EDITORIALS

Editorials are usually commissioned. We are, however, happy to consider and peer review unsolicited editorials

Where the latest US dietary guidelines are heading

So farewell dietary cholesterol and total fat as risk factors worth worrying about

Daan Kromhout emeritus professor, Wageningen University, 6700 EV Wageningen, Netherlands
daan.kromhout@wur.nl

Recently, the US Dietary Guidelines Advisory Committee released its recommendations for the next edition of *Dietary Guidelines for Americans*.[1] Two notable conclusions of the committee have attracted particular attention[2 3]: the elimination of dietary cholesterol as a "nutrient of concern" and the absence of a limit on total fat consumption. The committee's pronouncements will reverse nutrition policy because the low cholesterol, low fat diet has been the cornerstone of public health nutrition since 1980. In this editorial I will review the evidence for this change in policy from a historical perspective.

When fat was bad

The low cholesterol, low fat diet for preventing heart attacks was popularised in the first part of the 20th century. Classic animal experiments showed that feeding rabbits excessive cholesterol induced lipid containing lesions in the aorta. Anitschkow hypothesized that a high plasma cholesterol concentration caused atherosclerosis and its complications.[4] Observant medical doctors from the Netherlands noticed extraordinarily low numbers of patients with myocardial infarction in the East Dutch Indies (Cornelis de Langen) and China (Isodore Snapper).[5] The diets of these lean populations were low in cholesterol and fat and were associated with low plasma cholesterol levels, and these findings contributed to the diet-heart hypothesis.

But even at the time the diet-heart hypothesis could not explain all the known facts. For example, feeding animals excessive cholesterol did not induce atherosclerosis in all species, and populations with a high total fat intake, through a high consumption of olive oil or seafood, did not have a high number of people with myocardial infarction.

In the 1950s and 1960s it became clear that the type of fat is more important than the quantity. Controlled dietary experiments by Keys and colleagues and Hegsted and colleagues showed that saturated fat increased and polyunsaturated fat decreased plasma cholesterol whereas monounsaturated fat was neutral compared with a diet in which the fats were replaced with carbohydrates.[6 7]

One component of plasma cholesterol, low density lipoprotein (LDL) cholesterol, was identified as a causal risk factor for coronary heart disease,[8] and the intake of different types of fats was found to affect its concentration. A meta-analysis of 60 controlled dietary experiments carried out since 1970, showed that substituting saturated fats for carbohydrates as the source of 1% of energy intake increased LDL cholesterol by 0.032 mmol/L. Substitution with monunsaturated fats decreased LDL cholesterol by 0.009 mmol/L and substitution with polyunsaturated fats decreased it by 0.019 mmol/L.[9]

Off the hook

The strongest reductions in LDL cholesterol occurred when saturated fats were replaced by mono or polyunsaturated fats; monounsaturated fats reduced LDL cholesterol by 0.041 mmol/L and polyunsaturated fat by 0.051 mmol/L. Replacement of carbohydrates by all three types of fats increased high density lipoprotein (HDL) cholesterol (the "good"cholesterol) and decreased triglycerides levels.

> In large epidemiological prospective studies dietary cholesterol was not associated with a higher risk of coronary heart disease

Fatty acids are not the only determinants of blood lipid levels. Certain carbohydrates and dietary fibre can reduce LDL cholesterol. A meta-analysis of randomized controlled trials showed that replacement of 15% of energy of simple sugars with starch reduced LDL cholesterol by 0.27 mmol/L under isocaloric conditions.[10] Another meta-analysis of trials showed that 1 g/day of pectin, the water soluble fibre compound in fruit, reduced LDL cholesterol by 0.05 mmol/L.[11] Meta-analyses of studies of fibre rich foods have shown that 30-60 g of oats reduced LDL cholesterol by 0.18 mmol/L, 130 g of legumes reduced it by 0.17 mmol/L, and 35 g of nuts by 0.16 mmol/L.[12-14]

In 1981, Lewis and colleagues carried out a landmark dietary experiment.[15] They compared four diets varying in total fat, type of fat (polyunsaturated:saturated fat ratio), cholesterol, and fibre. They found that the most favourable lipid values were not obtained by the traditional low fat, low cholesterol, low fibre diet (as consumed by lean Asian populations) but by diets either high or low in total fat, with a polyunsaturated:saturated fat ratio of 1.0 and a high fibre content.

