WORLD FARMERS' ORGANISATION
SCIENTIFIC COUNCIL

Consumption of Unprocessed Red Meat Is Not a Risk to Health

SYNOPSIS PAPER
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ABSTRACT

A synopsis of five significant, recent and broad-scale scientific investigations on the health risks and health benefits of red meat consumption indicates that there is no convincing scientific evidence for assertions about harmful health effects of unprocessed red meat intake. If at all, the data very slightly lean toward an association of red meat consumption and protective health benefits. Overall, any of the statistical associations of up to 100 grams of red meat consumption per capita per day are so weak that they should be considered neutral. It is notable that less than 1% of the global population consumes more than 85 grams of red meat per day. From a global public health perspective, then, red meat consumption above the threshold of 85 grams is so negligible as to be irrelevant. National governments and supranational organizations such as the EU and UN, and their initiatives such as this year's UN Food Systems Summit, as well as international business and consumer associations, would be wrong to assume that a scientific consensus exists to justify policies to reduce red meat consumption in the general population for health reasons.

NOTE

This synopsis paper, while based on the latest high-quality evidence, is authored for the benefit of general readers interested in nutrition rather than nutrition scientists and related specialists. It has been prepared by a subcommittee of the Scientific Council of the World Farmers' Organisation (WFO).

The WFO Scientific Council is an independent scientific body composed of 15 scientists, experts and professors from across the globe, to equip WFO with the best scientific advice to enhance further the science-sound perspectives of the farmers' voice in the international debate around agriculture and food systems.

SUMMARY

A synopsis of five significant, recent and broad-scale scientific investigations on the health risks and health benefits of red meat consumption indicates that there is no convincing scientific evidence for assertions about harmful health effects of unprocessed red meat intake. If at all, the data very slightly lean toward an association of red meat consumption and protective health benefits. Overall, any of the statistical associations of up to 100 grams of red meat consumption per capita per day are so weak that they should be considered neutral. It is notable that less than 1% of the global population consumes more than 85 grams of red meat per day.

The five sources examined yield the following six summary observations.

1. The largest and most representative epidemiological study worldwide, with a cohort of 134,297 individuals enrolled from 21 low-, middle-, and high-income countries followed over 9.5 years, conducted by the global PURE consortium and published in March 2021, concludes that neither mortality nor cardiovascular disease risks was associated with unprocessed red meat consumption up to 100 grams per person per day.

2. Four systematic reviews of 122 studies and a corresponding dietary guideline conducted by the independent NutriRECS panel using internationally accepted standards for guideline methodology suggested by the Cochrane Handbook on systematic reviews, The Institute of Medicine and GRADE, published in October 2019, concludes that there are little to no health risks associated with red meat consumption, with the certainty of any health risks being low to very low.

3. The Global Burden of Disease Study (GBD 2017) published in November 2018, showed that red meat consumption is a negligible dietary health risk if at all, being, for instance, a factor 100 less dangerous to health than a diet low in fruit, and would be accounting for less than 0.1% of all deaths attributable to diet even under stretched assumptions.

4. The Global Burden of Disease Study (GBD 2019) published in October 2020, in stark contrast to GBD 2017, reported that red meat consumption had emerged as a significant dietary health risk, claiming to cause the equivalent of 896,000 deaths in the global population per year, which would represent a 36-fold increase over GBD 2017 estimates. The dramatic difference between the GBD 2017 and 2019 studies was achieved by an inexplicable transformation of the background data in the statistical evidence used. Without providing the relevant data, the study assumes a theoretical minimum risk exposure level (TMREL) of red meat intake of zero. In other words, the first bite of red meat would already be toxic. This 2019 study purporting to show the harmful health effect of red meat consumption is untransparent about its methods and appears to violate widely accepted and established scientific standards.

5. The WHO International Agency for Cancer Research (IARC) studies, published in November 2015 and 2018, concluded that red meat consumption has harmful health effects due to its probable cause of colorectal cancer. However, this widely cited 2015 classification of red meat being a class 2a cancer agent identifies 'hazards' rather than 'risks', the latter of which would have required a robust risk assessment and contextualization within overall dietary patterns and lifestyles. More worryingly, this conclusion is unsupported by the details of the underlying scientific evidence that were finally released in 2018. The evidence for red meat being classified as a cancer agent in 2015 appears to be a single scientific publication from 2011 by one of the IARC committee members. This 2011 publication suffers from a variety of technical shortcomings that violate widely accepted scientific standards, and is marred by an undisclosed conflict of interest.

6. Each of nine further high-profile scientific publications highlighted in this synopsis, state that an association between red meat and mortality cannot be established.

In conclusion, national governments and supranational organizations such as the EU and UN, and their initiatives such as this year's UN Food Systems Summit, as well as international business and consumer associations, would be wrong to assume that a scientific consensus exists to justify policies to reduce unprocessed red meat consumption in the general population for health reasons.

Red meat has many widely recognized nutritional benefits, which are not specifically deliberated on in this synopsis paper but are well laid-out in other places. For instance a recent UN Nutrition Report summarizes how especially vulnerable population groups such as babies in utero, infants and children of all ages, women of reproductive age, the ill and the elderly critically depend on livestock derived foods for their nourishment.[1] As there are no risks to general health to be expected, the consumption of unprocessed red meat at today's common levels should therefore be encouraged for all population groups as a significant source of dense and readily bio-available proteins, essential micro-nutrients and critically important bioactive substances and as part of an overall balanced diet combining different food groups.

[1] UN Nutrition Report: Livestock-derived foods and sustainable healthy diets, June 2021
https://www.unnutrition.org/wp-content/uploads/UN-Nutrition-paper-Livestock-derived-foods_19may.pdf
Press release and summary:
https://www.ilri.org/news/new-report-un-nutrition-untangles-risks-and-benefits-food-livestock-sustainable-healthy-diets

1 Evidence from the PURE Consortium Study published in March 2021 in the American Journal of Clinical Nutrition

1.1 Main conclusion by the 30 authors quoted verbatim from the study:

"We did not find significant associations between unprocessed red meat and poultry intake and mortality or major cardio-vascular disease."

1.2 Methods used by the authors

The Prospective Urban Rural Epidemiology (PURE) Study used data from its first two phases, with a cohort of 134,297 individuals, aged 35-70 years, enrolled from 21 low-, middle-, and high-income countries. Food intake was recorded using country-specific validated food frequency questionnaires. The primary outcomes were total mortality and major cardio-vascular disease. During a follow-up period of 9.5 years, the authors could record 7789 deaths and 6976 cardio-vascular disease (CVD) events. The hazard ratios (HR) were estimated using multivariable Cox frailty models with random intercepts. Higher unprocessed red meat intake (137 ± 76 g/day versus 5 ± 6 g/day, mean ± standard deviation) was not significantly associated with total mortality (HR: 0.93; 95% CI: 0.85, 1.02; P-trend = 0.14), or major CVD (HR: 1.01; 95% CI: 0.92, 1.11; P-trend = 0.72). Similarly, no association was observed between poultry intake and health outcomes.

1.3 Background on the authoring consortium and PURE

PURE stands for "Prospective Urban and Rural Epidemiology study". PURE is investigating the impact of modernization, urbanization, and globalization on health behaviours, how risk factors develop and influence cardiovascular disease, diabetes, lung diseases, cancers, kidney disease, brain health, and injuries.

PURE is by a long distance the largest, and most representative multinational study of its kind. Thanks to its inclusion of nearly every cultural and socioeconomic population strata around the world, it is better suited than any other epidemiological survey to identify confounding factors of health risks in statistical associations and eliminate them from the results. PURE began data capture in 2002, is conducted with partner universities in 25 countries on 5 continents, in 978 communities with 191,000 participants. PURE is coordinated by the Population Health Research Institute (PHRI) at McMaster University and funded by 35 different agencies.

PHRI has been directed by Prof Dr Salim Yusuf since its founding in 1999. Prof Yusuf was named an Office in the Order of Canada in 2013, is a fellow of the Royal Society of Canada, and was inducted into the Canadian Medical Hall of Fame in 2014. In 2011, he was the world's second-most cited researcher. He was the president of the World Congress of Cardiology in 2015 and 2016.

1.4 Citation:

Romaina Iqbal, Mahshid Dehghan, Andrew Mente, Salim Yusuf et al, on behalf of the PURE study, Associations of unprocessed and processed meat intake with mortality and cardiovascular disease in 21 countries [Prospective Urban Rural Epidemiology (PURE) Study]: a prospective cohort study, The American Journal of Clinical Nutrition, 2021;, nqaa448, https://doi.org/10.1093/ajcn/nqaa448

2 EVIDENCE FROM THE NUTRIRECS CONSORTIUM STUDY PUBLISHED IN OCTOBER 2019 IN THE ANNALS OF INTERNAL MEDICINE

2.1 MAIN CONCLUSION BY THE 19 AUTHORS QUOTED VERBATIM FROM THE STUDY:

"The panel suggests that adults continue current unprocessed red meat consumption."

