Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial[1–3]

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ABSTRACT

Background: Controversies persist concerning the association between intake of dietary saturated fatty acids (SFAs) and cardiovascular disease risk.

Objective: We compared the impact of consuming equal amounts of SFAs from cheese and butter on cardiometabolic risk factors.

Design: In a multicenter, crossover, randomized controlled trial, 92 men and women with abdominal obesity and relatively low HDL-cholesterol concentrations were assigned to sequences of 5 predetermined isoenergetic diets of 4 wk each separated by 4-wk washouts: 2 diets rich in SFAs (12.4–12.6% of calories) from either cheese or butter; a monounsaturated fatty acid (MUFA)–rich diet (SFAs: 5.8%, MUFAs: 19.6%); a polyunsaturated fatty acid (PUFA)–rich diet (SFAs: 5.8%, PUFAs: 11.5%); and a low-fat, high-carbohydrate diet (fat: 25%, SFAs: 5.8%).

Results: Serum HDL-cholesterol concentrations were similar after the cheese and butter diets but were significantly higher than after the carbohydrate diet (+3.8% and +4.7%, respectively; $P < 0.05$ for both). LDL-cholesterol concentrations after the cheese diet were lower than after the butter diet (−3.3%, $P < 0.05$) but were higher than after the carbohydrate (+2.6%), MUFA (+5.3%), and PUFA (+12.3%) diets ($P < 0.05$ for all). LDL-cholesterol concentrations after the butter diet also increased significantly (from +6.1% to +16.2%, $P < 0.05$) compared with the carbohydrate, MUFA, and PUFA diets. The LDL-cholesterol response to treatment was significantly modified by baseline values (P-interaction = 0.02), with the increase in LDL cholesterol being significantly greater with butter than with cheese only among individuals with high baseline LDL-cholesterol concentrations. There was no significant difference between all diets on inflammation markers, blood pressure, and insulin-glucose homeostasis.

Conclusions: The results of our study suggest that the consumption of SFAs from cheese and butter has similar effects on HDL cholesterol but differentially modifies LDL-cholesterol concentrations compared with the effects of carbohydrates, MUFAs, and PUFAs, particularly in individuals with high LDL cholesterol. In contrast, SFAs from either cheese or butter have no significant effects on several other nonlipid cardiometabolic risk factors. This trial was registered at clinicaltrials.gov as NCT02106208. *Am J Clin Nutr* 2017;105:800–9.

Keywords: cardiovascular risk factors, CVD, dairy products, men and women, randomized crossover controlled trial, SFA

INTRODUCTION

Most dietary guidelines have advocated for a restriction of dietary SFAs for the optimal management of cardiovascular health (1, 2). However, the association between SFAs and risk of cardiovascular disease (CVD)[12] remains controversial. On the one hand, several meta-analyses of observational studies have shown that self-reported intakes of SFAs were not associated with increased risk of all-cause mortality, CVD, coronary artery disease (CAD), or ischemic stroke (3, 4). In contrast, a systematic review of early randomized controlled trials (RCT) has shown a small but significant reduction in CVD risk when dietary SFAs have been substituted with PUFAs (5).

The controversy surrounding SFAs and CVD risk has been further fueled by data from studies that have shown that dietary SFAs may have different associations with CVD risk depending on the food source of SFA. For example, a 5% increase in energy from dairy SFAs in the Multi-Ethnic Study of Atherosclerosis has been associated with a 38% lower CVD risk, whereas a 5% increase in energy from meat SFAs was shown to predict a 69%

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[3] Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[12] Abbreviations used: apo B, apolipoprotein B; CAD, coronary artery disease; CVD, cardiovascular disease; INAF, Institute of Nutrition and Functional Foods; ITT, intent-to-treat; RCFFN, Richardson Center for Functional Foods and Nutraceuticals; RCT, randomized controlled trial.

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higher CVD risk (6). The food matrix may also modify the impact of SFAs on CVD risk factors. In a meta-analysis of RCTs, de Goede et al. (7) have shown that, for similar SFA intakes and ratios of PUFAs to SFAs, the consumption of hard cheese reduced LDL cholesterol and HDL cholesterol compared with the effect of butter.

Results from the meta-analysis by de Goede et al. (7) were limited in scope because they were based on data from only 5 RCTs, each of which had relatively small sample sizes (n = 14–49). All studies were conducted in Europe (8–11) or in Australia (12). To our knowledge, no previous study has compared the effects of SFAs from cheese and butter on cardiometabolic risk to those of MUFAs or PUFAs in a North American context. Finally, the majority of the available RCTs have focused on lipid risk factors. Therefore, there has been limited information regarding the impact of SFAs from different sources on nonlipid cardiometabolic risk factors.

The primary objective of this multicenter, randomized, crossover, controlled-consumption study was to compare the impact of SFAs from different dairy food sources, namely cheese and butter, on plasma lipid concentrations, blood pressure, and other cardiometabolic risk factors including factors that are related to glucose-insulin homeostasis and inflammation. As a secondary objective, we compared the impact of consuming SFAs from different dairy sources to that of other fat sources, including MUFAs and PUFAs, on cardiometabolic risk. On the basis of the available evidence, we hypothesized that the cheese matrix would attenuate the cardiometabolic effects associated with the consumption of SFAs.