In the 1980s, dietary guidelines around the world recommended restricting dietary cholesterol to 300 mg/day because controlled dietary experiments had shown that dietary cholesterol increased LDL cholesterol.[3] In a meta-analysis of four small prospective cohort studies dietary cholesterol was positively associated with coronary heart disease.[16] Subsequently, it became clear that the effect of dietary cholesterol on LDL cholesterol was smaller in diets with a high polyunsaturated:saturated fat ratio than in those with a low ratio, and in large epidemiological prospective studies dietary cholesterol was not associated with a higher risk of coronary heart disease.[3] More recent national food consumption surveys in the Netherlands and the US indicated that the average cholesterol intake was about 200 mg/day, considerably less than the recommended maximum of 300 mg/day. Because of the relatively small effect of dietary cholesterol on LDL cholesterol, the absence of a relation between dietary cholesterol and the risk of coronary heart disease, and the relatively low population intake of cholesterol, the 2006 Dutch guidelines committee[17] and the 2015 US committee concluded that it was no longer necessary to give quantitative advice on dietary cholesterol.

Nutritionally adequate, plant food based diets, rich in unsaturated fatty acids, such as the traditional Mediterranean style diets, not only have beneficial effects on blood lipid levels but also reduce cardiovascular risk and are associated with a lower risk of all cause mortality in prospective cohort studies.[18 19] In that context, guidelines for dietary cholesterol and total fat are not needed because they do not affect cardiovascular risk.

Cite this as: *BMJ* 2015;351:h4034

Should people eat spicy food? It is too early to say, but the debate and the research interest are certainly hotting up

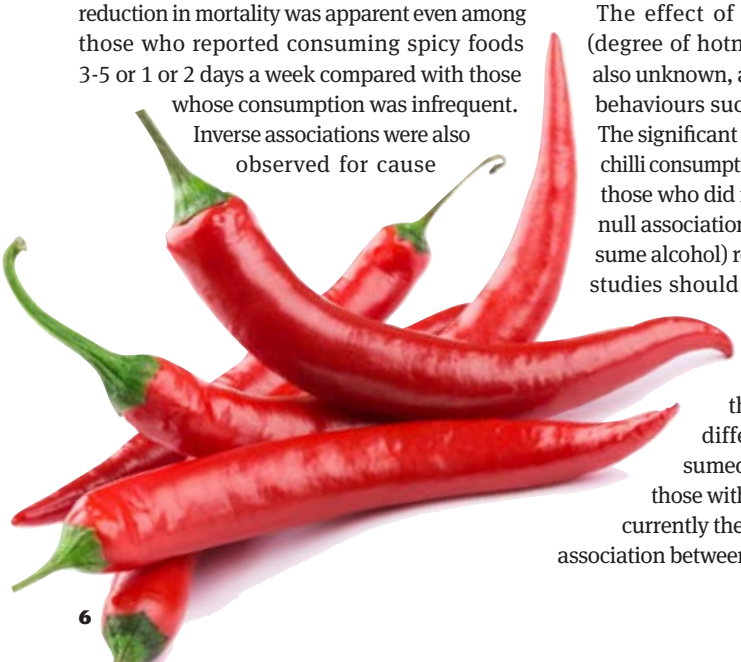
Consumption of hot spicy foods and mortality

Their benefits are plausible, but evidence is preliminary

Nita G Forouhi programme leader, MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge CB2 0QQ, UK
nita.forouhi@mrc-epid.cam.ac.uk

