The impact of diets rich in low-fat or full-fat dairy on glucose tolerance and its determinants: a randomized controlled trial

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ABSTRACT

Background: Dairy foods, particularly yogurt, and plasma biomarkers of dairy fat intake are consistently inversely associated with incident type 2 diabetes. Yet, few trials assessing the impact of dairy on glucose homeostasis include fermented or full-fat dairy foods.

Objectives: We aimed to compare the effects of diets rich in low-fat or full-fat milk, yogurt, and cheese on glucose tolerance and its determinants, with those of a limited dairy diet.

Methods: In this parallel-design randomized controlled trial, 72 participants with metabolic syndrome completed a 4-wk wash-in period, limiting dairy intake to ≤ 3 servings/wk of nonfat milk. Participants were then randomly assigned to either continue the limited dairy diet, or switch to a diet containing 3.3 servings/d of either low-fat or full-fat dairy for 12 wk. Outcome measures included glucose tolerance (area under the curve glucose during an oral-glucose-tolerance test), insulin sensitivity, pancreatic β-cell function, systemic inflammation, liver-fat content, and body weight and composition.

Results: In the per-protocol analysis ($n = 67$), we observed no intervention effect on glucose tolerance ($P = 0.340$). Both the low-fat and full-fat dairy diets decreased the Matsuda insulin sensitivity index (ISI) (means $\pm$ SDs -0.47 ± 1.07 and -0.25 ± 0.91, respectively) and as compared with the limited dairy group (0.00 ± 0.92) ($P = 0.012$ overall). Body weight also changed differentially ($P = 0.006$ overall), increasing on full-fat dairy ($+1.0$ kg; -0.2, 1.8 kg) compared with the limited dairy diet (-0.4 kg; -2.5, 0.7 kg), whereas the low-fat dairy diet ($+0.3$ kg; -1.1, 1.9 kg) was not significantly different from the other interventions. Intervention effects on the Matsuda ISI remained after adjusting for changes in adiposity. No intervention effects were detected for liver fat content or systemic inflammation. Findings in intent-to-treat analyses ($n = 72$) were consistent.

Conclusions: Contrary to our hypothesis, neither dairy diet improved glucose tolerance in individuals with metabolic syndrome. Both dairy diets decreased insulin sensitivity through mechanisms largely unrelated to changes in key determinants of insulin sensitivity. This trial was registered at clinicaltrials.gov as NCT02663544. *Am J Clin Nutr* 2021;113:534–547.

Introduction

Type 2 diabetes (T2D) is a major global health issue. In 2017, it was estimated that 451 million people had diabetes worldwide, with the vast majority having T2D (1), costing \$850 billion (1). Identifying modifiable determinants of T2D risk is therefore a major public health focus.

Diet is a modifiable lifestyle factor that affects glucose homeostasis and T2D risk (2, 3). Dairy is a food group that is inversely associated with T2D (4–10). This is particularly the case for low-fat dairy and yogurt (9, 11). Although full-fat dairy intake as assessed by questionnaire is mostly not associated with T2D (12, 13), biomarkers of dairy fat intake [i.e., phospholipid pentadecanoic acid (15:0), heptadecanoic acid (17:0), and *trans*-palmitoleic acid (*trans*-16:1n–7)] are consistently inversely associated with T2D (14, 15). These latter studies challenge the long-standing view that full-fat dairy foods may promote weight gain and cardiometabolic disease owing to their higher calorie and saturated fat content.

The limited experimental literature is largely inconsistent with the results from observational studies. Randomized controlled trials (RCTs) consistently indicate that increasing dairy intake does not affect glucose tolerance (16–19). Insulin sensitivity, a major determinant of glucose tolerance, also does not change in most RCTs (16–27). Outcomes of existing RCTs may differ from observational findings because they commonly relied on fasting measures of glucose homeostasis only, enrolled participants with normal baseline glucose homeostasis, did not control for changes in weight, and predominantly included low-fat unfermented dairy products (i.e., skim milk). The latter leads to a particular gap in our understanding, because biomarkers of dairy fat intake and yogurt have most consistently been linked to improved metabolic health and a reduced T2D risk (11–13, 28). Only 2 studies have directly compared the impact of low-fat and full-fat dairy on glucose homeostasis, 1 testing cheese (21) and the other milk (29). No RCT that we know of has comprehensively evaluated the impact of a wide variety of low-fat compared with high-fat dairy foods on glucose tolerance or its key determinants. As a result, it remains unclear whether dairy foods are protective against T2D, and whether this effect is dependent on the type of dairy consumed.

To address these gaps, we compared the effect of consuming 3.3 servings/d of low-fat or full-fat dairy foods with a diet limited in dairy on glucose tolerance and its major determinants. In contrast to previous studies, our trial included fermented dairy products in the form of both yogurt and cheese, in addition to milk. Our trial also included dynamic tests of glucose tolerance, insulin sensitivity, and pancreatic β-cell function. Assessment of major determinants of insulin sensitivity included liver fat content, biomarkers of systemic inflammation, and body weight and composition. We hypothesized that regularly consuming milk, yogurt, and cheese, particularly in their full-fat form, would improve glucose tolerance.

Methods

Trial registration

This trial was registered on clinicaltrials.gov on 26 January, 2016 (NCT02663544), before the enrollment of the first study participant. Changes were made after commencement of the study, but before the end of the trial and any laboratory or statistical analyses, to add several outcomes to broaden our ability to interpret trial effects on the primary endpoint. Specifically, we added glucose sensitivity, a measure of pancreatic β-cell function, as an additional secondary outcome measure. We also added fasting insulin, the HOMA-IR, and several measures of adiposity (trunk fat mass, peripheral fat mass, visceral fat mass, waist circumference, hip circumference, and the waist-to-hip ratio) as secondary outcome measures.

Study design

This parallel-design randomized controlled dietary intervention trial was conducted at the University of Washington (UW) and the Fred Hutchinson Cancer Research Center (Fred Hutch) in Seattle, WA. All participants completed a 4-wk wash-in diet period during which dairy food consumption was limited to ≤3 servings of nonfat milk per week ("limited dairy diet"). After completing a baseline clinic visit in the last week of the wash-in period, participants were randomly assigned to either continue the limited dairy diet or switch to a diet containing 3.3 servings/d of either low-fat or full-fat dairy foods in the form of milk, yogurt, and cheese, for 12 wk. Subjects completed a follow-up clinic visit in the final week of the intervention period.