METHODS

Participants

This study was undertaken as a multicenter RCT that involved the following 2 Canadian research centers: the Institute of Nutrition and Functional Foods (INAF) in Quebec City and the Richardson Center for Functional Foods and Nutraceuticals (RCFFN) in Winnipeg. Recruitment took place between May 2014 and May 2015. Advertisements were published in newspapers, circulated in local hospitals, and displayed on notice boards at companies near the university campuses. Invitations were also sent via mailing lists that were available in both centers. To be eligible, participants had to be 18–65 y old, have a waist circumference ≥94 and ≥80 cm for men and women, respectively, and have HDL-cholesterol concentrations below the age- and sex-specific 75th percentiles (≤1.34 and ≤1.53 mmol/L for men and women, respectively) to exclude individuals with high HDL-cholesterol concentrations, which was the primary study outcome. The study originally set out to recruit individuals on the basis of a high waist circumference and serum triglyceride concentration >1.7 mmol/L. However, this combination of inclusion criteria yielded an extremely low recruitment rate. The triglyceride criterion was modified to the aforementioned HDL-cholesterol criterion 3 mo into the study to facilitate recruitment. Participants had to have stable body weight (±2.5 kg) ≥6 mo before their inclusion in the trial. Menopausal status was defined as being without regular menses ≥1 y. Exclusion criteria were as follows: a history of CVD, type 2 diabetes, or monogenic dyslipidemia; the use of medications for hypertension, hyperlipidemia, or glycemic control; uncontrolled endocrine disorder such as hypothyroidism or hyperthyroidism; smoking; a Framingham-calculated CAD risk score >20%; any food allergies or aversion to foods that were included in the menu; particular nutritional habits such as vegetarianism; and women with menstrual irregularities including those who were experiencing perimenopause. The use of an anti-inflammatory drug was prohibited during the entire study period including the 4-wk preintervention period and washout periods. Other medications were allowed as long as the use and dosage had been stable over the 1 y that preceded the recruitment of the participants. The study protocol was thoroughly explained during the screening process, and written consent was obtained from all participants before undertaking the dietary phases. The study protocol was approved by local ethical boards and was registered on 4 April 2014 at clinicaltrials.gov at NCT02106208.

Experimental diet composition and study design

We used a single-blind crossover study design in which participants were randomly assigned to 8 predetermined sequences of the following 5 treatments: *1*) a diet that was rich in SFAs from cheese, *2*) a diet that was rich in SFAs from butter, *3*) a diet that was rich in MUFAs, *4*) a diet that was rich in PUFAs, and *5*) a high-carbohydrate, low-fat diet. The SFA content was matched in the cheese and butter diets. In the other diets, MUFAs, PUFAs, and carbohydrates replaced SFAs from the cheese and butter diets through dietary manipulations. Specifically, proteins from cheese in the cheese diet were replaced by increasing the serving sizes of meat and eggs in the other 4 diets. The grams of fat from cheese in the cheese diet were replaced by corresponding amounts of butter fat, refined olive oil, and corn oil in the butter, MUFA, and PUFA diets respectively. Carbohydrates from foods (vegetables, fruit, and grains) as well from added sugars (honey, sugar and brown sugar, jam, maple syrup, and 100% fruit juice) were substituted for fats in the 4 high-fat diets (cheese, butter, MUFA, and PUFA diets). Vegetables, fruit, and grain products with low-fiber contents were chosen in the carbohydrate diet to balance fiber intake across all diets. The identified foods and added sugars represented, on average, 77% and 23% of added carbohydrates, respectively, in the carbohydrate diet. More specifically, the carbohydrate diet provided a mean of 10.0 g added sugars (per 2500 kcal/d) compared with the amount in the cheese diet, whereas the remaining extra carbohydrates came from foods.

Diets were identical in terms of energy, protein, cholesterol, sodium, and fiber contents. Calcium and potassium contents were higher in the cheese diet than in the other 4 experimental diets (**Table 1**). Each of the 5 treatment phases had a 4-wk duration and was followed by a washout period ≥24 d. Three meals and 1 snack were provided each day to participants on the basis of a 7-d rotating menu, which was reproducible for the 5 diets and similar across the 2 participating research centers. The experimental diets were developed with the use of the Nutritional Database System for Research (2011; Nutrition Coordinating Center). Dietetic technicians prepared all recipes and meals in the metabolic kitchen of participating centers. Diets were provided under isoenergetic conditions to maintain a constant body weight. Energy needs for each participant were estimated with the use of validated equations (13) as well as from values that

TABLE 1
Nutritional composition of the 5 predetermined experimental diets[1]

	Cheese	Butter	MUFA	PUFA	CHO
Energy,[2] kcal	2654 ± 567	2615 ± 537	2647 ± 550	2649 ± 576	2618 ± 561
Cheese, g/2500 kcal	90.0[3]	0	0	0	0
Butter, g/2500 kcal	0	48.9	0	0	0
Lipids, %	32.0	32.0	32.0	32.0	25.0
SFAs	12.6	12.4	5.8	5.8	5.8
MUFAs	12.5	12.3	19.6	12.6	12.6
PUFAs	4.8	4.8	4.8	11.5	4.8
CHOs, %	51.9	52.0	51.9	51.9	58.9
Protein, %	16.0	16.0	16.0	16.0	16.0
Calcium, mg/2500 kcal	1261.0	811.1	812.2	811.7	841.6
Total fibers, g/2500 kcal	30.7	30.6	30.6	30.6	30.5
Cholesterol, mg/2500 kcal	272.1	272.4	271.5	272.2	272.4
Sodium, mg/2500 kcal	2482	2480	2479	2479	2485

[1] For the comparison between treatments, $P = 0.82$ (mixed models). Butter and cheese: $n = 77$; MUFAs: $n = 74$; PUFAs: $n = 76$; and CHO: $n = 72$. CHO, carbohydrate.
[2] All values are means ± SDs.
[3] Mean (all such values).

were estimated with the use of a validated, quantitative, web-based food-frequency questionnaire that was completed before the beginning of the trial (14). During each dietary phase, participants were asked to come to the INAF or RCFFN ≥3 times/wk to pick up the meals and snacks. Subjects were also encouraged, whenever possible, to consume either breakfast or lunch on site every weekday under staff supervision. Subjects were instructed to consume all of the food provided, and only that food, while limiting the consumption of caffeinated beverages and sugar-free beverages to 2 beverages/d. A discretionary amount of 0% fat fluid milk (105 g) was provided to subjects weekly if requested. Alcohol intake was not allowed 2 d before the beginning of the study and during each dietary phase. Body weight was monitored continuously throughout each dietary phase, and food provision was adjusted when subjects body weight fluctuated >2 kg over 1 wk. Subjects were instructed to maintain their usual physical activities except for the 4 d that preceded blood sampling at the various stages of the study, during which subjects were asked not to engage in any form of vigorous physical activity. Subjects could not be blinded to the cheese diet but were blinded to the other 4 diets.

