

Comment on the report ‘Dietary Fats and Cardiovascular Disease. A Presidential Advisory From the American Heart Association (AHA).’

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Recently, the American Heart Association (AHA) published a meta-analysis emphasizing their earlier recommendation to limit the intake of saturated fatty acids (SFA). SFA should be replaced with unsaturated fat, especially polyunsaturated fat, to lower the incidence of heart disease. Such replacement is claimed to reduce the risk for cardiovascular events by about 30%; a risk reduction comparable to treatment with statins. The AHA also advises against coconut oil consumption because it increases LDL-cholesterol and ‘has no known offsetting favorable effects’. We argue that the LDL-cholesterol concentration is still a soft endpoint, not a disease, while there are no studies showing unfavorable effects of coconut oil on hard endpoints. The AHA extensively motivates the exclusion of studies for their meta-analysis, but does not apply stringent criteria in the choice of the four trials that ultimately constitute the backbone of their meta-analysis. One of these was not a randomized controlled trial, while another suffered from ‘performance bias’. The largest negative trial was excluded, amongst others, because it did not last at least two years. The AHA meta-analysis conveys the notion of ‘cherry picking’. There are at present at least nine expert reviews that failed to find a clear link between SFA, cardiovascular mortality and total mortality. We argue that individuals with the metabolic syndrome should be careful with dietary SFA and carbohydrates, since they synthesize SFA de novo from carbohydrates and spare dietary SFA. The high risk of individuals with the metabolic syndrome is no reason to limit SFA intake of the genuinely healthy population. Some SFA are definitely pro-inflammatory, but a balanced diet also contains anti-inflammatory components.

Keywords:

Saturated fatty acids, cardiovascular disease, coconut oil, LDL-cholesterol, polyunsaturated fatty acids, metabolic syndrome, inflammation, CRP.

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Declaration of no conflict of interest:

None of the authors report a conflict of interest. FAJM received research grants from FrieslandCampina (Leeuwarden) for studies on nutrition in pregnancy, lactation and early infancy.

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The 2015-2020 ‘Dietary Guidelines for Americans’ advice to limit saturated fatty acid (SFA) intake to <10% of daily calories, while the 2013 American Heart Association (AHA)/American College of Cardiology lifestyle guidelines advice to further limit SFA to 5-6% of calories for individuals with elevated LDL-cholesterol (LDL-C) levels (1). In 2015, the Dutch Health Council abandoned the advice to consume less than 10% of energy as SFA, in favor of the ‘replacement of butter, hard margarines, and cooking fats by soft margarines, liquid cooking fats, and vegetable oils’ (2).

Recently, the AHA published a meta-analysis (1) emphasizing their earlier recommendation to limit SFA intake. In this 2017 ‘Presidential Advisory on dietary fats and cardiovascular disease (CVD)’, the AHA strongly recommends to lower SFA intake and replace SFA with unsaturated fat, especially polyunsaturated fat (PUFA), to lower the incidence of heart disease. Such replacement is claimed to reduce the risk for cardiovascular events by about 30%; a risk reduction comparable to treatment with statins. In addition, the AHA advises against the use of coconut oil because it increases LDL-C levels and ‘has no known offsetting favorable effects’ (1). The simultaneous raising of HDL-cholesterol (HDL-C) (3) is acknowledged but ignored because changes in HDL-C, either by drugs or diet, ‘can no longer be directly linked to changes in CVD, and therefore the LDL-C raising effect should be considered on its own’ (1).

We are at present confronted with even further deviating opinions regarding SFA and heart disease. For instance, a recent (2017) comment on currently available systematic reviews and meta-analyses of observational studies concluded that there is no association between SFA consumption and all-cause mortality, coronary heart disease (CHD), CHD mortality, ischemic stroke nor type 2 diabetes, in healthy adults (4), while a recent (2017) meta-analysis of randomized controlled trials (RCTs) (5) concluded that replacing SFA with mostly n-6 PUFA is unlikely to reduce CHD events, CHD mortality or total mortality. The latter meta-analysis claims to have excluded inadequately controlled trials and to have exclusively pooled the results of adequately controlled trials. The study found neither a beneficial nor an adverse effect on CHD events, CHD mortality and total mortality.