Subjects

We enrolled 18- to 75-y-old, weight-stable participants with the metabolic syndrome (30). Key exclusion criteria included regular recreational drug use; excessive alcohol consumption; recent use of antidiabetic medications or insulin; uncontrolled diabetes [glycated hemoglobin (HbA1c) >8.0%]; history of bariatric surgery; or recent use of medications or diagnosis of any medical condition likely to interfere with study endpoints.

Our primary recruitment strategy was based on automated screens of the UW electronic medical record system. Potentially eligible individuals were contacted by mail, followed by a telephone screening interview, and lastly an in-person screening visit at Fred Hutch. During this screening visit, eligibility was ascertained, the study design and procedures were discussed in detail, and participants sampled the intervention dairy foods. Informed consent was obtained from all participants before study initiation. The Fred Hutch institutional review board approved this study.

Study diets

During the wash-in period, participants were asked to not consume any dairy products other than a maximum of 3 servings (240 mL each) per week of nonfat milk ("limited dairy diet"). At the baseline clinic visit, participants were randomly assigned to 1 of 3 diets: to continue the limited dairy diet, or switch to a diet rich in either low-fat or full-fat dairy foods. The randomization was performed using a random number generator by MK and SH using a block randomization procedure, with a block size of 3, stratified by gender and the screening visit HOMA-IR (<5.0 compared with ≥5.0 or diagnosis of diabetes). Participants were enrolled and assigned to the intervention diets by KAS, GC,

MSB, or JNK. Blinding subjects to their randomly assigned diet was not possible because participants could easily discern which diet they had been assigned to based on the texture (i.e., full-fat compared with skim) or the amount (dairy compared with limited dairy) of study dairy provided. Those randomly assigned to stay on the limited dairy diet continued to not consume any dairy foods other than a maximum of 3 servings of nonfat milk per week. In the low-fat dairy diet, participants were asked to consume 3.3 servings/d of dairy in the form of nonfat milk and yogurt, and low-fat cheese. In the full-fat dairy diet arm, participants were asked to consume 3.3 servings/d of dairy in the form of whole milk (3.25% fat), full-fat yogurt (3.1% fat), and full-fat cheese. One serving was defined as 240 mL of milk, 170 g of yogurt, and 42.5 g of cheese. Nonfat and whole milk were produced by Darigold and nonfat and full-fat yogurt by Mountain High (General Mills). The low-fat and full-fat cheeses were chosen to be identical in terms of manufacturer and manufacturing processes, other than fat content, and included low-fat and full-fat cheddar cheese (21.2% and 32.9% fat, respectively; Sargento), gouda (18.0% and 32.2% fat, respectively; Beemster), and mozzarella (10.6% and 21.2% fat, respectively; Frigo/Saputo). The mean total amount of dairy fat in the administered dairy foods was 0 g/d in the limited dairy diet, 8 g/d in the low-fat dairy diet, and 29 g/d in the full-fat dairy diet. The Human Nutrition Laboratory at Fred Hutch provided all study dairy products. During all study diets, participants were instructed to not consume any dairy foods other than those provided by the study, and to otherwise continue to consume their habitual diet ad libitum. They were specifically instructed to incorporate the administered dairy products into their regular meals and snacks, and to consume provided dairy foods daily. On the low-fat and full-fat dairy diets, participants were not required to measure out exactly 3.3 servings of dairy per day, but rather were asked to consume all of the dairy provided before their next dairy food pick-up, such that their dairy consumption would average 3.3 servings/d. They were also asked to record their dairy consumption in a dairy log and to return any leftover dairy foods for weigh-backs.

Clinical procedures and data collection

At both clinic visits, we collected fasting blood; measured body weight and height, waist and hip circumference, and blood pressure; conducted a 3-h frequently sampled oral-glucose-tolerance test (FS-OGTT) to assess glucose tolerance, insulin sensitivity, and pancreatic β-cell function; conducted a whole-body DXA scan on a Lunar iDXA scanner (GE Healthcare) to assess body composition; and conducted an abdominal MRI scan to assess liver fat content.

Participants also completed an unvalidated modified Blair physical activity questionnaire (31) at baseline, clinic visit 1, and monthly during the 12-wk intervention period to assess habitual physical activity throughout the study. Twice during the wash-in diet period and 3 times during the intervention period, participants completed an unannounced 24-h dietary recall interview, administered by a staff member of the Fred Hutch Nutrition Assessment Shared Resource, who was otherwise not associated with the trial. Participants were told that their responses, including any indication of noncompliance, would not be shared with the study team before their completion of or dropout from the study.

Body weight and energy intake are key determinants of glucose tolerance and its determinants. Ad libitum energy intake cannot be measured reliably using subjective assessment methods. Therefore, participants completed a 5-d controlled feeding period during which they were provided with all of their food once during the last 3 wk of the wash-in diet period and again within the first 3 wk of the intervention period. These diets were standardized, based on the average American diet (other than dairy intake), and calibrated to offer 125% of each participant's estimated total energy expenditure. Participants were asked to consume all of the study dairy foods administered to them daily, but to eat the rest of the administered diet ad libitum, and to return all leftover foods to the Human Nutrition Laboratory at Fred Hutch. Returned foods were weighed and subtracted from the weight of the administered foods to calculate total energy intake during these 5-d periods. The purpose of the 5-d feeding periods was to assess whether participants randomly assigned to either the low-fat or full-fat dairy diets would be able to compensate for the energy content of the mandatory dairy foods by reducing their ad libitum consumption of nondairy foods provided by the standardized diet.

Laboratory procedures

High-sensitivity C-reactive protein (CRP), glucose, insulin, C-peptide, and total adiponectin in fasting plasma and HbA1c in fasting RBCs were measured at Northwest Lipid Research Laboratories (NWLRL) in Seattle, WA. CRP was measured by immunonephelometry (Behring Diagnostics), glucose on a Hitachi 917 autoanalyzer (Roche), and insulin and C-peptide on an AIA 600 II autoanalyzer (Tosoh Bioscience). HbA1c analysis was performed using HPLC-based G7 and G8 autoanalyzers (Tosoh Bioscience). Total adiponectin was measured in duplicate by an RIA (EMD Millipore Inc.). The interassay CV at NWLRL for this assay is 8%. High-sensitivity IL-6 was measured in duplicate in the Kratz laboratory by a high-sensitivity ELISA from R&D Systems. The interassay CV was 12%.