2.2 METHODS USED BY THE AUTHORS

The evaluation panel used the Nutritional Recommendations (NutriRECS) guideline development process based on a detailed a prior publicly available study protocol, which included rigorous systematic review methodology, dose-response meta-analysis and GRADE methods to rate the certainty of evidence for each outcome and to move from evidence to recommendations. A panel of 14 members, including 3 community members, from 7 countries voted on the final recommendations. Based on the average intake of red meat consumption (3 to 4 servings per week) in most middle to high income countries, the main conclusion was that adults should not reduce their red meat consumption given the lack of convincing evidence for health risks when assessed using the GRADE methodology (more on GRADE in the footnote)[2]. The authors summarized their review:

"*Evidence Summary for Harms and Benefits of Unprocessed Red Meat Consumption: For our review of randomized trials on harms and benefits (12 unique trials enrolling 54 000 participants), we found low- to very low-certainty evidence that diets lower in unprocessed red meat may have little or no effect on the risk for major cardiometabolic outcomes and cancer mortality and incidence. Dose–response meta-analysis results from 23 cohort studies with 1.4 million participants provided low- to very low-certainty evidence that decreasing unprocessed red meat intake may result in a very small reduction in the risk for major cardiovascular outcomes (cardiovascular disease, stroke, and myocardial infarction) and type 2 diabetes (range, 1 fewer to 6 fewer events per 1000 persons with a decrease of 3 servings/wk), with no statistically significant differences in 2 additional outcomes (all-cause mortality and cardiovascular mortality). Dose–response meta-analysis results from 17 cohorts with 2.2 million participants provided low-certainty evidence that decreasing unprocessed red meat intake may result in a very small reduction of overall lifetime cancer mortality (7 fewer events per 1000 persons with a decrease of 3 servings/wk), with no statistically significant differences for 8 additional cancer outcomes (prostate cancer mortality and the incidence of overall, breast, colorectal, esophageal, gastric, pancreatic, and prostate cancer). Similar to studies directly addressing red meat, cohort studies assessing dietary patterns (70 cohort studies with just over 6 million participants) provided mostly uncertain evidence for the risk for adverse cardiometabolic and cancer outcomes."*

2.3 BACKGROUND ON NUTRIRECS, QUOTED FROM THEIR WEBSITE:

"*NutriRECS is an independent group with clinical, nutritional and public health content expertise, skilled in the methodology of systematic reviews and practice guidelines who are unencumbered by institutional constraints and conflicts of interest, aiming to produce examples of trustworthy nutritional guideline recommendations based on the values, attitudes and preferences of patients and community members*." [3]

[2] More on GRADE here: https://www.gradeworkinggroup.org/
[3] https://nutrirecs.com/

2.4 CITATION:

Johnston BC, Zeraatkar D, Han MA, Vernooij RWM, Valli C, El Dib R, et al. Unprocessed Red Meat and Processed Meat Consumption: Dietary Guideline Recommendations From the Nutritional Recommendations (NutriRECS) Consortium. Annals of Internal Medicine [Internet]. 2019 Oct https://doi.org/10.7326/M19-1621

Supporting articles were also published in the Annals of Internal Medicine, related to the above

https://www.acpjournals.org/doi/10.7326/M19-0655

https://www.acpjournals.org/doi/10.7326/M19-0699

https://www.acpjournals.org/doi/10.7326/M19-1583

https://www.acpjournals.org/doi/10.7326/M19-0622

2.5 RESPONSES TO THE NUTRIRECS PUBLICATION

In an article in JAMA Network (Journal of American Medical Association), senior writer Rita Rubin illuminated the circumstances accompanying the publication of the NutriRECS recommendations in the Annals of Internal Medicine (AIM), which is among the world's top rated academic journals. It describes the tactics ranging from cyber-hooliganism to career abortion, which authors and editors are exposed to if they publish findings that are not congruent to the 'Red meat consumption must be reduced' narrative. Here excerpts from her article[4]:

"The Annals Editor-in-Chief Christine Laine said: 'We've published a lot on firearm injury prevention. The response from the NRA (National Rifle Association) was less vitriolic than the response from the True Health Initiative'….The True Health Initiative (THI) is a nonprofit founded and headed by David Katz, MD….Katz circulated the embargoed article among THI colleagues, telling them that the guideline 'looks like it's going to be a serious problem for us'….Katz compared the articles, which he called 'a great debacle of public health' to 'information terrorism' that 'can blow to smithereens…the life's work of innumerable careful scientists."

AIM also had to contend with several other attacks, among them that the email address of chief editor Laine was bot-attacked with thousands of emails so it ultimately needed to be shut down.

Another group called Physicians Committee for Responsible Medicine (PCRM) also launched campaigns against AIM and editor Laine. PCRM has 175,000 members, of who less than 10% are actually physicians according to their own website. Its mission is to be "***dedicated to saving and improving human and animal lives through plant-based diets and ethical and effective scientific research.***"[5] For instance, ***"PCRM asked the district of attorney of the City of Philadelphia where AIM's offices are located, 'to investigate potential reckless endangerment' resulting from the publication of the meat papers and recommendations."***. The monitoring organization 'Activist Facts' provides information on the tactics and activities of PCRM which the American Medical Association calls ***"unethical"***.[6]

Alongside these activist's campaigns, several high-profile academics also accused AIM and the article authors at scientific conferences of sensationalism, disinformation and tenuous conflicts of interests. Authors variously reported academic harassment at their scientific institutions.

[4] "Backlash Over Meat Dietary Recommendations Raises Questions About Corporate Ties to Nutrition Scientists" JAMA. 2020;323(5):401-404. doi:10.1001/jama.2019.21441

[5] https://www.pcrm.org/about-us

[6] https://www.activistfacts.com/organizations/23-physicians-committee-for-responsible-medicine/

2.6 BRIEF EXPLANATION ON LONGITUDINAL EPIDEMIOLOGICAL STUDIES

Longitudinal epidemiological studies such as the one conducted by PURE, or those reviewed by NutriRECS examine with statistical methods the occurrence of medical events and their association with various factors of lifestyle choices, socio-economic circumstances, genetic disposition and dietary intake. The more of these factors are known about the person that is being followed in the longitudinal study, the better can a statistical association be asserted instead of being confounded by unobserved factors. On the other hand, observing many factors makes a study design inherently expensive, so that typically fewer participants can be followed over the years. Fewer participants decrease the statistical certainty. As a result, there exist only a handful of epidemiological surveys that are both broad enough to have enough participants and capture at the same time a reasonable number of factors, from which valid statistical associations can be inferred.

In the sections 2.7 and 2.8 below, are shown graphical representations of the data from the most famous and most widely used epidemiological studies on for instance the statistical association between occurrence of cardiovascular disease events and different levels of red meat intake. The x-axis of the charts shows the average amount of red meat intake of a given person in the study. The y-axis shows the relative risk of suffering from a negative health effect (if the number is above 1), or the relative risk of being protected by a beneficial health effect (if the number is below 1).

To explain the relative risk (RR) concept: the average risk of suffering a coronary heart disease (CHD) event during the next 10 years for an average 55-year-old male US American with standard blood pressure of 120/80, is 5%. That means, one out of twenty of these US males will suffer a CHD until they are 65. The RR association of having diabetes and raised blood pressure of 140/90 with a CHD event for such a 55-year-old is 5. That means, 5% x 5 = 25%, or one out of four of such US males will suffer a CHD event in the next 10 years. The RR of having diabetes and raised blood pressure and being a cigarette smoker is 7.5. That means 5% x 7.5 = 37%, or more than one out of three of these US males will suffer a CHD event between 55 and 65 years of age.[7]

It is contested which levels of RR are statistically significant. The famous epidemiologist Samuel Shapiro observed: *"**we can hardly ever be confident about estimates of less than 2.0, and when estimates are much below 2.0, we are simply out of business**."* [8] In a famous example, as a demonstration for how unreliable RR statistics can be, researchers were able to "prove" among a population of 10 million people and 223 most common medical diagnoses, that for two of these medical conditions there existed a validated RR of 1.15 and 1.38 with the individual's astrological signs.[9] The authors conclude: "***Our analyses illustrate how the testing of multiple, non-prespecified hypotheses increases the likelihood of detecting implausible associations. Our findings have important implications for the analysis and interpretation of clinical studies***".

