

06-Sep-2020

BMJ-2020-060281 entitled "Red Meat Intake and Risk of Coronary Heart Disease Among US Men"

Dear Dr. Al-Shaar,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with it, provided you are willing and able to revise your paper to address matters raised by reviewers and editors, as described below.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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Sincerely,  
Dr Elizabeth Loder

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\*\*Report from The BMJ's manuscript committee meeting\*\*

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: Wim Weber (chair); Jamie Kirkham (statistician); John Fletcher; Jin-ling Tang; Tiago Villanueva; Elizabeth Loder

Decision: Put points

\* As with all dietary studies, we worry that the assessment of outcome (CHD) and exposure (FFQ) seem to have a lot of uncertainty.

\* There is also concern about generalisability since this a group of male only health-related professionals. Might you comment more on that?

\* Our statistician commented that the analysis seems well done and thought out. His only minor request is that in Table 1, would you please present n and % for categorical variables.

\* Although a reviewer asks for relative risks, we see these in the supplementary material. Perhaps they should be given more prominence in the paper itself.

\* In the methods section, could you please share what the barriers were to patient and public involvement. Please also include a dissemination plan, e.g. how will you share the results of the study with patients and the public? This could include blogs, press conferences, etc.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

#### Comments from Reviewers

Reviewer: 1

#### Comments:

This is a first class piece of work. It will be of much interest to readers of the BMJ. However there are a few minor corrections that are needed.

Page 12, line 1, the heading is rather misleading. A more appropriate heading is:  
Comparison of findings in relation to other studies

Page 13, line 45, the main implication of the findings is that people should reduce their intake of red meat in order to help prevent CHD. It can also be mentioned that this is also good for the environment.

Page 14, lines 18-20, the words (" whose socioeconomic status may not represent the overall population") should be written as follows: "whose socioeconomic status is almost certainly well above the overall population".

Many hyphens are missing. Examples are low fat, low density, follow up. Hyphens are sometimes used but in an inconsistent way.

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Reviewer: 2

Comments:

This manuscript is about Red Meat Intake and Risk of Coronary Heart Disease Among US Men. Red meat and processed meat are very timely subjects, as well as meat versus plant product and protein sources.

First, for the less informed reader it is important to understand that any association between red meat, or the replacement thereof, with CHD is only about CHD. Therefore excluding e.g. quality of life or all-cause mortality. All too often this is taken as an absolute measure. While avoiding just 'the risk of CHD' is a rather strange idea, however common.

Second, there appears already a lot of literature on this topic, as well as mechanistic evidence, therefore the information in itself (about red meat) is not new. It is assessed in a specific group of people, however in a sound way and with multiple additional analyses. Moreover, the replacement of red meat by plant products, albeit statistically, appears to be the sensible information, as this provides the extrapolation to 'general healthy eating' beyond the endpoint of CHD.

Third, it is rather strange that no word is mentioned considering interpretation of the HRs for processed red meat. What were the expectations, and why do we observe hardly any difference between processed and unprocessed red meat?

Fourth, while it is stressed throughout the manuscript that red meat is associated with an increased risk of CHD, it is rather the very high intake of red meat that appears to be associated with risk of CHD (only Q5 for the fully adjusted model). While we are not informed about the range of servings, the median serving of Q4 is 1.14 and Q5 is 1.72. Therefore the risk mainly lies with an intake of over 1.5 serving of red meat a day. If the authors like to overrule this information with the other analysis of HR per serving, they have to be more clear why and explain it to the reader. This may also explain the so-called

(introduction) inconsistency that this is not observed in populations with low red meat intake. This is not mentioned in the discussion.

Fifth, the message of less red meat and more plant protein sources is fine and fits in all current messages on healthy eating. However, many consumers that like to respond may tend to replace red meat by poultry, or even fish and eggs. Next to stressing plant protein sources as advantageous, stressing that poultry is not a good option should be considered. Maybe even that dairy is indeed helpful. The authors must know how impactful their publications are, the science is great, but you can also help in the gradual (!) transition towards healthy eating.