Compliance

Compliance to treatments was assessed via checklists that were filled out by participants on a weekly basis, which allowed for the identification of foods that were consumed and foods that were not consumed. Checklists provided information on beverage intake as well as on current medication use. Participants were asked to notify the coordinator who was in charge of the project from both centers before starting any new medication. Compliance was assessed during each dietary phase. Thus, a subject may have been compliant in some phases but not in others. It was decided a priori that we would exclude from the analyses all data points that were collected during a treatment phase for which the self-reported compliance was <80%.

Risk-factor assessment

Body weight, together with waist and hip circumferences, were measured according to standardized procedures throughout the study (15). The mean of the 2 postdiet values was used for the calculation of postdiet BMI. Body fat and composition were assessed with the use of dual-energy X-ray absorptiometry (GE Healthcare) at the end of each dietary phase. Systolic and diastolic blood pressures were determined at screening, beginning, and the end of each dietary phase from the mean of 3 consecutive measurements that were taken 10 min apart in the sitting position with the use of an automated blood pressure monitor (Digital BPM HEM-907XL model; Omron).

Analyses of cardiometabolic risk factors were performed on 12-h fasting blood samples that were collected from the antecubital vein. All cardiometabolic risk factors were measured twice on consecutive days at the end of each dietary phase, and the mean of the 2 measurements was used in all analyses. Treatment-specific baseline values were measured once. Laboratory analyses were carried out with staff blinded to study treatments.

Serum total cholesterol, triglyceride, and HDL-cholesterol concentrations were assessed with the use of a Roche/Hitachi Modular system (Roche Diagnostics) according to the manufacturer's specifications and with the use of proprietary reagents. Serum LDL-cholesterol concentrations were calculated with the use of the Friedewald equation except in 2 subjects who had serum triglyceride concentrations >4.5 mmol/L on 4 occasions, in which cases, LDL cholesterol was considered to be missing. Plasma total apolipoprotein B (apo B) concentrations were measured with the use of the a commercial ELISA kit (A70102; Alerchek). Serum high-sensitivity C-reactive protein concentrations were determined with the use of the Behring Latex-Enhanced highly sensitive assay on a Behring Nephelometer BN-100 (Behring Diagnostic) and the calibrators (N Rheumatology Standard SL) that were provided by the manufacturer as described previously (16). High-sensitivity C-reactive protein concentrations were considered to be missing when the mean of the 2 consecutive postdiet values was >10 mg/L. Adiponectin was measured with the use of a commercial ELISA kit for the human form (K1001-1; B-Bridge International). Fasting blood glucose concentrations were examined with the use of colorimetry, whereas insulin concentrations were tested with the use of electrochemiluminescence (Roche Diagnostics). Finally, the HOMA-IR was calculated with the use of the formula that was developed by Matthews et al. (17).