As an assessment of compliance with the dietary regimen, we measured the amounts of pentadecanoic acid, heptadecanoic acid, and *trans*-palmitoleic acid in plasma phospholipids (conducted in the Kraft Lab, Burlington, VT), because these are validated biomarkers of dairy fat intake (32, 33). Plasma phospholipids were extracted according to the method of Folch et al. (34). Plasma phospholipids were isolated from total plasma lipids via solid-phase extraction using aminopropyl cartridges (Thermo Fisher Scientific), and transmethylated with boron trifluoride solution in methanol (Sigma-Aldrich) to FAME (35). FAME were analyzed by GLC (35).

Study outcomes

The a priori–defined primary study outcome was change in glucose tolerance, as assessed by measuring the glucose AUC during a 3-h FS-OGTT. Secondary outcomes included changes in major determinants of oral glucose tolerance (i.e., systemic insulin sensitivity and pancreatic β-cell function) and major determinants of insulin sensitivity (i.e., liver fat content and low-grade chronic systemic inflammation). Systemic insulin sensitivity was assessed using the Matsuda–DeFronzo insulin

sensitivity index (ISI) based on data from the FS-OGTT (36). Pancreatic β-cell function was assessed using the insulinogenic index (37), the oral disposition index (oral DI), which is calculated as the product of the Matsuda ISI and the insulinogenic index, and modeled glucose sensitivity (38), all based on the FS-OGTT. Liver fat content was measured by an abdominal MRI scan in the UW Biomolecular Imaging Center on a Philips 3T Ingenia CX whole-body scanner (Philips). Dixon MRI with multiple echo times were obtained, and fat and water MRI images as well as a quantitative liver proton density fat fraction map were produced. The entire liver was segmented on every 10th slice of the fat MRI images to estimate liver fat content. For each slice, the percentage fat was weighted by the contour area as a percentage of the total contoured liver area (sum of the area of all segmented slices), and the weighted fat percentages were summed. Low-grade chronic systemic inflammation was assessed using the concentration of CRP and IL-6 in fasting plasma. Exploratory endpoints reported here to comprehensively assess intervention effects on glucose homeostasis included changes in HbA1c, HOMA-IR (39), and fasting plasma glucose, insulin, and total adiponectin concentrations as well as ad libitum energy intake during the two 5-d controlled feeding periods, body weight, body fat mass, trunk fat mass, peripheral fat mass, visceral fat mass, waist circumference, hip circumference, and the waist-to-hip ratio. We also assessed changes in the overall diet that resulted from the intervention.

Statistical analyses

We aimed to randomly assign 72 participants, with the goal of having ≥60 participants in the primary per-protocol analysis and ≥20 in each intervention group. Sample size was based on assumptions of a baseline 3-h AUC glucose of 24,000 mg/dL × min and an SD of the change of 2300 mg/dL × min, which was estimated to provide 80% power to detect a differential change in AUC glucose between any 2 intervention groups of 10% with a sample size of ≥20/group and an adjusted α-error level of 1.67% (adjusted to account for 3 post hoc tests). The baseline and variability estimates used in the sample size calculation were based on 2 prior pilot intervention trials by our group—1 in prediabetic individuals and the other in obese individuals without diabetes—from which 3-h FS-OGTT data were available.

Statistical analyses were performed using SPSS version 26 (IBM). The level of significance was set to $P < 0.05$ for all analyses. We conducted both an intent-to-treat (ITT) and a per-protocol analysis, with the latter defined a priori as the primary analysis. For the ITT analysis, we carried the baseline values forward for those time points where data were unavailable. For the per-protocol analysis for each endpoint, subjects were included if they *1*) completed the dietary intervention and all clinic visits; *2*) were compliant with the dietary regimen (defined as consuming ≥90% of the study dairy foods provided, and consuming ≤10 servings of nonstudy dairy foods during the intervention period); *3*) had no changes in medications that might affect the respective study endpoint; and *4*) remained free from any illness that might affect the respective study endpoint.

Logarithmic transformations were performed on all outcome variables that were not normally distributed. An unadjusted repeated-measures analysis of variance (RM-ANOVA) with time (clinic visit 1 compared with 2) as the within-subject variable and

diet group (limited compared with low-fat compared with full-fat) as the between-subjects variable, with primary emphasis on the time × diet group interaction, was considered model 1. Then, related baseline factors that differed by study arm as defined as a P value < 0.1 were included in the model as covariates, as appropriate (model 2 for glucose homeostasis–related endpoints). This was considered the primary model, because it was thought to more accurately reflect intervention effects (40). We also conducted sensitivity analyses adjusted for changes, defined as the difference between clinic visits 2 and 1, in habitual physical activity (model 2 for energy homeostasis–related endpoints) and those dietary variables that were differentially changed by the intervention diets. In addition, we conducted sensitivity analyses adjusted for our stratification variables: gender and HOMA-IR. For any glucose homeostasis–related variable for which we found differential changes by diet group, we conducted additional secondary analyses adjusting for changes in body fat mass (model 3 for glucose homeostasis–related endpoints) and any body weight or composition measure that changed differentially to determine to which extent any difference observed between the groups may be attributable to a change in measures of adiposity. If the global RM-ANOVA indicated significant time × diet differences between the diet groups for an outcome variable, we conducted post hoc independent-sample t tests comparing the change in that variable in each of the 3 diet groups, or 3 RM-ANOVAs that included only 2 diet groups at a time for post hoc tests. In these analyses, we adjusted for multiple testing according to Bonferroni. Again, post hoc tests were conducted on log-transformed data if the outcome variable failed the test for normality.