Minor points

methods

p5 line 15: FFQ is a relatively weak dietary intake assessment method, it may not be ideal for distinction of processed meat; there is some discussion, mainly the considerable advantage of repeated dietary assessments, which is great by the way; the authors could e.g. argue that for red meat it is in fact fine?

p5 line 55: correlation of FFQ with multiple records is relatively low, this is not discussed; if in fact the relationship is dose dependent, the quantification of the exposure (red meat) deserves some discussion.

p10 line 52: plant based protein exchange for red meat shows stronger associations in older men; this observation is not discussed.

p5 line 17: exclusion at baseline assumed, previous line is not about baseline, please specify.

p5 line 47: it may not be clear to readers why a hamburger is processed (cooked etc), and at the same time in the unprocessed category.

p12 line 1: this paragraph is hardly providing "Strengths and weaknesses in relation to other studies", it is a direct comparison with other finds.

p14 line 14: it is not clear why the measurement error of dietary assessment would underestimate the true effect of red meat, please specify.

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If you have any competing interests [please declare them here](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests): I have had research funds from food industry, not related to this topic. I have obtained speaking fees from food industry, not related to this topic. I have had consulting fees from food industry in the past, not related to this topic.

Reviewer: 3

#### Comments:

General comments: This manuscript by Al-Shaar and colleagues studies the association between intake of total, unprocessed, and processed red meat and risk of incident coronary heart disease (CHD) in the Health Professionals Follow Up Study cohort. The strengths include a large sample size with repeated dietary assessments and comprehensive analyses. However, there has been extensive work in the literature on this topic. Hence, it is important to address nuances to the existing evidence and interpret the results in ways to inform future directions in this line of work.

Given the study population consisting of health professionals, a population that is not representative in the US population, it will be helpful to present absolute risk in addition to the current results, so that the readers will have a better understanding of the actual magnitude of the relationship described.

The increased risk of CHD per serving of red meat daily is modest, ranging from 11%-15% in different types. It is important to explain why this is the case; and why the differences between unprocessed and processed red meat are small (4%), as we would expect a greater risk difference in processed meat which contains nitrates and a higher level of sodium. Also, the results suggest a higher risk in unprocessed than processed red meat for fetal CHD and for total CHD after controlling for the dietary quality index. These findings deserve further discussion to interpret the results. The earlier systematic review by Micha et al. (2010) published in *Circulation* reports different findings on the same topic.

The analyses include many exposures of interest and multiple outcomes. I think the 2-sided p-values may require a smaller value less than 0.05 if Bonferroni correction for multiple comparisons is not possible. Can you please add p-values for the results? Currently, only p for trend is presented. Also, there are many confounders adjusted in the model. After controlling for the dietary variables, the effect size attenuates. This is especially the case after adjustment for the healthy eating index shown in the supplemental results. Is controlling for AHEI for dietary quality a more conservative approach to use in this study?

In the substitute analyses, besides the different sources of plant-based foods, dairy products were also shown to have a beneficial association. The conclusion of the Abstract emphasized the protective association in plant-based protein. I think there are two problems here: 1. Plant-based protein is not the main exposure of interest in this study. Would that be more appropriate to summarize the findings for red meat consumption? 2. Plant-based protein did not show any association with CHD in participants aged younger than 65 years. Hence, the authors may want to carefully draw the conclusion in the Abstract as well as in the manuscript and point out this discrepancy in Results and Discussion.

Other comments/issues found in the manuscript:

Abstract:

Please check Results. There are a couple of typos there.

Main text:

Introduction:

Lines 17-31: I find it helpful if the authors can cite references to support the inconsistencies found in the literature. The argument made here is not convincing. I also find it difficult to understand the last two sentences in Lines 27-31.

Line 35: please specific "these issues."

Methods:

Page 5, Line 46: poultry is missing. Was seafood part of fish in the FFQ?