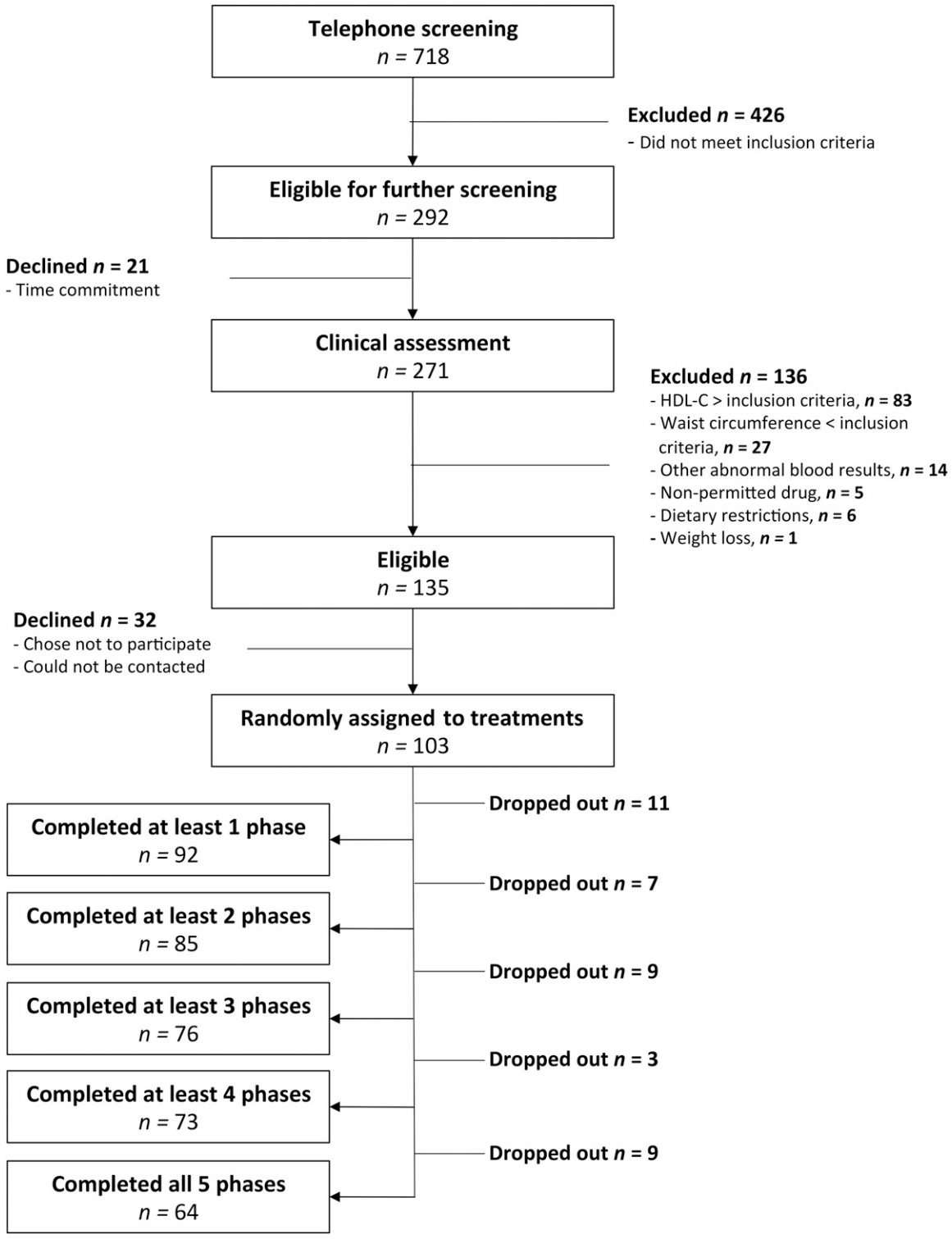

FIGURE 1 Flowchart diagram. Of 135 eligible subjects, 103 individuals were randomly assigned. The dropout rate was 37.9% (39 of 103 subjects who were randomly assigned). Reasons for dropping out were as follows: job, study, family, or travel constraints ($n = 12$); lost to follow-up ($n = 6$); loss of interest ($n = 5$); the protocol was too demanding ($n = 5$); diet issues (did not like the food; $n = 5$); health problems that were unrelated to the study protocol ($n = 3$); pregnancies ($n = 2$); and medical constraint ($n = 1$). A total of 92 subjects completed ≥1 phase, whereas 64 subjects completed all 5 phases. HDL-C, HDL cholesterol.

Sample-size calculations

The change in HDL cholesterol after cheese compared with after butter was considered as the primary analysis for a priori sample-size calculations. Accordingly, it was determined that a sample size of $n = 70$ would allow for the detection of a 6.3% between-diet difference in plasma HDL-cholesterol concentrations with a power of 90% ($P = 0.05$). A dropout rate of 20% was projected on the basis of our recent experience in a similarly

designed, multicenter, crossover consumption study that comprised 5 diets, each of which were separated by a 4-wk washout (18). The required sample size of $n = 90$ was slightly exceeded during recruitment.

Statistical analyses

Differences in study outcomes in treatments (postdiet values) were assessed with the use of mixed models for repeated measures in SAS software (v9.4; SAS Institute Inc.) with the treatment, sex, center, and sequence of treatments as fixed effects and subjects as a random effect. A pairwise comparison of treatments was examined only when the overall P value for the main treatment effect in the mixed models was <0.05. The Holm-Bonferroni procedure was used to adjust for multiple comparisons of the various treatments (19). This sequential step-down approach is considered one of the best-known techniques to control for a family-wise error rate. The method is similar to the classical Bonferroni correction. Specifically, the method ensures that the probability of ≥ 1 false discovery under the null hypothesis is fixed at the specified α level. However, the Holm-Bonferroni correction offers more statistical power without requiring any further assumption. Briefly, P values of the tests under consideration are rank ordered so that $P_1 \leq P_2 \leq \ldots \leq P_k$, where k is the number of tests. Original P values are sequentially adjusted; e.g., the adjusted value of P_1 is equal to k times the original value of P_1, and the adjusted value of P_2 is the maximum between the adjusted value of P_1 and $(k - 1)$ times the original value of P_2. Adjusted P values are evaluated against the criterion of $\alpha = 0.05$. The multiple comparisons under consideration were set a priori as follows: cheese compared with butter; cheese compared with carbohydrates, MUFAs, and PUFAs; and butter compared with carbohydrates, MUFAs, and PUFAs. MUFA, PUFA, and carbohydrate comparisons were not considered because they were not part of the primary aim of the study. With the use of a most parsimonious modeling approach, potential confounders of the changes in cardiometabolic risk factors with treatment, including baseline values of the selected outcome, center, sequence of treatments, sex, age, BMI, waist:hip ratio, and ethnicity and their interaction with treatment, were included in the final mixed models only when they were shown to be significant at $P < 0.05$. The normality in the distribution of all study outcomes was considered, and data were log transformed when required. In the primary analyses, multiple imputations of missing data were not used because mixed models have been shown to be robust even when a significant proportion of data are missing at random (20). However, data were also analyzed with the use of an intent-to-treat (ITT) approach with multiple imputation of missing data. More detailed information on how this analysis was conducted and the results are presented in **Supplemental Table 1**.

RESULTS

Figure 1 presents the study flowchart. Consumption by participants was initiated on 9 July 2014, and all participants completed the intervention on 18 February 2016. Of 135 eligible men and women, a total of 103 individuals were randomly assigned to the treatment sequences, 92 subjects completed ≥ 1 treatment phase, and 64 subjects completed all 5 treatments. Of 39 participants who dropped out, 20 individuals were from the INAF, and 19 individuals were from the RCFFN. The main reasons for dropping out were as follows: job, study, family, or travel constraints ($n = 12$); lost to follow-up or a loss of interest ($n = 11$); the dietary protocol was too demanding or because of diet issues ($n = 10$); and medical constraints, pregnancies, or other health problems ($n = 6$). A total of 14 treatment-specific data from 8 participants at the RCFFN with compliance $<80\%$ were excluded as per the eligibility criteria for analyses. The self-reported compliance of all participants at the INAF was $>80\%$ for all dietary phases. Characteristics at the screening of the 92 subjects who were included in the analyses are shown in **Table 2**. Participants from the INAF and RCFFN had a similarly low 10-y CVD Framingham risk score at baseline.