Results

Description of participants

The trial was conducted between January 2016 and October 2018, when the recruitment goal was met. Recruitment letters were sent to 4261 potentially eligible individuals identified by an automated screen and review of the UW electronic medical record system, and to 16 self-referred volunteers (**Figure 1**). We conducted telephone screening interviews with 354 individuals and invited 130 potentially eligible and interested participants to attend an in-person screening visit, where 90 were deemed eligible for the trial. Excluding individuals unwilling or unable to participate, 76 subjects began the wash-in period. After excluding individuals who either dropped out or were noncompliant with study procedures during the wash-in diet period, a total of 72 adults were randomly assigned to 1 of the 3 diet groups: 24 each to the limited dairy, low-fat dairy, and full-fat dairy diets. All randomly assigned participants were included in the ITT analyses. Five subjects were excluded from the per-protocol analyses of glucose tolerance and related endpoints ($n = 67$): 3 dropped out before the final clinic visit and 2 were excluded for noncompliance. For body weight– and body composition–related endpoints ($n = 66$), 1 additional participant was excluded from the per-protocol analyses due to a change in thyroid medication. For the analysis of biomarkers of inflammation ($n = 59$), an additional 8 participants were excluded for acute illness or a change in medication or supplement intake. For the analysis of liver fat content ($n = 61$), an additional 6 participants were excluded because they were unable to undergo
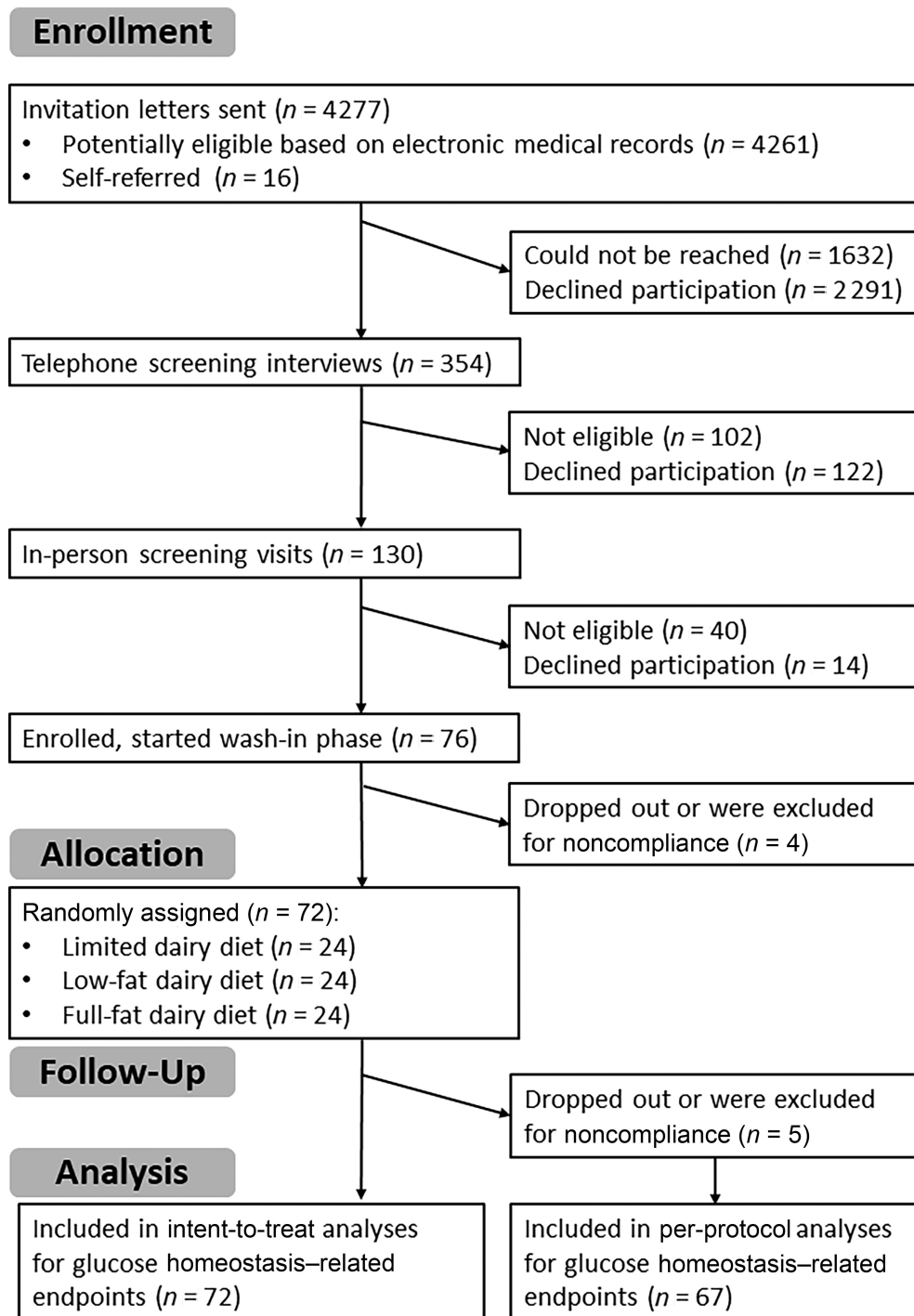
Enrollment

Invitation letters sent (*n* = 4277)
- Potentially eligible based on electronic medical records (*n* = 4261)
- Self-referred (*n* = 16)

Could not be reached (*n* = 1632)
Declined participation (*n* = 2291)

Telephone screening interviews (*n* = 354)

Not eligible (*n* = 102)
Declined participation (*n* = 122)

In-person screening visits (*n* = 130)

Not eligible (*n* = 40)
Declined participation (*n* = 14)

Enrolled, started wash-in phase (*n* = 76)

Dropped out or were excluded for noncompliance (*n* = 4)

Allocation

Randomly assigned (*n* = 72):
- Limited dairy diet (*n* = 24)
- Low-fat dairy diet (*n* = 24)
- Full-fat dairy diet (*n* = 24)

Follow-Up

Dropped out or were excluded for noncompliance (*n* = 5)

Analysis

Included in intent-to-treat analyses for glucose homeostasis–related endpoints (*n* = 72)

Included in per-protocol analyses for glucose homeostasis–related endpoints (*n* = 67)

FIGURE 1 Consolidated Standards of Reporting Trials flow diagram.

an MRI scan. **Table 1** shows the baseline characteristics, stratified by intervention group, for the per-protocol analysis. Baseline characteristics for those included in the ITT analyses can be found in **Supplemental Table 1**.

Adverse events

No subject withdrew from the study due to adverse events. Of 5 adverse events reported during the trial, 2 were rated as unrelated to study procedures. Three adverse events were rated as related to study procedures and classified as mild–moderate in

severity. One participant in the low-fat dairy group experienced hypoglycemia during both of their FS-OGTTs, with each incident being reported as a separate adverse event. A participant in the limited dairy intervention group experienced vertigo, nausea, and vomiting after the MRI scan.

