

31-Oct-2016

Dear Dr. Etemadi

BMJ.2016.035582 entitled "Mortality from different causes associated with meat, heme iron, nitrates and nitrites in a cohort of over half a million Americans: The NIH-AARP Diet and Health Study"

Thank you for sending us your paper which we sent for external peer review. I regret to say that after reviewing the comments of the reviewers we have decided not to publish it in The BMJ. As you will appreciate we receive a large number of articles and often have to reject valuable and worthwhile work. When making an editorial decision we take the comments of the reviewers into account and also consider whether a piece will interest and inform our readers and whether it adds sufficiently to previous work.

The reviewers' reports are available below. We hope they might be helpful in any resubmission to another journal.

Although The BMJ has an open peer review process, in which authors know who the peer reviewers were, we expect that you will keep the identity and comments of the peer reviewers for this paper confidential. You may, however, share the peer review comments in confidence (though not the names of the peer reviewers) with other journals to which you submit the paper. If you have any complaints about the peer review process or the conduct of the peer reviewers, please contact the editor who handled your paper. Please do not contact the peer reviewers directly.

Sincerely,

Kristina Fister  
kfister@bmj.com

Reviewer: 1

Recommendation:

Comments:

General comments:

Etemadi et al.'s manuscript should be should be withdrawn voluntarily by the authors. As explained below, their results and conclusions are meaningless, and this paper appears to be an attempt to distort the scientific record via either a failure of due diligence or simple ignorance of the extant literature.

Stated simply, these authors used methods that were demonstrated to lack validity and produce data that are physiologically implausible, incompatible with life, bear little relation to actual energy or nutrient consumption, and are inadmissible as scientific evidence.<sup>1-4</sup> Nevertheless, Etemadi et al. never cite nor even mention the rigorous contrary evidence that renders their methods invalid and their results and conclusions meaningless. These omissions mislead their readers about the results of the research.

Specifically, these authors used memory-based dietary data collection methods (M-BMs; questionnaires, interviews) but failed to inform their readers that the lack of validity of M-BMs was irrefutably established over the past 60+ years by a series of publications by Archer et al.,<sup>1 2 4-10</sup> evidence from U.S. Congressional hearings,<sup>11</sup> and an ever-growing coalition of nutrition and obesity researchers<sup>12-14</sup> who recognize the scientific and methodologic illiteracy of M-BMs.

The scientific record is clear that M-BM–data are inadmissible as scientific evidence because, first, they are derived from recalled memories. Uncorroborated, subjective recollections are nonempirical and therefore are not subject to independent observation, measurement, or the quantification of error; as such they cannot be falsified and therefore are "pseudoscientific."<sup>2 4</sup> Second, M-BM–derived data are physiologically implausible and often incompatible with life;<sup>1 3</sup> therefore these data cannot be representative of the respondent's dietary intake. Third, the error of M-BM–derived data is unknown, unknowable and non-quantifiable due to false memories,<sup>15 16</sup> omissions (i.e., forgetting),<sup>17</sup> intentional misreporting (i.e., lying),<sup>18</sup> and gross misestimation.<sup>1 2</sup> These biases are irremediable, and because M-BMs mimic protocols that are known to induce false memories,<sup>2</sup> neither the researchers nor the participants know the validity, reliability, or error structure of M-BM derived data. These facts support the conclusion that M-BM data are meaningless and the term pseudoscientific is applicable,<sup>2</sup> yet all of these facts are ignored by Etemadi et al.

Etemadi et al.'s research was funded by a number of NIH and NCI grants. As such it falls under the aegis of the US Department of Health & Human Services Office of Research Integrity (ORI) which defines "Research misconduct...as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results."<sup>19</sup> "Falsification is...omitting data or results such that the research is not accurately represented in the research record...the omission of data is considered falsification when it misleads the reader about the results of the research."<sup>19</sup>

It is clear that Etemadi et al.'s manuscript misled the reader via the omission of many decades of rigorous contrary evidence. Whether or not their behavior rises to the level of research misconduct is for the ORI to decide.

Specific comments:

The authors fail to list limitations to their study.

The authors state they excluded individuals with "extreme daily total energy intake" but do not define "extreme" nor do they inform the reader which protocol they used to determine their operational definition of "extreme." At a minimum, the Goldberg Cut-offs should be used.<sup>20-22</sup>

The authors present a dichotomy of "processed" vs. "unprocessed without defining either term. Given that any form of manipulation can be considered "processing" (e.g., cooking, use of salt and spices, etc.) the authors need to define their use of each term. For example, why are the meats in chili and lasagna in the "unprocessed category but ham in the processed? This appears to be purely subjective and arbitrary. The authors need to provide an objective definition of processing.