In this contribution, we comment on the recent AHA advice, discuss the major recent (2017) literature on the SFA-CHD connection and put the consumption of SFA in an evolutionary context.

Is coconut oil unhealthy?

There are, to our knowledge and that of others (6), no studies showing adverse effects of coconut oil on hard endpoints. Vijayakumar et al. (7) conducted a randomized study on the use of 'ordinary' coconut oil versus sunflower oil for cooking. The study population was composed of 200 patients with stable CVD on standard medical care, living in India. The oils were given to the subjects and their family members. After a two-year period, they did not find any differences in anthropometric, biochemical (e.g. total-, HDL-, LDL-cholesterol; triglycerides; and hsCRP) and vascular functions (flow mediated vasodilatation), or cardiovascular events. The AHA advisory does not mention this study, possibly because it did not last more than two years (see below).

We also argue that the LDL-C concentration is still a soft endpoint, not a disease, although many investigators are convinced by the causal involvement of the LDL-C concentration in CVD. However, an LDL-C concentration increase, observed in some RCTs and meta-analyses, might as well be linked with a lower CHD risk (e.g. in RCTs of fish oil and SGLT2 inhibitors), whereas an LDL-C decrease may be linked to a higher CHD risk (e.g. RCTs of hormone replacement therapy) (8). Statins reduce LDL-C levels and CVD risk but also reduce inflammation, as witnessed from the simultaneous drop of hsCRP. Inflammation changes our metabolism, including the compositions of LDL and HDL. The serum triglyceride concentration increases, HDL-C decreases and both 'small dense' LDL and 'dysfunctional' HDL emerge (8). The hypothesis of atherosclerosis being an inflammatory disease dates back to 1859 when R. Virchow noticed that 'an inflammation of the inner arterial coat is the starting point of the so-called atheromatous degeneration'. The concept became widely known by the paper of Ross in 1999 (9), that has been cited about 27,000 times. The recent CANTOS trial showed that targeting interleukin-1 beta in patients with previous myocardial infarction, with generally well-controlled LDL-C levels, and hsCRP above 2 mg/L, reduces hsCRP and the rate of recurrent cardiovascular events, without changing LDL- and HDL-cholesterol concentrations (10).

AHA meta-analysis accused of 'cherry picking'

Currently, there are at least nine expert reviews that have failed to demonstrate a clear link between SFA, cardiovascular mortality and total mortality. Short descriptions of the included trials in these meta-analyses and their conclusions can e.g. be found in references (11-13). Upon comparison, it should, however, be appreciated that the AHA advisory chose cardiovascular events, including myocardial infarction and angina, as endpoint, whereas the more conclusive 'hard' endpoints, including myocardial infarction, stroke and cardiovascular and total mortality, were mostly investigated by other meta-analyses (11). Selective omission of studies because of 'poor quality', possibly inspired by biased opinion, also named 'cherry picking' (11, 14), seems to have become the new trend and is in the center of the current discussion (4, 11-23).

The AHA advisory excluded most of the existing trials to arrive at a final selection of four and they did not provide clear detailed a priori inclusion criteria (11, 14). Exclusion of currently available studies is extensively explained, but they did not apply equally stringent criteria for choosing the four trials on which their meta-analysis is ultimately based (see below). Detailed a priori criteria are a prerequisite for a meta-analysis according to Cochrane guidelines. The following may be cited from the 'Study quality guide' of 'The Cochrane consumers and communication review group': 'A systematic review is only as good as the studies upon which it is built. Including biased studies in a systematic review can therefore produce misleading results. Even if high quality methods are followed for the conduct of the review itself, if studies with serious biases are included and these are not adequately accounted for or acknowledged, poor quality evidence will arise from the review' (24).