Adherence to the intervention and dietary intakes

Based on data from the Human Nutrition Laboratory on administered and returned study dairy foods as well as participants' entries regarding consumption of nonstudy dairy foods

TABLE 1 Baseline characteristics of study participants included in the primary per-protocol analyses for glucose tolerance and related endpoints[1]

Variable	Limited dairy (n = 22)	Low-fat dairy (n = 24)	Full-fat dairy (n = 21)	P value
Age, y	56 [46–68]	64 [58–71]	65 [58–68]	0.18
Male sex	54.5	58.3	57.1	0.97
Caucasian race	72.7	79.2	71.4	0.87
BMI, kg/m^2	33.6 ± 5.9	32.6 ± 7.3	32.8 ± 6.4	0.85
Body weight, kg	101 ± 16	96 ± 26	95 ± 17	0.58
Fat mass, kg	37.9 [32.2–45.1]	32.5 [23.6–52.1]	36.7 [27.4–48.8]	0.66
Lean mass, kg	57.7 ± 10.3	55.6 ± 14.0	53.8 ± 8.8	0.54
Visceral adiposity,[2] inch^3	148 [97–202]	104 [71–202]	124 [78–177]	0.35
Physical activity, MET-h/wk	37.2 [23.4–49.6]	41.0 [25.7–89.7]	37.8 [19.6–47.9]	0.29
2015 Healthy Eating Index	71.9 ± 9.2	72.3 ± 9.7	72.2 ± 8.5	0.95
HOMA-IR	2.5 [1.9–3.5]	3.3 [1.6–4.4]	3.0 [1.7–4.4]	0.98
Fasting glucose, mg/dL	101 [93–109]	110 [101–119]	107 [102–116]	0.09
Fasting insulin, μU/mL	9.8 [7.1–14.6]	12.3 [6.1–15.6]	11.3 [7.9–14.4]	0.86
Glycated hemoglobin, %	5.4 [5.0–5.5]	5.8 [5.5–6.2]	5.7 [5.4–5.9]	<0.001
Glucose AUC, mg/dL × min	25,195 [23,445–30,708]	29,895 [26,495–32,849]	27,888 [24,831–29,881]	0.07
Matsuda insulin sensitivity index	2.7 [2.0–3.8]	2.4 [1.8–3.8]	2.3 [1.9–3.4]	0.88
Insulinogenic index	1.0 [0.6–1.5]	0.7 [0.4–1.4]	1.2 [0.7–1.9]	0.51
Glucose sensitivity, pmol × min^{-1} × m^{-2} × L × mmol^{-1}	92 [64–120]	74 [41–103]	86 [68–110]	0.47
Oral disposition index	2.3 [1.4–4.5]	2.3 [1.4–3.2]	2.8 [1.5–4.8]	0.59
C-reactive protein, mg/L	1.2 [0.9–2.5]	0.9 [0.4–2.1]	1.5 [0.9–3.0]	0.52
IL-6, pg/mL	3.5 [2.5–4.2]	2.7 [1.8–4.1]	2.9 [1.6–4.2]	0.50
Total adiponectin, ng/mL	5150 [3838–7525]	6425 [3900–9300]	5900 [3925–9750]	0.86
Liver fat content,[3] % of total	5.2 [1.0–8.6]	4.4 [1.1–10.1]	3.7 [2.1–10.2]	0.60

[1] n = 67. Values are means ± SDs or medians [IQRs] for nonnormally distributed variables or percentages for categorical variables. P values are based on an ANOVA, except for gender and race, which were based on an independent-samples Kruskal–Wallis test. 1 inch = 2.54 cm. MET, metabolic equivalent of task.

[2] Sample size for visceral adiposity: limited, n = 21; low-fat, n = 22; full-fat, n = 20.

[3] Sample size for percentage liver fat: limited, n = 20; low-fat, n = 22; full-fat, n = 19.

on their dairy logs, per-protocol participants (n = 67) consumed (mean ± SD) 98.2% ± 1.8% and 97.9% ± 2.8% of the study dairy foods provided to them during the low-fat and full-fat dairy intervention diet periods, respectively (**Table 2**). During the limited dairy intervention period, participants consumed a mean ± SD of 74.9% ± 34.9% of the provided (nonmandatory) nonfat milk. Mean ± SD consumption of nonstudy dairy foods was 0.6 ± 1.0, 0.6 ± 0.9, and 1.3 ± 2.3 total servings over the entire 12 wk of the limited, low-fat, and full-fat dairy diet periods, respectively. Consistent data on total consumption of dairy foods were obtained from the mean of 3 unannounced 24-h dietary recall interviews conducted during the intervention period (Table 2). The percentage of 1 key biomarker of dairy fat consumption, pentadecanoic acid in the plasma phospholipid fraction, changed differentially (P = 0.004 for the time × diet interaction in the overall RM-ANOVA), with an increase in the full-fat dairy group compared with the limited dairy group (post hoc, adjusted P = 0.006) and a trend for an increase in the full-fat dairy group compared with the low-fat dairy group (post hoc, adjusted P = 0.075) (Table 2). No statistically significant differential changes were seen for 2 other established biomarkers of dairy fat intake, the plasma phospholipid concentrations of *trans*-palmitoleic acid and heptadecanoic acid (P = 0.104 and P = 0.203, respectively, for the time × diet interaction in the overall RM-ANOVA).

The dietary intervention also led to some changes in the participants' habitual diet, as measured by repeated unannounced 24-h dietary recall interviews (**Table 3**). The intake of SFAs increased in the full-fat dairy group compared with both the limited and the low-fat dairy groups (P < 0.01 in post hoc testing), and the intake of calcium increased in both dairy groups compared with the limited dairy diet (P < 0.001 in post hoc testing). The intake of MUFAs decreased in the low-fat dairy diet compared with both the limited and full-fat dairy diets (P < 0.05 in post hoc testing), but there was no differential change in PUFA intake. The intake of total sugars (percentage of energy) increased in the low-fat dairy group as compared with the limited dairy diet (P = 0.006, in post hoc testing). Nutrient density–adjusted fiber intake (g/1000 kcal) decreased in the full-fat dairy diet group as compared with the limited dairy diet group (P = 0.024, in post hoc testing), but there was no diet effect on total fiber intake (g/d). Carbohydrate intake (percentage of total energy) increased in the low-fat dairy arm compared with the full-fat dairy arm (P = 0.015 in post hoc testing) and fat intake increased in the full-fat dairy arm compared with the low-fat dairy arm (P < 0.001 in post hoc testing). Protein intake tended to increase in the low-fat dairy arm as compared with the limited dairy arm (P = 0.063 in post hoc testing). Total energy intake increased in the full-fat dairy arm compared with both the limited and low-fat dairy arms (P < 0.05 for both in post hoc testing), with no difference between the latter 2. The 2015 Healthy Eating Index increased in the low-fat dairy group compared with the full-fat dairy groups (P < 0.05 in post hoc testing), whereas the limited dairy group did not differ from either of the full-fat and low-fat dairy groups in post hoc testing.