The mean $\pm$ SD self-reported compliance to diets during each treatment phase on the basis of food-consumption checklists was high (98.7% $\pm$ 2.4%) and was similar between treatments ($P = 0.83$; Kruskal-Wallis test; data not shown) after the exclusion of data from noncompliant subjects. Self-reported compliance was significantly different between centers, although the difference was marginal [INAF: 99.4% $\pm$ 1.2%; RCFFN: 97.5% $\pm$ 3.4% ($P < 0.0001$; Kruskal-Wallis test)]. The mean duration of each dietary phase was 27.9 $\pm$ 0.9 d and was similar in treatments ($P = 0.60$; Kruskal-Wallis test). The median washout time between consecutive treatments was 33 d. No difference was observed between diets in terms of the frequency of self-reported, nonserious adverse events (**Supplemental Table 2**).

Table 3 presents the anthropometric and cardiometabolic risk profiles of participants after each diet. Waist circumference, BMI, and body fat were stable throughout the experiment, which reflected the isoenergetic nature of the trial. Serum HDL-cholesterol concentrations were similar after the cheese and butter diets but were significantly higher (+3.8% and +4.7%, respectively; $P < 0.05$ for both) than after the carbohydrate diet. After the cheese diet, LDL-cholesterol concentrations were significantly lower (−3.3%; $P < 0.05$) than after the butter diet but were higher (+2.6%, +5.3%, and +12.3%; $P < 0.05$ for all) than after carbohydrate, MUFA, and PUFA diets, respectively. LDL-cholesterol concentrations after the butter diet were significantly higher (+6.1%, +8.9%, and +16.2%; $P < 0.05$ for all) than after the carbohydrate, MUFA, and PUFA diets, respectively. The baseline LDL-cholesterol concentration significantly modified the LDL-cholesterol response to treatment (P-interaction = 0.02). As shown in **Figure 2**, the difference in LDL cholesterol between cheese and butter diets was significant in subjects with high baseline LDL cholesterol but not in those with lower baseline LDL cholesterol irrespective of the comparator nutrient. No such interaction was observed for other cardiometabolic risk factors.

Cheese led to higher serum triglyceride concentrations (+5.1% and +10.0%; $P < 0.05$ for both) compared with the effects of butter and PUFAs, respectively, but not compared with the effects of MUFAs or carbohydrates. Butter was associated with reduced serum triglycerides (−6.8%; $P < 0.05$) compared with the effect of carbohydrates but not compared with the effects of MUFAs and PUFAs. There was no difference between cheese and butter in terms of apo B concentrations and the cholesterol:HDL-cholesterol

TABLE 2
Characteristics at screening of subjects who completed ≥1 diet (n = 92)[1]

	INAF (n = 57)	RCFFN (n = 35)	P
Ethnicity, n (%)			<0.0001
Caucasian	55 (96.5)	11 (31.4)	—
Asian	0 (0)	10 (20.0)	—
African/African American	0 (0)	7 (28.6)	—
Hispanic	1 (1.8)	6 (17.1)	—
Other	1 (1.8)	1 (2.9)	—
Women, n (%)	32 (56.1)	17 (48.6)	0.48
Age, y	40.6 ± 13.6[2]	36.8 ± 13.3	0.19
Body weight, kg	86.5 ± 21.0	89.5 ± 19.8	0.51
BMI,[3] kg/m^2	30.3 ± 6.3	31.6 ± 5.6	0.23
Waist circumference, cm	100.6 ± 14.1	103.8 ± 13.9	0.29
Plasma lipids, mmol/L			
Total cholesterol	5.18 ± 1.00	4.70 ± 0.81	0.02
LDL cholesterol[4]	3.22 ± 0.84	2.79 ± 0.73	0.01
HDL cholesterol			
Women	1.30 ± 0.17	1.26 ± 0.21	0.56
Men	1.10 ± 0.19	1.04 ± 0.15	0.24
TG[3]	1.50 ± 0.83	1.64 ± 1.17	0.68
Total cholesterol:HDL cholesterol	4.37 ± 1.01	4.28 ± 0.89	0.67
Glucose,[3] mmol/L	5.21 ± 0.47	5.09 ± 0.54	0.21
Blood pressure, mm Hg			
Systolic	113.1 ± 12.0	115.6 ± 17.0	0.45
Diastolic	69.4 ± 10.1	77.1 ± 10.8	0.0008
10-y Framingham risk score, %	3.9 ± 4.3	3.5 ± 3.7	0.53

[1] P values were determined with the use of a chi-square test for categorical variables and a Student's t test for continuous variables. INAF, Institute of Nutrition and Functional Foods; RCFFN, Richardson Center on Functional Foods and Nutraceuticals; TG, triglyceride.
[2] Mean ± SD (all such values).
[3] Analyses were performed on log-transformed data.
[4] n = 56 for the INAF because of one missing value.

ratio. However, both diets significantly increased apo B and the cholesterol:HDL-cholesterol ratio compared with the effects of the MUFA and PUFA diets. Finally, there was no significant difference in blood pressure, inflammation markers, and indexes of glucose-insulin homeostasis across the experimental diets. There was also no significant interaction between treatment and sex or adiposity in the prediction of the response to diets for any cardiometabolic risk factors. As shown in Supplemental Table 1, results from the ITT and multiple imputation analysis and those from the per protocol analysis were similar with a few minor exceptions. Specifically, the ITT analysis revealed no significant treatment effect on postintervention HDL cholesterol, and there was no significant difference in postintervention LDL-cholesterol concentrations between cheese and carbohydrate diets.