More specifically, the AHA advisory notes that they limited the selection to trials that: 1) compared high SFA with high PUFA intake; 2) did not include trans unsaturated fat as a major component; 3) controlled the dietary intake of the intervention and control groups; 4) had at least two years of sustained intake of the assigned diets; 5) proved adherence by objective biomarkers such as serum cholesterol or blood or tissue levels of PUFA; and 6) collected and validated information on cardiovascular or coronary disease events. With these criteria, the included studies were: the study of the 'Wadsworth Hospital/Veterans Administration Center in Los Angeles' by Dayton et al. (846 men); the 'Oslo Diet Heart Study' (412 men), the study by the British 'Medical Research Council' (393 men) and the 'Finnish Mental Hospital Study' (1,222 men and women). The total number of subjects was 2,873 and the number of cases was 719 (1).

Given the above criteria and final choices, opponents criticize, amongst other, the inclusion of the poorly controlled 'Finnish Mental Hospital Study', which is not an RCT and has been omitted in all major reviews since 2014. The trial might e.g. have been biased by the use of an antipsychotic drug that was especially taken by the control group and was later found to increase the risk of cardiac death. Because of its large beneficial outcome and weight (31.66%), the inclusion of this study is likely to have driven the conclusions of the AHA advisory to a large extent (11).

On the other hand, the very large (originally 9,570 subjects) 'Minnesota Coronary Experiment' was excluded, among other reasons, because it did not last at least two years, while the outcomes of the 'Dietary Approaches to Stop Hypertension' (DASH; not aimed at fatty acids) study, not lasting for more than five months, were accepted as an example of an 'overall healthful dietary pattern' (11). In a recent reanalysis of the 'Minnesota Coronary Experiment', replacing SFA with linoleic acid effectively lowered serum cholesterol, but did not support the hypothesis that this reduction translated to a lower risk of death from CHD or all causes. More precisely, it was found that, in participants older than 65 years, a 30 mg/dL (0.79 mmol/L) decrease in serum cholesterol was associated with a 35% higher

risk of death (HR 1.35, 95% CI 1.18-1.54), whereas among people aged under 65 at baseline, there was no such relation (1.01, 0.88-1.16) (25).

The inclusion of the 'Oslo Diet Heart Study' into the AHA advisory is also criticized (14). This study holds 27.95% of the weight in the AHA meta-analysis, thus amounting 59.61% of the total weight when taken together with the afore-mentioned 'Finnish Mental Hospital Study'. The 'Oslo Diet Heart Study', though randomized, suffered from a 'performance bias' (26), with the intervention group receiving 'continuous instruction and supervision', while the control group received no counseling at all. This would be the equivalent of a drug trial without placebo control, and, moreover, unblinded, since the physicians who referred the studied patients to the main investigator were obviously aware of their assignment to either intervention or control. A resulting bias is plausible, since the intervention group reported a very low sugar intake (14).

Other comments regarding the four selected trials comprise the AHA endpoint of only CHD events. The absence of an analysis of total mortality raises questions about the occurrence of adverse effects (14).

Recent (2017) studies on dietary SFA and cardiovascular disease

The AHA advisory did not change our opinion (27-29) regarding the influence of dietary SFA on CHD. We still argue against the causality of the relation between SFA intake, cholesterol and CHD mortality. Our concern is the projection of this line of reasoning on the general, low-risk, healthy population (28,30). Individuals with the metabolic syndrome (insulin resistance syndrome) are known to de novo synthesize fat, notably palmitate, from polar precursors, especially glucose. In this condition, also referred to as pre-diabetes, the sparing of dietary fat and its de novo synthesis are among the various factors in the initiation of an inflammatory program, as recently extensively reviewed by Reilly and Saltiel (31). As discussed elsewhere (27-29) dietary- and de novo synthesized-palmitate interact with toll like receptor-4 to initiate an inflammatory cascade by as yet incompletely delineated mechanisms.