TABLE 2 Compliance with the dietary intervention of participants who were included in the per-protocol analysis for glucose tolerance and related endpoints[1]

	Limited dairy group (n = 22)		Low-fat dairy diet (n = 24)		Full-fat dairy diet (n = 21)	
	Wash-in diet period	Intervention period	Wash-in diet period	Intervention period	Wash-in diet period	Intervention period
Consumed study dairy foods (administered study dairy foods minus returned study dairy foods)						
Reduced-fat milk, servings/d	0.41 [0.22–0.42]	0.38 [0.17–0.42]	0.42 [0.36–0.42]	1.12 [1.08–1.12]	0.42 [0.37–0.42]	0.0 [0.0–0.0]
Reduced-fat yogurt, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.00 [0.97–1.01]	0.0 [0.0–0.0]	0.0 [0.0–0.0]
Reduced-fat cheese, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.14 [1.13–1.14]	0.0 [0.0–0.0]	0.0 [0.0–0.0]
Whole milk, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.12 [1.10–1.12]
Full-fat yogurt, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.01 [0.93–1.01]
Full-fat cheese, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.14 [1.13–1.14]
24-h dietary recall data [mean of unannounced 24-h dietary recall interviews in the wash-in (2 d) and intervention (3 d) periods]						
Reduced-fat milk, servings/d	0.59 [0.15–1.06]	0.53 [0.15–1.29]	0.74 [0.33–0.81]	1.11 [0.88–1.75]	0.50 [0.31–1.09]	0.0 [0.0–0.42]
Reduced-fat yogurt, cups/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.14 [0.59–1.63]	0.0 [0.0–0.0]	0.0 [0.0–0.0]
Reduced-fat cheese, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.25 [0.67–1.54]	0.0 [0.0–0.0]	0.0 [0.0–0.0]
Whole milk, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.35]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.06]	1.25 [0.93–1.92]
Full-fat yogurt, cups/d	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	1.35 [0.84–2.15]
Full-fat cheese, servings/d	0.0 [0.0–0.0]	0.0 [0.0–0.01]	0.0 [0.0–0.0]	0.0 [0.0–0.04]	0.0 [0.0–0.0]	1.19 [0.91–1.50]
Plasma phospholipid biomarkers of dairy fat intake						
15:0, % of total	0.19 [0.14–0.21]	0.16 [0.12–0.20]	0.16 [0.12–0.17]	0.14 [0.12–0.17]	0.15 [0.12–0.19]	0.19 [0.16–0.21]
17:0, % of total	0.28 [0.23–0.34]	0.27 [0.23–0.33]	0.28 [0.24–0.31]	0.28 [0.23–0.32]	0.29 [0.25–0.32]	0.30 [0.28–0.32]
$trans$-16:1n–7, % of total	0.017 [0.008–0.027]	0.013 [0.008–0.022]	0.016 [0.007–0.024]	0.015 [0.012–0.019]	0.012 [0.000–0.018]	0.024 [0.019–0.027]

[1] n = 67. Values are medians [IQRs]. One serving was defined as 240 mL for milk, 170 g for yogurt, and 42.5 g for cheese.

Glucose tolerance and its determinants

Our primary endpoint, glucose tolerance as assessed by AUC glucose, was not differentially affected by the intervention diets (**Figures 2**, **3**). This was the case in the unadjusted analysis (model 1 in **Supplemental Table 2**), as well as in model 2, which was adjusted for variables that differed or tended to differ across intervention groups at baseline (fasting glucose and HbA1c).

Intervention effects were seen for insulin sensitivity, as assessed by the Matsuda ISI ($P = 0.012$ for the overall time × diet interaction in model 2) (Figure 3, Supplemental Table 2). Specifically, the Matsuda ISI was significantly reduced in both dairy groups compared with the limited dairy group in post hoc tests, after Bonferroni correction (Figure 3B). Consistent with this reduction in insulin sensitivity, we observed a significant intervention effect for HOMA-IR and fasting insulin (overall time × diet interaction $P = 0.005$ and $P = 0.010$, respectively) (Figure 3C, Supplemental Table 2). Post hoc t tests showed that HOMA-IR significantly increased in both the low-fat and full-fat dairy groups compared with the limited dairy group ($P = 0.030$ and $P = 0.003$, respectively), with no difference between the 2 dairy intervention groups. There was also a significant increase in fasting insulin when comparing the low-fat dairy diet with the limited dairy diet ($P = 0.030$). The reduction in insulin sensitivity was also evident when assessing the change in plasma insulin concentrations during the 3-h FS-OGTT as compared with AUC glucose (Figure 2).

For measures of pancreatic β-cell function, we detected no overall intervention effect for the insulinogenic index and glucose sensitivity (Figure 3E, F, Supplemental Table 2). However, we detected an intervention effect for the oral DI (overall time × intervention interaction $P = 0.028$) (Figure 3G), with a statistically significant decrease in the full-fat group compared with the limited dairy group in post hoc testing ($P = 0.030$).

No intervention effects were seen for any of the major determinants of insulin sensitivity (**Figure 4**, **Supplemental Table 3**), including liver fat content (overall time × intervention interaction $P = 0.544$) and biomarkers of systemic inflammation, including CRP ($P = 0.213$), IL-6 ($P = 0.500$), and total adiponectin ($P = 0.789$).

We also assessed the impact of the intervention diets on other exploratory endpoints related to glucose homeostasis, fasting plasma glucose concentrations, and HbA1c. Whereas no intervention effect was seen for HbA1c (time × intervention interaction $P = 0.106$) (Figure 3I, Supplemental Table 2), we detected a trend for an intervention effect for fasting glucose ($P = 0.073$).

In sensitivity analyses, adjustment of models that indicated an intervention effect (Matsuda ISI, fasting insulin, HOMA-IR) for changes in body fat mass, body weight, or waist circumference did not fundamentally change the results, even though in some cases the intervention effects were slightly attenuated ($P \leq 0.070$ for all adjusted variables). Sensitivity analyses adjusting for the stratification variables similarly did not fundamentally change any of the results. The sensitivity analyses for the oral DI adjusting for both the changes in waist circumference and weight led to a more substantial attenuation, becoming nonsignificant ($P = 0.099$ and $P = 0.132$, respectively; data not shown). We also ran extensive sensitivity analyses adjusting for changes in dietary variables that were differentially changed by the

TABLE 3 Dietary intakes during wash-in and intervention phases, based on unannounced 24-h dietary recalls, for the participants included in the per-protocol analysis for glucose tolerance and related endpoints[1]