Figure 3 shows differences in observed values compared with values that were predicted on the basis of accepted equations (21) for changes in blood lipids and apo B when carbohydrates were replaced isoenergetically by SFAs from either cheese or butter. In the absence of a food-matrix effect, differences between observed and predicted changes should have been equal to zero. Observed LDL-cholesterol and HDL-cholesterol concentrations were significantly lower than predicted values when carbohydrates (6.8% of energy) were replaced by SFAs from cheese. This was not the case for butter. The replacement of carbohydrates by SFAs from cheese led to higher serum triglyceride concentrations than were predicted, whereas the replacement of carbohydrates by SFAs from butter led to higher-than-predicted apo B concentrations.

DISCUSSION

To our knowledge, this large, randomized, and carefully controlled consumption study provides new perspectives relative to the effects of dietary SFAs on cardiometabolic risk. One unique methodologic aspect of this investigation was that SFAs from cheese and butter were compared with carbohydrates but also with other control nutrients (i.e., MUFAs and PUFAs). First, the isocaloric replacement of carbohydrates by SFAs from both cheese and butter increased serum HDL-cholesterol concentrations. Although the changes in HDL cholesterol with cheese and butter were similar in magnitude, values that were recorded after the cheese diet were significantly lower than those that were predicted with the use of established equations (21). The different effects of SFAs from cheese and butter on LDL cholesterol were amplified in men and women with high baseline LDL-cholesterol concentrations irrespective of the comparator nutrient. Finally, SFAs from cheese and butter had no effect on several nonlipid cardiometabolic risk factors compared with the effects of carbohydrates, MUFAs, and PUFAs.

Only a few RCTs have compared the effects of SFAs from cheese and butter on LDL-cholesterol and HDL-cholesterol concentrations (8–12). All of the studies have used a crossover design with sample sizes that ranged from n = 14 to n = 49, and

TABLE 3
Anthropometric measures, plasma lipid profiles, and nonlipid cardiovascular disease risk factors at the end of each dietary intervention in 92 subjects[1]

	Cheese	Butter	MUFA	PUFA	CHO	*P*-between diets
Waist circumference, cm	100.8 ± 14.4	101.1 ± 14.0	100.3 ± 14.0	100.7 ± 14.5	100.6 ± 13.0	0.29
BMI,[2] kg/m^2	30.6 ± 6.2	30.6 ± 6.2	30.4 ± 6.1	30.6 ± 6.3	30.3 ± 5.5	0.93
Body fat, kg	32.6 ± 11.7	33.2 ± 11.6	32.5 ± 11.4	33.2 ± 11.9	31.9 ± 10.6	0.14
Total cholesterol, mmol/L	5.00 ± 0.94	5.10 ± 0.95	4.82 ± 0.89[3,4]	4.60 ± 0.81[3,4]	4.89 ± 0.92[3,4]	<0.0001
LDL cholesterol, mmol/L	3.19 ± 0.81	3.30 ± 0.84[3]	3.03 ± 0.78[3,4]	2.84 ± 0.69[3,4]	3.11 ± 0.79[3,4]	<0.0001
HDL cholesterol, mmol/L	1.10 ± 0.19	1.11 ± 0.21	1.10 ± 0.19	1.10 ± 0.20	1.06 ± 0.19[3,4]	0.0051
TG,[2] mmol/L	1.43 ± 0.70	1.36 ± 0.73[3]	1.38 ± 0.67	1.30 ± 0.62[3]	1.46 ± 0.71[4]	0.0007
Cholesterol:HDL cholesterol	4.67 ± 1.04	4.73 ± 1.18	4.50 ± 1.08[3,4]	4.28 ± 1.01[3,4]	4.71 ± 1.08	<0.0001
apo B, g/L	1.72 ± 0.50	1.74 ± 0.58	1.65 ± 0.50[3,4]	1.53 ± 0.50[3,4]	1.68 ± 0.50[4]	<0.0001
hs-CRP,[2] mg/L	2.82 ± 2.82	2.48 ± 2.40	2.15 ± 2.03	2.56 ± 2.53	2.53 ± 2.38	0.82
Adiponectin,[2] μg/L	7.01 ± 3.14	7.07 ± 2.91	7.05 ± 3.00	6.95 ± 2.89	6.86 ± 2.83	0.14
SBP, mm Hg	109.9 ± 13.4	109.0 ± 12.4	111.4 ± 12.9	109.9 ± 13.0	109.8 ± 12.6	0.20
DBP, mm Hg	70.0 ± 10.4	68.9 ± 9.8	68.7 ± 9.8	68.8 ± 11.3	69.9 ± 10.0	0.46
Fasting glucose, mmol/L	4.99 ± 0.57	4.96 ± 0.54	4.97 ± 0.51	4.99 ± 0.55	4.94 ± 0.55	0.85
Fasting insulin,[2] pmol/L	118 ± 70	118 ± 60	120 ± 81	118 ± 64	115 ± 55	0.83
HOMA-IR[2]	3.85 ± 2.57	3.78 ± 2.03	3.89 ± 2.88	3.82 ± 2.38	3.65 ± 1.88	0.82

[1] All values are means ± SDs. For all variables (except body fat and hs-CRP): cheese and butter, n = 77; MUFAs, n = 74; PUFAs, n = 76; and CHOs, n = 72; for body fat: cheese, n = 73; butter, n = 74; MUFAs, n = 71; PUFAs, n = 68; CHOs, n = 67; and for hs-CRP: cheese, n = 71; butter and PUFAs, n = 68; MUFAs, n = 66; and CHO, n = 64. P values were for the main treatment effects in mixed models. Pairwise comparisons of treatments were examined only when the P value of the main treatment effect was <0.05. Covariates (baseline values of the selected variable, sex, age, BMI, center, sequence, waist:hip ratio or waist circumference, and ethnicity) were included in the mixed models only when they were shown to be significant at $P < 0.05$. CHO, MUFA, and PUFA diets were not compared specifically because they were not part of the primary objectives of the study. apo B, apolipoprotein B; CHO, carbohydrate; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; SBP, systolic blood pressure; TG, triglyceride.
[2] Analyses were performed on log-transformed data.
[3] Significantly different from cheese, $P < 0.05$.
[4] Significantly different from butter, $P < 0.05$.

