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EDITORIAL

Saturated fatty acid intake and cardiovascular risk

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This editorial refers to 'Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: the JPHC Study'†, by K. Yamagishi *et al.*, on page 1225

Since the 1960s, clinical and animal studies have shown that reduction of dietary saturated fatty acid (SFA) consumption is associated with reduced risk of cardiovascular disease (CVD).[1,2] Thus, reduction of SFA intake is now one of the central strategies of dietary recommendations to reduce CVD worldwide.[1,2] For example, the World Health Organization and the US Dietary Guidelines recommend dietary consumption of $< 10\%$ of total energy intake from SFAs,[1] while the American Heart Association guidelines recommend even more strict dietary SFA consumption of $< 7\%$.[2] However, it has always been a matter of debate whether SFA consumption is truly associated with CVD risk, particularly with risk of stroke, because of insufficient evidence regarding the disorder. Recently, Siri-Tarino *et al*. performed a meta-analysis to summarize the evidence related to the association between dietary SFA intake and risk of coronary artery disease (CAD), stroke, and CVD (including stroke) in 21 prospective epidemiological studies, where 11 006 out of 347 747 subjects developed CAD or stroke during 5–23 years of follow-up.[3] Because the pooled relative risk (RR) estimate comparing extreme quantiles of SFA intake for CAD, stroke, and CVD was 1.07 [95% confidence inteval (CI) 0.96–1.19; $P = 0.22$], 0.81 (95% CI 0.62–1.05; $P = 0.11$), and 1.00 (95% CI 0.89–1.11; $P = 0.95$), respectively, they concluded that SFA intake was not significantly associated with increased risk of CAD, stroke, or CVD.[3] However, there seems to be an insignificant but mild trend for the relationship between dietary SFA intake and stroke (RR 0.81, $P = 0.11$), which may warrant further investigations.[3]

Yamagishi *et al*. have reported the results from the Japan Public Health Center-based prospective (JPHC) Study that examined whether dietary SFA intake is associated with risk of stroke and its subtypes as well as that of CAD amongst Japanese, whose average dietary SFA intake is lower than in Western populations.[4] The JPHC Study comprised a total of 38 084 men and 43 847 women from two subcohorts: Cohort I, aged 45–64 in 1995, and followed-up through 2009; and Cohort II, aged 45–74 in 1998, and followed-up through 2007. The major strengths of the JPHC Study include the large sample size, detailed evaluation of endpoints, and accurate diagnosis of stroke subtypes with computed tomography (CT)/magnetic resonance imaging (MRI). Consequently, the JPHC Study examined a larger number of cardiovascular events with more detailed analysis, giving a strengthened power in statistics and more useful clinical messages as compared with previous studies. After adjustment with multiple factors, including age, sex, energy intake, cohort, cigarette smoking status, alcohol intake, body mass index, sports at leisure time, walking and standing time, perceived mental stress, energy-adjusted dietary intakes of carbohydrate, protein, cholesterol, vegetables, fruit, and calcium, the JPHC Study revealed inverse associations of dietary SFA intake with total stroke [$n = 546$; adjusted hazard ratio (HR) (95% CI) for the highest vs. lowest quintiles = 0.77 (0.65–0.93), P for trend = 0.002], intraparenchymal haemorrhage [$n = 150$; 0.61 (0.43–0.86), P for trend = 0.005], and ischaemic stroke [$n = 319$; 0.84 (0.67–1.06), P for trend = 0.08], providing additional epidemiological evidence that dietary SFA intake is inversely associated with total stroke in a Japanese population.[4] This inverse relationship between SFA intake and stroke observed in the JPHC Study is consistent with the previous observation obtained in the Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk.[5] The JACC study comprised 58 453 Japanese men and women aged 40–79 years at baseline (1988–1990) with a 14.1-year follow-up and revealed inverse associations of SFA intake with mortality from total stroke [$n = 976$; multivariable HR (95% CI) for highest compared with lowest quintiles: 0.69 (0.53–0.89), P for trend = 0.004], intraparenchymal haemorrhage [$n = 224$; 0.48 (0.27–0.85), P for trend = 0.03], and ischaemic stroke [$n = 321$; 0.58 (0.37–0.90), P for trend = 0.01]. Thus, it may be concluded that there exists an inverse association between dietary SFA intake and both incidence and mortality from stroke at least in a Japanese population, where SFA levels are lower than in Western populations.

