Editorial

Red meat intake and cardiovascular risk: it's the events that matter; not the risk factors

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A meta-analysis reported in 2017 (1) that red meat intake did not significantly affect blood lipids and lipoproteins or blood pressure. The running title was misleading; it referred to cardiovascular risk. It is crucial to recognize that coronary risk factors, although they weakly predict risk (2), are not the same as the actual risk of cardiovascular events such as myocardial infarction, stroke and cardiovascular mortality.

The most important part of the paper is the Acknowledgements. The senior author reported that he "received research support from American Egg Board-Egg Nutrition Center, Beef Checkoff, Coca-Cola Foundation, National Dairy Council, National Institutes of Health, Pork Checkoff, and USDA and had a consulting arrangement with Coca-Cola Company". One of the other authors also "received support from the American Egg Board-Egg Nutrition Center".

Recently Thacker documented (3) that nutrition conferences for journalists on the topic of obesity were funded by Coca-Cola, likening the efforts to reshape obesity as being due to lack of exercise to the public relations campaign of the tobacco industry.

The role of the food industry in shaping the thinking of the public, nutritionists and physicians is pervasive and pernicious. The role of the sugar industry was the focus of a paper by Kearns and colleagues (4); an accompanying editorial (5) generalized the problem to the food industry. The abstract of the paper was as follows: "Early warning signals of the coronary heart disease (CHD) risk of sugar (sucrose) emerged in the 1950s.We examined Sugar Research Foundation (SRF) internal documents, historical reports, and statements relevant to early debates about the dietary causes of CHD and assembled findings chronologically into a narrative case study. The SRF sponsored its first CHD research project in 1965, a literature review published in *the New England Journal of Medicine*, which singled out fat and cholesterol as the dietary causes of CHD and downplayed evidence that sucrose consumption was also a risk factor. The SRF set the review's objective, contributed articles for inclusion, and received drafts. The SRF's funding and role was not disclosed. Together with other recent analyses of sugar industry documents, our findings suggest the industry sponsored a research program in the 1960s and 1970s that successfully cast doubt about the hazards of sucrose while promoting fat as the dietary culprit in CHD. Policymaking committees should consider giving less weight to food industry-funded studies and include mechanistic and animal studies as well as studies appraising the effect of added sugars on multiple CHD biomarkers and disease development".

The editorial said the following: "Industry-sponsored nutrition research, like that of research sponsored by the tobacco, chemical, and pharmaceutical industries, almost invariably produces results that confirm the benefits or lack of harm of the sponsor's products, even when independently sponsored research comes to opposite conclusions. Although considerable evidence demonstrates that those industries deliberately influenced the design, results, and interpretation of the studies they paid for, much less is known about the influence of food-company sponsorship

on nutrition research. Typically, the disclosure statements of sponsored nutrition studies state that the funder had no role in their design, conduct, interpretation, writing, or publication. Without a "smoking gun" it is difficult to prove otherwise. In this issue of *JAMA Internal Medicine*, Kearns and colleagues report on having found a smoking gun. From a deep dive into archival documents from the 1950s and 1960s, they have produced compelling evidence that a sugar trade association not only paid for but also initiated and influenced research expressly to exonerate sugar as a major risk factor for coronary heart disease (CHD)".

A similar smoking gun, though found in the hands of the American Egg Board, was obtained by Dr. Michael Greger under freedom of information legislation (http://nutritionfacts.org/video/egg-cholesterol-in-the-diet/). He obtained the email correspondence chain among the American Egg Board and its academic "friends", after colleagues and I published in 2010 (6) a review of the harmful effects of dietary cholesterol and egg yolk. In the correspondence was a discussion about what should be done about our paper, and an offer by one of the academic "friends" who is funded by the Egg Nutrition Center to write a letter to the Editor. The letter was indeed sent and published (7). Then colleagues and I published a paper reporting that egg yolk consumption was associated with carotid plaque (8), and additive to smoking, with approximately 60% of the effect of cigarette smoking (9). Subsequently someone sent emails to the chancellor of my university attempting to discredit me. The name at the end of the email appended M.D., Ph.D., M.B.A. When I replied, the astonished owner of that email address and name replied that he knew nothing about health, did not have those degrees, and Scotland Yard were investigating who hacked into his email account. (http://nutritionfacts.org/video/eggs-vs-cigarettes-in-atherosclerosis/).

Greger documents (http://nutritionfacts.org/video/eggs-and-cholesterol-patently-false-and-misleading-claims/) that the egg industry has spent hundreds of millions of dollars on advertising, after being convicted of false advertising on all seven counts, and losing the appeal in the Supreme Court. In the US their recent target has been the young mothers of children, presumably aiming to train up the next generation of egg consumers. He explains also how studies funded by the Egg Nutrition Center are designed to show benefits of eggs. (http://nutritionfacts.org/video/how-the-egg-board-designs-misleading-studies/).