Diet has long been regarded as central to health and longevity. Given human diets' vast variety and complexity, however, the challenge has been to identify the specific dietary components with a direct effect on health and mortality. The general consensus is that health gains for chronic disease are most likely from healthy dietary patterns that include adequate consumption of fruits, vegetables, whole grains, nuts, seeds, fibre, and fish and that are low in red and processed meats, sugary beverages, and salt.[1-3] Yet there remains a parallel interest in other common dietary components that may serve as functional foods. Hot spices are one such example and are the subject of a linked paper by Lv and colleagues .[4]

Among 0.5 million adults in the China Kadoorie Biobank the authors examined the prospective association of self reported consumption of spicy foods with total and cause specific mortality. Over a median of 7.2 years of observation with 3.5 million person years, during which 20 224 deaths occurred, they report a 14% lower risk (95% confidence interval 10% to 18%) in total mortality when comparing those who reported frequent consumption of spicy foods (6 or 7 days a week) with those who reported little consumption of spicy foods (less than once a week). A similar reduction in mortality was apparent even among those who reported consuming spicy foods 3-5 or 1 or 2 days a week compared with those whose consumption was infrequent. Inverse associations were also observed for cause specific deaths due to cancer, ischaemic heart disease, and respiratory disease. How should we interpret these novel findings and what are their implications for nutritional advice?



This research has several strengths, including a large sample size, the inclusion of 10 geographical regions of China representing both urban and rural settings, a prospective design, and sound application of statistical methods. The authors acknowledge limitations of measurement error, possible bias, confounding, and reverse causality, which are common problems in epidemiology, and indeed their efforts to minimise some of these limitations are notable.

Szechuan takeaway

The use of spices is an integral part of the Chinese diet[5] however, the authors only adjusted for three crudely measured dietary covariates (self reported consumption frequency of red meat, fresh vegetables, and fresh fruits) and were unable to account for energy intake or for other dietary habits that may be correlated with spicy foods. As the authors recognise, this could cause residual confounding. Their definition of spicy foods is synonymous with the frequency of consumption of types of chilli, fresh, dried, or as chilli oil or chilli sauce. It is unclear whether the observed associations are the direct result of chilli intake or whether chilli is simply a marker for other beneficial but unmeasured dietary components.

The effect of the quantity or strength (degree of hotness) of chilli consumed is also unknown, along with the effect of other behaviours such as alcohol consumption. The significant inverse association between chilli consumption and mortality only among those who did not consume alcohol (and a null association among those who did consume alcohol) remains unexplained. Future studies should explore if confounding or effect modification by other drinking habits might play a part, as it is highly likely that drinks such as water or different types of tea are consumed in greater amounts among those with a greater chilli intake. Concurrently there is evidence for an inverse association between tea consumption and mortality.[6] Lv and colleagues may be able to deal with some of these questions, using data collected on tea intake and other variables in their study.

So, should we encourage people to eat more chilli? As the authors acknowledge, a cause and effect relation cannot be inferred from their work. In this prospective study, Lv and colleagues have shown temporality of association, but we need to evaluate additional criteria to judge the strength of evidence.[7] Their findings should be considered hypothesis generating, not definitive, and will undoubtedly encourage further work.

The use of hot spices in food to enhance taste has captured the attention of the popular press as well as food outlets, fuelling a worldwide trend towards greater consumption.[8 9] In parallel, there is increasing scientific interest in spicy foods. Many potential benefits[4] have been suggested for chilli or its bioactive compound capsaicin, including but not limited to antimicrobial, anti-oxidant, anti-inflammatory, and anti-cancer properties, a beneficial influence on gut microbiota, and anti-obesity effects through thermogenesis and appetite,[10] energy balance,[11] and weight management.[12]

Despite a large published literature on capsaicin (a search of PubMed on 23 July 2015 listed 12 571 articles), a systematic appraisal of potential beneficial and adverse impacts of spicy foods and their bioactive compounds is warranted. Finally, although dietary modification trials are challenging for logistical reasons, adding or not adding spice to foods may be achievable, at least for short term trials reporting intermediate endpoints.[13]

Future research is needed to establish whether spicy food consumption has the potential to improve health and reduce mortality directly or if it is merely a marker of other dietary and lifestyle factors. The added contribution of spicy food intake to the benefits of a balanced healthy diet and healthy lifestyles also remains to be investigated. However, the current findings should certainly stimulate dialogue, debate, and further interest in research.

