Effect of changing the amount and type of fat and carbohydrate on insulin sensitivity and cardiovascular risk: the RISCK (Reading, Imperial, Surrey, Cambridge, and Kings) trial1–4

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ABSTRACT

Background: Insulin sensitivity (Si) is improved by weight loss and exercise, but the effects of the replacement of saturated fatty acids (SFAs) with monounsaturated fatty acids (MUFAs) or carbohydrates of high glycemic index (HGI) or low glycemic index (LGI) are uncertain.

Objective: We conducted a dietary intervention trial to study these effects in participants at risk of developing metabolic syndrome.

Design: We conducted a 5-center, parallel design, randomized controlled trial [RISCK (Reading, Imperial, Surrey, Cambridge, and Kings)]. The primary and secondary outcomes were changes in Si (measured by using an intravenous glucose tolerance test) and cardiovascular risk factors. Measurements were made after 4 wk of a high-SFA and HGI (HS/HGI) diet and after a 24-wk intervention with HS/HGI (reference), high-MUFA and HGI (HM/HGI), HM and LGI (HM/LGI), low-fat and HGI (LF/HGI), and LF and LGI (LF/LGI) diets.

Results: We analyzed data for 548 of 720 participants who were randomly assigned to treatment. The median Si was 2.7 × 10⁻³ mL · μU⁻¹ · min⁻¹ (interquartile range: 2.0, 4.2 × 10⁻³ mL · μU⁻¹ · min⁻¹), and unadjusted mean percentage changes (95% CIs) after 24 wk treatment (P = 0.13) were as follows: for the HS/HGI group, −4% (−12.7%, 5.3%); for the HM/HGI group, 2.1% (−5.8%, 10.7%); for the HM/LGI group, −3.5% (−10.6%, 4.3%); for the LF/HGI group, −8.6% (−15.4%, −1.1%); and for the LF/LGI group, 9.9% (2.4%, 18.0%). Total cholesterol (TC), LDL cholesterol, and apolipoprotein B concentrations decreased with SFA reduction. Decreases in TC and LDL-cholesterol concentrations were greater with LGI. Fat reduction lowered HDL cholesterol and apolipoprotein A1 and B concentrations.

Conclusions: This study did not support the hypothesis that isoenergetic replacement of SFAs with MUFAs or carbohydrates has a favorable effect on Si. Lowering GI enhanced reductions in TC and LDL-cholesterol concentrations in subjects, with tentative evidence of improvements in Si in the LF-treatment group. This trial was registered at clinicaltrials.gov as ISRCTN29111298. Am J Clin Nutr 2010;92:748–58.

INTRODUCTION

Weight loss and increased physical activity improve insulin sensitivity (Si) and several of the features of metabolic syndrome (1–3), but the evidence with regard to the type and nature of fat and carbohydrate in the diet is less clear.

Dietary guidelines (4, 5) for cardiovascular disease (CVD) prevention advocate a reduction in saturated fatty acids (SFAs) and trans isomeric fatty acids (TFAs) to ≤10% and 1% of energy, respectively. The replacement of SFAs with cis monounsaturated fatty acids (MUFAs) lowers LDL cholesterol concentrations and may improve Si (6–8); replacement with high–glycemic index (HGI) carbohydrates lowers HDL cholesterol concentrations (9) and might impair Si, although lower GI carbohydrates may prevent the fall in HDL cholesterol concentrations, promote weight loss, and improve Si (10, 11).

The RISCK (Reading, Imperial, Surrey, Cambridge, and Kings) study tested the hypothesis that replacing SFAs with MUFAs or carbohydrates and lowering the GI would improve Si and other CVD risk factors in subjects at risk of developing metabolic syndrome.

SUBJECTS AND METHODS

Subjects

Ethical approval for the RISCK study was obtained from the National Research Ethics Service, and written informed consent was given by participants.

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2 RISCK is an acronym derived from the study center names: Reading, Imperial, Surrey, Cambridge, and Kings.

3 Supported by the UK Food Standards Agency (project NO2031). Foods were supplied by Unilever Food and Health Research Institute (Unilever R&D, Vlaardingen, Netherlands), Cereal Partners UK (Welwyn Garden City, Hertfordshire, United Kingdom), Grampian (Banff, United Kingdom), Weetabix Ltd (Kettering, United Kingdom), and Sainsbury’s Supermarkets Ltd (London, United Kingdom).

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Received December 17, 2009. Accepted for publication July 8, 2010. First published online August 25, 2010; doi: 10.3945/ajcn.2009.29096.

Am J Clin Nutr 2010;92:748–58. Printed in USA. © 2010 American Society for Nutrition
Men and women (age range: 30–70 y), who were recruited from the general population, attended a clinic at the participating centers in a fasting state for measurement of height, weight, waist, seated blood pressure (BP), liver function test, glucose and lipid concentrations, and hematology. A score of ≥4 points was required to qualify for entry into the study according to the following point system: a fasting glucose concentration >5.5 mmol/L or insulin concentration >40 pmol/L = 3 points; body mass index (BMI; in kg/m²) >30 or waist >102 cm for men and >88 cm for women = 2 points; BMI of 25–30 or waist >94 cm for men and >80 cm (women) = 1 point; treated hypertension = 2 points; systolic BP >140 mm Hg = 1 point; diastolic BP >90 mm Hg = 1 point; HDL cholesterol concentration <1.0 mmol/L for men and <1.3 mmol/L for women = 2 points; and serum triacylglycerol concentration >1.3 mmol/L = 1 point. A small remeasurement was given to subjects for participation in the study. Baseline measures were made from August 2004 to April 2006. Exclusion criteria for this study were as follows: a medical history of ischemic heart disease; a >30% 10-y risk of CVD (5); diabetes mellitus; cancer; pancreatitis, cholestatic liver disease, or renal disease; use of lipid-lowering drugs; systemic corticosteroids, androgens, phenytoin, erythromycin, or drugs for regulating hemostasis (excluding aspirin); exposure to any investigational agent ≤30 d before the study; presence of gastrointestinal disorder or use of a drug that is likely to alter gastrointestinal motility or nutrient absorption; a history of substance misuse or alcoholism; a current pregnancy, planned pregnancy, or given birth in the past 12 mo; an unwillingness to follow the protocol or to give informed consent; a weight change of >3 kg in the 2 mo before the study; intake of >1 g eicosapentaenoic and docosahexaenoic acids/d; or smoking ≥20 cigarettes/d.