In the above example, it would be wrong to conclude from the little information provided that diabetes or smoking ***causes*** CHD events. There could also be unobserved confounding factors that are not mentioned. For instance, it does not cover whether the diabetic smoker with a 37% chance of a CHD event is potentially also more likely to be drinking alcohol, being divorced, consuming too few vegetables and fruits, having poor living conditions, working in a hard-labor job environment, being exposed to environmentally hazardous substances,

[7] Data from American Heart Association, Mozaffarian 2015, Framingham Heart Study
www.heart.org/idc/groups/heart-public/@wcm/@sop/@smd/documents/downloadable/ucm_449846.pdf

[8] Shapiro, 2004: Looking to the 21st century: have we learned from our mistakes, or are we doomed to compound them? https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.903. Shapiro was the co-founder of the Epidemiology center of Boston University.

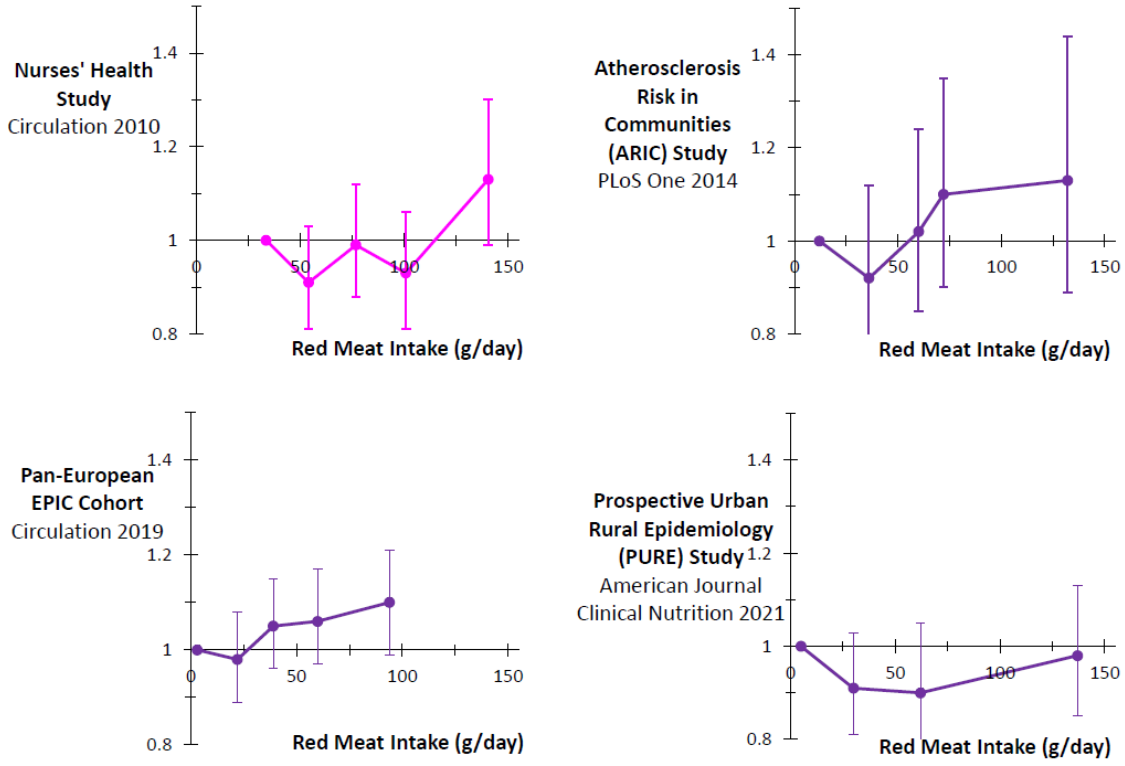
[9] Austin PC, Mamdani MM, Juurlink DN, Hux JE. Testing multiple statistical hypotheses resulted in spurious associations: a study of astrological signs and health. J Clin Epidemiol. 2006 Sep;59(9):964-9.
doi: 10.1016/j.jclinepi.2006.01.012. Epub 2006 Jul 11

conducting too little exercise, having a family history of CHD-events, and more. In order to state that diabetes or smoking causes CHD events, it is also necessary to separate out all these other possibly confounding factors, and to understand the causal biochemical mechanism by which diabetes or smoking causes CHD events in the body of a person. For diabetes or smoking the causality mechanism has been well achieved, but the principle remains the same: correlation is not causation.

With regards to red meat consumption, no widely recognized scientific investigation could so far establish a convincing causal mechanism, i.e., the biochemical pathway through which red meat would cause damage in a normally healthy body and thus cause negative health effects.

2.7 Statistical associations expressed as Relative Risk between red meat consumption and myocardial infarction (colloquially known as heart attack) in four widely known studies

Fig 1) Red meat consumption and its relationship with myocardial infarction, in RR



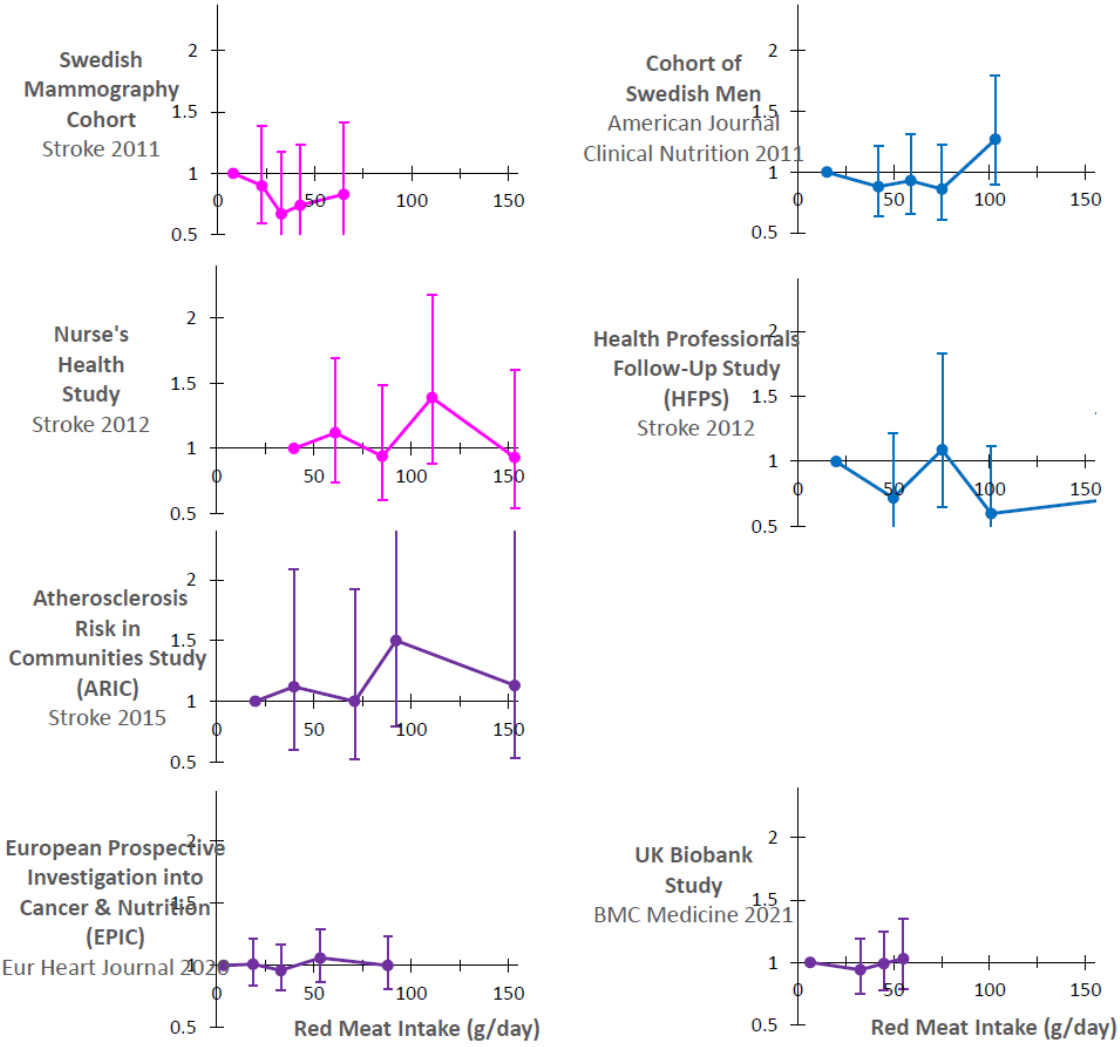
Source: Graphics prepared on basis of data of respective studies, y-axis is relative risk

Commentary: No relevant statistical association

All four of these studies show de facto a flat line profile, with relative risk (RR) fluctuations around plus/minus 10% which are statistically not significant. The PURE study is the only multinational multicultural investigation among these four. Nurses Health and ARIC are US American, and EPIC is a European investigation. Each of them stays well below the standard of a relative risk (RR) of 2, only above of which epidemiologists such as Shapiro would claim to identify any significance.

