Symposium on ‘The challenge of translating nutrition research into public health nutrition’

Session 4: Challenges facing the food industry in innovating for health
Impact on CVD risk of modifying milk fat to decrease intake of SFA and increase intake of cis-MUFA

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Despite the acknowledged benefits of reducing SFA intake few countries within the EU meet recognised targets. Milk and dairy products represent the single largest source of dietary SFA in most countries, yet epidemiological evidence indicates that milk has cardioprotective properties such that simply reducing consumption of dairy foods to meet SFA targets may not be a sound public health approach. The present paper explores the options for replacing some of the SFA in milk fat with cis-MUFA through alteration of the diet of the dairy cow, and the evidence that such changes can improve the indicators for CHD and CVD in general for the consumer. In addition, the outcome of such changes on risk factors for CHD and CVD at the population level is examined in the light of a modelling exercise involving data for eleven EU member states. Given the current and projected costs of health care, the results indicate that urgent consideration should be given to such a strategy.

Abbriviations: EI, energy intake.

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The replacement of SFA by both cis-MUFA and PUFA not only brings about favourable changes in plasma cholesterol pools but may have other beneficial outcomes. Whilst most attention has focused on the hypercholesterolaemic effect of SFA and associated increases in CVD risk, there is now some evidence that high intakes of SFA may also be related to reduced insulin sensitivity, which is a key factor in the development of the metabolic syndrome. In epidemiological studies high intakes of SFA have been associated with a higher risk of impaired glucose tolerance and higher fasting plasma glucose and insulin concentrations. A 3-month intervention study involving 162 healthy subjects given diets rich in SFA (from butter and margarine) or cis-MUFA (from high-oleic sunflower oil) showed that the subjects on the SFA diet had significantly impaired insulin sensitivity (−10%) whilst those on the cis-MUFA diet showed no change (Table 1). Also of note in this study is that additional dietary inclusion of n-3 fatty acids from fish oil had no effect on insulin sensitivity or insulin secretion and the favourable effects of the cis-MUFA diet were not seen in individuals with a high fat intake (>37% energy intake (EI)). Against these benefits there have been concerns that cis-MUFA may also have some anti-cancer benefits. For example, in vitro studies suggest that oleic acid may be involved in inhibiting the growth of breast cancer cells and it is of note that in the Greek cohort of the European Prospective Investigation into Cancer and Nutrition Study the only single dietary characteristic of the Mediterranean diet shown to be significantly protective to a range of cancers was MUFA:SFA, with increased values being beneficial.

Despite the recognised benefits of limiting SFA intake, it has been reported that in the UK men and women currently exceed the Department of Health mean population target for SFA intake (<11% total food energy) by 22% and 20% respectively and indeed few countries within the EU achieve such a target. The proportion of UK children exceeding the target is even greater. Whilst on average UK adults do not achieve the population target for cis-MUFA intake (13% total food energy), deviation from the target is much less than that for SFA, with cis-MUFA intakes of 12.1% and 11.5% EI for men and women respectively. There is, however, still considerable scope for improvement.

### Milk and dairy products as sources of saturates

A comprehensive study across fourteen western European countries has shown that milk and dairy products are key sources of total fat (24%) and the single largest source of SFA (39%) in the UK diet (Fig. 1). More recently, the UK National Diet and Nutrition Survey has confirmed the primary role of milk and dairy products as sources of dietary SFA. Thus, conceptually, a simple strategy to reduce intake of SFA would therefore be to advise that consumption of milk and dairy products should be substantially reduced. This approach, however, would ignore the fact that these foods also supply up to approximately 30% of dietary cis-MUFA in a number of EU countries and are key sources of other key nutrients including vitamin B12 and Ca.

There is also good epidemiological evidence that increased consumption of milk can provide cardiovascular protective benefits. Based on an analysis of ten cohort studies the reported risks in subjects with the highest
intakes of milk, relative to those with the lowest consumption, were 0.87 (95% CI 0.74, 1.03) for CHD and 0.83 (95% CI 0.77, 0.90) for ischaemic stroke\(^*\). Also, the high milk consumers had a reduced incidence of the metabolic syndrome\(^*\). Thus, simply reducing milk and dairy consumption in order to reduce SFA intake is not likely to produce benefits overall.