Study design

A parallel 2 × 2 factorial design compared with a control intervention was used. The primary outcome was a change in Si, and the secondary outcomes were changes in CVD risk factors including lipid profiles and BP associated with metabolic syndrome. Power calculations were based on 113 subjects per group completing the study to give an 80% power to detect a difference in means of 1 (completing the study to give an 80% power to detect a difference). Power calculations were based on 113 subjects per group including lipid profiles and BP associated with metabolic syndrome. The primary outcome was a change in Si, pentaenoic and docosahexaenoic acids/d; or smoking ≥20 cigarettes/d.

The target differential between the HGI and LGI groups was =11 and =13 GI points respectively. Participants were advised that the dietary advice was designed for weight maintenance. For practical reasons, participants and the nutritionist advising on the dietary changes were not blinded to the treatment allocation. The dietary intervention is described in detail elsewhere (12). In brief, dietary targets were successfully achieved by using a food-exchange model where exchangeable fats and carbohydrates in the habitual diet were replaced by study foods with a specific fatty acid profile and measured GI. Specially formulated fat spreads, cooking and baking fats, and mayonnaises were provided by Unilever Food and Health Research Institute (Unilever R&D, Vlaardingen, Netherlands) and pasta or potatoes, breakfast cereals, breads, rice, and biscuits of appropriate GI were provided. Participants were offered sufficient quantities of study foods for their whole household at fortnightly intervals and given counseling and support to maintain dietary compliance. Unweighed 4-d food diaries (3 weekdays and 1 weekend day) were collected to record the habitual diet (before run-in) of subjects, dietary intakes at baseline, and dietary intakes in the third and the final month of the intervention. Nutrient intakes were estimated by using the food-composition database software DINO (Medical Research Council Human Nutrition Research Unit, Elsie Widdowson Laboratory, Cambridge, United Kingdom), which includes the UK food-composition tables (13) and is supplemented with additional data obtained from manufacturers and from in-house analyses and calculations. The database contained GI values for carbohydrate-containing foods (14). The fatty acid composition of the study fats and oils was based on chemical analyses provided by the suppliers (Unilever Best Food, Unilever R&D).

Participants provided a 24-h urine collection at baseline and follow-up for determination of the urinary microalbumin:creatinine ratio before attending the clinic for the intravenous glucose tolerance test (IVGTT). The day before each clinic visit, advice was given to subjects to avoid fatty foods, refrain from consuming alcohol, and engage in exercise, and participants were provided with a choice of light LF evening meals (2 to 3 MJ; <10 g fat) with the same meal provided on each occasion and were advised to consume the type of carbohydrate to which they had been allocated (HGI or LGI) and with vegetables as required. Subjects were asked to consume the meal before 2200 as described in a previous study (15), after which time they fasted overnight and attended the clinic between 0800 and 1100. Weight (in light clothing) and height (without shoes) and seated BP (16) were measured, and an indwelling venous cannula was inserted into the forearm. Fasting blood samples were collected and a short IVGTT was performed (17). Blood samples were separated at ≤2 h and stored at −80°C pending analysis.

IVGTT

Glucose effectiveness (Sg) and Si were estimated with the MINMOD Millennium program (version 6.02; MINMOD Inc, Pasadena, CA). Two fasting blood samples were taken to measure glucose and insulin. A bolus (0.3 g/kg body weight) of 50%
A glucose solution (Phoenix Pharma Ltd, Gloucester, United Kingdom) was infused into one cannula over a 1-min period. Insulin (Novo Nordisk Pharmaceuticals Ltd, West Sussex, United Kingdom) was given as a bolus (30 mU/kg body weight) into the same cannula 20 min after administration of the glucose. Blood samples were collected over a 3-h period (2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 min after the start of the glucose infusion). The area under the plasma insulin curve C20 was computed as an indicator of endogenous insulin secretion (AIRG). Each modeled IVGTT was examined to establish the goodness of fit, and if observed glucose and insulin profiles were atypical and/or the fractional SD for Si was >0.2, the result was excluded from the analysis. The Revised Quantitative Insulin Sensitivity Check Index (RQUICKI) index of Si was calculated from fasting glucose, insulin, and nonesterified fatty acid concentrations (18).

**Analytic methods**

Glucose concentrations were measured with a hexokinase assay (Dimension clinical chemistry system; Dade Behring, Milton Keynes, United Kingdom) (interassay CV: 2.4%), insulin concentrations were measured with an electrochemiluminescence immunoassay (Roche, Indianapolis, IN) on a Roche Elecsys analyzer (Roche) (interassay CVs were 4.5% at 169 pmol/L and 3.6% at 552 pmol/L), and nonesterified fatty acid concentrations were measured with an enzymatic colorimetric assay (Roche Diagnostics, Penzberg, Germany). The following assays were determined in the Department of Clinical Chemistry, King’s College Hospital (London, United Kingdom). Total cholesterol (TC), HDL cholesterol, and triacylglycerol concentrations were measured by using enzymatic assays on a Bayer Advia Model analyzer (Bayer Diagnostics Europe Ltd, Newbury, United Kingdom) by using reagents supplied by the manufacturer (CVs for TC were 1.1%, 1.5%, and 1.0% at 3.9, 5.2 and 5.7 mmol/L, respectively; CVs for HDL cholesterol were 2.2%, 2.1%, and 2.5% at 0.91, 1.39, and 1.95 mmol/L; CVs for triacylglycerol were 2.5% and 1.5% at 1.32 and 2.36 mmol/L, respectively). LDL cholesterol concentrations were calculated by using the Friedwald formula only if fasting plasma triacylglycerol concentrations were <4.49 mmol/L; intercellular adhesion molecule-1 concentrations were measured by using an enzyme-linked immunosorbent assay (R&D Systems Europe, Abingdon, Oxon) (interassay CV: 6%); C-reactive protein high-sensitivity assay concentrations were measured by using reagents (Rapackiego19, 20–150; PZ Cormay, Lublin, Poland) (interassay CV: 6.97%, 3.34%, and 1.23% at concentrations of 0.047, 0.218, and 0.976 mg/dL, respectively; urinary microalbumin concentrations were measured by using reagents (Bayer Diagnostics Europe Ltd) (CVs were 5.3% at 19 mg/L and 2.8% at 56 mg/L; the minimum detectable concentration of urinary albumin was 6 mg/dL); urinary creatinine was measured by using the kinetic Jaffe method with rate blank correction by using reagents (Bayer Diagnostics Europe Ltd) (CVs were 2.1% at 7.1 mmol/L and 1.4% at 17.7 mmol/L). Plasma apolipoprotein B and A1 were measured by immunoprecipitation assays (Randox Laboratories, Crumlin, United Kingdom) on an ILAB-650 analyzer (Instrumentation Laboratory, Warrington, United Kingdom), and the proportion of small dense LDL (sdLDL) was measured by ultracentrifugation on the LDL fraction on an iodixanol gradient (19) at the University of Surrey. Fibrinogen concentrations were measured by the Clauss method, and factor VII coagulant (FVIIc) was measured by a clotting assay as previously described (15) by using an assay where the deficient plasma was depleted in protein S and protein C (20) in the Hemophilia Centre Laboratories St Thomas’s Hospital (London, United Kingdom); interassay CVs were 2% and 3%, respectively. Plasminogen activator inhibitor type 1 (PAI-1) concentrations were measured by using an in-house chromogenic assay (21) at the Institute of Medical Sciences, University of Aberdeen (Aberdeen, United Kingdom) (interassay CV: 8.4%).