	Limited dairy group (n = 22)		Low-fat dairy diet (n = 24)		Full-fat dairy diet (n = 21)		RM-ANOVA (time × diet interaction)[2]
	Wash-in diet period	Change during intervention period	Wash-in diet period	Change during intervention period	Wash-in diet period	Change during intervention period	
Energy intake, kcal/d	1998 [1624–2307]	81 ± 544^a	2041 [1526–2625]	224 ± 375^a	1712 [1364–2098]	554 ± 467^b	0.003
Carbohydrates, %E	46.1 ± 11.4	−0.7 [−4.4 to 0.9]^a,b	47.7 ± 8.6	1.6 [−4.3 to 6.2]^a	46.3 ± 7.1	−4.1 [−7.6 to −0.8]^b	0.020
Total sugars, %E	18.0 ± 7.0	−1.9 ± 5.6^a	18.5 ± 6.6	3.4 ± 5.0^b	17.1 ± 6.2	0.9 ± 4.7^a,b	0.004
Added sugars, %E	9.3 ± 4.5	−0.5 ± 3.3	8.5 ± 4.1	0.7 ± 4.3	9.1 ± 6.1	−0.9 ± 4.1	0.349
Fiber, g/d	23.9 ± 8.9	1.5 ± 7.9	25.7 ± 9.0	−0.3 ± 6.2	21.5 ± 9.0	0.2 ± 5.8	0.650
Fiber, g/1000 kcal	12.3 ± 5.0	0.3 ± 3.8^a	12.6 ± 3.4	−1.4 ± 2.5^a,b	12.2 ± 4.4	−2.8 ± 3.3^b	0.011
Fat, %E	34.0 ± 8.1	1.3 [−2.7 to 5.7]^a	34.2 ± 7.7	−2.5 [−8.2 to 0.0]^b	35.0 ± 9.0	4.4 [0.6–7.3]^a	<0.001
SFAs, %E	8.0 ± 2.0	0.7 [−0.3 to 3.8]^a	8.2 ± 2.1	0.6 [−1.5 to 2.1]^a	8.7 ± 2.6	5.2 [3.4–6.9]^b	<0.001
MUFAs, E%	14.1 ± 4.3	−0.3 ± 3.8^a	14.0 ± 3.9	−3.1 ± 3.8^a	13.7 ± 4.1	−0.2 ± 4.6^a	0.014
PUFAs, %E	9.2 ± 2.8	0.3 ± 2.3	9.3 ± 3.1	−1.8 ± 3.0	9.7 ± 3.5	−1.1 ± 3.4	0.058
Protein, %E	15.4 [12.5–18.1]	0.0 ± 0.1	16.2 [13.7–17.7]	0.1 ± 0.1	15.3 [14.1–18.6]	0.0 ± 0.1	0.024
2015 Healthy Eating Index	71.9 ± 9.2	−2.5 ± 10.0^a,b	72.8 ± 9.7	2.9 ± 8.7^a	72.2 ± 8.5	−5.6 ± 7.6^b	0.008
Calcium, mg/1000 kcal	307 [222–440]	−9 ± 150^a	298 [252–358]	401 ± 167^b	338 [276–426]	277 ± 194^b	<0.001

[1] n = 67. Values are means ± SDs or medians [IQRs] for nonnormally distributed variables. RM-ANOVA, repeated-measures analysis of variance; %E, percentage of total energy intake. Values with different superscript letters are statistically significantly different in Bonferroni-adjusted post hoc testing (P < 0.017).

[2] Reflects an overall comparison of the 3 dietary phases by RM-ANOVA.

intervention diets (Table 3). The intervention effects for fasting insulin, HOMA-IR, the Matsuda ISI, and the oral DI tended to be very robust and remained significant even after adjustment for changes in percentage energy from carbohydrates, added sugars, total fat, SFAs, MUFAs, and protein; the change in fiber intake (g/1000 kcal); and the change in the 2015 Healthy Eating Index. With the exception of the oral DI, all intervention effects also remained significant after adjustment for change in energy intake. Similarly, sensitivity analyses that excluded 1 outlier in the full-fat dairy group for several of the variables (Figure 3) or adjusted for changes in physical activity did not affect any of the results.

The ITT analysis (n = 72) yielded results consistent with the per-protocol analyses for all endpoints.