2.8 Statistical associations expressed as Relative Risk between red meat consumption and haemorrhagic stroke in seven widely known studies

Fig 2) Red meat consumption and its relationship with haemorrhagic stroke, in RR



SOURCE: GRAPHICS PREPARED ON BASIS OF DATA OF RESPECTIVE STUDIES, Y-AXIS IS RELATIVE RISK

Commentary: No relevant statistical association

The studies on the statistical association between red meat consumption and haemorrhagic stroke are even less conclusive than on heart attacks, with neither protective effects nor harmful effects observable across the studies. Three studies (Cohort of Swedish Men, Nurses Health Study and Atherosclerosis in Communities Study) appear to demonstrate a non-statistically significant rise in haemorrhagic stroke at around 100 grams per day, but the risk clearly falls again for higher intakes up to 150 grams per day in two out of these three studies.

3 EVIDENCE FROM THE GLOBAL BURDEN OF DISEASE (GBD 2017) STUDY IN NOVEMBER 2018 IN LANCET

3.1 DESCRIPTION OF THE STUDY:

The massive international scientific GBD effort involving several hundred institutions and authors from around the world, has provided standardized and comprehensive assessments of the global burden of diseases, injuries and risk factors at regular intervals for the past 30 years. Publications from the GBD 2017 analysis have highlighted the considerable impacts of malnutrition and dietary risk factors on deaths and disease burden. The authors describe the method as such:

"The main inputs to this analysis included the intake of each dietary factor, the effect size of the dietary factor on disease endpoint, and the level of intake associated with the lowest risk of mortality. Then, by use of disease specific population attributable fractions, mortality, and disability-adjusted life-years (DALYs), we calculated the number of deaths and DALYs attributable to diet for each disease outcome."

One of the 21 designated dietary risk factors is high red meat consumption. In the supplement, the authors list the only two sources by which they assessed the riskiness factor of high red meat consumption. The two sources are from 2010 and 2011 respectively:

a) World Cancer Research Fund, American Institute for Cancer Research, Imperial College London. WCRF/AICR Systematic Literature Review Continuous Update Project Report: The Associations between Food, Nutrition and Physical Activity and the Risk of Colorectal Cancer. Oct 2010.
b) Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. Am J Clin Nutr 2011; 94: 1088–96.

Both sources are problematic. The first source by WCRF is de facto the same as the IARC source which will be described further below in section 5, and which is compromised in various ways.

The second source describes on its page 3 that ***"for both men and women, red meat intake was negatively associated with physical activity, but positively associated with BMI and smoking. In addition, a high red meat intake was associated with a high intake of total energy and a worse diabetes dietary score."*** Despite these strong indications of confounding factors by proven causes for diabetes, the study claims to have identified diabetes association above and beyond those confounding factors for both processed and unprocessed red meats. The statistical tests that were performed in this investigation to prove additional association, cannot be considered sufficient.

3.2 COMMENTARY: RED MEAT RISKS WERE DE FACTO PROVEN TO BE NEGLIGIBLE

Regardless of relying merely on these two problematic sources instead of taking a broader and more recent spectrum of investigations into account, the GBD 2017 study could identify a global annual death burden of just 25,000 deaths due to high red meat consumption, out of a total 22 million deaths due to all 21 dietary risk factors, so only around 0.1% of the total. Red Meat would be a hundred times less dangerous than a diet low in fruit for instance. The GBD 2017 study showed that high red meat intake would be a negligible dietary risk factor.

3.3 Citation:

Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017; Roth, Gregory A et al. The Lancet, Volume 392, Issue 10159, 1736 – 1788; DOI: https://doi.org/10.1016/S0140-6736(18)32203-7

Health Effects of Dietary Risks in 195 Countries, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study. Christopher JL Murray & GBD 2017 Diet Collaborators. The Lancet 2019, Volume 393: 1958–72; DOI: https://doi.org/10.1016/S0140-6736(19)30041-8

4 Evidence from the Global Burden of Disease (GBD 2019) Study in October 2020 in Lancet

4.1 Description of the study:

The essentially same international consortium as in 2017, reviewed in 2019 a slightly updated data set in comparison to the GBD 2017 study. In the GBD 2019 study the data covered the years 1990 to 2019, whereas in the GBD 2017 study the data ranged from 1990 to 2017.

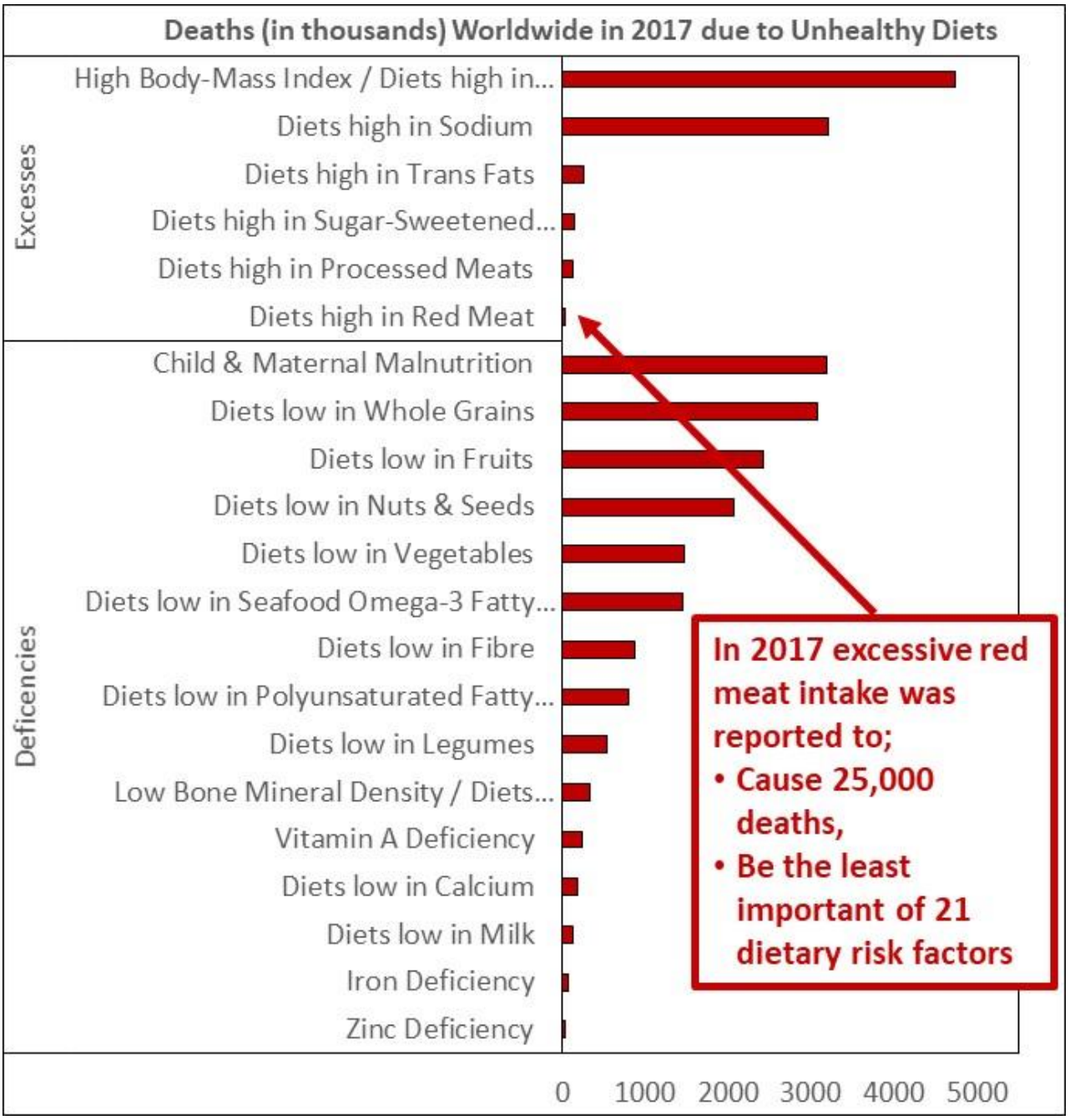
While changes occurred in many categories of the assessment, the most substantial change in the estimates was the disease burden attributed to diets high in unprocessed red meat. In the GBD 2019 analysis, a diet high in red meat was reported to be responsible for 896,000 deaths and 23.9 million DALYs (disability-adjusted life years), and to be the seventh-leading dietary risk factor for attributable DALYs. By contrast, the GBD 2017 analysis only attributed 25,000 deaths, and 1.3 million DALYs, to diets high in red meat, so that red meat intake was the least important of 21 dietary risk factors. Hence, by comparison with the GBD 2017 estimates, the GBD 2019 estimates of deaths and DALYs attributable to unprocessed red meat intake have increased 36-fold and 18-fold, respectively (see below figure 3).

