Meta-analysis of effect of saturated fat intake on cardiovascular disease: overadjustment obscures true associations

Dear Sir:

The recent article by Siri-Tarino et al (1), which reported on a meta-analysis of prospective cohort studies evaluating the association of saturated fat with coronary heart disease (CHD), stroke, and cardiovascular disease (CVD) observed that “there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD.” This finding has generated some interest in the media (2, 3). However, we believe that the interpretations of the results presented in this article are overstated and could be a result of flaws in the methodologic design of the study.

The meta-analysis involves data from 16 studies that evaluate the effect of saturated fat intake on CHD incidence or mortality and from 8 studies that evaluate the effect of saturated fat intake on stroke incidence or mortality. The results for CVD include any events for either CHD or stroke. The authors state that “wherever possible, risk estimates from the most fully adjusted models were used in the estimation of the pooled [relative risks].” It is well established that saturated fat intake is associated with increased concentration of serum cholesterol (4), and that serum cholesterol concentrations are associated with CHD and CVD (5). Therefore, serum cholesterol concentrations lie on the causal chain between saturated fat intake and CHD and CVD and to adjust for serum cholesterol concentrations in a meta-analysis will obscure the effect of saturated fat intake on these health outcomes. Yet 7 of the 16 studies included in the meta-analysis of CHD events, and 4 of the 8 studies included in the meta-analysis of stroke events, were adjusted for serum cholesterol concentrations. These studies accounted for nearly half of all CHD and CVD events included in the meta-analyses (see Table 1). Adjustment for serum cholesterol concentrations will inevitably bias the estimates of effect of saturated fat intake toward the null hypothesis. A meta-analysis of nonadjusted data would have produced different (and more informative) results.

Siri-Tarino et al (1) do not mention this as a potential limitation of their study, nor do they calculate estimates of the effect of saturated fat intake on CHD and CVD using unadjusted data from the identified cohort studies. Without this further analysis, the conclusion that, “our meta-analysis showed that there is insufficient evidence from prospective epidemiologic studies to conclude that dietary saturated fat is associated with an increased risk of CHD, stroke, or CVD” is unsupported.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies adjusted for serum cholesterol concentrations</th>
<th>Total no. of studies</th>
<th>Individuals included from studies adjusted for serum cholesterol concentrations</th>
<th>Total no. of individuals</th>
<th>Events from studies adjusted for serum cholesterol concentrations</th>
<th>Total no. of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>7</td>
<td>16</td>
<td>59,428</td>
<td>214,182</td>
<td>3640</td>
<td>8644</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>8</td>
<td>138,769</td>
<td>179,436</td>
<td>1101</td>
<td>2362</td>
</tr>
<tr>
<td>CVD (CHD or stroke)</td>
<td>10</td>
<td>21</td>
<td>188,430</td>
<td>347,747</td>
<td>4641</td>
<td>11,006</td>
</tr>
</tbody>
</table>

1 CHD, coronary heart disease; CVD, cardiovascular disease.

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Peter Scarborough  
Mike Rayner  
Department of Public Health  
University of Oxford  
Old Road Campus  
Headington  
Oxford OX3 7LF  
United Kingdom  
E-mail: peter.scarborough@dphpc.ox.ac.uk

Ineke van Dis  
Research Department  
Netherlands Heart Foundation  
PO Box 300  
2501 CH The Hague  
Netherlands

Kaare Norum  
Department of Nutrition  
Faculty of Medicine  
University of Oslo  
PO Box 1046  
0316 Blindern  
Oslo  
Norway
FBH declared no conflicts of interest. Research support from the National Dairy Council, National Cattleman’s Beef Research. FBH’s work is supported by NIH grant HL60712. RMK receives on the contrary, such a replacement was associated with a slightly fat by carbohydrate was not associated with decreased risk of CHD; a recent pooled analysis of 11 American and European cohort studies (1) suggests that the overall results from the meta-analysis are robust and adjusted risk estimates for intake of saturated fat 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.

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).

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Patty W Siri-Tarino

Children’s Hospital Oakland Research Institute
Oakland, CA

Qi Sun
Frank B Hu

Harvard School of Public Health
Boston, MA

References


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).