Should people eat spicy food? It is too early to say, but the debate and the research interest are certainly hotting up.

Cite this as: *BMJ* 2015;351:h4141

RESEARCH, p 10

It is time now to take stock of how much patient centered research we are doing, how well we are doing it, and whether it improves healthcare

Can patient centred outcomes research improve healthcare?

We believe it can; now we should put it to the test

Thomas W Concannon senior policy researcher, The RAND Corporation, 20 Park Plaza, Suite 920, Boston, MA 02116, USA tconcann@rand.org

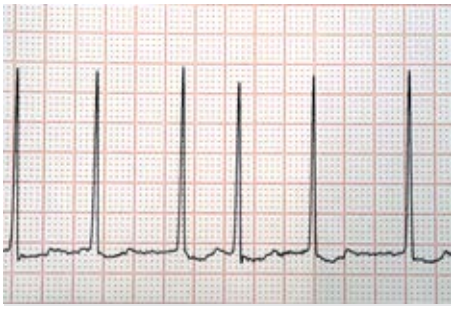
The Patient-Centered Outcomes Research Trust Fund (PCORTF) was established in 2009 to support research that is funded, designed, carried out, and put into practice within a culture of patient centeredness.[1] A legislatively mandated review in 2017 of the "adequacy and use of funding" will be used to determine whether PCORTF funding levels should be continued or adjusted after its authorization runs out in autumn 2019. As 2017 approaches, researchers ought to begin taking stock of our work in patient centered outcomes research: how well are we are doing and what might we do better?

In the linked paper, Xian and colleagues present a solid example of how to refocus research on questions, outcomes, and approaches that could help patients and clinicians to make better healthcare decisions. The team studied prescribing of warfarin for patients with ischemic stroke who were discharged from hospital between 2009 and 2011 with persistent or paroxysmal atrial fibrillation or flutter.[2] This study was funded by the Patient-Centered Outcomes Research Institute (PCORI) in 2013.

This team's preliminary work with patients resulted in prioritization of an outcome that actually matters to people with ischemic stroke: time "alive at home, without recurrent stroke, and without being hospitalized for complications."[2] The team also measured major adverse clinical events (MACE), as well as other clinical indicators as secondary outcomes. Their continued work with patients as co-investigators assured involvement throughout the research process, allowing patients to participate in research design and provide input into the statistical analysis plan.

The study focused on patients who were older and at higher risk than those in previous efficacy studies and was conducted in settings where patients go for care. Treatment settings included 1487 hospitals with expertise in stroke, or nearly a quarter of the 6300 hospitals that treat adults in the United States.[3]

Since its establishment in 2010, PCORI has funded hundreds of studies through its regular call for proposals.[4] This work reflects a large nationwide effort in what was essentially a start-up venture only a few years ago. Measurement of performance in this effort should track along three streams.



DR P MARAZZI/SPL

The trigger

Firstly, we need an ongoing and public inventory to explain how trust fund dollars earmarked for patient centered outcomes research have been spent. PCORI already provides a great deal of inventory information on its website. Each quarter, the organization publishes an online dashboard of funded projects, results, publications, and other milestones.[4] The most recent dashboard shows that many more studies are on their way to reporting in the next few years.

The dashboard also accounts for a range of other activities, including milestones reached in PCORnet, a program designed to establish new infrastructure for ongoing patient centered research. Inventory assessments of other trust fund programs are also needed, such as the inclusion of patient centered outcomes research in the portfolios of the National Institutes of Health and the Agency for Healthcare Research and Quality.