It defies credulity to think that a finite list of 124 food items can be representative of dietary intake or "usual consumption" when there are more than 100,000 food items in the US Food Supply. For example, as of the date of this review, there are 77,413 foods listed in the USDA Food Composition Databases alone,<sup>23</sup> and new food and beverage items are added every day. How can a list of 124 items accurately characterize an individual's usual consumption?

Stated simply, the authors used a questionnaire that includes 0.16% of the possible foods and beverages that could be consumed and yet they assumed that they accurately characterized the respondent's diet? This is indicative of unscientific credulity.

How do the authors know any of the dietary information the respondents provided on the questionnaire is accurate? Surely, these authors do not simply take each response on faith. Or do they? As above, this is indicative of unscientific credulity.

The authors use caloric intake from a questionnaire. It is well-established that energy-adjustment cannot correct for differential recall,<sup>24</sup> and there is a general discipline-wide prohibition against using self-reported energy intake as a measure of actual energy intake.<sup>12-14</sup>

The statistical model contains an odd mix of objective, subjective, and irrelevant variables, many of which are highly correlated and measured with extremely poor accuracy (e.g., energy intake, self-reported health histories and perceptions of health status). As such, residual confounding is a major statistical issue that does not appear to be considered by these authors.

In conclusion, if published, this paper would significantly distort the scientific record and mislead the reader about the results of the research.<sup>19</sup> As such, it should be voluntarily withdrawn by the authors.

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**Additional Questions:**

Please enter your name: Edward Archer

Job Title: Chief Science Officer

Institution: EnduringFX

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: No

Funds for research?: Yes

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If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='\_new'> (please see BMJ policy) </a> please declare them here: From 2014-2016 Dr. Archer received research support from the NIDDK and received speaking fees from industry and non-profit organizations.

Reviewer: 2

Recommendation:

Comments:

Dr. Etemadi and colleagues have comprehensively investigated the association between red meat, white meat and meat ingredients (heme iron, nitrates and nitrites) and risk of mortality in a very large cohort study of American adults. Several previous studies have reported that red and processed meat intakes have been shown to be associated with increased rates of premature death. However, few studies have examined the mortality risk associated with white meat and meat ingredients. The authors have also replacement of red meat by white meat, as well as the mediation effect of meat ingredients on the associations. In this regard, the study has its novelty and unique contribution to the literature. The study has a very large sample size of over half million and has a reasonable follow-up duration of about 16 years, thus the authors were able to evaluate the associations with total mortality and nine specific causes of mortality. Overall, the manuscript has been well written and the analyses seem appropriate.

Some comments:

1. The authors have used energy density method as the exposures. Maybe some other methods could also be tried, e.g., residual method.
2. The exposures have been measured only once at baseline, thus whether the exposures could represent the long-term intake levels remains unclear, particularly if the meat products and intake patterns have changed in the past several decades. Any studies to evaluate the reproducibility and variability of the DHQ in assessing dietary intakes? How about the validity of DHQ in assessing meat intake in the calibration study?
3. The authors have included chicken, turkey, and fish in the same category of white meat, however, it might be better to do a sensitivity analysis to examine the associations separately. Fish and chicken may have different impact on the mortality risk. Some previous literature should also be discussed and compared in the Discussion section.
4. In the final model, the authors only included fruit and vegetables intake. Meat intake could be related to other dietary habits, and more fine adjustment of dietary habit could be considered, such as certain dietary patterns (without meat component).
5. In the substitution model, if total meat and red meat were both included in the model, the meaning of red meat was

the change in mortality risk by substituting red meat with white meat, while the meaning of total meat in this model was the change in mortality risk by increase of white meat holding red meat constant. Therefore, for white meat, this is the addition model and the results should be comparable to the "addition model" the authors have used. Furthermore, in the substitution model, the increased mortality risk of replacing red meat by white meat should be the reciprocal of the decreased mortality risk of replacing white meat by red meat. Theoretically, this should be the case, and the authors could examine their data and make sure they have used the correct method.

6. Heme iron can also come from white meat, and the authors can test the relations of heme iron from red meat and heme iron from white meat with the mortality risk. Or the authors can test whether the risk related to red meat was mediated by total heme iron or heme iron from red meat.

7. Table 1, it is better to show the total number of participants in each quintile of red meat intake. The current table 1 shows the number of deaths in each quintile, and is somewhat confusing.