Manipulating the fatty acid composition of dairy foods to replace some SFA with \textit{cis}-MUFA may therefore prove a valuable means of reducing SFA intake whilst retaining the cardioprotective benefits of milk. This hypothesis is supported by two intervention studies with such modified milk and milk products\(^{23,24}\). A summary of the main findings from these two studies is shown in Table 2. In the first of the studies, which used an 8-week randomised cross-over design with thirty-three men and women, diets containing normal dairy products with 65 and 23% fatty acids as SFA and \textit{cis}-MUFA respectively were compared with diets in which the fat in the dairy products had been modified to contain 50% SFA and 35% \textit{cis}-MUFA\(^{23}\). Broadly similar percentages of SFA and \textit{cis}-MUFA were used in the second study, which involved thirty-one men and women with three sequential intervention periods each of 18 days\(^{24}\). Whilst the latter study used both subjects who were normocholesterolaemic and hypercholesterolaemic\(^*\), it is of note that the control values for total cholesterol and LDL-cholesterol for the subjects in the first of the studies\(^{23}\) were somewhat higher than those for the hypercholesterolaemic group of the second study\(^{24}\). Despite this difference, overall responses were greater in the second study\(^{24}\), which also interestingly reports a more significant \((P>0.01)\) increase in HDL-cholesterol (+22%) in the normocholesterolaemic group than in the hypercholesterolaemic group (+6%; \(P>0.05\)). This finding suggests benefits of the modification in subjects generally regarded as normocholesterolaemic. Serum concentrations of LDL-cholesterol were significantly decreased in both studies whilst HDL-cholesterol was increased only in the second study\(^{24}\), leading to a decreased LDL-cholesterol:HDL-cholesterol. In the second study the dietary manipulation resulted in reduced concentrations of lipoprotein \((a)\), leading the authors to conclude that modifying the milk fat composition has positive effects on both LDL-cholesterol:HDL-cholesterol and lipoprotein \((a)\) concentrations, both of which have been established as risk factors for CHD\(^{24}\). Based on the observed reduction (−4.3%) in total cholesterol, it was proposed that this outcome could lead to a 9% reduction in death from CHD\(^{23}\).

Whilst these two studies do provide support for the concept of modifying milk fatty acid composition in the way described, it is noteworthy that both studies involved small numbers of participants, were of short duration and had only a limited number of outcomes measured with no estimates of insulin sensitivity or vascular function included\(^{23,24}\). More detailed and longer-term studies are urgently needed.

### Modifying milk fatty acid composition

#### Decreasing the SFA content of milk

The main technique used to decrease the SFA content of milk fat is to include supplements of plant oils or oilseeds rich in unsaturated C18 fatty acids in the diet of the dairy cows (for review, see Givens & Shingfield\(^{25}\)). Specifically, this approach can be used to reduce the proportion of SCFA and medium-chain fatty acids (6:0–16:0) and increase the concentrations of long-chain fatty acids in milk\(^{26,27}\). These changes are believed to occur as a result of long-chain fatty acids (C\(≥\)16) inhibiting the \textit{de novo} fatty acid synthesis of short- and medium-chain SFA in the mammary gland, and because lipid supplements increase the amount of long-chain unsaturated fatty acids in plasma available for incorporation into milk fat. Normally, including plant oils (other than palm oil rich in 16:0) in the cows’ diet has little effect on milk fat content of 4.0 but consistently increases 18:0 concentrations at the expense of 16:0\(^{28,29}\). In all cases, inclusion of plant oils and oilseeds in the diet of the cow leads to an unavoidable increase in milk \textit{trans}-18:1 content as a result of extensive lipolysis and biohydrogenation of C18 PUFA in the rumen.

