Author’s response to reviews

Title: The association between adherence to the Mediterranean diet and hepatic steatosis: cross-sectional analysis of two independent studies, the United Kingdom Fenland Study and the Swiss CoLaus Study

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Author’s response to reviews:

Dr Lin Lee, DPhil
Chief Editor, BMC Medicine

Dr Diana Samuel, PhD
Associate Editor, BMC Medicine

Re: Manuscript ID: BMED-D-18-01223 “The association between adherence to the Mediterranean diet and hepatic steatosis: cross-sectional analysis of two independent studies, the United Kingdom Fenland Study and the Swiss CoLaus Study”

Dear Dr Lee and Dr Samuel,

We are pleased to have the opportunity to revise and resubmit this manuscript. We appreciate the valuable comments from the reviewers of our work. We have revised our manuscript according to editorial board and reviewers’ comments and suggestions.
Please find enclosed a point-by-point response to yours and the reviewers’ comments. We believe that the manuscript is now much improved.

As requested, we provide two versions of the manuscript: one in which all changes have been ‘tracked’ (submitted as a supplementary file), and one ‘clean’ version (submitted as main article file). We look forward to hearing from you.

Yours sincerely,

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Responses to comments from the committee members

Comment #0-1. If provided, please include the ethical approval numbers obtained from the local ethics committees.

OUR RESPONSE: Thank you. As suggested, we have now included this as follows:

(1) Methods section (Lines 76 & 84, page 5 & 6):

“The Cambridge Local Research Ethics Committee approved the study (04/Q01008/19) and all participants provided written informed consent.”

“The institutional Ethics Committee of the University of Lausanne, which later became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the CoLaus study (reference 16/03) and all participants provided written informed consent.”
(2) Ethics approval and consent to participate section (Page 23):

“The Fenland Study was approved by the Cambridge Local Research Ethics Committee (NRES Committee East of England-Cambridge Central – 04/Q0108/19). The institutional Ethics Committee of the University of Lausanne, which afterwards became the Ethics Commission of Canton Vaud (www.cer-vd.ch) approved the CoLaus study (reference 16/03).”

Comment #0-2. This work is very well done. So the reviewers are correct, this is a well analysed and well written piece of work.

OUR RESPONSE: Thank you.

Comment #0-3. My only concern is novelty since, since this was submitted, a number of other papers, including trials in this space, have been published and have confirmed the same finding, as below. Thus, for me, novelty of this work is less than perhaps originally considered, though these other studies do add more support for their findings being correct and as they repeated in two cohorts, then they do have some advantages, plus their analyses suggesting findings tally with change in adiposity. I do think they should however include these references in their introduction and discussion, and edit to see how they fit with their data or otherwise.

OUR RESPONSE: We have now revised the introduction and discussion to address the concern about novelty. We have added references to the recent publications as helpfully suggested by the editorial team and the other reviewer. Please note the following changes:

(1) In the Introduction section, we included the two recently published clinical trials in patients with existing hepatic steatosis (assigning Reference#16 to Katsagoni et al., Br J Nutr 2018; and Reference#17 to Properzi et al., Hepatology 2018) in the reference list of the following sentence (Lines 51-54, page 4):

“Higher adherence to the Mediterranean diet has beneficial effects on progression of hepatic steatosis, but this evidence was derived from small-scale trials (n<90 followed up for <6 months) in patients with existing hepatic steatosis [12-17].”

(2) We have also modified the relevant paragraph and extended our introduction related to existing literature by adding the suggested reference (Ref#20, Ma et al., Gastroenterology 2018.) as follows (Lines 54-61, pages 4 & 5):

“Among adults free from clinically manifest hepatic steatosis, evidence from three studies is available, but still inconclusive. Two cross-sectional studies reported conflicting results: one among obese Spanish adults with high cardiovascular risk (n=794) reported an inverse association [18]; and the other among apparently healthy Chinese adults (n=332) reported a null association [19]. The Framingham Heart Study, only one longitudinal study thus far, has recently
reported a significant inverse association of greater adherence to the Mediterranean diet with incident hepatic steatosis (n=1521 adults over 6 years follow-up) [20].”

(3) We also modified the paragraph related to the aim of our study as follows (Lines 62-66, page 5):

“Given the limited and inconsistent evidence, which is mainly restricted to a single study or country, we aimed to investigate the cross-sectional association of adherence to the Mediterranean diet with hepatic steatosis among middle-aged healthy adults in two independent population-based cohorts: Fenland (East England, UK) and CoLaus (Lausanne, Switzerland).”

(4) In the Discussion section (Lines 346-349, page 17), we added a new statement:

“Moreover, our results are in agreement with the only prospective study to date reported a significant inverse association between adherence to the Mediterranean diet and incident hepatic steatosis among healthy individuals without hepatic steatosis [20].”

Comment #0-4. PS I don’t like their last line in the paper – “Future research should extend these findings by characterizing the longitudinal relationships between adherence to the Mediterranean diet or other dietary patterns, whole-body and central adiposity, and the risk of developing hepatic steatosis.” Rather clinical trials are needed as below, these are now emerging as per two of the refs below – it’s the only way to sort out cause and effect.