**Statistical analyses**

Data were analyzed by using analysis of covariance (ANCOVA) according to a prespecified analysis plan of regressing follow-up
measures against baseline measures with center, ethnicity, baseline waist, baseline age, baseline HDL cholesterol, sex, and diet as covariates. Box Cox regression models were used to select suitable data transformation. Outliers were excluded from the ANCOVA and were defined as points >2.5 times the interquartile range from the median on the transformed scale at baseline, follow-up, or change from baseline. However, inclusion of these points did not materially affect the findings. The unadjusted effect of each diet is expressed as the percentage change from the median value at baseline with 95% CIs. A global test of between-diet differences with 4 df providing a $P < 0.05$ was prespecified as a condition to be met before further between-diet differences were explored. Additional sensitivity analyses were conducted. The effect of weight change as a covariate was examined post hoc. Correlations are presented as Spearman’s $r$.

RESULTS

Study participation

The CONSORT (22) flowchart for recruitment is shown in Figure 1. A total of 549 subjects completed the study, and data from 548 subjects were analyzed (one subject was excluded for statin use in the LF/HGI group). The ethnic mix of subjects was typical of England and predominantly white, with about one-fifth of subjects from ethnic minorities. The details of the participants at screening are shown in Table 1. Few participants were smokers (6.6%); 80% of participants had central obesity; 63% of participants had BP $>130/85$ mm Hg or were receiving medication for BP (17.5%); 25.5% of participants had low HDL cholesterol concentrations ($<1.29$ mmol/L in men and $<1.03$ mmol/L in women); 27.5% of participants had serum triacylglycerol concentrations $>1.7$ mmol/L; and 72% of participants had serum TC concentrations $>5.0$ mmol/L; 47.5% of the subjects had metabolic syndrome according to the criteria of the International Diabetes Federation (23). Their habitual diets provided 35.3%, 13.0%, 11.6%, 1.2%, and 6.2% of energy from total fat, SFAs, MUFAs, TFAs, and polyunsaturated fatty acids.

Body weight was relatively stable but decreased with the LF diets by 0.8 kg (95% CI: 0.4, 1.2 kg) compared with the HM diet (Table 2). This change was correlated with a decrease in reported energy intake ($P = 0.206$; $P < 0.0001$).

The dietary intake of energy from total fat, SFAs, and MUFAs were close to the target values with the HS/HGI reference diet and LF (LF/HGI and LF/LGI) diets (Table 3). With the HM (HM/HGI and HM/LGI) intervention diets the intake of MUFA was slightly lower than planned, and the intake of polyunsaturated fatty acid was slightly higher than planned. The proportion (mean $\pm$ SD) of energy supplied by stearic acid (18:0) with the HS/HGI, HM, and LF diets were $4.0 \pm 0.8\%$, $2.3 \pm 0.7\%$, and $2.1 \pm 0.7\%$ of energy, respectively. The intakes (mean $\pm$ SD) of TFA with the HS/HGI, HM, and LF diets were $1.0 \pm 0.4\%$, $0.6 \pm 0.4\%$, and $0.6 \pm 0.4\%$ of energy, respectively, and were derived primarily from naturally occurring sources (dairy fat, lamb, and beef). The GI was $\approx 8$ GI points lower with the LGI diets than with the HGI diets compared with the target of 11–13 GI points. Further information is provided in Table 3 and elsewhere (12).

Insulin sensitivity

Modeling was successfully achieved for 510 participants out of 544 sets of complete IVGTT data; the number of subjects on whom data were excluded were as follows: 5 subjects in the HS/HGI group, 4 subjects in the HM/HGI group, 12 subjects in the HM/LGI group, 3 subjects in the LF/HGI group, and 10 subjects in the LF/LGI group. The correlations between baseline and follow-up measures of Si, Sg, AIR G, and RQUICKI were 0.70, 0.29, 0.82, and 0.73 in the HS/HGI group. The median Si in the subjects indicated that most subjects were moderately insulin resistant (Table 2).

Unadjusted mean percentage changes (95% CIs) after 24 wk treatment were as follows: $-4\%$ (–12.7%, 5.3%) in the HS/HGI group, $2.1\%$ (–5.8%, 10.7%) in the HM/HGI group; $-3.5\%$ (–10.6%, 4.3%) in the HM/LGI group, $-8.6\%$ (–15.4%, –1.1%) in the LF/HGI group, and 9.9% (2.4%, 18.0%) in the LF/LGI group. A global test of between-diet differences revealed no significant effect of the dietary interventions on Si ($P = 0.13$). Likewise, there were no significant effects of dietary intervention on Sg, AIR G, or the fasting index of Si (RQUICKI) (24). Adjustment for weight change did not alter these statistical conclusions. A post hoc analysis that excluded subjects whose weight changed $>3$ kg ($n = 93$) showed an inverse relation between changes in Si with changes in body weight ($P = -0.112$; $P = 0.019$).