#### Increasing the \textit{cis}-MUFA content of milk

As result of extensive metabolism of dietary unsaturated fatty acids, 18:0 is the most abundant long-chain fatty acid available for incorporation into milk fat. However, the secretion of \textit{cis}-9 18:1 in milk is in excess of mammary 18:1 uptake as a result of the activity of stearoyl-CoA (Δ9) desaturase activity in mammary secretory cells. Desaturation of 18:0 to \textit{cis}-9 18:1 is the predominant precursor–product of the Δ9 desaturase, converting approximately 40% of 18:0 uptake by the mammary gland\(^{29}\). It is therefore feasible to exploit the endogenous desaturation in the mammary gland to enhance the \textit{cis}-MUFA (18:1 in particular) content of milk fat by supplementing diets with

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal dairy products</th>
<th>Modified dairy products</th>
<th>% change</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noakes et al(^{23}) (n 33)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total chol</td>
<td>6.50</td>
<td>6.22</td>
<td>-4.3</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>4.49</td>
<td>4.25</td>
<td>-5.3</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.30</td>
<td>1.28</td>
<td>NS‡</td>
<td></td>
</tr>
<tr>
<td>Total chol:HDL-cholesterol*</td>
<td>5.0</td>
<td>4.9</td>
<td>-2.0</td>
<td></td>
</tr>
<tr>
<td>TAG</td>
<td>1.57</td>
<td>1.54</td>
<td>-1.9</td>
<td>NS‡</td>
</tr>
<tr>
<td>Seidel et al(^{24}) (n 31)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total chol</td>
<td>5.06</td>
<td>5.02</td>
<td>NS‡</td>
<td></td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>2.98</td>
<td>2.66</td>
<td>-10.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>1.45</td>
<td>1.77</td>
<td>+22.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL-cholesterol:HDL-cholesterol</td>
<td>2.22</td>
<td>1.79</td>
<td>-19.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total chol:HDL-cholesterol*</td>
<td>3.49</td>
<td>2.84</td>
<td>-18.6</td>
<td></td>
</tr>
<tr>
<td>Lipoprotein ((a)) (mg/l)</td>
<td>210.4</td>
<td>187.3</td>
<td>-11.0</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

*Not presented by authors.
†Subjects who were normo-and hypercholesterolaemic together.
‡\(P>0.05\).
lipids rich in 18:0, although this approach does not normally alter the cis-9 18:1/18:0 (29). However, feeding plant oils or oilseeds rich in cis-9 18:1 can be used to enhance milk fat cis-9 18:1 content. Care is needed to ensure that as far as possible such material is protected from rumen microbial biohydrogenation, thus providing maximum enhancement of cis-MUFA in milk fat whilst minimising the concentrations of trans-18:1 in milk (25). Supplements of cis-9 18:1 acyl amides (30,31) or high levels of whole cracked rapeseeds in the diet (32) have been shown to dramatically increase the cis-9 18:1 content of milk fat, although this approach can be associated with some reduction in voluntary diet intake and hence milk yield. With a rapeseed diet 18:1 in milk fat increased from 20.1% total fatty acids to 41.3% total fatty acids, although the rather extreme treatment diets used were associated with reduced milk production (32). This approach would therefore need to be balanced by a premium paid for milk of altered fatty acid composition.

Modelling the impact of changes in milk composition on the risk of CVD at EU population level

As part of the Lipgene project (33) a series of studies have been undertaken to produce milk with reduced SFA (typically from 70% total fatty acids to 55% total fatty acids) and increased cis-MUFA (typically from 20% total fatty acids to 32% total fatty acids). The background to this modification has been discussed (34) but essentially it has been achieved by the use of oleic acid-rich rapeseeds in the diet of the dairy cow. A number of models based mainly on changes in the concentration of serum cholesterol pools has been proposed to assess the impact of changes in the amount and composition of dietary lipids on the risk of CHD and CVD in general. Within the Lipgene project (33) these models have been used to develop five approaches to assess the impact at EU population level of reducing SFA and increasing cis-MUFA content of milk fat. Lack of data currently prevents such modelling of the effects on insulin sensitivity or the metabolic syndrome as a whole.

Baseline data employed

The intakes of SFA and cis-MUFA by males and females in eleven EU member states as reported in the TRANSFAIR study (18) were used to represent current baseline intakes. Similarly, data for the percentage of total intake of these fatty acids derived from milk fat were also taken from the same study. These baseline data are summarised in Table 3. The effect on intake of these fatty acids in each of the eleven EU member states was calculated assuming that all milk and dairy products consumed had SFA reduced from 70% total fatty acids to 55% total fatty acids and cis-MUFA increased from 20% total fatty acids to 32% total fatty acids. It was assumed that the total fatty acid content of these foods remained the same as in unmodified products.

