Diet-heart: a problematic revisit[1–3]

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The diet-heart revisit in this issue of the Journal (1, 2), concerning saturated fatty acids (SFAs) and coronary heart disease (CHD), is problematic in its thrust; it relates to numerous questions as follows, none of which are explicitly spelled out:

1) In univariate analyses of population-based observational data, are there direct relations of dietary SFAs to CHD?
2) In multivariate analyses controlled for possible confounders, are there independent direct relations of dietary SFAs to CHD?
3) Is the SFA-CHD relation similar for ''hard'' fatal CHD and ''soft'' total CHD?
4) Do limitations in quality of dietary data in epidemiologic studies on SFA-CHD influence results?
5) What are the findings from randomized controlled trials on SFA-CHD?
6) Is the SFA-CHD relation mainly attributable to adverse SFA influence on serum cholesterol (total cholesterol, LDL cholesterol)?
7) What about possible effects of dietary cholesterol?
8) With lower dietary SFA, which macronutrients are preferable to replace SFA?
9) Are dietary influences on serum lipoprotein particles clear or relevant? Do particle measurements enhance CHD risk assessment independent of serum lipids?
10) Do dietary SFAs or other macronutrients influence metabolic traits other than LDL cholesterol, particularly HDL cholesterol and triglycerides, independent of caloric balance (obesity)? Do these traits predict CHD risk independently of established major metabolic risk factors such as adverse total cholesterol and LDL cholesterol, blood pressure (BP), body mass, and hyperglycemia/diabetes?
11) Do these dietary traits influence BP?
12) On the basis of all of the evidence, what are optimal dietary recommendations to reduce CHD risk?

Regarding item 1 above, the issue of whether SFA relates to CHD in univariate analyses is relevant. If findings on this subject are positive but the association is markedly reduced or ceases in multivariate analyses, this may be due to confounding (eg, by dietary cholesterol) and/or overadjustment (eg, by inclusion in analyses of serum total or LDL cholesterol, a major CHD risk factor influenced by SFA intake). Assessment of such possibilities enlightens understanding of SFA-CHD relations, but the 2 current articles (1, 2) do not address these issues.

Limited information on these issues is extractable from tables in the meta-analysis (2). Of 15 studies that unequivocally concern the SFA-CHD relation, 4 did not include other dietary lipids or serum lipids among covariates. Their CHD relative risks

(RRs) ranged from 1.22 to 2.77—ie, >1.07, which was the estimated CHD RR in the meta-analysis (2). Do these larger RRs reflect freedom from confounding and overadjustment? Analyses are needed to clarify this; the 2 current articles (1, 2) give no such data.

The meta-analysis (2) states briefly that the Ni-Hon-San Study and the Seven Countries Study found significant cross-population relations between SFA and CHD, as have multiple ecological analyses (3). The authors ignore these findings in their assessments and conclusions.

Regarding item 2, in multivariate analyses the question is: Does SFA relate to CHD independently of multiple covariates (including dietary and serum lipids)? The 2 articles (1, 2) never make this clear. Thus, the Abstract in the meta-analysis simply states, ''Intake of saturated fat was not associated with an increased risk of CHD'' (2). A precise characterization is as follows: There was a statistically nonsignificant relation of SFA to CHD (RR: 1.07) independent of other dietary lipids, serum lipids, and other covariates.

As to item 3, the meta-analysis did not compare SFA–fatal CHD and SFA–total CHD outcomes (total CHD is undefined). This merits exploration. My calculations, from data for 16 CHD studies (meta-analysis tables), with RRs weighted by person-years of exposure, yielded contrasting CHD risks: for ''hard'' fatal CHD (11 studies), the RR was 1.32; for ''soft'' total CHD (5 studies), the RR was 0.99; and for all 16 studies, the RR was 1.09 (compared with the meta-analysis RR estimate of 1.07).

Regarding item 4, the meta-analysis (2) reported its findings as independent of a quality score including diet assessment. Of the 16 CHD studies, 4 relied on one 24-h dietary recall; the SFA-CHD RR was >1.00 for only one of these studies. Seven used a food-frequency questionnaire (FFQ); the RR was >1.00 in 3 of these studies. Five used dietary history or multiday food record; the RR was >1.00 in all 5 studies, even though 3 were adjusted for serum or dietary lipids (2). These facts, which were unnoted in the meta-analysis (2), prompt the question: Did low-level reliability (reproducibility) of dietary SFA data drive RR

values toward 1.00 (the regression-dilution bias problem)? No data on SFA reliability are given.

As shown in Table 1 of the meta-analysis (2), whether a study "validated" dietary data (a misnomer) is noted; the procedure was a comparison of 2 methods, the study's and another method (eg, FFQ and 7-d record), which is an assessment of reliability, not validity (concordance of data with external objective reality). The ability to evaluate the validity of dietary data on free-living people is limited (4); validity was not assessed in the meta-analysis. Also, the meta-analysis says nothing about the problem for the 16 studies of possible bias in SFA-CHD findings due to dietary change (eg, reduced SFA intake) in people with higher serum total cholesterol seeking to lower total cholesterol/CHD risk (as occurred for the earliest of the 16 studies).