Page 8, lines 4-5: is it possible to conduct stratified analysis by BMI ( $\geq 25$  and  $< 25$ ) and by fiber intake ( $\geq 28$ g/d and  $< 28$ g/d)

Page 8, lines 12-22: as repeated dietary assessments are available, it will be helpful to comment whether there is any difference in red meat consumption at baseline, the most recent diet and the cumulative average in the Results.

Page 9, lines 31-33: please specify the units or categories of the dietary variables adjusted for in the model.

Page 9, line 42: "a one serving per day"?

Page 10, line 37: I find dark meat fish is an unusual term. On this line, tuna is part of it. But in Supplementary Table 6, tuna is in its own category. Why is this the case? Is it possible to use a more general term such as fatty fish and non-fatty fish? Also, does fish include seafood in this study?

Page 10, lines 48-54: please add the results of plant-based protein sources for men younger than 65 years.

Page 11, lines 12-14: please comment on why a weaker association was found in the more recent diet in Discussion.

Discussion:

Page 11, lines 35-37: I think this should be clear that the protective association was only found in men older than 65 years. Also, I find the term "high-quality plant-based protein" confusing. How was the quality of plant-based protein determined? Were other sources such as quinoa and seeds included in the estimated intake of plant-based protein? If only a few groups (nuts, legumes and soy) were assessed, please say so.

Page 12, line 1: the subtitle "Strengths and weaknesses in relation to other studies" does not seem appropriate. Why would these be strengths and weakness when the results are compared with those in the existing literature?

Page 12, line 39: I find these mechanisms are not helpful or not directly connected to the findings in this paper. For example, it points to fats and cholesterol are responsible for the risk of CHD, but red meat is a whole food. Or if heme iron is culprit, I think iron intake should be tested to see its association with CHD risk. For TMAO, it can come from red meat, eggs, dairy products, and salt-water fish? So this speculation did not make sense here, as the relationship for eggs, dairy products and fish tend to have a protective association in the analysis.

Page 12, lines 37-39: this statement needs a reference, please.

Page 14, lines 16-20: "may not"?

Page 14, lines 31-33: The results suggest that other animal sources such as eggs and dairy products also showed a significantly lower risk for CHD, and plant-based protein was protective in men older 65 years. Please be accurate in the concluded statement.

Page 16, lines 23-30: for the added information: first, I don't think this topic is new; second, the stratified analysis shows only plant-based protein is protective in men older than 65 years. Perhaps add something more nuanced from the findings.

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Reviewer: 4

Comments:

Meat Intake and Risk of Coronary Heart Disease Among US Men

Thank you for this study on an interesting and relevant subject. The paper is well read, the analyses are solid and well performed, and the conclusions are clear. Specifically, using the substitution models reveal very interesting results. Below some suggestions for improvement. I would especially try to make a better focus in statistical analysis and results towards your research question so your analysis are really focused on answering the question, which will make it easier to read.

Page 1:

-Title: In your abstract and introduction it becomes clear that the main new information your study adds is that plant based protein sources are a good substitution for red meat. You could consider to add this in the title. Especially since meat intake is already correlated to CHD in multiple other studies as you mention in your introduction and discussion.

Page 3:

-Besides plant based foods also dairy and whole grains reduce risk for CHD. Why is this not in the conclusion?

Page 4:

-3-10 I would suggest to change beginning to: "Substantial evidence from randomized trials and observational studies suggests that high consumption of red meat, especially processed red meat, is associated with increased risk of mortality<sup>2-4</sup> and major chronic diseases<sup>5-10</sup>, including the coronary heart disease (CHD)<sup>11-13</sup>

-14-15: 'not seen in a population'.

Page 5

-The study is performed among the Health Professional study, why is the Nurses Health study not included?

- For those unfamiliar with the Health Professional study a few details on the population would be helpful (e.g. health status, what why health professionals, how were they recruited, region were they live). A reference to a design paper of the cohort would be helpful as well.

-15-17 '70 items blank on FFQ or intake <800 or >4200'? Could you support this approach by a reference?

