelines of the Institutional Review Board of Hallym University Sacred Heart Hospital and principles in the Declaration of Helsinki. We described the conduct of this study at METHODS including ethical issues (page 5 line 12). We also enclosed STROBE report in this revision for better understanding.

The following are our responses to reviewers’ comments:

**Reviewer 1 Comments**

**Major Compulsory Revisions 1.**

How was the initial screening question of having more than 10 times of HAMP in the last one year being justified? There could exist high possibility of erroneous or false memory in such long period (one year) led by such questions. The authors may wish to discuss this.

**Authors’ response**

We used an initial questionnaire survey to screen HAMP. At initial questionnaire survey, the participants were asked their HAMP during last one year and there was a possibility of erroneous memory of their headache. In the
present study, most participants with HAMP reported their HAMP appeared frequently during or after MP use (Figure 2). These findings suggested that most participants with HAMP answered positively at initial questionnaire survey and little possibility of underreporting of HAMP. In addition, the prevalence of HAMP in the present study was similar to previous reports of HAMP. We added a description regarding this issue at DISCUSSION (page 14 line 8 - line 14).

**Major Compulsory Revisions 2.**
Was there difference in gender distribution among HAMP sufferers and non-sufferers?

*Authors’ response*
There was no difference between age, gender distribution between HAMP participants and those without HAMP. We added description on gender distribution among HAMP suffers and non HAMP suffers in RESULTS (page 7 line 16) and TABLE 1.

**Minor Essential Revisions 1.**
The abbreviation HAMP should be defined in the introduction when being firstly introduced but not in the method section. Similarly, in second line of abstract, the sentence should be revised as “The causal relationship of headache associated with MP use (HAMP) is currently undetermined…”

*Authors’ response*
Thank you for your kind comments. We included the definition of HAMP at INTRODUCTION (page 4 line 23). We revised as “The causal relationship of headache associated with MP use (HAMP)” at ABSTRACT (page 3 line 4).

**Minor Essential Revisions 2.**
Following the previous point, the title can be streamlined as "Clinical features of headache associated with mobile phone use: a cross-sectional study in university students."

*Authors’ response*
Thank you for important comments. We revised the tile of this study as “Clinical features of headache associated with mobile phone use: A cross-sectional study in university students” after your comment.

**Discretionary Revisions**
1. Typos: Page 3, Line 18: Thirteen eight -> should be thirty eight (also same issue in line 20)
2. Page 12, line 13: reported "by" only one participant…

*Authors’ response*
Thank you for your kind comments for our typo errors. We corrected as ‘thirty seven’ (page 3 line 18) and ‘reported by only one participant’ (page 12 line 19).

**Reviewer 2 Comments**

**Major Compulsory Revisions 1.**

In at least two places in the paper, the authors mention that “the headache features and associated symptoms of HAMP were not reported yet” (abstract) and that “to the best of our knowledge, this is the first report on the headache features and associated symptom of HAMP” (page 10). In fact, several previous studies have attempted to characterise the headache features and associated symptoms of people who report symptoms that are associated with mobile phones. From memory, these include:

- Hocking 1998 (Reference 3 in the authors’ manuscript)
- Roosli et al 2004 (Reference 5)
- Stovner et al Nocebo as headache trigger: evidence from a sham-controlled provocation study with RF fields. Acta Neurol.Scand. 2008; 117 (suppl 188); 67-71

I think it would be useful to acknowledge these papers and discuss the results in relation to them.

**Authors’ response**

Thank you for your great and important comments. We revised our manuscript after your comments and deleted inadequate sentences for HAMP such as ‘the headache features and associated symptoms of HAMP were not reported yet’ (ABSTRACT) and ‘to the best of our knowledge, this is the first report on the headache features and associated symptom of HAMP’ (INTRODUCTION and DISCUSSION). We also cited your suggesting references and included them in REFERENCES (No. 3, 4, 25).

**Major Compulsory Revisions 2.**

The authors say that “recent randomized double-blind provocation studies have indicated that there is no causal relationship between MP use and hypersensitivity symptoms” (Discussion, third para). First, I think this reads better if the word “hypersensitive ty” is dropped. More importantly, this is not quite accurate. These studies do not generally deny that there could be causal relationship between MP use and symptoms. But they do call into question what the mechanism is. In particular they suggest that MP use causes symptoms through mechanisms that are not related to the radiofrequency fields.
produced by the MP, and they suggest that psychological mechanisms (including a nocebo effect) may provide the causal mechanism. I realize that this is mentioned later on, but this particular sentence isn’t quite accurate as it stands.

Authors’ response
We dropped the word “hypersensitivity” and revised as idiopathic environmental hypersensitivity to electromagnetic fields (IEI-EMF). We also revised descriptions on IEI-EMF and nocebo effect at DISCUSSION (page 11 line 7– line 15, page 13 line 9- line 13).

