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de Medeiros GCBS, Mesquita GXB, Lima SCVC, et al. Associations of the consumption of unprocessed red meat and processed meat with the incidence of cardiovascular disease and mortality, and the dose-response relationship: A systematic review and meta-analysis of cohort studies. Critical Reviews in Food Science and Nutrition.

What We Know, Think We Know, or Are Starting to Know

And we're back to red meat. When it comes to debates about diet and nutrition, we can perhaps distil two levels of controversy: nutrient-based and food-based. These are tightly correlated debates. For example, the debate about saturated fat is inseparable from the debates about the healthfulness of foods like red meat and butter.

To add to the ideological mess that is nutrition, the health effects of these foods are judged by the two dominant, diametrically opposed dietary paradigms through a moral value lens. This means that, where there may be some ambiguity in the research, they will reconcile that ambiguity through the prism of that dietary paradigms' beliefs.

And so it is with red meat, on both sides. While the research on processed meat increasing risk for adverse health outcomes is difficult to push back against [1–3], there *is* some nuance to the literature on unprocessed red meat intake. In a previous Research Lecture, we discussed the potential dose thresholds ate which risk for unprocessed meat may be observed.

Leaving aside the absurdity of meat-only diets, there are plenty of sensible voices who would argue that unprocessed red meat intake in the context of a wider healthy dietary pattern is likely not any concern. Indeed, we have covered a study that is often cited in support of that position in a previous Deepdive.

The study we dig into today concluded little to association between both unprocessed and processed meat intake and cardiovascular disease [CVD] risk. It was posted in our Facebook group and has subsequently done the rounds on social media. Let' s get into it…

The Study

The investigators conducted a systematic review and meta-analysis of studies published up to February 2021, with the following inclusion criteria:

1. The study was a prospective cohort design
2. The participants were disease-free at baseline
3. The exposure of interest was red and/or processed meat intake
4. The outcome of interest was CVD events and/or mortality

"Red meat" was provided the following definitions:

- **Unprocessed red meat:** unprocessed muscle meat from mammals [beef, veal, pork, lamb], including minced and/or frozen meat.
- **Processed meat:** meat that has been processed by salting, curing, fermentation, smoking or other processes that enhance the flavour or improve preservation, and includes products such as bacon, sausages, ham, chicken nuggets, poultry deli meats and other deli meats and pâté.

The quality of the included studies was assessed using the Newcastle-Ottawa Scale [NOS]*, which is a tool to assess the quality of prospective cohort studies included in a meta-analysis.

*Geek Box: The Newcastle-Ottawa Scale

The Newcastle-Ottawa Scale (NOS) is a grading tool to assess the quality of non-randomised trials included in a meta-analysis. Observational studies of exposures may have small relative risks, but a large population attributable fraction (PAF): the PAF is the reduction in risk of disease across the whole population from changing an exposure. This potential population benefit means that it is important to have tools which can assess the quality of observational studies, to arrive at conclusions which may result in shifting the burden of disease in the population. The NOS uses three domains to assess the quality of cohort studies: selection of the cohorts (4 'stars' maximum), comparability of the cohorts (2 'stars' maximum) and assessment of outcome (3 'stars' maximum). 9 stars is therefore the maximum available score for a given study. Selection considers the representativeness of the exposed and non-exposed groups, the ascertainment of the exposure (for example, dietary assessment method), and clear demonstration that the entire group was free of the outcome (i.e., disease) at the start of the study. Comparability assesses the design and analysis of the cohorts, specifically what variables the study controlled/adjusted for. Outcome considers the assessment of the outcome (i.e., medical records), the follow-up duration, and the numbers included in the follow-up. The NOS is a straightforward, convenient tool to assess the quality of prospective cohort studies included in a meta-analysis.

Results: A total of 21 studies published over the period 1994 to 2020, including cohorts from North America, Europe, and Asia. The follow-up period of the included studies ranged from 4yrs to 30yrs. Of the included studies, 19 investigated associations for unprocessed red meat intake and 18 investigated associations for processed red meat intake. The main outcomes in the meta-analysis were coronary heart disease [CHD] mortality, total stroke, ischaemic stroke, and haemorrhagic stroke.

- ***CHD Mortality*:** There was no statistically significant association for unprocessed meat [HR 1.20, 95% CI 0.94 to 1.56] or processed meat [HR 0.92, 95% CI 0.67 to 1.26]. If we look at the HR and confidence intervals, the direction of effect toward higher risk was more evident for unprocessed meat, however, for processed meat the confidence intervals are spread across the 1.0.
- ***Total Stroke*:** There was a statistically significant 10% increase in risk for unprocessed meat [HR 1.10, 95% CI 1.01 to 1.19] and 17% increase in risk for processed meat [HR 1.17, 95% CI 1.08 to 1.26]. If we look at the HR and confidence intervals, the finding for unprocessed meat intake is less robust [the lower bound close to 1.0] than that for processed meat.
- ***Ischaemic Stroke*:** There was no statistically significant association for unprocessed meat [HR 1.04, 95% CI 0.94 to 1.17] or processed meat [HR 1.05, 95% CI 0.79 to 1.39]. Again, for processed meat the confidence intervals are spread across the 1.0 and there is little signal in this noise.
- ***Haemorrhagic Stroke*:** There was a statistically significant 25% lower risk for unprocessed meat [HR 0.75, 95% CI 0.57 to 0.99]. No analysis was conducted for processed meat and this outcome. If we look at the HR and confidence intervals, the direction of effect is evident, however, the confidence intervals are wide and close to 1.0, indicating a lack of precision in the estimate of effect.