In the documentation, the GBD Risk Factors collaborators acknowledge the substantial changes in the estimates for many of the dietary risk factors. They list three major sources for these changes: a) changes in the crosswalks between alternative and reference methods for estimating diet intake, b) new systematic reviews and meta-regressions, and c) more empirical standardized methods for selecting the theoretical minimum risk exposure level (TMREL). For red meat, all three sources influence the estimates, and the latter two appear to be of particular importance.

4.2 Commentary: Departure from required scientific principles render study unconvincing

In contrast to all previous GBD analyses, where published peer-reviewed systematic reviews and meta-analyses were utilized, the GBD 2019 Risk Factors collaborators have performed or updated their own systematic reviews for each dietary risk and its related outcomes. Based on these reviews they found for instance "***sufficient evidence supporting the causal relationship of red meat intake with ischaemic heart disease, breast cancer, haemorrhagic stroke, and ischaemic stroke***", and added these outcomes to previously found relationships with diabetes mellitus and colon cancer. However, the authors provide very little information concerning their self-conducted systematic reviews. This violates a number of established and required scientific principles.

Fig 3a) Dietary risks and deaths according to GBD 2017 analysis



SOURCE: GRAPHIC PREPARED ON BASIS OF DATA IN GBD 2017 AND 2019 STUDIES

Fig 3b) Dietary risks and deaths according to GBD 2019 analysis

SOURCE: GRAPHIC PREPARED ON BASIS OF DATA IN GBD 2017 AND 2019 STUDIES

The publisher, The Lancet, along with all top ranked medical journals, rightly requires that global health estimates be reported according to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement. [10] Indeed, both the Editor-in-Chief of The Lancet, Dr Richard Hoorton, and the lead author of the GBD 2019 study, Professor Christopher Murray, are co-authors of the GATHER statement. GATHER recognizes that accurate interpretation and responsible use of health estimates, by both decision makers and researchers, requires understanding of the input data on which estimates were based, including their quality, and of the methods used to derive the estimates from the input data. GATHER comprises a checklist of 18 items which are organized into four sections: objectives and funding, data inputs, data analysis, and results and discussion. With regard to data inputs, GBD 2019 does indicate that 92 sources are used in the estimations of relative risk of diets high in red meat. However, those 92 publications are not specifically identified. Moreover, there is no reporting of GATHER items 3-6, which pertain to how the data from each source were identified and accessed, the inclusion and exclusion criteria, the characteristics of the populations, the data collection methods, and any potentially important biases.

Furthermore, since the GBD 2019 study undertook new and/or updated systematic reviews and meta-analyses, The Lancet requires that each of these reviews be reported according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 guidelines.[11] In these guidelines there is for instance a requirement to specify the methods used to assess the risk of bias in the included studies; a shift from assessing "quality" to assessing "certainty" in the body of evidence; and a recommendation that systematic review protocols are prospectively registered with a publicly accessible repository. However, there is no record of PRISMA documentation in the main paper, nor in the appendices, of the GBD 2019 systematic review protocols, nor of the required peer-reviewed publications which comprehensively address the 27 item PRISMA (2009 or 2020) checklists.

There is also no explanation provided for what is meant by "***more empirical standardized***" methods for selecting the TMREL for risk factors. The TMREL for risk factors viewed as harmful, was, by default, set to zero. Hence, the red meat TMREL was likewise set to 0 g/day, implying that the first bite of red meat would already be toxic. The assumption of a red meat TMREL of zero is counterintuitive given the role of meat in evolutionary diets, and in contemporary hunter-gatherer populations, where cardiometabolic diseases were and are uncommon.[12] [13] It is also not congruent with the statistical evidence from the major epidemiological studies as shown in section 2.7 and 2.8, which were available to the GBD collaborators.

Finally, there seems to have been no accounting for the totality of nutritional effects of red meat in the meta-regressions. If the TMREL is assumed to be zero, red meat would then *de facto* be presented as an inherently harmful food. This would ignore the well documented nutritional benefits with respect to the supply of essential nutrients and bioactive components. [14] [15] In summary, the transformation of the data that led to the dramatic rise of harmfulness of red meat consumption are not made transparent in the study, which violates every principle of good scientific practice, and furthermore violates the standards which The Lancet requires for its publications.

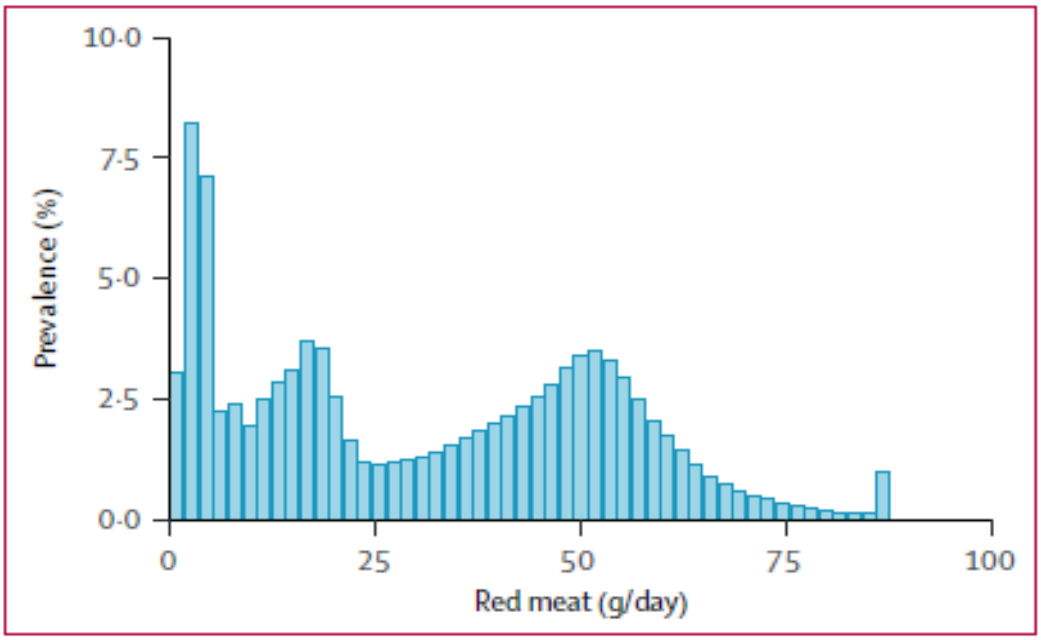
[10] Stevens GA, Alkema L, Black RE et al (The GATHER Working Group). Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. Lancet 2016; 388: e19–23.
[11] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9.
[12] Mann NJ. A brief history of meat in the human diet and current health implications. Meat Sci. 2018; 144: 169
[13] Cordain TL, Eaton SB, Brand Miller J, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. Eur J Clin Nutr 2002; 56 Suppl 1:S42-2.
[14] Wyness L. The role of red meat in the diet: nutrition and health benefits. Proc Nutr Soc 2016; 75: 227–32.
[15] Adesogan AT, Havelaar AH, McKune SL et al. Animal source foods: Sustainability problem or malnutrition and sustainability solution? Perspective matters. Global Food Security 2020; 25: 1003252.

4.3 GLOBAL PREVALENCE AND DISTRIBUTION OF RED MEAT CONSUMPTION

It is not well known how much red meat is consumed by the global population. The most uniform and authoritative database on the subject could be the New Food Balance Sheets compiled annually by FAOstat. These balance sheets capture the data in a consistent methodology across all countries worldwide. However, the balance sheets only show how much of the respective food stuffs are produced and available on average per person per country. They do not show the intra-country distribution of amounts of red meat intake, nor do they account for a difference between food that is available and food that is consumed. Moreover, the food balance sheets do not distinguish between processed meats and unprocessed or minimally processed meats. A second data source are so-called food frequency questionnaires (FFQ). They ask what people are actually eating. However, the results from FFQ's often show large divergencies to the FAO food balance sheets. This is particularly the case for meat products, which tend to be eaten relatively more frequently in food service settings rather than at home, and are therefore harder to capture with the FFQ's.