Major Compulsory Revisions 3.
The authors provide a description of the requirements we might look for before assuming a causal role between MP use and headaches. They then go on to say (Discussion, p12, second para) that “Rare headache provocation by regular telephones suggests that HAMP is related to the use of MP per se, even if the nocebo effect does play a role in HAMP provocation.” Why “even if”? Surely satisfying the criteria listed for assuming causation merely tell us that use of a mobile phone seems to trigger headaches. It says nothing about why use of mobile phone triggers headaches. It could be purely due to psychological mechanisms, purely due to radiofrequency fields, purely due to heat or sound, or some other factors or combination of factors. The causation criteria by themselves really tell us nothing about the mechanism involved.

Authors’ response
Thank you for important comments for describing the results of symptom provocation tests by RF exposure. We revised the sentences to describe the exact meaning of the findings (page 12 line 17- line 22) after your kind comments.

Major Compulsory Revisions 4-1.
Later in the same paragraph, the authors say that “The lack of HAMP occurrence when using hands-free equipment also suggests that certain factors nullified by hands-free equipment are related to HAMP provocation. In light of these recent reports using RF provocation and findings in our study RF may not be the sole cause of MP-associated headache, and the nocebo effect could play a role in provoking headache. However these findings do not exclude the possible role of MP in headache provocation.” I think there are several comments to make here.

First, I am concerned about the use of the word “sole” in “RF may not be the
sole cause…” This takes for granted that RF is indeed one of the causes. But as the authors know, this is not supported by the large body of experimental data in this field.

**Authors’ response**

Thank you again for important comments for interpretation of the results in symptom provocation tests by RF exposure. We revised the description ‘The lack of HAMP occurrence when using hands-free equipment~ However, these findings do not exclude the possible role of MP in headache provocation’ as ‘The lack of HAMP occurrence when using hands-free equipment also suggests that certain factor(s) nullified by hands-free equipments are related to HAMP provocation’ to avoid misunderstanding at DISCUSSION (page 12 line 20- line 22).

**Major Compulsory Revisions 4-2.**

Second, the following juxtaposition is not appropriate: “RF may not be the sole cause… However these findings do not exclude the possible role of MP in headache provocation.” It may be that this is just poorly worded, but the implication seems to be this study supports the assertion that RF fields are a cause of symptoms. I do not believe that the data presented here support that. The authors’ data could be said to be entirely consistent with a nocebo-based mechanism. Likewise, their data might also be seen as largely consistent with RF being the cause (although the single participant who gets symptoms from landline phones would still need to be explained), or heat from a phone being to blame. Making causal statements with these data is difficult.

**Authors’ response**

Authors agreed with reviewer’s comments and revised inadequate descriptions in interpretation of results of the previous studies and the present study. We deleted the sentence ‘RF may not be the sole cause… However these findings do not exclude the possible role of MP in headache provocation’ and revised descriptions regarding RF and symptom provocation at DISCUSSION (page 12 line 17 – line 22, page 13 line 14 – line18.

**Major Compulsory Revisions 4-3.**

Third, by saying that these findings “do not exclude the possible role of MP in headache provocation” the authors again do not clearly differentiate between an understanding of whether mobile phone use can trigger headaches (they can) and an understanding of what the mechanisms behind this might be. This distinction is important.
**Authors’ response**

Similarly as response above (*Major Compulsory Revisions 4-2*), authors agreed with reviewer’s comments and revised inadequate descriptions in interpretation of results of the previous studies and the present study. We deleted the sentence ‘do not exclude the possible role of MP in headache provocation’ and revised descriptions regarding RF and symptom provocation at DISCUSSION (page 12 line 17 – line 22).

**Minor Essential Revisions 1.**
The authors note in the first paragraph of the introduction that “Several epidemiological studies have suggested that MP use may be related to the occurrence of these symptoms.” While I agree I am not entirely convinced that references 3, 4 and 5 support this assertion. As a review paper, reference 6 is probably sufficient on its own to support the statement.

**Authors’ response**

Thank you for your careful review and important comment. We reviewed the references again for adequacy and revised after your comment. We deleted inadequate references and only included adequate reference (page 4 line 8- line 9).

**Minor Essential Revisions 2.**
Similarly, in the first paragraph of the introduction, the authors say that “a series of double-blind, sham controlled provocation studies have reported no significant difference in headache provocation between control and HP radiofrequency fields among participants who experienced some of the aforementioned symptoms during MP use.” References 11 to 15 are cited in support. Of these, references 11 and 12 are not provocation studies while reference 14 did not assess participants who experienced symptoms in connection with MP use. As far as I know, the most up to date review on this area is still that by our group. It cites several additional studies which do support the statement.


**Authors’ response**
Thank you again for your careful review and kind comment. We carefully reviewed your suggesting reference (Rubin GJ, Nieto-Hernandez R & Wessely S [2010]. Idiopathic environmental intolerance attributed to electromagnetic fields [formerly ‘electromagnetic hypersensitivity’]) and revised references after your comment and reference (page 4 line 17).

