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doi: 10.3945/ajcn.2010.29504.

Reply to P Scarborough et al

Dear Sir:

We agree with Scarborough et al that it is appropriate to consider the possibility that inclusion of serum cholesterol concentrations in multiple regression models may attenuate the relation of saturated fat to cardiovascular disease (CVD) in observational cohort studies. However, using data from the subset of studies in our meta-analysis in which the models did not include blood cholesterol concentration [9 coronary heart disease (CHD) studies and 6 stroke studies; $n =$ 291,126], the results did not differ significantly from those that we reported for all 21 studies ($n = 347{,}747$) (1). The calculated relative risk estimates and 95% CIs for saturated fat intake in the subset were 1.13 (0.96, 1.33) for CHD, 0.84 (0.63, 1.10) for stroke, and 1.02 (0.86, 1.19) for total CVD. This secondary analysis suggests that the overall results from the meta-analysis are robust and are not affected by different analytic strategies. They corroborate a recent pooled analysis of 11 American and European cohort studies ($n = 344{,}696$ persons) that showed that replacement of saturated fat by carbohydrate was not associated with decreased risk of CHD; on the contrary, such a replacement was associated with a slightly increased risk of CHD (2).

QS is supported by a Postdoctoral Fellowship from Unilever Corporate Research. FBH's work is supported by NIH grant HL60712. RMK receives research support from the National Dairy Council, National Cattleman's Beef Association, and the Robert & Veronica Atkins Foundation. PWS-T, QS, and FBH declared no conflicts of interest.

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doi: 10.3945/ajcn.2010.29752.

Saturated fat and heart disease

Dear Sir:

In a meta-analysis of observational studies, Siri-Tarino et al (1) concluded that there was no association of intake of saturated fat with risk of cardiovascular disease. There are several weaknesses in their report, which question the validity of their conclusions.

First, the notion that there exists such a thing as ''the effect of saturated fat'' is flawed. A lower intake of saturated fat implies an increased intake of some other source of calories to maintain caloric balance. Different substitutions for saturated fat have different effects on risk of coronary heart disease (CHD) and need to be discussed separately.

Replacement of saturated fat by polyunsaturated fat lowers both plasma concentrations of LDL cholesterol and the LDL/HDL-cholesterol ratio (2). Moreover, replacement of saturated fat by polyunsaturated fat is also associated with a lower risk of CHD in prospective cohort studies (3) and with lower risk of CHD in randomized trials (4). Thus, the benefit of replacing saturated by polyunsaturated fat is proven beyond reasonable doubt. However, Siri-Tarino et al failed to find this effect in their meta-analysis, just as they failed to find a significant association of saturated fat with CHD in general. The null results of their meta-analysis may reflect a lack of statistical power or an overreliance on mathematical models. To estimate the effect of replacing saturated by polyunsaturated fat, Siri-Tarino et al selected 5 studies that reported relative risks adjusted for intake of carbohydrate, protein, and fats but not of polyunsaturated fat. They then combined these 5 numbers and presented the outcome as the effect of replacing saturated by polyunsaturated fat. It requires a leap of faith to assume that the outcome of such a calculation truly represents what happens when saturated fat is replaced by polyunsaturated fat.

A major weakness of the meta-analysis is the imprecision of dietary assessment methods used in the underlying studies. About half of the studies used 1-d dietary assessments or some other unvalidated method. Food intake varies from day to day, and there is a substantial literature showing that a single 24-h recall provides a poor estimation of the usual dietary intake of an individual (5). Such methods cannot reliably rank individuals by their long-term intake, especially within populations with a uniformly high saturated fat intake. Such imprecision in the assessment of disease determinants systematically reduces the strength of association of determinants with the disease. This is referred to as *attenuation* (6) or *regression dilution bias* (7).