Secondly, procedural assessments are needed to examine whether investigators are getting the principles of patient centeredness right. This will involve comparing patient centered work against quality standards. PCORI publishes a range of standards on its website, including a rubric that can guide newcomers through the tasks of involving patients and other stakeholders in a study.[5] A recently published framework lists four principles of patient centeredness that could help to ensure that we are getting it right: patient centered outcomes research should be relevant, pragmatic, feasible, and participatory.[6]

Making a difference?

Finally, we need to evaluate whether patient centered outcomes research is making a difference to healthcare quality and outcomes. We have seen a growing commitment to patient centeredness in part because we believe it can help us to create new evidence that is relevant to patients and other decision makers, research methods that are more transparent to decision makers, and findings that are usable in a wider range of settings.[7] This belief needs to be put to the test with carefully designed evaluation protocols.

The team led by Xian has performed exceedingly well in all of these streams. The project was reported on schedule and according to a pre-specified analytic plan. The study gets the basics of patient centeredness right: investigators took on a question and measured outcomes that matter, designed a pragmatic study to answer the question, and used a robust and participatory approach in conducting the research. Whether this study results in improved uptake of warfarin among older and higher risk patients is yet to be seen. However, we can already see how it might change patient-clinician dialogue about treatment options.

Patients leaving the hospital may be better able to remember that taking warfarin could help them to stay healthy and at home longer. Many, on the other hand, will not understand or remember what MACE stands for.

Recent investments in patient centered research have been large and rapidly scaled up. On one level, the United States has embarked on this course because we believe it is the right thing to do; it may help us to meet the important goal of supporting broad participation in the use of public dollars. However, we also do it in the belief that it will change healthcare by supporting patients and clinicians to make better decisions. It is time now to take stock of how much patient centered research we are doing, how well we are doing it, and whether it improves healthcare.

Cite this as: *BMJ* 2015;351:h3859

RESEARCH, p 9

thebmj.com
Cardiology updates from *BMJ* at bmj.co/cardiology

Delivering thrombectomy for acute stroke using cardiology services

Why should the location of an acutely occluded artery affect who gets treated?

Andrew Apps cardiology registrar
drandyapps@gmail.com
Soroosh Firoozan cardiology consultant, Department of Cardiology, High Wycombe Hospital, Bucks, HP11 2TT, UK
Tito Kabir cardiology consultant, Harefield Hospital, Middlesex, UK

Evidence is mounting for the supplementary benefit over thrombolysis of endovascular therapy in selected patients with acute stroke. Mechanical percutaneous removal of intracerebral clot using an aspiration catheter ensures that the artery is recanalised. Like thrombolysis, the benefits are greater with early treatment, and we need to think about how to achieve this. Evidence on the benefits of rapid primary percutaneous coronary intervention in patients presenting with ST segment elevation myocardial infarction (STEMI) led to a network being set up in the United Kingdom to provide 24 hour care.[1] Teams staffing these networks, skilled in opening arteries quickly, could also provide endovascular therapy to selected patients with acute stroke.

The most recent meta-analysis comparing thrombolysis with conservative management[3] found that, if administered within three hours, the number needed to treat (NNT) to achieve one further independent patient (modified Rankin score of 0-2) is 11.[3] Delay diminishes benefit; if thrombolysis is given within six hours this number increases to 24. The potential for long term functional benefit comes with a significant increase in the risk of early (seven day) symptomatic intracranial haemorrhage and death, with numbers needed to harm of 17 for haemorrhage and 40 for death.