### Table 1

| Characteristic | M (n = 230) | F (n = 318) |
|---------------|------------|------------|
| Age (y)       | $52 \pm 10^2$ | $51 \pm 9$ |
| Postmenopause [n (%)] | — | 167 (53.5) |
| Race or ethnic group [n (%)] | White | 192 (83.5) |
|               | South Asian | 21 (9.1) |
|               | Black | 12 (5.2) |
|               | Other | 5 (2.2) |
| BMI (kg/m$^2$) | 28.3 $\pm$ 3.8 | 28.6 $\pm$ 5.3 |
| Waist circumference (cm) | 102 $\pm$ 10 | 94 $\pm$ 12 |
| BMI $>30$ kg/m$^2$ or waist $>94$ cm (M) or 84 cm (F) [n (%)] | 186 (80.9) | 254 (79.9) |
| Fasting insulin (pmol/L) | 60 $\pm$ 35.7 | 59.5 $\pm$ 31.3 |
| >40 mmol/L [n (%)] | 196 (87.5) | 272 (87.5) |
| Fasting glucose (mmol/L) | 5.5 $\pm$ 0.7 | 5.3 $\pm$ 0.6 |
| >5.6 mmol/L [n (%)] | 97 (42.4) | 107 (33.8) |
| Systolic BP (mm Hg) | 138 $\pm$ 16 | 129 $\pm$ 17 |
| Diastolic BP (mm Hg) | 84 $\pm$ 10 | 80 $\pm$ 9.3 |
| BP $>130/85$ mm Hg or BP medication [n (%)] | 168 (73.0) | 177 (55.7) |
| Total cholesterol (mmol/L) | 5.5 $\pm$ 0.9 | 5.5 $\pm$ 1.0 |
| >5.0 mmol/L [n (%)] | 164 (71.6) | 229 (72.0) |
| HDL cholesterol (mmol/L) | 1.2 $\pm$ 0.3 | 1.5 $\pm$ 0.4 |
| <1.03 mmol/L (M) or <1.29 mmol/L (F) [n (%)] | 49 (21.4) | 90 (28.3) |
| TAG (mmol/L) | 1.4 $\pm$ 0.8 | 1.2 $\pm$ 0.7 |
| >1.7 mmol/L [n (%)] | 75 (32.8) | 75 (23.6) |
| TAG $>1.7$ mmol or HDL cholesterol $<1.03$ mmol/L (M) or 1.29 mmol/L (F) [n (%)] | 97 (42.4) | 136 (42.8) |
| Cigarette smokers [n (%)] | 18 (7.8) | 18 (5.6) |
| BP medication [n (%)] | 44 (19.1) | 51 (16.3) |
| Hormone replacement therapy [n (%)] | — | 35 (11.0) |
| Oral contraceptive [n (%)] | — | 12 (3.8) |
| Thyroxine [n (%)] | 2 (0.9) | 23 (7.2) |

1 BP, blood pressure; TAG, triacylglycerol.
2 Geometric mean $\pm$ SD (all such values).
Inclusion in the analysis plan of a gate-keeping condition \( (P < 0.05) \) in the global test of between-diet differences before further between-diet differences can be explored constrained the false-positive rate at 5%. However, it may have concealed further between diet differences. Because the unadjusted 95\% CIs of the changes in Si after consumption of the LF/HGI and LF/LGI diets did not overlap, an additional ANCOVA analysis tested for evidence of an interaction between the fat content of the diet and GI \( (P = 0.017) \); adjusted for weight change \( P = 0.027 \). In the LF condition, a reduction of the GI of the diet increased Si by 12\% \( (P = 0.016) \); adjusted for weight change \( P = 0.027 \) compared with a 5\% decrease in Si with a reduction in GI in the HM condition \( (P = NS) \). These additional analyses were not adjusted for multiple comparisons. Further additional analyses did not reveal any convincing between-diet differences in any measures of Si, including the type \( (P = 0.7) \) or amount \( (P > 0.18) \) of fat.

**Cardiovascular risk factors**

TC and LDL cholesterol concentrations were significantly lower after consumption of all diets with a reduced intake of SFAs than after consumption of the HS/HGI reference diet \( (P < 0.001 \) and \( P < 0.001; \text{Table 1}) \). Reductions in TC \( (P = 0.01) \) and LDL cholesterol \( (P = 0.03) \) concentrations were greatest in the LGI groups. Apolipoprotein B concentrations differed between treatment groups \( (P < 0.001) \) and were lower with the HM diets and lower still with the LF diets than with the HS/HGI reference diet (Figure 2B). HDL cholesterol concentrations were lower with the LF diets than with the HS/HGI reference diet or HM diets \( (P < 0.001 \) and \( P = 0.002 \), respectively) (Figure 2A). These changes were reflected by similar changes in apolipoprotein A1 concentrations (Figure 2B). There was no difference between the LGI and HGI diets. Only a minority of the subjects showed a preponderance of sdLDL (19\% of the men and 4\% of the women), which was not affected by the dietary intervention. The TC:HDL cholesterol ratio was significantly lower in the HM groups than after consumption of the HS/HGI reference diet \( (P < 0.001 \) and \( P = 0.001; \text{Table 1}) \). Reductions in TC \( (P = 0.01) \) and LDL cholesterol \( (P = 0.03) \) concentrations were greatest in the LGI groups. Apolipoprotein B concentrations differed between treatment groups \( (P < 0.001) \) and were lower with the HM diets and lower still with the LF diets than with the HS/HGI reference diet (Figure 2B). HDL cholesterol concentrations were lower with the LF diets than with the HS/HGI reference diet or HM diets \( (P < 0.001 \) and \( P = 0.002 \), respectively) (Figure 2A). These changes were reflected by similar changes in apolipoprotein A1 concentrations (Figure 2B). There was no difference between the LGI and HGI diets. Only a minority of the subjects showed a preponderance of sdLDL (19\% of the men and 4\% of the women), which was not affected by the dietary intervention. The TC:HDL cholesterol ratio was significantly lower in the HM group than in the LF group \( (P = 0.003) \), but the ratio of apolipoprotein B and A1 was significantly lower in both HM and LF groups \( (P = 0.002 \) and \( P = 0.02 \), respectively) than it was for subjects who consumed the HS/HGI reference diet. BP fell in all groups from baseline to follow-up, but there were no treatment effects (Table 5). Fibrinogen was positively correlated with BMI.
TABLE 3