However, the Global Burden of Disease 2019 publication provides a helpful estimation of the global distribution of red meat consumption. This estimate shows a three-modal distribution, with one group of the global citizenry consuming around 5 grams per day, a second group consuming around 20 grams per day, and a third cluster consuming around 50 grams per day. Only 1 % of the global population consumes more than 85 grams per day. The statistical distribution suggests that the number of persons around the world who consume more than 100 grams per day are immeasurably and inestimably small.

Fig 4: GBD estimation of red meat consumption 2019



SOURCE: GRAPHIC PREPARED ON BASIS OF DATA GBD STUDIES ESTIMATION

4.4 CITATION:

Murray, Christopher J L et al.; Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019 The Lancet, Volume 396, Issue 10258, 1223 – 1249 https://doi.org/10.1016/S0140-6736(20)30752-2

5 EVIDENCE FROM THE WHO IARC IN NOVEMBER 2015 AND DOCUMENTATION RELEASED IN 2018

5.1 MAIN OBSERVATION OF THE IARC COMMITTEE MEMBERS AS COMMUNICATED IN 2015:

"No clear association was seen in several of the high-quality studies, and residual confounding from other diet and lifestyle risk is difficult to exclude. The Working Group concluded that there is limited evidence in human beings for the carcinogenicity of the consumption of red meat."

5.2 COMMENTARY

Closer inspection of the evidence documented in the IARC Monograph #114 which was subsequently published in 2018, suggests that the above is an overly careful wording of the state-of-the-art science. Of 32 observations highlighted in studies referred to in the Monograph, 3 show a statistically significant reduction of colorectal cancer risk with red meat consumption, 21 show no statistical association, and only 8 claim a significant association of increased risk. The only double-blind placebo-controlled study showed no association. Two of the three studies showing cancer risk reduction, were the two largest cohort studies, one with 73,214 participants in Shanghai, and three separate investigations of a large number of health professionals in USA. The only cohort study with a large and representative number of participants showing a cancer risk increase, could show such positive association only after applying a statistical manipulation of the numbers, and then only for pork meat consumption.

5.3 THE CIRCUMSTANCES OF THE STUDY

The International Agency for Research on Cancer (IARC) is the specialized cancer agency of the World Health Organization. The objective of the IARC is to promote international collaboration in cancer research.[16]

On the basis of the recommendations of an independent Advisory Group of international experts, the IARC Monographs Programme evaluates agents that are suspected to cause cancer. Agents are recommended for evaluation when there is evidence that people may be exposed, and when there is also scientific evidence available to evaluate carcinogenicity.[17]

An Advisory Group of 21 scientists from 13 countries met in April, 2014, to recommend topics for assessment in 2015–19 and to discuss strategic matters for the International Agency for Research on Cancer (IARC) Monographs programme.[18] Among 24 high priority topics, one of them was: ***"Processed and unprocessed red meat—consumed worldwide; several epidemiological studies of colorectal and some other cancers."*** (A further topic was coffee and maté, on which IARC Monograph #116 was published.[19]) The Rapporteur of that meeting was Prof Bernard Stewart, Scientific Advisor to Cancer Australia and Conjoint Professor at University New

[16] https://www.iarc.who.int/cards_page/about-iarc/
[17] https://monographs.iarc.who.int/wp-content/uploads/2018/07/QA_ENG.pdf
[18] https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70168-8/fulltext
Future priorities for the IARC Monographs
DOI: https://doi.org/10.1016/S1470-2045(14)70168-8
[19] Monograph #116 concluded that against the previous classification of coffee in 1991 being possibly carcinogenic, evidence now shows that coffee is not classifiable as carcinogenic. However, drinking very hot beverages is: https://www.iarc.who.int/wp-content/uploads/2018/11/Monographs-QA_Vol116.pdf

South Wales.[20] Prof Stewart then became the Meeting Chair of the Working Group members for the meat investigation, which started swiftly.

The Working Group members published the summary of their findings in The Lancet Oncology on 26 October 2015. They said that 22 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France. The Working Group had *"**assessed more than 800 epidemiological studies that investigated the association of cancer with consumption of red meat or processed meat in many countries, from several continents, with diverse ethnicities and diets.**"*[21] Despite the claim of having assessed 800 studies, in reality only one study was used to arrive at the main conclusion, as will be shown below in section 5.5.

Both in that summary[22], and in the same day press release and a Q&A document by WHO/IARC, the authors claimed that: *"**An analysis of data from 10 studies estimated that every 50 gram portion of processed meat eaten daily increases the risk of colorectal cancer by about 18%.... data from the same studies suggest that the risk of colorectal cancer could increase by 17% for every 100 gram portion of red meat eaten daily**."* [23]

In contradiction to the above statement, in the summary the Working Group members also wrote that: *"**Chance, bias, and confounding could not be ruled out with the same degree of confidence for the data on red meat consumption, since no clear association was seen in several of the high quality studies and residual confounding from other diet and lifestyle risk is difficult to exclude. The Working Group concluded that there is limited evidence in human beings for the carcinogenicity of the consumption of red meat**."* [24]

Nonetheless, as a result of its findings, overall the Working Group classified *"**consumption of red meat as "probably carcinogenic to humans" (Group 2A). In making this evaluation, the Working Group took into consideration all the relevant data, including the substantial epidemiological data showing a positive association between consumption of red meat and colorectal cancer and the strong mechanistic evidence**."* [25]

In contradiction to the "***strong mechanistic evidence***", the WHO/IARC Q&A document makes clear that a causal mechanism between red meat consumption and cancer is not proven: *"**Eating red meat has not yet been established as a cause of cancer.**"* [26] The Working Group did not elucidate how a *"**limited evidence**"* in the 5th paragraph becomes *"**substantial epidemiological data**"* in the 13th paragraph of the same document. It also did not explain how there can be "***strong mechanistic evidence***", if causality has not been established.

Evidently, the overall headline conclusion of the Working Group in the year 2015, was not supported by their own self-pronounced findings.

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[20] https://www.cancer.org.au/people/bernard-stewart
https://research.unsw.edu.au/people/professor-bernard-w-stewart

[21] 5th paragraph in: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00444-1/fulltext; Carcinogenicity of consumption of red and processed meat;
DOI: https://doi.org/10.1016/S1470-2045(15)00444-1

[22] 6th paragraph in: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00444-1/fulltext;
Carcinogenicity of consumption of red and processed meat;
DOI: https://doi.org/10.1016/S1470-2045(15)00444-1

[23] 12th question in: https://www.who.int/news-room/q-a-detail/cancer-carcinogenicity-of-the-consumption-of-red-meat-and-processed-meat

[24] 8th paragraph in: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00444-1/fulltext; Carcinogenicity of consumption of red and processed meat;
DOI: https://doi.org/10.1016/S1470-2045(15)00444-1

[25] 13th paragraph in: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00444-1/fulltext; Carcinogenicity of consumption of red and processed meat;
DOI: https://doi.org/10.1016/S1470-2045(15)00444-1

[26] 11th question in: https://www.who.int/news-room/q-a-detail/cancer-carcinogenicity-of-the-consumption-of-red-meat-and-processed-meat

5.4 The IARC Monograph #114, 2018

The release of the detailed documentation for the Working Group findings, IARC Monograph #114, was published three years later in the year 2018, and could shed more light on the scientific evidence which the Working Group was evaluating. However, the findings in this 511-pages long document neither correspond to the Working Group summary published in The Lancet in October 2015, nor to the WHO press release and its Q&A document.

For instance, with regards to statistical associations between red meat and colorectal cancers, the section 2.2.1 a) of the monograph, starting on page 107, describes in brief 24 cohort studies and case-control studies from across the world. Of 32 observations made in these studies, 3 show a statistically significant reduction of colorectal cancer risk with red meat consumption, 21 show no statistical association, and 8 show a significant association of increased risk. The only double-blind placebo-controlled study showed no association. Two of the three studies showing cancer risk reduction, were the two largest cohort studies, one with 73,214 participants in Shanghai, and three separate investigations of large numbers of health professionals in USA. The only study with significant number of participants showing a cancer risk increase, could only show such positive association after applying a statistical processing enhancement of the numbers, and then only for pork consumption (see Annex 3, respectively #9, #14 and #13).

In summary, most of the studies cannot prove any association, including all of the broadest and best conducted studies. Each study that could show a positive association between red meat consumption and colorectal cancer, suffers from shortcomings of potentially confounding data or data processing enhancement.