In contrast, however, the results regarding CAD are inconsistent between the JPHC Study and the JACC Study; the JPHC Study

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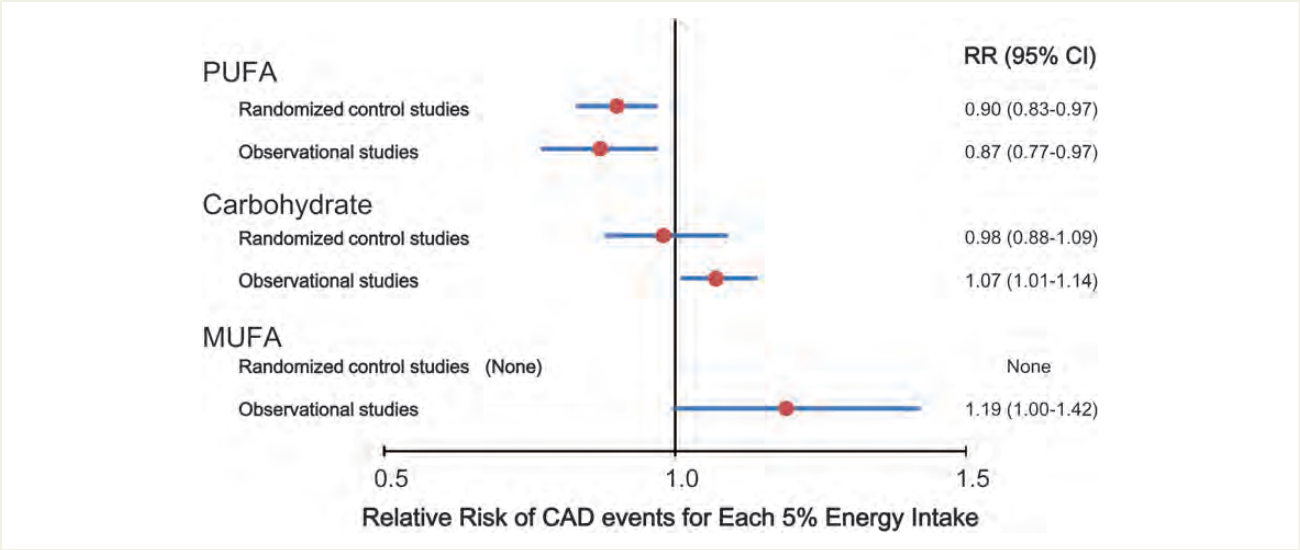

Figure 1 Relative risk (RR) for the effects of dietary changes on actual coronary artery disease (CAD) events is obtained from the meta-analysis of eight randomized clinical trials (RCTs) for polyunsaturated fatty acids (PUFAs) replacing saturated fatty acids (SFAs),[7] the Women's Health Initiative RCT for carbohydrate replacing SFAs,[9] and a pooled analysis of 11 prospective cohort studies.[8] CI, confidence interval; MUFA, monounsaturated fatty acids.

revealed a positive association of dietary SFA intake with myocardial infarction [$n = 124$; 1.39 (0.93–2.08), P for trend = 0.046], particularly among men,[4] whereas the JACC Study found no association of dietary SFA intake with mortality from ischaemic heart disease [$n = 836$; 0.89 (0.68–1.15), P for trend = 0.59] or myocardial infarction [$n = 330$; 0.85 (0.56–1.29), P for trend = 0.40].[5] Possible explanations for the discrepancy include the facts that a relatively younger population was examined in the JPHC Study and that the incidence and mortality of myocardial infarction as an endpoint were different between the two studies. In other words, the discrepancy could be due, at least in part, to the increase in the incidence of, but not that in mortality from, myocardial infarction in a relatively younger generation in Japan, particularly in males. In addition, there might have been a difference in food sources of SFAs between the two studies, such as meat, plants, and dairy products, because individual SFAs may affect CAD risk differently and most SFA-rich foods contain other constituents related to CAD risks.[6]

Another strength of the JPHC Study is an approach searching for a cut-off level of dietary SFA intake. To explore the optimal level of dietary SFA intake to prevent CAD or stroke, the authors included the results obtained from previous studies by plotting dietary SFA intake and crude incidence of and mortality from haemorrhagic stroke, ischaemic stroke, and CAD. By this approach, they suggested a threshold of ~20 g/day of dietary SFA intake for the inverse relationship of SFA intake with stroke, especially with haemorrhagic stroke. Although the present results should be confirmed by future studies including meta-analyses, dietary SFA intake >20 g/day could be an optimal cut-off level to prevent stroke. However, it should be underlined that dietary SFA intake >20 g/day could also be a risk for development of CAD, particularly of myocardial infarction, despite controversies even in the Japanese population, where dietary SFA intake is lower than in Western populations. It remains to be examined whether reduction of dietary SFA to ~20 g/day could actually reduce CAD in Western populations as well as in Asian populations.