Changes in energy, source of dietary energy, and carbohydrate quality during the run-in period with a high–saturated fatty acid and a high–glycemic index (HS/HGI) reference diet and at the end of a 24-wk dietary intervention

| Energy (MJ) | Fat (% of energy) | SFA (% of energy) | MUFA (% of energy) | PUFA (% of energy) | Carbohydrates (% of energy) | NSP (g/d) | Glycemic index |
|------------|------------------|------------------|-------------------|-------------------|-------------------------|----------|--------------|
| 8.59 ± 2.11 | 37.9 ± 3.0 | 22.8 (21.2, 23.2) | 6.0 (5.9, 6.2) | 5.5 (5.3, 5.7) | 43.0 ± 3.0 | 17.6 ± 5.8 | 63.5 ± 3.6 |

4 wk run-in on HS/HGI (n = 95)

LPHG (n = 110)

LPHG (n = 110)

| Energy (MJ) | Fat (% of energy) | SFA (% of energy) | MUFA (% of energy) | PUFA (% of energy) | Carbohydrates (% of energy) | NSP (g/d) | Glycemic index |
|------------|------------------|------------------|-------------------|-------------------|-------------------------|----------|--------------|
| 8.59 ± 2.11 | 37.9 ± 3.0 | 22.8 (21.2, 23.2) | 6.0 (5.9, 6.2) | 5.5 (5.3, 5.7) | 43.0 ± 3.0 | 17.6 ± 5.8 | 63.5 ± 3.6 |

2 wk lam in on HS/HGI (n = 95)

After the 24-wk dietary intervention

LPHG (n = 110)

| Energy (MJ) | Fat (% of energy) | SFA (% of energy) | MUFA (% of energy) | PUFA (% of energy) | Carbohydrates (% of energy) | NSP (g/d) | Glycemic index |
|------------|------------------|------------------|-------------------|-------------------|-------------------------|----------|--------------|
| 8.59 ± 2.11 | 37.9 ± 3.0 | 22.8 (21.2, 23.2) | 6.0 (5.9, 6.2) | 5.5 (5.3, 5.7) | 43.0 ± 3.0 | 17.6 ± 5.8 | 63.5 ± 3.6 |

DISCUSSION

Participants without preexisting CVD or type 2 diabetes, but who were likely to be insulin resistant, were recruited into the RISCK trial. The criteria were purposefully set to identify individuals at an increased risk of developing metabolic syndrome but at a lower level than clinical definitions. The dietary manipulations were smaller than many previous studies but represent achievable public health goals. Measurements of food intake and changes in TC predicted by the Keys equation (Figure 3) indicated good compliance to the changes in dietary fat intake. Although the dietary advice aimed to maintain body weight, there was a small decrease (≈1 kg) after the LF than after the HM diets. This is consistent with the measured reduction in energy intake on the LF diet and reflects incomplete compensation for the reduction in food energy from fat. In contrast, there was no evidence of any effect of GI on body weight.

Insulin sensitivity

Two smaller studies that used a glucose suppression test reported favorable effects of MUFA compared with SFA on Si (28, 29). However, these prescribed specific meals were consumed by individuals in a metabolic ward-type regimen. The current study used the IVGTT method, which focuses on the peripheral actions of insulin and is largely unconfounded by the hepatic and gastrointestinal contributions observed in measures such as the oral glucose tolerance test. Our results do not confirm the findings of the KANWU study (7), which also used an IVGTT and a similar dietary prescription to replace SFAs with MUFA for 3 mo. The KANWU study reported a 5.2% difference in TC between diets and noted that Si fell from 4.13 to 3.71 (×10^{-6} \text{mL} \cdot \mu \text{U}^{-1} \cdot \text{min}^{-1}) on the SFA diet, and on the MUFA diet it increased from 4.76 to 4.86 (×10^{-6} \text{mL} \cdot \mu \text{U}^{-1} \cdot \text{min}^{-1}); the difference between treatments was of borderline statistical significance (P = 0.053). Further analysis suggested a significant difference (P = 0.03) in subjects who consumed <37% of energy as fat during the study period, but the justification of conducting this post hoc comparison is questionable (30) because there was no evidence that the treatment effects differed in the different subgroups (P = 0.26; Lars Berglund, personal communication, 2008). A recent small (n = 60) intervention trial that compared an HS diet to an HM or Mediterranean diet, showed no effect on Si measured by homeostatic model assessment of IR or by the euglycemic clamp method in a subset of (30) subjects after 8 wk intervention (31). Findings from LIPGENE, a large (n = 417) pan-European study, concur with that of RISCK.
### TABLE 4
Serum lipid and lipoprotein concentrations at baseline [high–saturated fatty acid and high–glycemic index (HS/HGI) diet] and at follow-up¹