Overall, the documentation in monograph #114 does not appear to be able to satisfy the definition of: *"**substantial epidemiological data**",* which supposedly led to classifying red meat consumption as *"**probably carcinogenic to humans**".*

5.5 Dr Teresa Norat, member of the IARC Working Group, Imperial College London

Not a single one of the studies mentioned in the IARC Monograph #114 corroborate the statement that there is an increased risk of colorectal cancer by 17% for every 100 gram of red meat eaten daily, as was pronounced in 2015 in The Lancet Oncology Summary. Indeed, this finding does not derive from the analysis of the IARC Working Group. Instead, it is the conclusion of an investigation which one of the members of the Working Group, Dr Teresa Norat, had already published in the year 2011, resting on a meta-analysis of just 10 out of the potentially available 21 studies as per the IARC working group (3 of the 24 were published after 2011).[27]

Besides this 2011 study being a meta-analysis rather than being direct epidemiological evidence, which is potentially problematic in itself, there are various methodological shortcomings in Dr Norat's analysis from the year 2011, and how she arrived at the conclusions. Her authoring team selected data from 10 studies and gave them various weights of significance. Five of these studies had concluded that there is no association between red meat consumption, and five showed a positive association. It is obvious that by biassing the inclusion sample of studies for meta-analysis towards positive association studies (most available studies also in 2011 showed no association), the overall result automatically is more likely to show a positive association as well.

Furthermore, the authoring team gave Dr Norat's own study from 2005 as one of the ten studies included, an outsized weight of 38% in the sample. This is the same study mentioned above (also mentioned in section 5.7,

[27] https://pubmed.ncbi.nlm.nih.gov/21674008/
Red and Processed Meat and Colorectal Cancer Incidence: Meta-Analysis of Prospective Studies
https://doi.org/10.1371/journal.pone.0020456

#13) which could only arrive at a positive association for colorectal cancer after enhanced data processing, and then could show it only for pork meat consumption.

In essence, the 2011 paper by Dr Norat shows strong symptoms of p-hacking, which is the processing of statistical data for long enough, until the pre-conceived desired results emerge. The 2011 paper by Dr Norat is thus compromised and should not be considered sufficient scientific evidence.

Nonetheless, it was this flawed 2011 investigation, which then supplied the summary findings for the IARC Working Group in 2015 and the headline conclusions in all WHO announcements.

5.6 World Cancer Research Fund International

The 2011 paper by Dr Norat is also flawed in another way. The authors have declared on its cover page that no competing interests exist. That is not true.

Each of the seven authors except one, have been members[28] of the *"Continuous Update Project"* supported and funded by the World Cancer Research Fund International (WCRFI): *"The Continuous Update Project is an ongoing programme to analyse global research on how diet, nutrition and physical activity affect cancer risk and survival."* [29] WCRFI has as its mission to be: "*a leading authority on cancer prevention research related to diet, weight and physical activity",* and its vision is *"to live in a world where no one dies of a preventable cancer."* [30]

The WCRFI has been created by the WCRF UK, where it was founded by Ms Marilyn Gentry in 1990. WCRF UK is a privately owned and privately managed company limited by guarantee registered as a charity in England and Wales.[31] WCRF operates similar affiliates in the US (there called American Institute for Cancer Research), Netherlands and Hong Kong. Ms Gentry is President of each of them. According to the Form 990 for FY 2019 for the US affiliate, Ms Gentry earned above USD 240,000, while the CEO Kelly B. Browning earned above USD 470,000.[32] The US affiliate had income of USD 18 million in FY 2019, while the UK affiliate had an income of GBP of 8.8 million.[33]

Independent of WCRFI being a charity for a noble cause – self-evidently, the WCFRI is a financial donations-dependent organization and an interested party in carcinogenicity. The affiliation of Dr Norat of the Imperial College London and her authoring team with WCRFI and its financial support, should have been declared in the 2011 publication.

Moreover, since it was de facto Norat's 2011 paper which served as a basis for the IARC Working Group findings and communications, that interest should have been declared as well as part of the IARC documentations. Given her association with the WCRFI, it is also doubtful, to what degree Dr Norat could be considered an independent expert and was therefore possibly not qualified as being a member of the Working Group for the IARC.

5.7 Findings in IARC Monograph #114 on association of red meat and colorectal cancer

The following excerpts are taken from the IARC documentation report #114 that was the basis for the WHO/IARC decision in 2015, and which was published in 2018. Highlighted sections are direct quotes from the

[28] https://www.wcrf.org/diet-and-cancer/continuous-update-project/acknowledgements/
[29] https://www.wcrf.org/diet-and-cancer/continuous-update-project/
[30] https://www.wcrf.org/latest/about-us/our-network/
[31] https://www.wcrf-uk.org/uk/about-us/who-we-are
[32] https://www.aicr.org/wp-content/uploads/2020/08/FY-2019-Form-990.pdf
[33] https://www.wcrf-uk.org/uk/about-us/annual-publications/impact-report-2019-2020

text. Comments are in […]. The sequence which does not seem to follow any apparent logic, is the same as in the monograph.

1. Kato et al, 1997; cohort study: New York University Women's Health Study, 100 cases: "**Colorectal cancer was not significantly associated with red meat intake**" (p.107)
2. Tiemersma et al 2002; nested case-control study: Cardiovascular Disease Risk Factors in Netherlands, 102 incidental colorectal cancer cases during 8.5 years matched against 537 random sample control: "**positive association was observed in men, but not in women**" (p.107)
3. Oba et al, 2006; cohort study: 30,221 subjects in Japan, of which 213 colon cancer cases over 8 years: "**Red meat intake was unrelated to colon cancer risk**" (p.108) [the conclusion is not correct: for women, red meat intake was significantly associated with LESS colon cancer risk]
4. Singh & Fraser, 1998; cohort study: 32,051 subjects in a non-hispanic Adventist Health Study in California, of which 157 colon cancer cases over 6 years: **"increased risk of colon cancer", however: "residual confounding could not be ruled out that other lifestyle differences could at least partially explain the association**" (p.108)
5. Pietinen et al, 1999; double-blind, placebo-controlled trial on prevention of lung cancer in Finnish male smokers, of which 185 colorectal cancers over 8 years: **"Colorectal cancer was not associated with intake of beef, pork and lamb…intake of fried meats was not related to colorectal cancer"** (p.108)
6. Bostick et al, 1994; cohort study: Iowa Women's Health Study in postmenopausal women, of which 212 colon cancer cases over 5 years: **"Consumption of total red meat as defined was not associated with colon cancer…lack of association was observed in women with or without a family history of colon cancer"** (p.109)
7. Andersen et al, 2009; case-cohort nested study in a Danish Diet, Cancer and Health cohort study: 372 cases versus 765 controls: **"Null association between intake of red meat and colorectal cancer risk"** (page 109)
8. Sorensen et al, 2008; case-cohort nested study in the Danish Diet, Cancer and Health cohort study: 379 colorectal cases versus 769 controls: **"colorectal cancer was not significantly associated"** (p 109)
9. Lee et al, 2009; cohort study: 73,224 women in the Shanghai Women's Health Study, of which 394 colorectal cancer cases over 7.4 years: **"The risk of colorectal cancer was not related to the amount of red meat intake"** (p 109). [Indeed the relative risk of colorectal cancer was reduced by 20% for highest quintile red meat consumers versus the lowest quintile at almost significant levels].
10. English et al, 2004; cohort study: Melbourne Collaborative Cohort Study with 451 colorectal cancers: **"a positive association with rectal cancer"** (p 110)
11. Larsson et al, 2005; cohort study: Swedish Mammography Cohort, of which 733 colorectal cases: **"Unprocessed beef and pork was associated with almost twofold risk of distal colon cancer"** (p 110)
12. Butler et al, 2008; cohort study: Singaporean Chinese, of which 941 colorectal cases over 10 years: [no conclusion was given, however the Hazard Ratio of 1.01 means there is no hazard, and also no statistical significance] (p110)
13. Norat et al, 2005; cohort study: European Prospective Investigation into Cancer and Nutrition (EPIC) of which 1329 colorectal cancer cases across 10 European countries. [A barely significant risk association was found for red meat and colorectal cancer. Only after a statistical processing enhancement could a positive association be identified:], **"if expressed as a continuous increment of 100 gram red meat per day, a significant association was observed."** [When mutually adjusted for different type of meats, only pork consumption was significant]. (p 110)