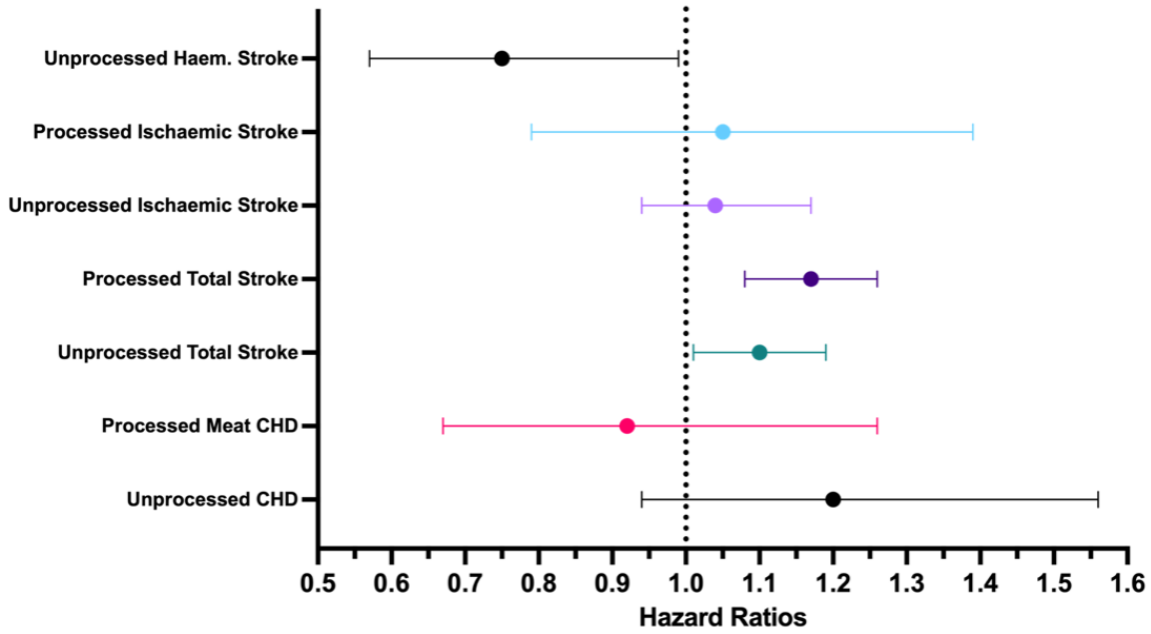

Figure *summarising the hazard ratios [bold colour circle] and corresponding 95% confidence intervals [left-right arms from circle] for each of outcomes associated with unprocessed and processed meat intake in the present meta-analysis. The only statistically significant finding of increased risk was in relation to total stroke, for both unprocessed and processed meats. The only statistically significant finding of decreased risk was in relation to haemorrhagic stroke, for unprocessed meat only.*

The Critical Breakdown

Pros: The inclusion criteria was clear for study design, population, and exposure and outcome. The investigators did attempt to make the meta-analysis more of a comparison of similar studies, confining inclusion to studies that carried out a 'high vs. low' comparison of intake levels and reported meat intake in grams per day [or a metric easily converted to grams per day]. The meta-analysis was stratified by sex, allowing for further insights into potential sex differences in risk. All but one primary study assessed diet using food-frequency questionnaires [FFQ] [although 4 studies did not mention validation of the FFQ].

Cons: Of the 21 included studies, only 9 were included in the meta-analysis in total, and this was further reduced to 2 to 3 studies included in meta-analysis of specific outcomes, e.g., stroke. The included studies quantified the comparators for meat intake differently, including dividing participants into quintiles, categorising based on frequency of intake, and categorising by portion size. While it is a 'Pro' that the authors did their best have comparable studies in the meta-analysis, the comparator groups from the primary included studies were not given sufficient consideration regarding dose of intake, and the substantial regional differences in background diets [e.g., Asian cohorts vs. American] which influenced the findings [more on this below].

Key Characteristic

When a study is published with largely 'null' findings, how do we think about it? Part of the ongoing issue with nutrition science isn't that nutritional epidemiology is unreliable, it is that sufficient attention to important concepts is not given by investigators. For example, the majority of included studies for this meta-analysis compared "high vs. low" intake. But what is "high"? What is "low"? How do these levels relate to prior knowledge, in particular to knowledge of risk at different thresholds?