The propaganda of the egg industry rests on a red herring, and a half-truth. The red herring is that eating eggs does not increase fasting levels of cholesterol; the half-truth is that eggs do not increase cardiovascular risk. By focusing on fasting lipids, the egg industry is engaging in misdirection. Although eating eggs does not increase fasting cholesterol by much (~10%, with a wide range of inter-individual differences), the main effect of diet is not on the fasting state, but the fed state. For ~4 hours after a high-cholesterol/high fat meal, the arteries are inflamed, with a marked increase in oxidative stress, and endothelial dysfunction (6).

The slogan "eggs can be part of a healthy diet for healthy people", often part of egg advertising in Canada, is the half-truth. It is based on two US studies that enrolled healthy people, followed them over time, and reported that only among participants who became diabetic during follow-up could harm be shown: an egg a day doubled cardiovascular risk (10,11). However, there were two key problems with these studies: the participants were not old enough at the end of the studies to carry a high enough cardiovascular risk so that it would be evident, and the US diet is so bad that it is hard to show that anything makes it worse. The American Heart Association statistical report of 2015 revealed that diet is the worst of the lifestyle and risk factor issues in that country: only 0.1% of Americans eat a healthy diet, and only 8.3% eat a moderately healthy diet. In Greece, however, where the Mediterranean diet prevails, among diabetics an egg a day increased coronary risk 5-fold, and even 10 grams/day of egg (a sixth of a large egg) increased coronary risk by 50% (12).

It is well-known that vegetarians have a lower cardiovascular risk than meat-eaters (13-15). Reduction of cardiovascular risk with a vegetarian diet would probably be even greater but for the elevation of total homocysteine resulting from B12 deficiency (16-18). What is less well appreciated is that the diet for which there is the best evidence of reduced cardiovascular risk, the Cretan Mediterranean diet, has a much lower intake of animal flesh than a usual Western diet. Keys, in a retrospective paper (19), described it as follows: "the heart of this diet is mainly vegetarian, and differs from the American and Northern European diets in that it is much lower in meat and dairy products and uses fruit for dessert".

It would be difficult/impossible to persuade meat-eaters in my clinic to participate in a randomized trial in which they stood a chance of being randomized to a vegetarian diet, and even more difficult to obtain adherence. However, it is easier to compare a Mediterranean diet with a low-fat diet. The Israeli diet study comparing a low-carbohydrate

vs. a low-fat *vs.* a Mediterranean diet obtained 95% adherence at 1 year and 86% at 2 years; it showed very clearly that the Mediterranean diet was equal to the low-carbohydrate diet with regard to weight loss, and both were significantly better than the low fat diet. It also showed that the Mediterranean diet was the best among diabetics, with the greatest reduction of fasting glucose and insulin, and in insulin resistance.

Studies of the effect of the Mediterranean diet on cardiovascular outcomes show a much greater effect than most physicians or the public appreciate. The Lyon Diet Heart study (20), in secondary prevention, reported a greater than 60% reduction of cardiovascular risk in four years, with a Mediterranean diet compared to a prudent Western diet that amounted to a low-fat diet. This was twice the effect of simvastatin in the contemporaneous Scandinavian Simvastatin Survival Study—a 40% reduction of recurrent myocardial infarction in six years (21).

More recently in a Spanish trial (PREDIMED), a Mediterranean diet was shown to significantly reduce cardiovascular risk compared to a low-fat diet, in high-risk primary prevention participants. Stroke was reduced by nearly half in five years, in the arm of the study that was fortified with mixed nuts (22).

Besides the high content of cholesterol and saturated fat in red meat, and the very high cholesterol content of egg yolk, another important factor has come to the fore in the recognition of the interaction between diet, the intestinal microbiome and renal function (23). Carnitine in red meat (24) and phosphatidylcholine in egg yolk (25) are converted to trimethylamine, in turn oxidized in the liver to trimethylamine n-oxide (TMAO). Among patients referred for coronary angiography, plasma levels of TMAO after a test dose of two hard-boiled eggs strongly predicted coronary risk (26). Besides TMAO, other toxic metabolites of the intestinal microbiome, produced from amino acids, accumulate in renal failure. These include p-cresyl sulfate, indoxyl sulfate and indole 3-acetic acid (27). Meat intake should be limited, and red meat and egg yolk should therefore be avoided particularly by persons with renal impairment. This includes the elderly; in vascular patients above age 80 the average estimated glomerular filtration rate is below 60 mL/min per 1.73 m^2 (27).

As discussed above, studies sponsored by the egg industry and/or meat industry must be regarded with great skepticism. As importantly, a focus on risk factors such as fasting lipid levels is beside the point. What matters is the risk of cardiovascular events. It is clear that a high intake of meat increases the risk of cardiovascular events. The intake of any animal flesh should be limited, and because red meat contains ~4 times as much carnitine as other animal flesh, intake of red meat should be rare. As with egg yolk, red meat should be avoided by persons at risk of cardiovascular events. This essentially includes all persons in the Western world who hope to attain an advanced age (28).

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