14. Wei et al, 2004; Fung et al, 2010; and Bernstein et al, 2015, two cohort studies of Nurses Health Study (NHS) and Health Professionals Follow-Up Study of which 2731 colorectal cancer cases: **"the cumulative average intake of unprocessed red meat was not associated with colorectal cancer risk, similar when analysed in grams of intake."** [indeed, for distal colon cancer the risk was reduced by 25% for red meat consumption with high statistical significance]. (p 111)
15. Chan et al, 2005; nested case-control of the same NHS cohorts, with 183 colorectal cancer cases versus 443 controls: **"No association was observed in all women."** (p 111)
16. Nöthlings et al, 2009; Ollberding et al, 2012; multiethnic cohort study in Hawaii and California, of which 3404 colorectal cases: **"Red meat intake was not associated with colorectal cancer risk."** (p 112)
17. Spencer et al, 2010; nested case-control in UK Dietary Cohort Consortium based on seven cohort studies with 579 colorectal cases: **"Red meat intake was not related to risk of colorectal cancer"**. (p 112)
18. Kantor et al, 2014; Figuerido et al, 2014; pooled analysis of the Genetics and Epidemiology of Colorectal Cancer Consortium, with 9160 cases of colorectal cancer and 9280 controls for all studies combined: Kantor: **"Relative Risk increased by 33% for each serving per day in intake of red meat"**. Figueiredo: "**Relative Risk of 23% higher**". (p 112)
19. Gaard et al, 1996, prospective study: Norwegian National Health Screening Service, of which 143 colon cancer cases: **"Consumption of meatballs, meat stews, and fried or roasted meats was unrelated to colon cancer risk"** (p 112)
20. Lin et al, 2004; randomized trial: Women's Health Study with 202 colorectal cases after 8.7 years: **"positive association between white meats and colorectal cancer"** (p 113)
21. Brink et al, 2005; case cohort analysis of 2948 participants with 608 cases of colorectal cancer in the Netherlands Cohort Study: **"Intake of beef, pork, minced meat and liver was not significantly associated with colon or rectal cancer risk"** (p 113)
22. Gilsing et al, 2015; full cohort analysis of the Netherlands Cohort Study – Meat Investigation Cohort after 20.3 years: **"no clear association was observed with colon or rectal cancer."**
23. Sato et al, 2006, cohort study in Japan with 47,605 residents, of which 474 cases of colorectal cancer after 11 years: **"No associations were observed with risk of cancers of the colon, proximal or distal colon, and rectum."** (p 113)
24. Takachi et al, 2011: prospective study in Japan with 1145 cases of colorectal cancer after seven years: **"In women a significant association between beef intake and colon cancer, and a non-significant association for pork. No significant association was observed in men."** (p 113)

6 SELECTED FURTHER EVIDENCE FROM SELECTED HIGH PROFILE SCIENTIFIC INVESTIGATIONS AND PUBLICATIONS

6.1 TITLE OF PUBLICATION: RED MEAT AND COLON CANCER: A REVIEW OF MECHANISTIC EVIDENCE FOR HEME IN THE CONTEXT OF RISK ASSESSMENT METHODOLOGY

"In conclusion, the methodologies employed in current studies of heme have not provided sufficient documentation that the mechanisms studied would contribute to an increased risk of promotion of preneoplasia or colon cancer at usual dietary intakes of red meat in the context of a normal diet."

laire Kruger, Yuting Zhou, Red meat and colon cancer: A review of mechanistic evidence for heme in the context of risk assessment methodology, Food and Chemical Toxicology, Volume 118, 2018, Pages 131-153, ISSN 0278-6915, https://doi.org/10.1016/j.fct.2018.04.048

(https://www.sciencedirect.com/science/article/pii/S0278691518302655)

6.2 TITLE OF PUBLICATION: THE ROLE OF RED AND PROCESSED MEAT IN COLORECTAL CANCER DEVELOPMENT: A PERSPECTIVE

"Epidemiological and mechanistic data on associations between red and processed meat intake and CRC are inconsistent and underlying mechanisms are unclear."

Marije Oostindjer, Jan Alexander, Gro V. Amdam, Grethe Andersen, Nathan S. Bryan, Duan Chen, Denis E. Corpet, Stefaan De Smet, Lars Ove Dragsted, Anna Haug, Anders H. Karlsson, Gijs Kleter, Theo M. de Kok, Bård Kulseng, Andrew L. Milkowski, Roy J. Martin, Anne-Maria Pajari, Jan Erik Paulsen, Jana Pickova, Knut Rudi, Marianne Sødring, Douglas L. Weed, Bjørg Egelandsdal: The role of red and processed meat in colorectal cancer development: a perspective, Meat Science, Volume 97, Issue 4, 2014, Pages 583-596, ISSN 0309-1740, https://doi.org/10.1016/j.meatsci.2014.02.011.

(https://www.sciencedirect.com/science/article/pii/S0309174014000564)

6.3 TITLE OF PUBLICATION: PROCESSED MEAT INTAKE AND INCIDENCE OF COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE OBSERVATIONAL STUDIES

"The overall judgment showed that two out of 29 studies had a moderate risk of bias, 25 had a serious risk of bias, and 2 had a critical risk of bias."

Händel, M.N., Rohde, J.F., Jacobsen, R. et al. Processed meat intake and incidence of colorectal cancer: a systematic review and meta-analysis of prospective observational studies. Eur J Clin Nutr 74, 1132–1148 (2020). https://doi.org/10.1038/s41430-020-0576-9

6.4 Title of publication: Red Meat and Colorectal Cancer: A Quantitative Update on the State of the Epidemiologic Science

"In conclusion, the state of the epidemiologic science on red meat consumption and CRC is best described in terms of weak associations, heterogeneity, an inability to disentangle effects from other dietary and lifestyle factors, lack of a clear dose-response effect, and weakening evidence over time."

Dominik D. Alexander, Douglas L. Weed, Paula E. Miller & Muhima A. Mohamed (2015) Red Meat and Colorectal Cancer: A Quantitative Update on the State of the Epidemiologic Science, Journal of the American College of Nutrition, 34:6, 521-543, DOI: 10.1080/07315724.2014.992553

6.5 Title of publication: Red Meat Intake and Cardiometabolic Disease Risk: An Assessment of Causality Using The Bradford Hill Criteria

"Weakness of associations between total and unprocessed red meat intake and cardiometabolic diseases and lack of coherence with short-term experimental evidence on cardiometabolic disease risk factors reduces confidence that associations are causal."

Erica Hill, Yu Wang, Caroline Clark, Bethany McGowen, Lauren O'Connor, Wayne Campbell, Red Meat Intake and Cardiometabolic Disease Risk: An Assessment of Causality Using The Bradford Hill Criteria, Current Developments in Nutrition, Volume 4, Issue Supplement_2, June 2020, Page 31, https://doi.org/10.1093/cdn/nzaa040_031

6.6 Title of publication: Association between red meat consumption and colon cancer: A systematic review of experimental results

"Because of these limitations in the existing literature, there is currently insufficient evidence to confirm a mechanistic link between the intake of red meat as part of a healthy dietary pattern and colorectal cancer risk."

Turner ND, Lloyd SK. Association between red meat consumption and colon cancer: A systematic review of experimental results. Experimental Biology and Medicine. 2017;242(8):813-839. doi:10.1177/1535370217693117

6.7 Title of publication: Should dietary guidelines recommend low red meat intake?

"We argue that claims about the health dangers of red meat are not only improbable in the light of our evolutionary history, they are far from being supported by robust scientific evidence."

Frédéric Leroy & Nathan Cofnas (2020) Should dietary guidelines recommend low red meat intake?, Critical Reviews in Food Science and Nutrition, 60:16, 2763-2772, DOI: 10.1080/10408398.2019.1657063

6.8 Title of publication: Mortality in vegetarians and comparable nonvegetarians in the United Kingdom

"There was no significant difference in overall (all-cause) mortality between the diet groups of low meat eaters, fish eaters, and vegetarians compared with regular meat eaters."

Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. Am J Clin Nutr. 2016 Jan;103(1):218-30. doi: 10.3945/ajcn.115.119461. Epub 2015 Dec 9. PMID: 26657045; PMCID: PMC4691673.

6.9 Title of publication: Vegetarian diet and all-cause mortality: Evidence from a large population-based Australian cohort – the 45 and Up Study

"Following extensive adjustment for potential confounding factors there was no significant difference in all-cause mortality for vegetarians versus non-vegetarians. There was also no significant difference in mortality risk between pesco-vegetarians or semi-vegetarians versus regular meat eaters. We found no evidence that following a vegetarian diet, semi-vegetarian diet or a pesco-vegetarian diet has an independent protective effect on all-cause mortality."

Mihrshahi S, Ding D, Gale J, Allman-Farinelli M, Banks E, Bauman AE. Vegetarian diet and all-cause mortality: Evidence from a large population-based Australian cohort - the 45 and Up Study. Prev Med. 2017 Apr;97:1-7. doi: 10.1016/j.ypmed.2016.12.044. Epub 2016 Dec 29. PMID: 28040519.