|                      | HS/HGI     | HM/HGI     | HM/LGI     | LF/HGI     | LF/LGI     | P          |
|----------------------|------------|------------|------------|------------|------------|------------|
| **Total cholesterol (mmol/L)²** |            |            |            |            |            | —          |
| Baseline [median (IQR)] | 5.6 (4.8, 6.2) | 5.7 (4.9, 6.3) | 5.6 (5.0, 6.4) | 5.5 (5.0, 6.3) | 5.5 (4.8, 6.3) | —          |
| Follow-up [median (IQR)] | 5.3 (4.9, 6.1) | 5.5 (4.6, 6.1) | 5.4 (4.6, 6.1) | 5.3 (4.6, 5.9) | 5.2 (4.6, 5.8) | —          |
| Percentage change [mean (95% CI)] | -1.2 (-3.1, 0.6) | -3.9 (-5.7, -2.1) | -7.0 (-8.9, -5.0) | -5.7 (-7.4, -4.0) | -6.7 (-8.5, -4.8) | 0.0001³ and 0.0006⁴ |
| **LDL cholesterol (mmol/L)⁵** |            |            |            |            |            | —          |
| Baseline [median (IQR)] | 3.4 (3.0, 4.0) | 3.6 (3.1, 4.1) | 3.6 (3.0, 4.1) | 3.6 (3.1, 4.2) | 3.5 (2.8, 4.1) | —          |
| Follow-up [median (IQR)] | 3.4 (3.0, 4.1) | 3.5 (2.9, 4.1) | 3.3 (2.7, 3.9) | 3.4 (2.8, 3.9) | 3.2 (2.7, 3.7) | —          |
| Percentage change [mean (95% CI)] | -0.6 (-3.4, 2.1) | -5.2 (-7.8, -2.6) | -7.8 (-10.2, -5.5) | -7.0 (-9.2, -4.8) | -7.0 (-9.5, -4.5) | 0.0005⁵ and 0.0015⁶ |
| **Plasma sdLDL (%)⁶** |            |            |            |            |            | —          |
| Baseline [median (IQR)] | 18.8 (12.9, 30.0) | 20.9 (14.2, 31.1) | 20.1 (14.6, 35.5) | 19.2 (12.9, 26.1) | 20.2 (13.2, 31.3) | —          |
| Follow-up [median (IQR)] | 20.6 (13.8, 30.7) | 22 (15.8, 37.9) | 21.8 (14.8, 36.7) | 19.5 (12.9, 30.0) | 19.7 (14.3, 35.2) | —          |
| Percentage change [mean (95% CI)] | +4.3 (-20.0, 10.8) | +9.8 (38.3, 16.0) | +1.9 (-37.7, 7.6) | +5.2 (0.0, 10.6) | +2.4 (-34.3, 8.3) | 0.50⁷ and 0.39⁸ |
| **HDL cholesterol (mmol/L)⁹** |            |            |            |            |            | —          |
| Baseline [median (IQR)] | 1.3 (1.2, 1.5) | 1.3 (1.1, 1.5) | 1.3 (1.1, 1.6) | 1.3 (1.1, 1.6) | 1.3 (1.2, 1.6) | —          |
| Follow-up [median (IQR)] | 1.3 (1.2, 1.4) | 1.3 (1.1, 1.5) | 1.3 (1.1, 1.5) | 1.3 (1.1, 1.5) | 1.2 (1.1, 1.4) | —          |
| Percentage change [mean (95% CI)] | -2.0 (-43.0, 0.3) | -2.7 (-46.0, -0.9) | -4.3 (-63.2, -2.2) | -5.9 (-77.4, -4.0) | -7.2 (-89.5, -5.5) | 0.0004⁹ and 0.0009⁹ |
| **Triacylglycerols (mmol/L)⁶** |            |            |            |            |            | —          |
| Baseline [median (IQR)] | 1.4 (1.0, 1.7) | 1.4 (1.1, 1.8) | 1.5 (1.1, 1.9) | 1.2 (0.9, 1.7) | 1.4 (1.0, 1.7) | —          |
| Follow-up [median (IQR)] | 1.3 (1.0, 1.7) | 1.4 (1.1, 1.8) | 1.3 (0.9, 1.9) | 1.2 (0.9, 1.8) | 1.3 (1.0, 1.8) | —          |
| Percentage change [mean (95% CI)] | -0.6 (-7.1, 6.3) | +1.5 (-37.7, 0.2) | -4.8 (-96.0, -2.2) | +2.9 (-20.8, 0) | +0.3 (-44.5, 2.2) | 0.74⁴ and 0.34⁴ |
| **Total:HDL-cholesterol ratio** |            |            |            |            |            | —          |
| Baseline [median (IQR)] | 4.2 (3.6, 4.8) | 4.4 (3.7, 4.9) | 4.3 (3.5, 5.0) | 4.2 (3.5, 4.8) | 4.2 (3.3, 4.7) | —          |
| Follow-up [median (IQR)] | 4.2 (3.5, 4.8) | 4.3 (3.7, 4.8) | 4.0 (3.3, 4.7) | 4.1 (3.6, 4.8) | 4.1 (3.4, 4.8) | —          |
| Percentage change [mean (95% CI)] | +0.6 (-15.2, 28.0) | -2.4 (-43.0, -0.5) | -2.8 (-47.0, -0.9) | +0.1 (-17.2, 0.0) | -0.8 (-11.1, 2.8) | 0.037⁷ and 0.0043⁷ |

¹ HM/HGI, high–monounsaturated fatty acid and HGI diet; HM/LGI, HM and low–glycemic index diet; LF/HGI, low-fat and HGI diet; LF/LGI, LF and LGI diet; IQR, interquartile range; sdLDL, small dense LDL. Transformations: log(HDL cholesterol), square root(cholesterol), log(triacylglycerol), and square root(total:HDL cholesterol ratio). Outliers were removed. Mean (95% CI) changes were calculated from ANCOVA of transformed follow-up measures on transformed baseline measures adjusted for sex, center, and ethnicity and baseline waist, (log)HDL, and age.

² Adjusted for weight change.

³ n = 83 (HS/HGI), 109 (HM/HGI), 111 (HM/LGI), 112 (LF/HGI), and 120 (LF/LGI).

⁴ From ANCOVA of transformed follow-up measures on transformed baseline measures adjusted for sex, center, and ethnicity and baseline waist, (log)HDL, and age.

⁵ n = 83 (HS/HGI), 108 (HM/HGI), 112 (HM/LGI), 112 (LF/HGI), and 120 (LF/LGI).

⁶ Adjusted for weight change.

⁷ n = 83 (HS/HGI), 108 (HM/HGI), 112 (HM/LGI), 112 (LF/HGI), and 120 (LF/LGI).

⁸ n = 81 (HS/HGI), 108 (HM/HGI), 110 (HM/LGI), 109 (LF/HGI), and 114 (LF/LGI).

⁹ n = 87 (HS/HGI), 107 (HM/HGI), 112 (HM/LGI), 108 (LF/HGI), and 104 (LF/LGI).

⁰ n = 83 (HS/HGI), 110 (HM/HGI), 108 (HM/LGI), 113 (LF/HGI), and 121 (LF/LGI).

"n" indicates the number of participants in each group.
LIPGENE examined the effect of a similar dietary intervention on Si, as measured by IVGTT, in the metabolic syndrome, and showed no significant change in Si after SFA-rich and MUFA-rich diets (32). Taken together, these findings do not provide convincing evidence that the isoenergetic replacement of SFA with MUFA improves Si.

Reports of the effect of GI on Si are inconsistent, and intervention studies have varied widely in their duration, sample size, subject characteristics and health status, intervention diet, and methods for assessing Si (33, 34). We achieved a reduction in GI similar to the range reported in prospective observational studies (35). To achieve a greater reduction in GI, it would have been necessary to replace a substantial amount of added sugar with starch foods with a LGI that would have resulted in other, poorly controlled, dietary changes. In the current study, there was no overall effect between diets on Si as determined by the prespecified statistical analyses. However, additional sensitivity analyses provided tentative evidence to suggest an improvement on the LF/LGI diet than on the LF/HGI diet, but further research is needed to test if this observation is robust.