**Minor Essential Revisions 3.**

3. In the “questionnaire survey” section of the methods, the authors note that “we defined HAMP if headache developed during MP use or within 1 hour after MP use and … if he or she experienced HAMP more than ten time during last one year in this study.” Yet in the “current headache status of participants” section of the results, the authors say that only 37 of 40 participants with HAMP had experienced a headache in the past year. I am having trouble understanding why the remaining 3 participants were placed in the HAMP group if they had not had a headache in the past year. Could the authors clarify this?

*Authors’ response*

At initial questionnaire survey, we assessed participants’ current MP use status, HAMP and headache not associated with mobile phone use (HNAMP). Three participants with HAMP reported that they did not experienced HNAMP during last year and only suffered HAMP. We revised this circumstance at RESULTS for better understanding (page 7 line 25- page 8 line 1).

**Minor Essential Revisions 4.**

The authors report “phonophobia” as being more prevalent among people who experience symptoms which they attribute to mobile phones. I found this interesting, as it might indicate a possible mechanism through which use of a mobile can cause symptoms. But as a psychologist I was slightly unsure whether I interpret the term “phonophobia” in the same way as the authors. It might be useful to see a translation of the exact wording of the question used by the authors. This would prevent any ambiguity for other readers.

*Authors’ response*

We assessed phonophobia of HANMP using a question ‘Was your headache more painful when you are in noisy circumstances’ at initial questionnaire No. 13. We included the initial screening questionnaire at this revision as additional file 1 for better understanding of evaluation process for phonophobia.

**Minor Essential Revisions 5.**

5. I liked the suggestion that a different mechanism (or possibly it is a
complementary mechanism that both initiates the nocebo effect and then exacerbates it?) is the noise and heat produced by a mobile phone. However, the authors then suggest (p 11) that this theory could be explored by using “more refined provocation tests that include all actual mobile phone conditions” and “conditions similar to actual MP use” (conclusions). Would it not be better to have a test in which these various proposed causal elements are separated out? E.g.a noise condition, a heat condition, an RF condition, and then combinations of them. Would that not provide a better way to demonstrate whether these are responsible for triggering the symptoms?

Authors’ response
Regarding results of previous randomized controlled provocation tests and reports for effects of local temperature change and noise in headache provocation, headache provocation test to examine the effects of altering conditions by MP use including noise, local temperature change as well as RF exposure and then their combinations, are needed. We added our suggestions at CONCLUSIONS (page 14 line 21- line 24).

Discretionary Revisions 1.
1. The manuscript is well written, but there are a few places where it would benefit from being read through by someone who is a native English speaker. Note also that in the Results (clinical features of HAMP) it should presumably be thirty eight participants from 40, rather than thirteen eight participants as currently appears.

Authors’ response
We carefully proofread again and corrected misspellings and grammatical errors. We used track change all our edits.

Discretionary Revisions 2.
2. I thought the use of pie charts (Figure 3) was very helpful. I wondered whether Figures 2 and 4 might also best be expressed in the same format, for consistency? I don’t have particularly strong views on that however.

Authors’ response
Thank you for careful comment. We revised our Figure 2, 3, 4 as pie charts after your comment for better understanding.

Discretionary Revisions 3.
3. I note that one participant mentioned that a normal telephone also triggered headaches. Did the authors ask about any other electrical triggers for symptoms? They will be aware of the broader condition of idiopathic
environmental intolerance attributed to electromagnetic fields and that symptoms attributed to mobile phones makes up a possible subgroup within this condition. It might be worth broadening the discussion to include this? See, e.g., Rubin GJ, Cleare AJ & Wessely S (2008). Psychological factors associated with self-reported sensitivity to mobile phones. Journal of Psychosomatic Research, 64, 1-9.

Authors’ response
We reviewed the HAMP participant who reported headache provocation by regular telephone use considering your suggesting reference. We described her HAMP and HNAMP in detail and suggested two possible mechanisms for her headache provocation by regular telephone use (chronic headache disorder and IEI-EMF) at DISCUSSION (page 12 line 25 – page 13 line 14).

Discretionary Revisions 4.
4. The authors note in the discussion that “discrepancies in the proportion of MP users who experience HAMP may be due to differences in MP types, and demographic features.” It may also be due to differences between different countries in levels of concern about mobile phones or media reporting about them (see, e.g. Mortazavi et al, Bioelectromagnetics 2007;28:326-330).

Authors’ response
Thank you for kind comment. We revised the sentences about discrepancy in proportion of HAMP after your comments and included your suggesting reference (page 10 line 15 – line 18).

Discretionary Revisions 5.
5. Unless I missed it (and apologies if so) no funding statement is provided.

Authors’ response
This study did not receive any financial support. We included this statement at ACKNOWLEDGEMENT AND FUNDING (page 15 line 5 – line 8).

We hope to hear from you soon.

Thanking you in anticipation,

Sincerely,
Byung-Chul Lee MD, PhD