Author's response to reviews

Title: A pilot placebo-controlled, double-blind, and randomized study on the cognition-enhancing benefits of a proprietary chicken meat ingredient in healthy subjects

Authors:

Zain M Azhar (azharmz@hotmail.com)
Jamil O Zubaidah (zujamil@gmail.com)
Khin ON Norjan (noorjan30@yahoo.com)
Candy YJ Zhuang (cyyi@cerebos.com.sg)
Fai Tsang (ptf1@cerebos.com.sg)

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Author's response to reviews: see over
Dear Dr. Kumagai,

Re: MS: 1825039980901549

Title of Manuscript: A pilot placebo-controlled, double-blind, and randomized study on the cognition-enhancing and anti-stress benefits of a proprietary chicken meat ingredient in healthy subjects Zain M Azhar, Jamil O Zubaidah, Khin ON Norjan, Candy YJ Zhuang and Fai Tsang

Thank you very much for considering our manuscript for publication in the Nutrition Journal. We greatly appreciate the additional advice that has helped us to further improve our manuscript. We would like to submit the appropriately revised manuscript based on the advice and seek your acceptance. Together with the revised manuscript, we have also prepared the point-to-point responses to the referee.

Overall, we have made the following major revisions:

1. We have clarified the usage of psychological assessments as an assessment to ensure the psychological well-being of the subjects. We have also removed parts of the text that discuss about stress and focus on discussion on the cognition-enhancing effects of CMI-168.
2. We have added the details of subject recruitment to provide clear descriptions of the subject features.

Dr. Hiromichi Kumagai
The Nutrition Journal Editorial Team
Nutrition Journal
c/o BioMed Central
236 Gray's Inn Road
London WC1X 8HB
United Kingdom

29th Jul 2013
3. We have explained the usage of Digits Forwards test in this study as a basic measurement of short-term memory storage capacity.

4. We have made appropriate changes in the results and discussion sections based on the advice from the referee.

Together with this cover letter, we have also appended the point-by-point responses to the referee. We sincerely thank the editors and referees for the highly constructive advice on our manuscript and hope we have complied with the requirements sufficiently for acceptance of the revised manuscript.

Sincerely yours,

Fai TSANG
RESPONSES TO THE CONCERNS RAISED BY REFEREE

Referee 3: Jonathan Ling

Major Compulsory Revisions

Abstract
The first section of the background (from ‘Globalization…’ to ‘On the other hand…’) should be deleted as this information is not appropriate for an abstract. The abstract should start with ‘It has long been postulated’.

Our response:
Thanks to the referee for pointing out this. We have changed the Abstract following his advice.

We do not know whether the participants were mildly stressed as none of the data related to the BDI are presented anywhere in the manuscript.

Our response:
We acknowledge that the focus of this study was to investigate the cognition-enhancing properties of CMI-168 instead of its anti-stress effects. As such, we have deleted the wordings “mildly stressed” and changed to “healthy” to avoid confusion.

Background
P3 Where is the evidence on ‘accelerated ageing’? A reference to some of the debate on the ethical and safety concerns would be helpful.

Our response:
As advised, we have added in references to support the association of lifestyle stress with aging. A couple of references to the discussion on the ethical and safety concerns have also been included. Below are the references we have added to the manuscript.

References in the revised manuscript:

‘Swirled vigorous debate’ is a slightly odd construction. There is no reference to any ‘evidence
supporting the efficacies of foods and supplements in cognition enhancement’. It is difficult for anything to be entirely conclusive (end of P3), however several studies have found facilitation effects for cognitive tasks and at least some of these should be referenced.

Our response:
Thanks very much for the advice. We have amended the text and added some references on the efficacies of foods and supplements in cognition enhancement.

References in the revised manuscript:

P4 ‘In the preclinical analyses, CMI-168 demonstrated selective cognition-enhancing efficacies, particularly in the areas of working memory and spatial memory.’ Is there a reference that could be cited to support this point?
Where the facilitation effects compared to EOC – did they differ?