**Cardiovascular risk factors**

This study confirmed the effect of SFA reduction on TC, LDL cholesterol, and apolipoprotein B concentrations and an effect of fat reduction on lowering HDL cholesterol and apolipoprotein A1 concentrations. The current study did not observe the change in serum triacylglycerol concentrations reported in a previous meta-analysis (36). This was probably because participants were provided with a light LF meal on the day that preceded measurement to exclude the acute effects of variations in fat intake. We previously showed that fasting triacylglycerol concentrations do not differ between an HM diet and a high-carbohydrate diet when dietary antecedent intake is standardized (37) and also showed, by using the same model, that changes in fasting and postprandial triacylglycerol (15) and small dense LDL concentrations occur after an increased intake of long-chain n-3 fatty acids (38). The dietary interventions did not alter the proportion of small dense LDLs, which are believed to be the key proatherogenic lipoprotein particle associated with the dyslipidemia of metabolic syndrome, and this finding is consistent with previous reports (39, 40). In contrast to the conclusions of a meta-analysis (33), the current study showed an additional reduction in TC and LDL cholesterol concentrations with lowering GI. However, lowering GI did not prevent the fall in HDL cholesterol or apolipoprotein A1 concentrations. On the basis of a meta-analysis of prospective cohort studies (41), it was argued that the ratio of TC:HDL cholesterol is twice as informative at predicting CVD risk than is TC. In this context, the LF diets did not influence the ratio, but the ratio was lower on the HM diet than on the HS/HGI reference diet.

Elevated CRP, fibrinogen, and PAI-1 activity independently predict the risk of acute coronary syndromes. In line with previous reports (25, 26), a relation between these risk factors and measures of adiposity was shown. However, the current intervention study was unable to show any effects of the type of fat or GI on hemostatic and inflammatory markers of CVD risk, which suggests that diet composition has little effect on these risk factors. This is consistent with the review of the effects of fat conducted for the WHO/FAO, which could find no probable or convincing evidence to indicate that exchanging SFAs for MUFAs, or carbohydrates for SFAs, influenced CRP concentrations (40). An elevated FVIIc concentration is associated with an increased risk of fatal CHD (42, 43) and associated with fasting triacylglycerol and cholesterol concentrations. The Women’s Health Initiative (44) reported a 4% fall in FVIIc in women consuming an LF diet. However, FVIIc changes rapidly in response to meals high in fat (≤3 h and persisting for ≤24 h) the findings of this RISCK study, where the measurements were preceded by a light LF meal, indicate that there is no chronic change in dietary FVIIc caused by variations in total and monounsaturated fat intake in agreement with a short-term study (37).
|                        | HS/HGI   | HM/HGI   | HM/LGI   | LF/HGI   | LF/LGI   | \(P\) |
|------------------------|----------|----------|----------|----------|----------|------|
| **Systolic BP (mm Hg)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 126 (117, 138) | 126 (115, 137) | 130 (120, 140) | 130 (120, 143) | 128 (118, 138) |      |
| Follow-up [median (IQR)]| 126 (119, 137) | 124 (114, 134) | 128 (116, 136) | 127 (115, 142) | 124 (116, 137) |      |
| Percentage change [mean (95% CI)]| -1.5 (-3.2, 0.3) | -2.0 (-3.6, -0.3) | -2.5 (-4.0, -1.0) | -1.7 (-3.1, -0.4) | -1.5 (-3.0, 0.0) | 0.73\(^7\) and 0.33\(^8\) |
| **Diastolic BP (mm Hg)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 77.8 (71.8, 86.0) | 78 (73.0, 85.0) | 79 (72.5, 84.5) | 81 (74.0, 87.0) | 79.5 (74.0, 87.0) |      |
| Follow-up [median (IQR)]| 79 (71.5, 84.0) | 78.5 (72.0, 84.0) | 78.5 (72.5, 85.0) | 78.5 (71.5, 87.0) | 79.3 (73.5, 85.0) |      |
| Percentage change [mean (95% CI)]| -0.5 (-2.6, 1.5) | -1.6 (-3.3, 0.0) | -0.9 (-2.6, 0.8) | -1.5 (-2.9, -0.1) | -1.7 (-3.1, -0.2) | 0.99\(^7\) and 1.00\(^6\) |
| **Fibrinogen (g/L)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 2.68 (2.28, 3.14) | 2.71 (2.40, 3.10) | 2.55 (2.30, 3.03) | 2.79 (2.28, 3.14) | 2.65 (2.32, 3.11) |      |
| Follow-up [median (IQR)]| 2.66 (2.34, 3.17) | 2.76 (2.37, 3.24) | 2.70 (2.27, 3.13) | 2.82 (2.43, 3.15) | 2.76 (2.40, 3.21) |      |
| Percentage change [mean (95% CI)]| +0.5 (+3.1, 4.1) | +1.6 (+1.2, 4.5) | +1.6 (+1.0, 4.2) | +2.1 (+0.8, 5.0) | +2.4 (+0.3, 5.0) | 0.85\(^7\) and 0.98\(^8\) |
| **CRP (mg/L)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 0.7 (0.16, 2.30) | 0.54 (0.20, 1.90) | 0.4 (0.14, 1.10) | 0.5 (0.10, 1.95) | 0.57 (0.16, 1.90) |      |
| Follow-up [median (IQR)]| 0.95 (0.30, 1.85) | 0.65 (0.20, 2.30) | 0.7 (0.20, 2.00) | 0.7 (0.20, 2.40) | 0.6 (0.20, 1.70) |      |
| Percentage change [mean (95% CI)]| +21.3 (+5.8, 55.2) | +3.8 (+21.4, 35.6) | +36.3 (3.0, 78.2) | +22.4 (+7.6, 60.3) | +8.0 (+13.5, 33.9) | 0.86\(^7\) and 0.90\(^7\) |
| **ICAM-1 (μg/L)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 242 (206, 288) | 240 (218, 283) | 242 (219, 283) | 240 (206, 283) | 247 (207, 284) |      |
| Follow-up [median (IQR)]| 241.4 (215, 287) | 247.6 (214, 278) | 242 (210, 274) | 242 (214, 273) | 249 (214, 280) |      |
| Percentage change [mean (95% CI)]| +0.3 (+3.0, 3.7) | -0.4 (+3.0, 2.3) | +2.2 (+4.9, 0.6) | -0.6 (+3.4, 2.2) | -0.3 (+3.2, 2.6) | 0.59\(^7\) and 0.57\(^7\) |
| **PAI-1 (IU/L)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 17.0 (12.0, 23.4) | 18.0 (13.4, 22.4) | 17.8 (13.6, 23.0) | 16.7 (12.3, 21.0) | 17.9 (13.6, 21.9) |      |
| Follow-up [median (IQR)]| 19.2 (13.0, 24.1) | 19.4 (15.0, 24.8) | 19.6 (14.5, 24.9) | 18 (12.9, 23.4) | 18.4 (14.0, 22.1) |      |
| Percentage change [mean (95% CI)]| +7.5 (+1.1, 16.1) | +11.3 (4.6, 18.0) | +7.0 (0.3, 13.8) | +6.4 (+1.1, 13.8) | +2.2 (+4.8, 9.3) | 0.48\(^7\) and 0.72\(^7\) |
| **FVIIc (%)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 135 (118, 153) | 138 (116, 153) | 133 (110, 150) | 127 (105, 148) | 135 (116, 156) |      |
| Follow-up [median (IQR)]| 127 (108, 150) | 133 (111, 155) | 132 (110, 157) | 127 (101, 143) | 128 (103, 149) |      |
| Percentage change [mean (95% CI)]| -0.9 (-5.0, 3.2) | -0.6 (-4.4, 3.3) | +1.3 (-2.4, 5.0) | +2.8 (+1.2, 6.8) | -2.7 (-6.2, 0.7) | 0.85\(^7\) and 0.98\(^8\) |
| **Microalbumin/creatinine (mg/mmol)**|          |          |          |          |          |      |
| Baseline [median (IQR)]| 1.27 (0.93, 1.82) | 1.17 (0.83, 1.58) | 1.22 (0.80, 1.62) | 1.2 (0.78, 1.62) | 1.13 (0.82, 1.76) |      |
| Follow-up [median (IQR)]| 1.19 (0.78, 1.50) | 1.08 (0.78, 1.58) | 1.11 (0.72, 1.88) | 1.22 (0.80, 1.88) | 1.3 (0.86, 2.00) |      |
| Percentage change [mean (95% CI)]| -1.2 (-2.1, -2.8) | -0.6 (-3.4, 0.7) | -4.3 (-11.8, 3.8) | +0.3 (-8.1, 13.8) | +5.8 (-17.1, 33.8) | 0.0016\(^7\) and 0.017\(^7\) |