Once again, the key characteristic of a meta-analysis of prospective cohort studies of diet is plagued by these issues. Let's take the finding in relation to processed meat and CHD mortality. The lack of association between processed meat intake and CHD mortality was driven by two Japanese cohorts, Nagao et al. 2012 and Saito et al. 2020. The former had a "highest" category of 13.9g/d in men 10.4g/d in women; the latter had a "highest" category of 8.4g/d and 11.7g/d in men and women, respectively. Both respective "high" categories are far below the ~50g/d threshold at which processed meat appears to significantly increase risk [1,4].

Is this lack of association truly a reflection of no increased risk, or a null finding related to a lack of sufficient contrast in exposure relative to baseline levels of already low intake? Given the totality of evidence, a more prudent bet would be the latter. And let us continue this theme under ***Interesting Finding...***

Interesting Finding

So, what about the lower risk of haemorrhagic stroke associated with unprocessed meat intake? Given that unprocessed meat intake was associated with a 10% higher risk of total stroke, this finding is one which warrants further scrutiny.

The first thing to note is that the studies included in the analyses of total stroke and haemorrhagic stroke differed; the three studies included in the analysis of total stroke were European (Sweden and Spain; *n* = 2) and US (*n* = 1). Although almost all cohorts included in the systematic review had <100g/d unprocessed red meat intakes, the cohorts included in the total stroke analysis were all at the higher end: the "high" category in the European cohorts was >80g/d, while the US cohort was >150g/d.

However, the two cohorts included in the analysis of unprocessed meat and haemorrhagic stroke were both Japanese cohorts. Based on the ***Key Characteristic***, above, you can see where this is going, right? But in fact, it goes beyond this regional distinction alone, because the overall significance was driven by a significantly lower risk in women, not men [data from both sexes was derived from the same two cohorts]. And in women, the "high" category levels of unprocessed meat intake were 23g/d (Saito et al., 2020) and 94g/d (Takata et al., 2013). If we think about the background knowledge on this topic, we typically see some positive direction of effect in these ranges in the Japanese cohorts [(5)]. Let' s think about why under ***Relevance***, below.

Relevance

In nutritional epidemiology, the comparator groups are important beyond just the actual levels of intake, because wider factors matter for the comparison in terms of what is consumed in the wider diet, and wider non-dietary lifestyle behaviours. For example, if you look at US cohorts, for example, high red meat often correlates with wider unhealthy dietary and lifestyle factors [(6)]. But if you look at some of the Japanese cohorts, the "high" [bear in mind <100g/d] red meat categories often have the highest vegetable and fruit intakes, higher fish intake, and healthy bodyweights [(5)].

And while we would expect these important factors to be adjusted for in statistical analysis, statistical adjustment doesn' t mean, for example, that an individual never smoked or ate their vegetables. These wider factors matter for the potential direction of effect when a certain level of intake is compared to another, particularly where that level of intake may be in a range at which we do not see any clear relationship with risk [(3)].

We have seen this play out in populations beyond Asian shores. As we covered in a previous Deepdive, a Canadian cohort showed that levels of intake around ~460g/week were not associated with adverse health outcomes in the context of high fruit and vegetable intakes. But as we highlighted in that Deepdive, if we break that weekly threshold down to daily intake, it averages ~65g/d, consistent with the wider evidence suggesting little influence of unprocessed red meat intakes in these ranges [(3)].

To be fair to the authors, they highlight the wide variance in what is considered "high", and the fact that there was substantial variability in how studies presented levels of intake. And they did attempt to have appropriately matched studies in the meta-analysis. Nevertheless, it is not sufficient simply to match studies based on whether they conducted a "high vs. low"

analysis and had similar outcome measures. It is important to go further than this in using background knowledge to inform the analysis, and in this respect, being clear on what doses are being compared and in what populations.

We clearly still have a long way to go to improve meta-analytic methodology for nutrition research.

Application to Practice

So, what about the present study doing the rounds? The first is that the increase in total stroke from both unprocessed and processed meat has been shown before, but similar to the present study, with regional differences between Japan and the US in strength of association [(7)]. Given that 2/3 studies in the analysis of total stroke were <100g/d in comparison, would higher levels provide more robust strength of associations for total stroke than the present study? This is always arguable, and the wider body of evidence does suggest that unprocessed meat intake does start to more consistently indicate risk at levels of >150g/d, as we discussed in this previous Research Lecture.

Secondly, the lack of association for the processed meat other outcomes and inverse association for haemorrhagic stroke must be considered in the context of the included studies: primarily Japanese cohorts with very low levels of processed meat and <100g/d unprocessed meat intakes. When papers like this get splashed around as "no association" without this addition context [ahem, Menno Henselmans], they are not an accurate representation of the study.

I'm going to stick the general proposition, based on the totality of evidence, that there is likely little cause for concern for unprocessed red meat intakes <100g/d on average in the context of a wider healthful dietary pattern. But the purported lack of association for processed meat in the present study, except for total stroke, should not be taken as representative of the risk posed by processed meat intakes of >50g/d.

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