3 of the 5 studies provided all foods to the participants (9–11). Results, which were very consistent between studies, have been summarized in a recent meta-analysis (7). For a similar ratio of PUFAs to SFAs, the consumption of cheese compared with that of butter significantly reduced HDL cholesterol by 0.05 mmol/L (95% CI: 0.02, 0.09 mmol/L) and LDL-cholesterol concentrations by 0.22 mmol/L (95% CI: 0.14, 0.29 mmol/L) (7). In our study, the consumption of SFAs from cheese and butter led to similar HDL-cholesterol concentrations, which were higher than those after consumption of the low-fat, high-carbohydrate diet, but were similar to the values after consumption of the MUFA and PUFA diets. In contrast, after consumption of the cheese diet, serum HDL-cholesterol concentrations were lower than those that were predicted on the basis of established predictive equations (21), which was a result that was consistent with a small food-matrix effect that modulated the impact of SFAs on

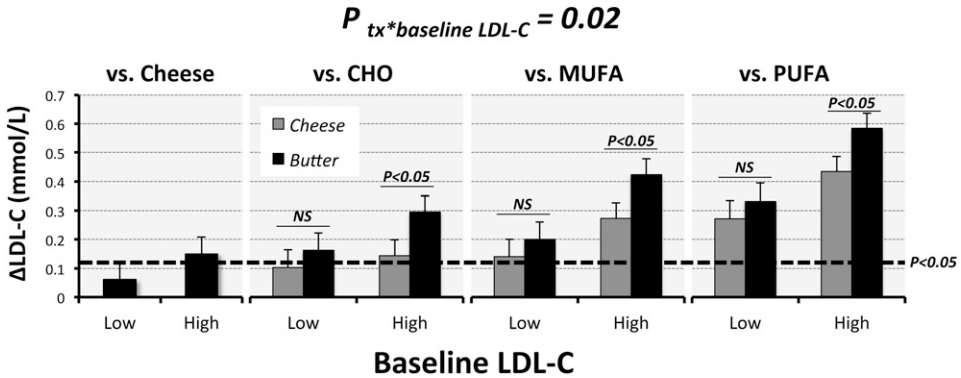

FIGURE 2 Interaction between baseline LDL-C concentrations and diet-induced changes in LDL-C. Values are presented as means ± SEMs. Subjects were classified as having relatively high or low LDL-C at baseline with the use of the median (3.1 mmol/L) LDL-C concentrations in all subjects at screening. The dotted line identifies the value above which the change in LDL-C concentrations with SFAs from cheese or butter was significant compared with that of other nutrients as determined with the use of mixed models. The tx*baseline LDL-C interaction was significant whether LDL-C was analyzed as a continuous variable or as a categorical variable (high compared with low). CHO, carbohydrates; LDL-C, LDL cholesterol; tx*baseline, treatment × baseline.

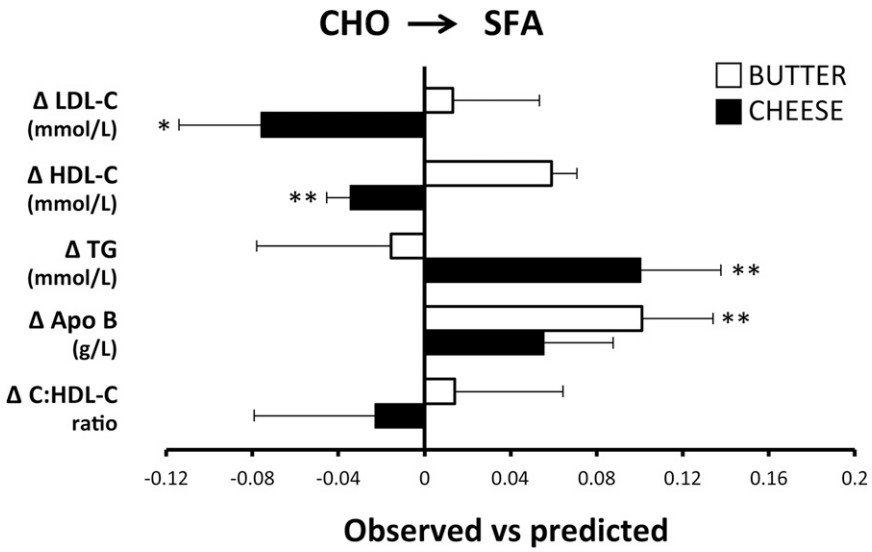

FIGURE 3 Mean ± SEM predicted compared with observed changes in blood lipids with SFAs from butter ($n = 66$) and cheese ($n = 70$) as determined on the basis of the equations of Mensink et al. (21). A paired t test was used to determine P values for the difference in observed compared with predicted changes in blood lipids when SFAs from cheese (6.8% of energy) or from butter (6.6% of energy) replaced CHO. *·**For the difference between observed and predicted changes in blood lipids: $^*P < 0.05$, $^{**}P < 0.01$. Apo B, apolipoprotein B; C, cholesterol; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TG, triglycerides.

HDL cholesterol. In previous RCTs, Tholstrup et al. (8) reported the smallest difference in HDL cholesterol between butter and cheese (mean difference: 0.03 mmol/L; NS), and the study participants had the lowest baseline HDL-cholesterol concentrations (mean: 1.23 mmol/L). In our study, participants also had relatively low HDL cholesterol as per our recruitment criteria (HDL cholesterol below age- and sex-specific 75th percentiles), which suggested that the food-matrix effects that mediate the impact of SFAs on HDL cholesterol may be attenuated when baseline HDL cholesterol is lower. It has become clear that HDL-cholesterol concentrations may poorly reflect the antiatherogenic properties of HDL particles (22). More studies are needed to investigate whether SFAs from different sources have an effect on the cholesterol efflux capacity as well as on HDL anti-inflammatory and antioxidant properties.