A recent paper by Chiu et al. (8) strengthens the above notion that especially individuals with 'LDL phenotype B', a feature of the metabolic syndrome, should limit both their SFA- and carbohydrate-intakes, since dietary SFA and carbohydrates are likely to interact. Individuals with the LDL phenotype B present high levels of small-dense LDL particles. The latter, and also medium sized LDL particles, are components of 'atherogenic' dyslipidemia, and associate with CVD outcomes more strongly than larger LDL particles. It was concluded that 'saturated fat may have heterogeneous effects on levels of atherogenic LDL particles that may depend on the amount of saturated fat consumed, the dietary context, particularly concomitant carbohydrate intake, and/or predisposition to atherogenic dyslipidemia'. We conclude that there is no convincing evidence that the current recommendations for SFA should apply to healthy subjects with LDL phenotype A with predominance of large, buoyant LDL particles, who do

not suffer from the metabolic syndrome and are at low CHD risk.

Other recent studies published in the Lancet (32-34), seem to have debunked the 'lipid hypothesis' that started in 1958 with the advent of the 'Seven Countries Study' of Ancel Keys. These Lancet papers on the 'Prospective Urban Rural Epidemiology' (PURE) study did, however, meet serious criticism (see below). The PURE study is a very large, epidemiological cohort study of individuals aged 35-70 years in 18 countries in five continents. The study includes high-income, medium-income and low-income nations. Enrolment was from 2003-2013 and the median follow-up was 7.4 years. The authors associated dietary intakes of 135,335 individuals with cardiovascular mortality, disease and events and non-CVD mortality. A very high carbohydrate intake (>70 energy%) was associated with a higher risk of total mortality, but not with CVD risk, whereas total fat, SFA, MUFA and PUFA were related to a lower total mortality. Total fat, SFA, MUFA and PUFA were not associated with CVD, myocardial infarction nor cardiovascular disease mortality, whereas SFA exhibited an inverse association with stroke (32, 34). In addition, the PURE study investigated the association between nutrients and CVD risk markers in 125,287 participants (33, 34). The outcome confirmed that SFA intake is associated with higher LDL-C but also with higher HDL-C and lower triglycerides, total cholesterol/HDL-C ratio, triglycerides/HDL-C ratio and ApoB/ApoA1 ratio. Modelling studies showed that replacing SFA for unsaturated fats might improve some risk markers (total cholesterol, LDL-C, triglycerides/HDL-C ratio and blood pressure) but may also worsen others (HDL-C and triglycerides). It was concluded that 'focusing on a single lipid marker such as LDL-C alone does not capture the net clinical effects of nutrients on cardiovascular risk. Based on the lipid profile, a reduction of SFA intake below 10 energy% was not supported (33, 34).

It must be noted that, based on its design, lack of causality and data analysis, the PURE study has been seriously criticized (35, 36). Some of the findings, e.g. the LDL-C raising effect of PUFA, are at odds with well-controlled feeding trials (36). The strength of the PURE study, comparing dietary data with disease outcomes across a broad range of countries and geographical regions, constitutes at the same time its weakness, since such a design with many variables profoundly increases the chance of residual confounding from parameters like wealth, socioeconomic status and access to health care (35, 36). For instance, the relation of SFA intake with lower total mortality might as well reflect an association between higher consumption of animal fat (i.e. wealth) and access to either a hospital or medical care (35).

Evolutionary approach

From an evolutionary point view, there is also no reason to reduce the consumption of a nutrient that we have always eaten, in favor of the consumption of an amount of linoleic acid (advice 5-10 energy% (37)) that we have never eaten in our whole evolutionary past (38,39). There should be good scientific evidence for such a recommendation, which is currently not the case.

The 'precautionary principle' to risk management is applicable here. This principle states that if an action or policy has a suspected risk of causing any harm, either to the public or to the environment, in the absence of scientific consensus, the burden of proof that it is not harmful falls on those taking that action (40).