As an effort to reduce SFA consumption, previous observational and randomized clinical trials have tried to show benefits of replacement of SFAs with other substitutes to reduce CAD risk.[7–9] Among such substitutes examined, polyunsaturated fatty acids (PUFAs) are the most promising candidates to reduce CAD risk despite some controversies (*Figure 1*).[7] In populations consuming a Western diet, the replacement of 1% of energy from SFAs with PUFAs is associated with a reduction in CAD incidence of 2–3%.[7] In contrast, there is little evidence to support the effect on CAD risk of replacing SFAs with monounsaturated fatty acids (MUFAs), although MUFAs have been reported to reduce LDL-cholesterol levels.[10] The benefit of substituting carbohydrates for SFAs is also unclear or limited, even though unrefined carbohydrate with a low glycaemic index might be beneficial.[11] Thus, to date, the best candidate substitutions of SFAs could be PUFAs, particularly *n*-3 PUFAs, because a series of studies have shown that a high intake of fish oil and *n*-3 PUFAs could reduce the incidence of myocardial infarction, ischaemia–reperfusion injury, ventricular arrhythmias, and death, including sudden cardiac death, despite some controversies.[12–16] Further studies are warranted to determine whether specific foods could be appropriate alternatives for SFAs and also whether *n*-3 PUFAs could be appropriate supplement to reduce cardiovascular risks.

Conflict of interest: none declared.

References

1. US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans, 2010*. Washington, DC: US Government Printing Office, 2010.

2. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;**114**:82–96.
3. Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *Am J Clin Nutr* 2010;**91**:535–546.
4. Yamagishi K, Iso H, Kokubo Y, Saito I, Yatsuya H, Ishihara J, Inoue M, Tsugane S. Dietary intake of saturated fatty acids and incident stroke and coronary heart disease in Japanese communities: the JPHC Study. *Eur Heart J* 2013;**34**: 1225–1232.
5. Yamagishi K, Iso H, Yatsuya H, Tanabe N, Date C, Kikuchi S, Yamamoto A, Inaba Y, Tamakoshi A, for the JACC Study Group. Dietary intake of saturated fatty acids and mortality from cardiovascular disease among Japanese: the JACC Study. *Am J Clin Nutr* 2010;**92**:759–765.
6. de Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR Jr, Nettleton JA. Dietary intake of saturated fat by food source and incident cardiovascular disease. *Am J Clin Nutr* 2012;**96**:397–404.
7. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. *PLoS Med* 2010;**7**:e1000252.
8. Jakobsen MU, O'Reilly EJ, Heitmann BL, Pereira MA, Bälter K, Fraser GE, Goldbourt U, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. *Am J Clin Nutr* 2009;**89**: 1425–1432.
9. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA* 2006;**295**: 655–666.
10. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;**370**:1829–1839.
11. Jakobsen MU, Dethlefsen C, Joensen AM, Stegger J, Tjønneland A, Schmidt EB, Overvad K. Intake of carbohydrates compared with intake of saturated fatty acids and risk of myocardial infarction: importance of the glycemic index. *Am J Clin Nutr* 2010;**91**:1764–1768.
12. Kromhout D, Yasuda S, Geleijnse JM, Shimokawa H. Fish oil and omega-3 fatty acids in cardiovascular disease: do they really work? *Eur Heart J* 2012;**33**:436–443.
13. Tsuburaya R, Yasuda S, Ito Y, Shiroto T, Gao JY, Ito K, Shimokawa H. Eicosapentaenoic acid reduces ischemic ventricular fibrillation via altering monophasic action potential in pigs. *J Mol Cell Cardiol* 2011;**51**:329–336.
14. Gao JY, Yasuda S, Tsuburaya R, Ito Y, Shiroto T, Hao K, Aizawa K, Kikuchi Y, Ito K, Shimokawa H. Long-term treatment with eicosapentaenoic acid ameliorates myocardial ischemia–reperfusion injury in pigs *in vivo*. Involvement of Rho-kinase pathway inhibition. *Circ J* 2011;**75**:1843–1851.
15. Hara M, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, Hamasaki T, Doi Y, Nishino M, Sato H, Kitamura T, Nanto S, Hori M, Komuro I; for the Osaka Acute Coronary Insufficiency Study (OACIS) Investigators. Low levels of serum n-3 polyunsaturated fatty acids are associated with worse heart failure-free survival in patients after acute myocardial infarction. *Circ J* 2012;**77**:153–162.
16. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K. Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicospentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;**369**:1090–1098.