In our study, the mean reduction in LDL cholesterol after consumption of the cheese diet compared with after consumption of the butter diet was 0.11 mmol/L ($P < 0.05$), which was one-half of what was observed (−0.22 mmol/L; 95% CI: −0.29, −0.14 mmol/L) in the meta-analysis by de Goede et al. (7). The food-matrix effect in our study was further evidenced by the fact that the substitution of SFAs from cheese by carbohydrates led to lower LDL cholesterol than was predicted on the basis of the established predictive equations (21). This outcome was not the case for SFAs from butter. Our data also suggest that the LDL-cholesterol–raising effect of SFAs from butter compared with that of SFAs from cheese is amplified in individuals with higher LDL-cholesterol concentrations. The extent to which baseline LDL cholesterol modifies the response to dietary changes has been documented in the past, and our results further support this notion (23). Some of the variability in the LDL-cholesterol response to dietary SFAs has been attributed to interindividual differences in the rate of catabolism of LDL particles. Individuals in whom LDL-cholesterol concentrations are high because of a reduced fractional catabolic rate of LDL particles may be particularly sensitive to changes in dietary SFAs, which are known to downregulate the LDL-receptor activity (24). Single nucleotide polymorphisms in the apolipoprotein E gene and other genes that are involved in cholesterol metabolism may also influence the LDL-cholesterol response to changes in dairy SFAs (25), but it is unclear how different sources of SFAs may modify these effects. Finally, it has been suggested that the effects of dietary SFAs and cholesterol on the lipid profile may be attenuated in obese and insulin-resistant individuals and those with metabolic syndrome (26, 27). In our study, interindividual variations in body weight, waist circumference, or the HOMA index did not modify the impact of SFAs (irrespective of source) on LDL cholesterol compared with that of the substitute nutrients.

Very few studies have compared the impact of cheese and butter on nonlipid risk factors. The current study revealed no differences in nonlipid cardiometabolic risk factors between the cheese and butter diets. Thus, the food-matrix effects appeared to be very specific to cholesterol metabolism. It has been shown that the calcium content in cheese may alter the whole-body cholesterol pool by reducing lipid absorption in the intestine, thereby enhancing the excretion of SFAs and cholesterol through feces and by suppressing endogenous cholesterol synthesis in the liver (28–30). The difference in calcium intake between butter and cheese diets (∼400 mg/2500 kcal) was less than one-half that in previous RCTs (8–12), but this reduction may have been enough to induce different LDL cholesterol responses to the cheese and butter. The phospholipids that are present in milk-fat globule membranes of all dairies except butter as well as the bacterial content of cheese have also been evoked as potential mechanisms that may underlie the differential effects of SFAs from cheese and butter on LDL-cholesterol concentrations (31–33). Finally, the extent to which differences in the relative contents of specific SFAs in cheese and butter are responsible for the food-matrix effect is unclear (7).

As expected, the replacement of SFAs from either cheese or butter by MUFAs and PUFAs reduced serum LDL-cholesterol and apo B concentrations (21, 34). In contrast, SFAs, irrespective of the dietary source, had no effects on HDL cholesterol,

inflammation markers, indexes of insulin-glucose homeostasis, or blood pressure compared with the effect of MUFAs and PUFAs. In general, cheese consumption has shown no association with risk of CAD or hypertension and may even be associated with reduced risks of stroke and type 2 diabetes (35). Recent data from a systematic review and meta-analysis also suggested that butter shows relatively small or neutral overall associations with mortality, CVD, and diabetes (36). The reconciliation of data from RCTs and observational studies is challenging. Further studies are needed to explore how the neutral effects of SFAs from cheese and butter on several cardiometabolic risk factors, compared with the effects of MUFAs and PUFAs, possibly abrogate their LDL-cholesterol raising effects on CAD-related outcomes.

This study has several strengths. First, to our knowledge, it is the largest trial thus far to have compared SFAs from butter and cheese. The large sample size combined with the controlled-consumption conditions and crossover nature of the study provided statistical power to detect very small effects in treatments. To our knowledge, this is the first study to compare effects of SFAs from both cheese and butter with those of carbohydrate-, MUFA-, and PUFA-rich diets, simultaneously. Weaknesses include a limited capacity to assess true compliance, which was based on self-reporting. The high dropout rate is also a limitation, although it was not entirely unexpected considering the duration and the commitment that were needed to complete the protocol. However, mixed models are robust when data are missing at random, which was very probable in this study. Sensitivity analyses with the use of data from the center with the lowest dropout rate yielded similar results (data not shown). Further ITT analyses also supported the notion that there is a food-matrix effect that modulates the impact of SFAs on LDL-cholesterol concentrations as well as no effect of SFAs, irrespective of the food source, on nonlipid cardiometabolic risk factors (Supplemental Table 1).

In conclusion, data from this large, carefully controlled RCT suggest that there is a significant food-matrix effect that modulates the impact of SFAs on blood lipids. This food-matrix effect on LDL cholesterol may be exacerbated in individuals with high baseline LDL cholesterol and appears to be independent of whether SFAs from both cheese and butter are substituted for carbohydrates, MUFAs, or PUFAs. These findings reinforce the importance to consider whole foods and food sources as opposed to single nutrients when assessing the impact of diet on health. Finally, data indicate that SFAs from cheese have no significant effect on several nonlipid cardiometabolic risk factors, which may partly explain why cheese intake has not been associated with increased risk of CAD in observational studies (35).

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