An alternative advice to the healthy population might be to take a statin, aspirin, antihypertensive, or even an SGLT2 inhibitor, to lower CVD and other risks. There is basically no difference in the required level of evidence for such drugs in primary prevention, compared with a dietary advice that is remote from what we are based on from an evolutionary point of view. The 'unnatural' advice to lower SFA in favor of notably linoleic acid should be regarded as 'treatment of the healthy population'. It may be argued that such options, i.e. drugs or unnatural diet, are nowadays needed for prevention because of our deviation from a healthy lifestyle, which is more than diet alone (30). We contend that lifestyle changes, not the masking of an unhealthy lifestyle with unnatural diets or drugs, are definitively better choices, both from the point of view of the individual and the society as a whole.

New studies?

What does it take to settle the differences? It is unlikely that new, impeccable, studies will be conducted for many reasons, including high costs, 20,000-30,000 participants needed, feasibility to deliver diets to such large numbers, adherence to intervention for at least five years, declining CVD incidence rates because of improved lifestyle, and better medical treatment (1,14). The current intervention studies are what they are and, for all practical purposes, one has to reach a(n) (interim) conclusion.

Conclusions

Individuals with the metabolic syndrome should be advised to limit dietary SFA intake, since they synthesize SFA de novo from carbohydrates and spare dietary SFA (27-29). The high risk of individuals with the metabolic syndrome is no reason to limit SFA intake by the genuinely healthy population. Some SFA, for example palmitate, are definitely pro-inflammatory, but a balanced diet also contains anti-inflammatory components, as extensively outlined elsewhere (27-30, 41).

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Samenvatting

Muskiet FAJ, Ruiz-Núñez B, Dijck-Brouwer DA. Commentaar op het rapport “Voedingsvetten en Cardiovasculaire Ziekte. Een presidentieel advies van de American Heart Association (AHA)”. *Ned Tijdschr Klin Chem Labgeneesk*. 2017; 42: 224-228

Recent heeft de ‘American Heart Association’ (AHA) een meta-analyse gepubliceerd die hun eerdere aanbeveling benadrukt om de inname van verzadigde vetzuren (SFA) te beperken. SFA moeten worden vervangen door onverzadigd vet, met name meervoudig onverzadigd vet, om de incidentie van hartziekten te verlagen. Gesteld wordt dat een dergelijke verandering het risico op cardiovasculaire incidenten met ongeveer 30% kan verlagen; een risicoreductie vergelijkbaar met een behandeling met statines. De AHA adviseert ook tegen de consumptie van kokosnootolie omdat dit het LDL-cholesterol verhoogt en geen ‘bekende compenserende gunstige effecten kent’. Wij beargumenteren dat de LDL-cholesterol concentratie nog steeds een zacht eindpunt is, geen ziekte, terwijl er geen studies zijn die ongunstige effecten van kokosnootolie tonen op harde eindpunten. De AHA motiveert op uitgebreide wijze de exclusie van studies voor hun meta-analyse maar past geen strenge criteria toe op de keuze van de vier trials die uiteindelijk de ruggengraad vormen van hun meta-analyse. Eén van deze betrof geen gerandomiseerd onderzoek, terwijl een andere leed aan een “performance bias”. De grootste, negatief uitpakkende, trial werd onder andere geëxcludeerd omdat deze niet tenminste twee jaar duurde. De AHA meta-analyse ademt een gevoel van “het halen van de krenten uit de pap”. Er zijn momenteel tenminste negen reviews van experts die geen duidelijke link vonden tussen SFA, cardiovasculaire mortaliteit en totale mortaliteit. Wij beargumenteren dat personen met het metabool syndroom voorzichtig moeten zijn met de inname van SFA en koolhydraten omdat ze SFA de novo synthetiseren uit koolhydraten en SFA uit de voeding sparen. Het hoge risico van mensen met het metabool syndroom is geen reden om de SFA inname van de werkelijk gezonde populatie te beperken. Sommige SFA zijn zonder twijfel pro-inflammatoir, maar een gebalanceerde voeding bevat eveneens anti-inflammatoire componenten.