Baseline values for the mean total serum cholesterol concentrations in the population of the same eleven member states were taken from a WHO study carried out in 2002 (35) (Table 3) whilst the latest records on annual deaths from CHD, stroke and other CVD-related causes in the selected member states and for the total EU27 (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Republic of Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, UK) were obtained from Allender et al. (35).

### Table 3. Baseline values for SFA, cis-MUFA intakes, the percentage supplied by dairy products and total serum cholesterol in eleven EU member states (adapted from Hulshof et al. (18) and Allender et al. (35))

<table>
<thead>
<tr>
<th>Country</th>
<th>SFA intake</th>
<th>MUFA intake</th>
<th>Total serum cholesterol (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (g/d)</td>
<td>From dairy (%) total</td>
<td>Total (g/d)</td>
</tr>
<tr>
<td>Belgium</td>
<td>45.0</td>
<td>30.2</td>
<td>34.3</td>
</tr>
<tr>
<td>Finland</td>
<td>32.9</td>
<td>44.9</td>
<td>26.7</td>
</tr>
<tr>
<td>France</td>
<td>34.2</td>
<td>56.7</td>
<td>27.3</td>
</tr>
<tr>
<td>Germany</td>
<td>49.0</td>
<td>57.1</td>
<td>25.3</td>
</tr>
<tr>
<td>Greece</td>
<td>22.6</td>
<td>27.4</td>
<td>25.0</td>
</tr>
<tr>
<td>Italy</td>
<td>30.9</td>
<td>47.3</td>
<td>19.4</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>40.0</td>
<td>33.9</td>
<td>37.3</td>
</tr>
<tr>
<td>Portugal</td>
<td>28.1</td>
<td>32.5</td>
<td>29.6</td>
</tr>
<tr>
<td>Spain</td>
<td>30.7</td>
<td>33.9</td>
<td>22.1</td>
</tr>
<tr>
<td>Sweden</td>
<td>37.7</td>
<td>48.5</td>
<td>46.6</td>
</tr>
<tr>
<td>UK</td>
<td>27.1</td>
<td>38.8</td>
<td>29.1</td>
</tr>
<tr>
<td>Overall mean</td>
<td>33.5</td>
<td>41.3</td>
<td>28.0</td>
</tr>
</tbody>
</table>

M, males; F, females.

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Approaches used

Model 1. The reduction in EI from SFA (as % total EI) that would result from the change in milk fat composition was calculated and this value was used in the model of Keys et al.\(^{(36)}\) to predict the absolute reduction in serum total cholesterol (mmol/l) that would result:

\[
\text{change in serum cholesterol concentration (mmol/l)} = 0.031(2\Delta S - \Delta P) + 1.5\Delta C/C,
\]

where \(\Delta S\) is change in % EI from SFA, \(\Delta P\) is change in % EI from PUFA and \(\Delta C\) is change in dietary cholesterol intake. It was assumed that \(\Delta P\) and \(\Delta C\) were zero.

Using the calculated reduction in total cholesterol, the risk of an incidence of CHD was calculated from a risk analysis\(^{(37)}\), which predicts the maximum risk reduction to be 30% per 0.6 mmol/l reduction in serum total cholesterol.

Model 2. The reduction in EI from SFA (as % total EI) was calculated from the model of Keys et al.\(^{(36)}\) and together with the serum cholesterol values reported by Allender et al.\(^{(35)}\) the percentage reduction in serum cholesterol was predicted. To calculate the likely percentage reduction in CHD events the percentage reduction serum cholesterol was then used in the model of Lipids Research Clinics Program\(^{(38)}\), which proposes that a 4% reduction in cholesterol will result in a 9% reduction in risk of developing CHD.

Model 3. The percentage reduction in serum cholesterol was calculated as for model 2 and this value was used in the model of Sacks & Katan\(^{(39)}\) to predict the percentage reduction in risk of a cardiac event. The latter model proposes that the risk of a coronary event is reduced by 2% for each 1% reduction in total cholesterol.