8. Some of the results are unexpected and deserves more discussions. For example, why stronger associations were the mortality from chronic liver diseases and respiratory diseases, rather than cardiovascular disease or cancer? The authors have talked about oxidative stress and other pathways, but those mechanisms are not specific for liver or respiratory system.

9. For the mediation analysis, could you examine the proportion of the increased mortality risk associated with processed red meat mediated by nitrate/nitrite and heme iron together?

10. In table 2, it will also be better to show the proportions mediated by heme iron for total red meat and unprocessed red meat.

11. The interaction results were not comprehensively discussed in the Discussion section. Are the significant interactions by chance or there are biological rationales for the interactions? How to explain the results?

Additional Questions:

Please enter your name: An Pan

Job Title: Professor

Institution: Huazhong University of Science and Technology

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:

This manuscript provides evidence about a question of diet and health which is important to clinicians advising their patients and to public policy makers on the environmentally sensitive issue of red meat production. The AARP cohort is large but not well known. Follow-up in the present study was for 16 y and 7.5 M person-years. The cohort was set up with diet-health hypotheses in mind, utilizing eight US populations served by a cancer registry to identify incident cancer cases. The response rate at baseline was rather low (~16%) and there is a question of generalizability of the findings. There are two parts to this question. First, estimating incidence or mortality rates is not the focus of the study, therefore the low response rate is not a problem per se. Second, because the research hypotheses concern the causal relationships of meat and associated dietary intakes with mortality, distortion of the results due to selection bias will occur if the probability of study participation is associated with the exposure-outcome relationship. The logic is that non-participation at a particular level of meat intake will distort the diet-mortality effect estimate if mortality risk differs between those present in the study and those not present, and further that the probability of participation differs across quintiles of meat intake. This situation may arise despite the prospective study design, as a consequence of the differing propensities of individuals to participate in health research according to their pattern of health behaviour. Although subjects were recruited (and thus diet was measured) many years before disease onset and death, we would need to know something about the life styles and health of those who refused to participate in the study (or at least a subset) before we could exclude selection bias as a partial explanation of the findings.

Separately, there is a question about the lack of specificity of the observed health effects of meat intake (see Fig 1). The pattern of risks is remarkably constant across all 10 cause groups, such that red meat intake appears to increase the hazard of death from any cause except Alzheimer's, including infectious causes. This finding suggests that there is some common method error linked with the use of a food frequency questionnaire. For example, the apparently adverse effects of higher red meat intake (and generally protective effects of higher white meat intake) could be the result of reporting bias or what can be called 'behaviour bias'. In other words, it is difficult to distinguish between causal

explanation, bias and confounding. Health conscious people have lower mortality risk because they behave well in general, and they may have reported falsely low red meat intake. Other people may genuinely have had lower red meat intake because they were health conscious and believed low intake would be salutogenic. Both explanations undermine the claims of causality made in the study, and they should be discussed along with high quality null findings which suggest that a higher red meat diet is not a risk factor for colorectal cancer, one of the health outcomes most firmly linked with red meat intake in popular science. Thus, Spencer et al Cancer Causes and Control 2010 used a prospective case-control design based on food diaries. Ananthakrishnan et al Cancer Epidemiol Biomarkers Prev 2015 in a pooled analysis of 11 studies showed the same association was seen only in retrospective studies, again pointing to the challenges of nutritional epidemiology which are barely mentioned in the manuscript. A related question: was there life before the BMJ? It seems likely this US manuscript has been rejected by JAMA or NEJM or both, for reasons related to the points above. Yet the discussion in the paper still does not build in the reflections on causal interpretation that are needed. Despite the fact that it would be 'cool' to show that red meat is bad for health, and to strengthen the case that the ecological disaster of intensive beef production is not justified on human health grounds, the findings of this study are too open to alternative interpretation to provide that evidence.

#### Specific points

1. The results of the "addition models" (Supplementary Table 2) are adjusted for total energy intake while total meat intake is not held constant. This effect size from these models can be interpreted as a substitution of the meat source in question with non-meat food sources. To estimate the effect of increased intake of meat the model should adjust for the sum of energy intake from all other sources rather than the total energy intake (energy partition method).
2. Subgroup analysis (Figure 2) mentions the association is stronger for never smokers and never/mild alcohol drinkers. This is true for red meat but not white meat.
3. Typo in title of Table 1: should be quintiles.
4. The idea that white meat should be substituted for red is promoted (e.g. see Abstract conclusion), perhaps accidentally, in the manuscript. There is no need to eat meat for health reasons, and this substitution idea needs no encouragement.

#### Additional Questions:

Please enter your name: Eric Brunner

Job Title: Prof

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Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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