Regarding item 5 above, the Clinical Trials section in the Opinion article (1) is almost entirely uncritical, noting only in regard to 2 trials that "these studies may have been limited by a small sample size and/or a limited duration of follow-up." This section discusses the Women's Health Initiative Trial uncritically, without attention to key aspects or implications of design and findings. That trial primarily explored the effects of low total fat on breast and colon cancer, not the effects of improved dietary lipid composition on CHD; reported improvements in dietary lipid composition by the intervention group were small; improvements in total and LDL cholesterol, BP, and so forth were miniscule or nil, yielding nonsignificant effects on CHD (predictably)—eg, for a combined "hard" CHD endpoint [in women without baseline cardiovascular disease (CVD) history], the hazard ratio for the intervention group was 0.94 (95% CI: 0.86–1.02). As Howard et al (5) have noted, "Trends toward greater reductions in CHD risk were observed in those with lower intakes of saturated fat or *trans* fat or higher intakes of vegetables/fruits." The investigators concluded that "more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk" (5). This inference is concordant with extensive data that show CHD rates lower by 90% and life expectancy years longer for the small minority of adult Americans with favorable levels of the 4 readily measured diet-dependent major CHD risk factors [total cholesterol, BP, body mass index (BMI), glycemia/diabetes] and non-smoking status (6).

There is a 50-y history on diet-heart trials involving multiple studies, including the National Diet-Heart Study and the Multiple Risk Factor Intervention Trial, with extensive findings, conclusions, and recommendations that are not mentioned in the current 2 articles (1, 2). Suffice it to note here that no definitive diet-heart trial has been done, and it is unlikely that one will ever be done. Enhancement of public policy for CHD/CVD prevention has to proceed on the basis of all of the other evidence, as it has successfully since 1960, a key matter only touched on one-sidedly in the 2 current articles (1, 2).

Regarding item 6, the current articles (1, 2) contain formulations that imply skepticism regarding the importance of the influence of SFA on serum total and LDL cholesterol (eg, reference 1, first sentence of Introduction). The authors' precise intent is unclear: Do they doubt the validity of the equations of Keys et al (University of Minnesota) and Hegsted et al (Harvard), which are based on dozens of metabolic ward–type feeding experiments, showing independent relations of dietary SFA and cholesterol (direct) and polyunsaturated acid (PUFA) (inverse) to total cholesterol (*see* Bibliography in reference 6: articles by Clarke et al, Hegsted et al, Keys et al), findings that are repeatedly confirmed in observational and interventional studies in free-living people? (The 2 current articles do not cite these references.) Are the briefly described (1) interactive influences on total and LDL cholesterol among the dietary lipids validly established? Do they bring into question the classical findings?

As to item 7, the current articles (1, 2) barely touch on influences of dietary cholesterol. The meta-analysis mentions the 1933 Anitschkow chapter, stating (inaccurately) that early animal studies showed high SFA and cholesterol intakes induced hypercholesterolemia/atherosclerosis. In fact, the decisive dietary modification for experimental atherogenesis, the *sine qua non* or *materia peccans* (Anitschkow's term), is *cholesterol ingestion*. This has been the prerequisite since the 1908–1912 breakthrough by Anitschkow et al (a centennial anniversary meriting celebration and discussion) in thousands of experiments in mammalian and avian species—herbivorous, carnivorous, and omnivorous—including nonhuman primates. To neglect this fact in a review about humans is to imply that the Darwinian foundation of biomedical research is invalid and/or that there is a body of substantial contrary evidence in humans. Neither is the case. Dietary cholesterol (as well as SFA) adversely influences human serum lipid concentrations, per cited equations. And several prospective epidemiologic studies found direct relations of dietary cholesterol to CHD independent of serum total cholesterol (6). The SFA-CHD relation can be soundly elucidated only with concurrent consideration of dietary cholesterol (as well as PUFA, carbohydrate, etc). The quality of the current 2 articles (1, 2) is impaired by inadequate attention to dietary cholesterol.