\(^5\) HM/HGI, high–monounsaturated fatty acid and HGI diet; HM/LGI, HM and low–glycemic index diet; LF/HGI, low-fat and HGI diet; LF/LGI, LF and LGI diet; ICAM-1, intercellular adhesion molecule-1; PAI-1, plasminogen activator inhibitor type 1; FVIIc, factor VII coagulant. Transformations: log. Outliers were removed. Mean (95% CI) changes were calculated on a transformed scale but expressed as the percentage change from median values at baseline. \(P\) values refer to the global test of significance between the groups. Relevant post hoc analysis results are referred to in Results.

\(^6\) Adjusted for weight change.

\(^7\) From ANCOVA of transformed follow-up measures on transformed baseline measures adjusted for sex, center, ethnicity, and baseline waist circumference, (log)HDL cholesterol, and age.

\(^8\) n = 80 (HS/HGI), 89 (HM/HGI), 111 (HM/LGI), and 108 (LF/LGI).
Conclusions

This study did not support the hypothesis that isoenergetic replacement of SFAs with MUFAs or carbohydrates improves SI but confirms the favorable effect of reductions in SFA on TC:HDL ratio. Lowering GI enhanced the reduction in TC and LDL cholesterol concentrations, with preliminary evidence from additional analyses of an improvement in SI in the LF treatment.

We acknowledge the contributions of the additional RISCK Study Group members—University of Reading: Hannah Farrant (local coordinator); Claire Lawrence, Edel Magee, and Kii Tsoi (research assistants); Darren Cole (database manager); Steve Austin, Hanneke Mfuni, and Kate Guberg (sample analyses of glucose, insulin, and nonesterified fatty acid); Anna Gent, Celia Greenberg, and Caroline Stokes (coding and analyses of dietary data); Mario Siervo and Rosemary Hall (clinicians); Celia Walker (supplementary analyses, Medical Research Council Human Nutrition Research); Imperial College London: Louise Goff (local coordinator); Claire Howard, Namrata Dhopatkar, and Bushra Siddiqui (research assistants); Anne Dornhurst (clinician); Kings College London: Fiona Lewis (local coordinator) Samantha Bowen, L Chen, and Robert Gray (research assistants); Nuala Booth (sample analyses of PAI-1); Rachel Gitau (local coordinator); Katie Newens and Sean Lovegrove (research assistants); Ana Rodriguez-Mateos (sample analyses of plasma fatty acids); University of Reading and University of Surrey: John Wright (clinician); Ana Rodríguez-Mateos (sample analyses of plasma fatty acids); University of Reading and University of Surrey: John Wright (clinician); University of Surrey: Margaret Griffin (local coordinator) and Nicola Harman (lead for lipid subclasses).

The authors’ responsibilities were as follows—SAJ: chief investigator and is the guarantor for this article and had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analyses; JAL: principal investigator; CMW: co-investigator for the University of Reading; BAG: principal investigator for University of Surrey; GSF: principal investigator for the Imperial College London; CSM: scientific co-ordinator; MDC: statistician; LJB: responsible for insulin sensitivity modelling and analysis; and TABS: principal investigator for the Kings College London. The authors and their research groups have a number of links with the food industry. In a personal capacity, GSF is a consultant to Coca-Cola, Premier Foods, and Unilever and TABS has acted as a consultant to Seven Seas and is a member of the Scientific Advisory Committee for the Global Dairy Platform and external scientific review committee of the Malaysian Palm Oil Board, and chairs Cadbury’s Global Nutrition Advisory Panel.

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