Evidence supporting endovascular therapy as an adjunct to thrombolysis in people with ischaemic stroke is compelling and perhaps should not surprise us because the rate of recanalisation of the proximal cerebral artery after thrombolysis can be as low as 30%.[7] Five randomised studies comparing endovascular treatment with thrombolysis alone were published earlier this year. All used a primary outcome of 90 day functional independence (modified Rankin score of 0-2) and reported an absolute benefit of 13.5% to 31% for patients with a proximal anterior circulation occlusion.[8-12]

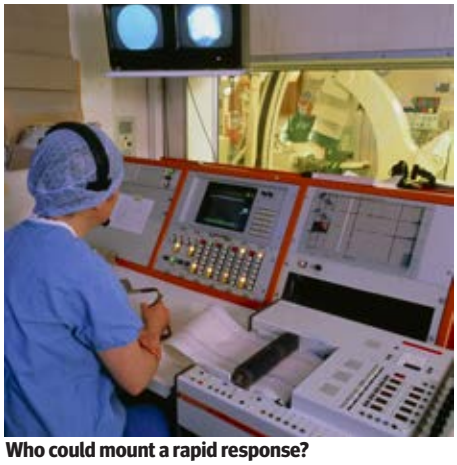
This translates to an NNT of 3-7. In response to the results of the Multicenter Randomised Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN),[8] the other trials were stopped early when interim analyses showed clear benefit. Only one trial reported any reduction in death rates (90 day mortality 19% *v* 10.4%, P=0.04),[10] although these are small trials randomising between 70 and 500 patients. Thrombectomy did not increase rates of intracranial haemorrhage (suggesting that onsite neurosurgical facilities are not mandated for the procedure).

Benefit from early endovascular therapy for acute stroke with proximal cerebral occlusion may be at least as great as that from percutaneous coronary intervention for STEMI. Percutaneous coronary intervention has been shown to reduce the short term risk of death from 9% to 7%, of reinfarction from 7% to 3%, and of stroke from 2% to 1% compared with thrombolysis.[13] The human cost of stroke is catastrophic and easily compares with the morbidity from acute myocardial infarction. Why should one group of patients get poorer outcomes simply because their acutely occluded artery lies within a different circulation? The primary angioplasty network for STEMI may be ideally placed to address this unmet need.

Call in the artery openers

However, the correct framework of care means nothing without the appropriate operator to perform the procedure. To date, only interventional neuroradiologists have provided thrombectomy, and there has been no analysis of safety if it is performed by other specialists. The limited number of neuroradiologists has implications for providing a timely intervention. After local imaging, many patients with proximal occlusion must be moved long distances to a regional centre for treatment. Alternatively, other interventionists, including cardiologists and vascular radiologists, could be trained to do the procedure in selected primary angioplasty centres.

Evidence is mounting for the supplementary benefit over thrombolysis of endovascular therapy in selected patients with acute stroke



SIMON FRASER/FREEMAN HOSPITAL/SPL

Who could mount a rapid response?

This would allow treatment to be offered on a round the clock, on-call basis. The ingrained culture of speed could help get door to groin times, which were at best 90 minutes in the thrombectomy trials, down to below 60 minutes, considered a reasonable door to balloon (that is, reperfusion) time in primary angioplasty. This would maximise clinical benefit since the frequency of 90 day functional independence increases with faster intervention.[11]

Whereas clear cut ST segment elevation is a reliable indicator of occlusion of a coronary artery, diagnosing cerebral artery occlusion is less straightforward. It requires computed tomographic angiography as well as input from a stroke physician. The proportion of people admitted with stroke who are likely to be suitable for thrombectomy is not clear, but it may be small given that the technology is of proved benefit only in proximal arterial occlusion.[14]

Further research to quantify this group is needed to guide potential reorganisation of the thrombolysis network into, or around, thrombectomy centres. Eligible patients are those with the most catastrophic strokes, who are least likely to achieve recanalisation with thrombolysis.[7] With the potential to avoid functional dependence in one in five patients treated, there is an urgent need to ensure access to this treatment. Integration of stroke and cardiac services may allow appropriate patients to access this treatment through the established angioplasty network; after all, time saves brain, not just myocardium.

Cite this as: *BMJ* 2015;351:h3969