Our response:
Our preliminary studies focused on in vivo models of learning and memory; the data for which was not published. We acknowledge that this could be too preliminary to justify our statement as mentioned above. As such, we have removed the sentence without affecting the original meaning of the text.

Methods
Subjects – the number of participants should be clearly stated in this section. Details of stress should not be presented here (as presumably this was not an inclusion criterion – if it was then we need to know much more about the selection process). We also need to know how many males and females there were – much recent research has highlighted sex differences in cognitive abilities so this would be helpful for future researchers. In my previous review I asked that further information related to recruitment be added, and other information: “This information should be placed in the subject section, and not in a separate section on sample characteristics in the results. Where were they recruited from? How were they recruited? Did any drop out (we only have the final numbers in the study presented in the results)? Was compliance measured (e.g. were participants encouraged to return any unused capsules to the research team)? Were participants asked if they had complied?” Information about whether participants were asked to return capsules has been added, however other information is still needed.
Our response:
We have added details of the total number of participants and more details of the participants including the number of males and females in each group, recruitment details, compliance details, and withdrawals. We have also removed the discussion on stress to avoid confusion. We sincerely hope the additional information will help to provide sufficient information to the readers for a clear understanding of the subject characteristics and the study.

Thanks to the authors for clarifying that participants were on a mixed diet – presumably this means that they consumed meat - this should be added to the text. How was this data collected? I don’t see a reference to this in the materials section.

Our response:
Thanks very much for the comment. We have added more details about the diet in the revised manuscript.

Study Design
It is good to know that participants were asked to return any unused materials – did any bring some back?
Although I understand the authors’ reasons for including the digit span backwards task, it is unusual to only give this and omit the forwards version. Was data also collected on this? If so, this should be reported. If it wasn’t a justification for why it was excluded should be made.

Our response:
We have added details of compliance of subjects to the supplementation regime and have clarified that only the data from the fully compliant subjects were used for statistical analyses in this study. Thanks to the referee for pointing out the usage of Digits Forwards task. We have clarified that we have conducted both Digits Forwards and Digits Backwards tasks. We have also reported in the revised manuscript that Digits Forwards was recorded as a clinical note and there was no significant change in the scores of all subjects in Digits Forwards throughout the study, implicating that the supplementation of CMI-168 did not have any impact on the basic short-term memory storage capacity in the subjects. In contrast, the Digits Backwards and Letter-Number-Sequencing tests provided information on the benefits of CMI-168 supplementation in attention and working memory.

Sample size
Thank you for adding reference to the sample size, however could you also add the appropriate details of this calculation, anticipated effect sizes, power, confidence level, etc.

Results
Psychological profiles
The participants completed a battery of tests. These should have allowed the researchers to determine whether they were stressed; it seems odd to have relied on the judgment of psychiatrist to make this judgment and omit reporting of the BDI, etc. which were detailed at length in the method. Can these data please be added.

(1) Attention and working memory
There is much detail on digit span tasks; this should be moved to the method (everything down to ‘As shown in Figure 1’).
Were there any sex differences?
Discussion
Statistical references (eg p < .001) should be removed from the discussion.
Our response:
Sample size
Thanks to the referee for the comment. We have added details on the samples size calculation including anticipated effect size, power and confidence level.
Psychological profiles
We have taken the advice and clarified that the psychological profiling was intended to ensure the psychological well-being of the subjects and was not part of the data to assess the stress status of the subjects.
Attention and working memory
We have taken the advice and have shifted the discussion on Digit Span to the Method section.
As the current study was intended as a preliminary examination of the cognition-enhancing characteristics of CMI-168, we think that the sample size of the current study may not be sufficient to provide any conclusive indication of the gender differences in the cognitive performance in this study.
Discussion
As advised, we have removed the statistical references from the Discussion section.

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Our response:
We greatly appreciate the referee’s highly constructive advice for our manuscript.