Model 4. The absolute reduction in serum total cholesterol (mmol/l) was estimated from the model of Keys et al.\(^{(36)}\) followed by an estimate of the percentage reduction in death from CHD derived from the data of Lloyd-Williams et al.\(^{(40)}\). The data derived indicate that for men and women a reduction in serum cholesterol of 0.063 mmol/l would result in a 1.4 and 0.89% reduction in CHD deaths respectively. These estimates were used with the EU death rate data\(^{(35)}\) to predict the absolute yearly reduction in deaths from CHD. The absolute yearly reduction in deaths from stroke and other CVD-related causes was estimated using the same reduction in risk as for CHD and the estimates for the whole EU 27 was based on the mean reduction in risk of the eleven selected member states.

Model 5. The model of Mensink et al.\(^{(7)}\), which predicts changes in cholesterol pools from isoenergetic replacement of carbohydrate with SFA, MUFA and PUFA was rearranged to predict the effect on serum total cholesterol: HDL-cholesterol of isoenergetic replacement of SFA with cis-MUFA. Minor balancing with PUFA was included to maintain equal lipid exchanges:

\[
\text{change in serum total cholesterol: HDL-cholesterol} = (\Delta S - 0.003) - (\Delta M + 0.026) - (\Delta P + 0.032),
\]

where \(\Delta S\) is reduction in % EI from SFA, \(\Delta M\) is increase % EI from cis-MUFA and \(\Delta P\) is balancing change in % EI from PUFA.

It has been proposed that changes in serum total cholesterol: HDL-cholesterol have greater prediction power for CHD events than changes in either total cholesterol or LDL-cholesterol\(^{(7)}\). The estimated reduction in this ratio was then used to predict the percentage reduction in CHD events on the basis that a one unit change in total cholesterol: HDL-cholesterol is associated with a 53% change in the risk of myocardial infarction\(^{(41)}\).
provided by model 5 may be more realistic than those from
the other models, although it has been commented that
epidemiological observations often suggest a much greater
effect of dietary fat composition change than the choles-
terol-based model(7).

Table 5 gives the predicted reduction in deaths estimated
by model 4. This model suggests a reduction of about 7900
and 2700 deaths from CHD and stroke per year respectively
in the eleven selected member states, which compares
favourably with predicted respective reductions of 7000 and
2000 for fifteen member states(40); the authors of the latter
study have proposed a slightly more conservative dietary
change(40). Table 5 predicts reductions of approximately
10 500 and 3900 deaths from CHD and stroke per year
respectively in the EU27. Of note is the fact that the predicted
reduction in deaths from CHD in the UK is broadly in line

![Fig. 2. Relationships between (a) total SFA and (b) SFA from milk and dairy products and total serum cholesterol in eleven EU member states. (■), Males; (▲), females; (●), males and females. (a) \(R^2 = 0.51\); (b) \(R^2 = 0.53\). (Adapted from Hulshof et al(18) and Allender et al(80).)
with the reduction that has been predicted for England and Wales if value added tax was to be extended to dietary SFA (42), although interestingly in a commentary on the value added tax idea it was suggested that substituting a modified food for a traditional food may represent a more-consumer-friendly intervention (43).

Ultimately, the direction of any population-directed diet modification will depend on cost–benefit analysis and political will. However, since CVD is currently estimated to cost the EU in the order of €169 × 10^9/year (44) and €192 × 10^9/year (35) and likely to rise because of an ageing population, the economic scope for some dietary change would appear to be large.

### Conclusions

Despite the recognised benefits of reducing SFA intake, the UK target that intake should not on average exceed 11% total food energy (16) is met by few countries within the EU. Whilst milk and dairy products are the single largest source of SFA in most diets, epidemiological evidence suggests cardioprotective and other benefits of milk such that reducing consumption to meet SFA targets may be counterproductive. There is evidence to suggest that modifying the fatty acid content of milk fat by reducing SFA and increasing cis-MUFA will reduce risk factors for CHD, and such changes can now be achieved through alteration of the diet of the dairy cow. Modelling of the effects of such changes at an EU population level points to the potential for substantial reductions in coronary events and deaths, although implementation of such a widespread policy will require major changes in the agro-food industry at both economic and political levels. Given the current and projected costs of health care such a process requires urgent consideration.

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### References