OUR RESPONSE: In line with your helpful suggestion, we have now revised the last sentence of the conclusion. Based on the references, we indicate importance of further evidence for the
primary prevention in terms of efficacy and effectiveness of potential intervention to improving adherence to the Mediterranean diet (Lines 431-434, page 21 & 22):

“The cross-sectional findings from our population-based cohorts warrant further interventional or observational studies to test whether improvement of adherence to the Mediterranean diet is efficacious and effective in diverse settings for the primary prevention of hepatic steatosis.”

We also thank the editors committee for listing the recent publications. We have cited these accordingly in Introduction and Discussion sections. Please find Katsagoni et al., 2018 (Ref#16) and Properzi et al., 2018 (Ref#17) in the Introduction section (Lines 51-54, page 4); and Ma et al., 2018 (Ref#20) in both Introduction (Lines 58-61, page 5) and Discussion (Lines 346-349, page 17) sections.

Responses to comments from the reviewers

Comments from Reviewer #1: Ludovico Abenavoli

Comment #1-1. Introduction section: The Author report that obesity is the main driver of hepatic steatosis, particularly NAFLD. This is a correct sentence. However I suggest to improve it, and to report that: NAFLD is the hepatic border of metabolic syndrome. Several scientific advances in understanding the association between NAFLD and metabolic syndrome have identified insulin resistance as the key aspect in the pathophysiology of both diseases (Abenavoli et al. World J Gastroenterol 2016)

OUR RESPONSE: We thank the reviewer for this comment. We have added the suggested reference and updated the relevant sentence as follows (Introduction section, lines 37-40, page 4):

“NAFLD is the primary hepatic outcome of metabolic syndrome and further cardiometabolic diseases, which include insulin resistance as well as dyslipidaemia and obesity as key pathologic mechanisms according to recent scientific advances [3, 4].”

(Ref #3 is EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease, J Hepatol 2016; and #4 is a review of metabolic aspects of adults with NAFLD by Abenavoli L et al., World J Gastroenterol 2016.)

Comment #1-2. Methods section: I suggest to describe briefly the dietetic profile of both the studied population. This is important to help the reader to better understand the founded data. In fact MD is efficacy in England and Swiss people, to population not include in the Mediterranean area.

OUR RESPONSE: In table 1 we have provided the overall dietary profile of each of the two populations in the UK and Switzerland. Specifically, we have described total energy intake and
macronutrient intakes (protein, carbohydrate, and fat intakes) by quintiles of adherence to the Mediterranean diet score. In the Results section, in the first paragraph, we summarized the characteristics of adherence to the Mediterranean diet being higher among women and those of higher socio-economic status, in both cohorts. We have now revised the Methods and Results sections to address the validity of the diet score and dietary profile of each of the two cohorts. Please note the following changes:

(1) We have taken the opportunity to update the relevant paragraph in the Methods section as follows, to highlight the validity of our diet scores in non-Mediterranean settings (Method section, lines 109-116, page 7):

“We evaluated the pyramid-based MDS (pyrMDS) [32] based on the Mediterranean dietary pyramid [33] as our primary exposure. The Mediterranean dietary pyramid was proposed by the Mediterranean Diet Foundation to be applied to both Mediterranean and non-Mediterranean countries [33]. We previously confirmed the content validity of pyrMDS in a non-Mediterranean setting, with its higher scores being associated with lower incidence of cardiovascular disease, cardiovascular and all-cause mortality in a UK population [32].”

(2) We have also added overall comparison of mean adherence to the pyrMDS in each of the two cohort in the Results section (Lines 255-256, page 13):

“The mean pyrMDS score was 9.07±1.43 and 8.45±1.24 in Fenland and CoLaus, respectively.”

Comment #1-3. Discussion section: I suggest the Author to stress the importance of non-invasive tools to detect NAFLD in a large population study.

OUR RESPONSE: We agree and we have added the following statement in the discussion section to acknowledge the importance of non-invasive tools to detect NAFLD in large epidemiological studies (Limitation section, lines 414-417, page 20):

“These validated markers of hepatic steatosis are based on non-invasive and easily ascertained measurements which make them suitable for large epidemiological studies [37, 38, 59, 60], and the results were consistent irrespective of the marker used.”

We have also taken the opportunity to add the recent validity study of using ultrasound in epidemiological studies (Reference#36, De Lucia Rolfe E et al., PLoS One 2018) in the Methods and Limitations sections as follows:

(1) In the Methods section (Lines 141-143, page 8):

“The diagnostic accuracy of ultrasound was previously assessed against proton magnetic resonance spectroscopy, with sensitivity and specificity of 96% and 94%, respectively [36].”
(2) In the Limitation section (Lines 412-414, page 20):

“In the Fenland study, hepatic steatosis was based on ultrasound, a valid method for detecting hepatic steatosis [36], supplemented with an algorithm based FLI, while in the CoLaus study two hepatic steatosis indices were used.”

Comments from Reviewer #2: Stefano Bellentani

Comment #2-1. The authors compared 2 validated and large cohorts to verify if the Mediterranean Diet could be useful to prevent steatosis. They used a well-validated markers (FLI= Fatty liver Index) and hepatic US to reach the diagnosis and a semi-quantitative Food Questionnaire to check the diet of the population. They found that a greater adherence to the Mediterranean diet was associated with lower likelihood of hepatic steatosis, and clearly showed that improving dietary quality via the Mediterranean diet could be an effective strategy to prevent the occurrence and development of hepatic steatosis. The paper is a good paper and it deserves publication without any other modification.

OUR RESPONSE: Thank you for the positive appraisal of our manuscript.