- Why are patients with cancer excluded? And why not patients with for example Diabetes Mellites or COPD etc?

Page 6

-12: Why are data censored at January 31, 2016? Is there no more up to date information known on incidence CHD?

- How was physical activity assessed? Using a validated questionnaire?

Page 7

- 23: please report the covariates.

- The AHEI is not mentioned in the paragraph on covariates.

- To improve the readability of the statistical analyses I would suggest to first clearly mention all the analyses directly required to answer the research questions. After that the sensitivity analyses can be described.

- Did the authors consider BMI as an effect modifier or causal interference by BMI? Data are stratified for age categories, but not for BMI. It would be of value to spend more time and analyses to better understand the possible interference of BMI with the results - more that only adjusting for BMI groups in the models.



page 8

-3-5: what is the reason you stratified by calendar time and why the year 2000?

27: I assume the proportional hazards assumption was made? Please make this statement.

Page 9

-Please give some demographics about participants in first sentence of the results or minimally average age and age range.

Page 10

- 29: The novelty of this paper mainly lies in the substitution models. In the results, the HR for plant protein sources is mentioned. Yet for dairy and fish we are redirected to the supplementary results. I would suggest to provide these results a more prominent place in the result section.

Page 11

Clear summary of the most important results.

Page 12

In the part on strengths and weaknesses in relation to other studies I do not really see how the current study is compared to other studies. It is more a summary of previous findings. But how would you explain differences and/or similarities? And are there weaknesses or strengths in the current design compared to other studies/results? E.g. do you expect other results among females? Other methods to measure diet etc?

Page 12

The describes mechanisms are clear and useful. However, I miss some implications of these extremely important results. For example:

-Your results provide opportunity to optimize dietary advice.

-The current situation in the world asks for serious changes in the use of resources. The observed results do not only offer plenty of opportunity to improve health, but also to do so in a sustainable manner.

-What future research steps are required before this finding can be made more 'official'. Or is it already possible to advice policy makers, health care workers etc?

-Taking a broader view; red meat is clearly associated with higher CHD risks. What about other health outcomes? Would you expect that your results apply to other outcomes? Cancer, sarcopenia etc?

These results are very important! And I would take the opportunity to highlight the possible implications of these results in more detail (not only the conclusion).

Page 13

The part on the weaknesses apply generally to all observational studies and could be made more specific to the current study. Also, how could these weaknesses have effected the results? For example, do you expect different results in other ethnicities? What kind of residual confounding can be expected (any specific covariates that are yet known to influence the association).

Page 14

- In the conclusion only the reduced CHD of substitute plant based foods are mentioned not dairy and whole grains, why is this?

Page 16

- Based on the studies you mention in your discussion I would state that point 3 was already known and that your study confirms this. Your study especially adds new information on plant based protein sources that reduce CHD as substitution of red meat.

Page 17

-Why is chosen to not report quantile 2 and 4?

- what is the reason that for instance fruit and vegetable intake is energy adjusted and red meat intake is not?

-why is substitution of whole grains in supplementary material and not in figure 1?

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v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

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Occasionally the outcomes that are prespecified in a trial registry do not match up with those included in the trial protocol. When there are discrepancies between protocol and registry specified outcomes, we expect the paper to report and interpret the registry specified outcomes. You may also report any protocol specified outcomes, but if you do please be sure to include the date of the protocol and the point at which each outcome was added to the protocol, and explain why the registry entry differed from the protocol and why the registry was not updated to reflect any protocol changes.

f. Discussion: To minimise the risk of careful explanation giving way to polemic, please write the discussion section of your paper in a structured way. Please follow this structure: i) statement of principal findings of the study; ii) strengths and weaknesses of the study; iii) strengths and weaknesses in relation to other studies, discussing important differences in results; iv) what your study adds (whenever possible please discuss your study in the light of relevant systematic reviews and meta-analyses); v) meaning of the study, including possible explanations and implications for clinicians and policymakers and other researchers; vi) how your study could promote better decisions; vi) unanswered questions and future research

g. Footnotes and statements

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