Regarding item 8 on macronutrient alternatives to SFA, the current articles (1, 2) express concern about possible unfavorable metabolic influences of carbohydrate—eg, on triglycerides, HDL cholesterol, and small LDL particles. No mention is made of the fact that international epidemiologic data cast doubt as to the generalizability of "carbohydrate-induced dyslipidemia": eg, Seven Countries Study baseline data (1960s) on Italy and Japan, the latter with dietary total fat of ≈10% of kcal (≈3% SFA, 3% MUFA, 3% PUFA); high, mostly complex, total carbohydrate; favorable serum lipid concentrations; and low CHD rates. Similarly, in the late 1990s (4), macronutrient intakes in Japan and China compared with the United States were higher in total available carbohydrate (54%, 65%, and 49% of kcal, respectively), starch, vegetable protein, alcohol (men); lower (Japan, China compared with the United States) in total fat and SFA (6% and 5% of kcal, respectively), *trans* fatty acids, cholesterol (China), Keys dietary lipid score, sugars; also lower in BMI (4). Note the amount of SFA (5–6% of kcal), which was an *observed* finding for the Chinese/Japanese population samples (4); the authors (1) are incorrect in describing recommendations for this amount of SFA as an "extrapolation" without a database. Serum total cholesterol, LDL cholesterol, triglycerides, glycated hemoglobin, uric acid, and fibrinogen were lower in Japanese in Japan than in Japanese Americans in Hawaii, and HDL cholesterol was higher (in men) or as high (in women)—ie, with no evidence of carbohydrate-induced dyslipidemia/metabolic syndrome. Other studies have reported corresponding data from China (7) and from Italy. The current articles (1, 2) also neglect the 3 DASH (Dietary Approaches to Stop Hypertension)/OmniHeart feeding trials (8, 9) in regard to the likely benefit

of replacing SFA with complex carbohydrate. The authors are inaccurate in concluding (Abstract; 1) that "there are few epidemiologic or clinical trial data to support a benefit of replacing saturated fat with carbohydrate."

Regarding item 9, concern is expressed (1) about differential effects of dietary SFA and carbohydrate on amounts of larger and smaller LDL particles. Limited data exist on these effects and on whether lipoprotein particle measurement enhances CHD risk assessment independent of serum lipids. Initial findings do not warrant proposals to overturn recommendations—which were developed and refined over decades on the basis of massive concordant evidence—on population-wide improved nutrition to prevent CHD. They pose questions, but they do not give solid answers; more research is essential.

As to item 10, the concern (1) about influences of dietary composition on triglycerides, HDL cholesterol, glycemia/diabetes, and "metabolic dyslipidemia" is also one-sided. The evidence is overwhelming that the main "driver" of these traits is caloric imbalance producing overweight/obesity (10). These metabolic traits all respond favorably to even modest weight reduction with diets of varied nutrient composition, including heart-healthy fare (*see* below) (11, 12). Data are limited or inconsistent on influences of dietary composition (SFA compared with carbohydrates, etc) (*see* item 8 above) and on "metabolic dyslipidemia"/metabolic syndrome as an independent predictor of CHD risk. Current findings do not warrant modification of recommendations for improved nutrition, beyond intensified emphasis on prevention and control of obesity (ie, on caloric balance as well as on nutrient composition).

Regarding item 11, recent epidemiologic and feeding trial findings (8, 9, 13) indicate that multiple macro-/micronutrients independently influence BP in addition to the established adverse effects of high salt, excess alcohol, and caloric imbalance/obesity and the favorable effects of potassium. These include vegetable protein, glutamic acid, ω-3/ω-6 PUFAs, oleic acid/monounsaturated fatty acid (MUFA), and minerals (calcium, nonheme iron, magnesium, phosphorus) inversely and red meat, glycine, cholesterol, and sugars in sweetened beverages directly. Combined effects—estimated from epidemiologic data and shown by feeding trials—are sizable and important for medical care and public health. The authors' paragraphs on BP mention only a few macronutrients (1).

Finally, as to item 12 recommendations the authors offer only the following: "dietary efforts to improve the increasing burden of CVD risk associated with atherogenic dyslipidemia should primarily emphasize the limitation of refined carbohydrate intakes and a reduction in excess adiposity" (1; Abstract and Conclusions). Coupled with the statement in the Abstract and Conclusions in the meta-analysis (2), "there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD," the authors seem to be dissociating themselves from prevailing national and international dietary recommendations to the general population for primordial, primary, and secondary prevention of CHD/CVD and the established major metabolic risk factors. But they are not explicit. Is that their intent? Specifically, do they disagree with the merits of heart-healthy fare on the basis of DASH-, OmniHeart-,

Mediterranean-, East Asian–type eating patterns, which emphasize vegetables, fruit, whole grains, legumes/seeds/nuts, fat-free/low-fat dairy products, fish/shellfish, lean poultry, egg whites, seed oils in moderation, alcohol (if desired) in moderation, and portion size/calorie controlled and deemphasize red and processed meats, cheeses, ice cream, egg yolks, cookies/pastries/pies/cakes/other sweets/sweetened beverages, snacks, and salt/commercial foods with added salt. Estimated nutrient composition of this fare is as follows: total fat $\approx$20–25% of kcal, SFA 6–7%, MUFA 7–9%, PUFA 7–9%, cholesterol <100 mg/1000 kcal, total protein 18–25%, vegetable protein 9–12%, carbohydrate 55–60% (mostly complex), fiber 30–35 g/d, 50–65 mmol Na/d (2900–3770 mg NaCl/d), mineral/vitamin intake high (6). A vast array of concordant multidisciplinary research evidence is the sound foundation for these recommendations.

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