Energy intake, body weight, and body composition

During the 5-d controlled feeding period conducted during the intervention period as compared with the 5-d controlled feeding period during the wash-in period, participants received 281 kcal/d and 463 kcal/d more in the form of mandatory dairy foods in the low-fat and full-fat dairy groups, respectively. Comparing intakes from the 5-d controlled periods (intervention compared with wash-in), mean ± SD energy intake remained stable in individuals randomly assigned to stay on the limited dairy diet (mean ± SD: −21 ± 317 kcal/d), increased by +166 ± 267 kcal/d in those who switched to the low-fat dairy diet, and increased by 384 ± 175 kcal/d in participants who switched to the full-fat dairy diet (P < 0.001 in the overall RM-ANOVA; adjusted P < 0.01 in post hoc tests comparing full-fat dairy with both limited dairy and low-fat dairy, with no significant difference between low-fat dairy and limited dairy). Similarly, total energy intake as measured by the repeated 24-h dietary recall interviews increased by (mean ± SD) 224 ± 375 kcal/d and 554 ± 467 kcal/d in the low-fat and full-fat dairy intervention groups, respectively, compared with the wash-in period, whereas it stayed relatively stable in the limited dairy group during the intervention period (P = 0.003 in the overall RM-ANOVA; adjusted P < 0.05 in post hoc tests comparing full-fat dairy with both limited dairy and low-fat dairy, with no significant difference between low-fat dairy and limited dairy) (Table 3). Consistent with these increases in total energy intake, we observed an overall intervention effect for body weight (time × intervention interaction P = 0.005), with a statistically significant increase in the full-fat dairy group compared with the limited dairy group (**Figure 5**A, **Supplemental Table 4**), with the low-fat dairy group not significantly different from either after Bonferroni correction. There was a significant overall effect on fat mass (overall time × intervention interaction P = 0.024), but no 2 diets differed from one another after adjustment for multiple comparisons in post hoc testing (Figure 5B, Supplemental Table 4). Further, there was a trend for a difference in lean mass (overall time × intervention interaction P = 0.082) (Figure 5C, Supplemental Table 4). An overall intervention effect was seen for waist circumference (overall time × intervention interaction P = 0.015) (Figure 5D), with a significant increase in both dairy groups compared with the limited dairy group in post hoc testing. No significant intervention effects were seen for hip circumference, the waist-to-hip ratio, or measures of fat distribution including trunk fat, peripheral fat, or visceral fat (Figure 5E–I). As with measures of glucose homeostasis, sensitivity analyses adjusted
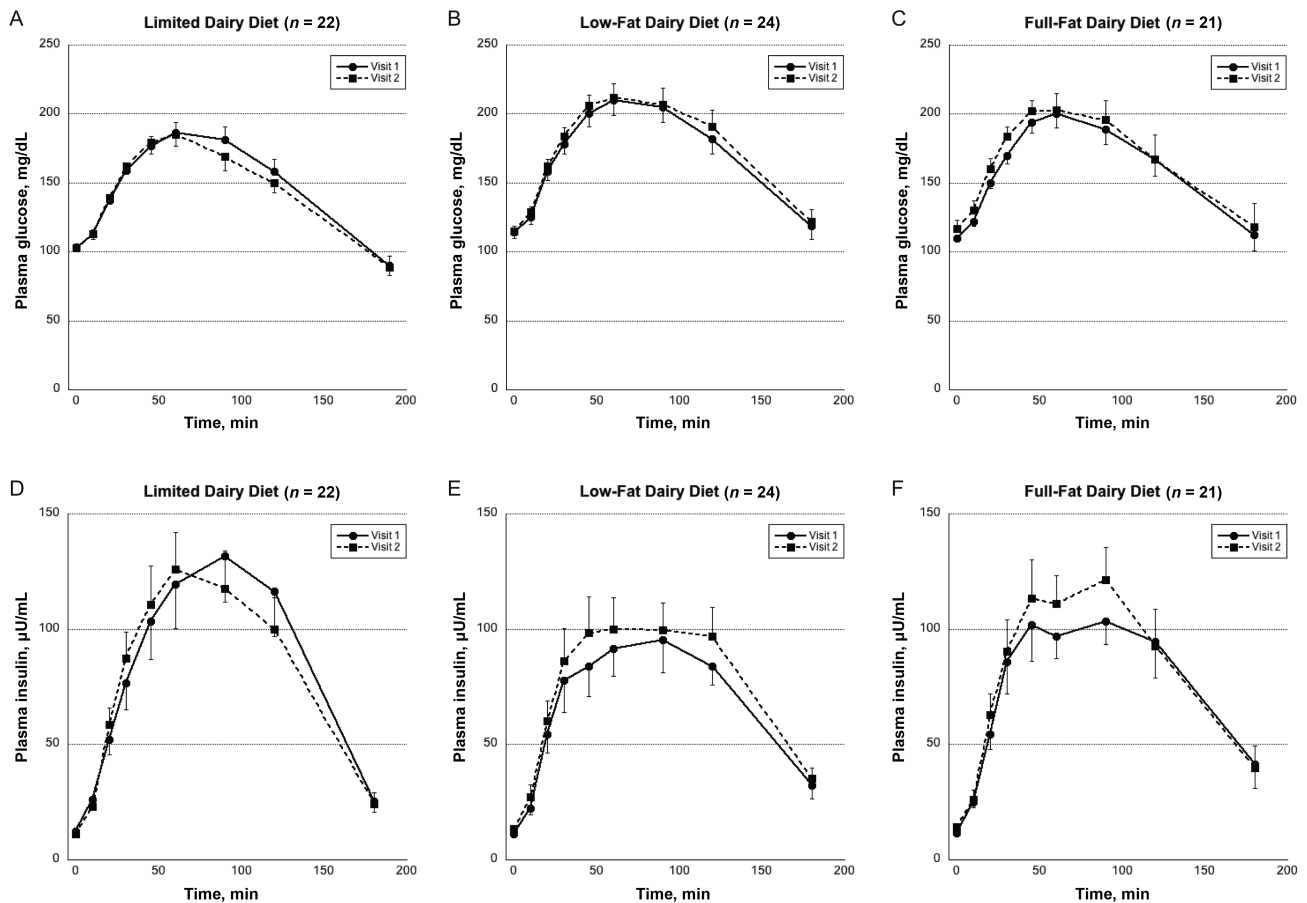
FIGURE 2 Impact of diets limited in dairy (*n* = 22, A, D) or rich in low-fat dairy (*n* = 24, B, E) or full-fat dairy (*n* = 21, C, F) on plasma glucose (A–C) and insulin (D–F) concentrations in 3-h frequently sampled oral-glucose-tolerance tests. Circles and squares represent means at baseline (visit 1) and after the 12-wk dietary intervention (visit 2), respectively. Error bars represent SEMs.

for changes in physical activity (model 2 in Supplemental Table 4), stratification variables, or key dietary factors, as listed in Table 3, or excluding 1 major outlier in the full-fat dairy group yielded very similar results. The ITT analysis (*n* = 72) yielded results that were consistent with the per-protocol analyses for all endpoints.

Discussion

In contrast to our hypothesis, consuming 3 servings/d of low-fat or full-fat dairy in the form of milk, yogurt, and cheese did not improve glucose tolerance in men and women with metabolic syndrome. In fact, insulin sensitivity was reduced on both dairy diets compared with the control diet limited in dairy, and this effect was very robust in sensitivity analyses. This reduction in insulin sensitivity was also associated with a reduced oral DI in the full-fat dairy group, suggesting that pancreatic *β*-cell insulin secretion in response to the standardized glucose load did not increase sufficiently to fully compensate for the decrease in insulin sensitivity. It is possible that this reduction in insulin sensitivity could lead to a reduction in glucose tolerance over time, thereby increasing T2D risk. However, it is curious that the decrease in insulin sensitivity did not seem to be explained by changes in known determinants of insulin

sensitivity (i.e., body weight, fat mass, liver fat content, or systemic inflammation), indicating that another mechanism is at play. One potential mechanism that was not explored in this study is that the observed reduction in insulin sensitivity in the dairy groups could plausibly be a physiological response to prevent hypoglycemia after dairy-rich meals. Dairy foods acutely trigger insulin responses far in excess of what would be expected based on their modest glycemic index (41). This insulinotropic effect of dairy may be triggered by branched-chain amino acids found in dairy, which may act directly on the pancreatic *β*-cell and have also been shown to promote the release of the incretin glucagon-like peptide-1 in intestinal cells in vitro (42–44). Sustained hyperinsulinemia causes insulin resistance (45, 46). Possibly, repeated postprandial hyperinsulinemia triggered by regular dairy consumption could similarly lead to insulin resistance. However, future investigations are needed to assess the impact of the hyperinsulinemia produced by dairy consumption and its potential to affect insulin sensitivity. It therefore remains unclear how the combination of dairy-induced insulin resistance coupled with the acute insulinotropic effect of dairy seen in previous studies affects glucose tolerance and T2D risk in the long term. Another potential mechanism not explored in this study are potential alterations in the gut microbial composition that may have resulted from following our dairy interventions,
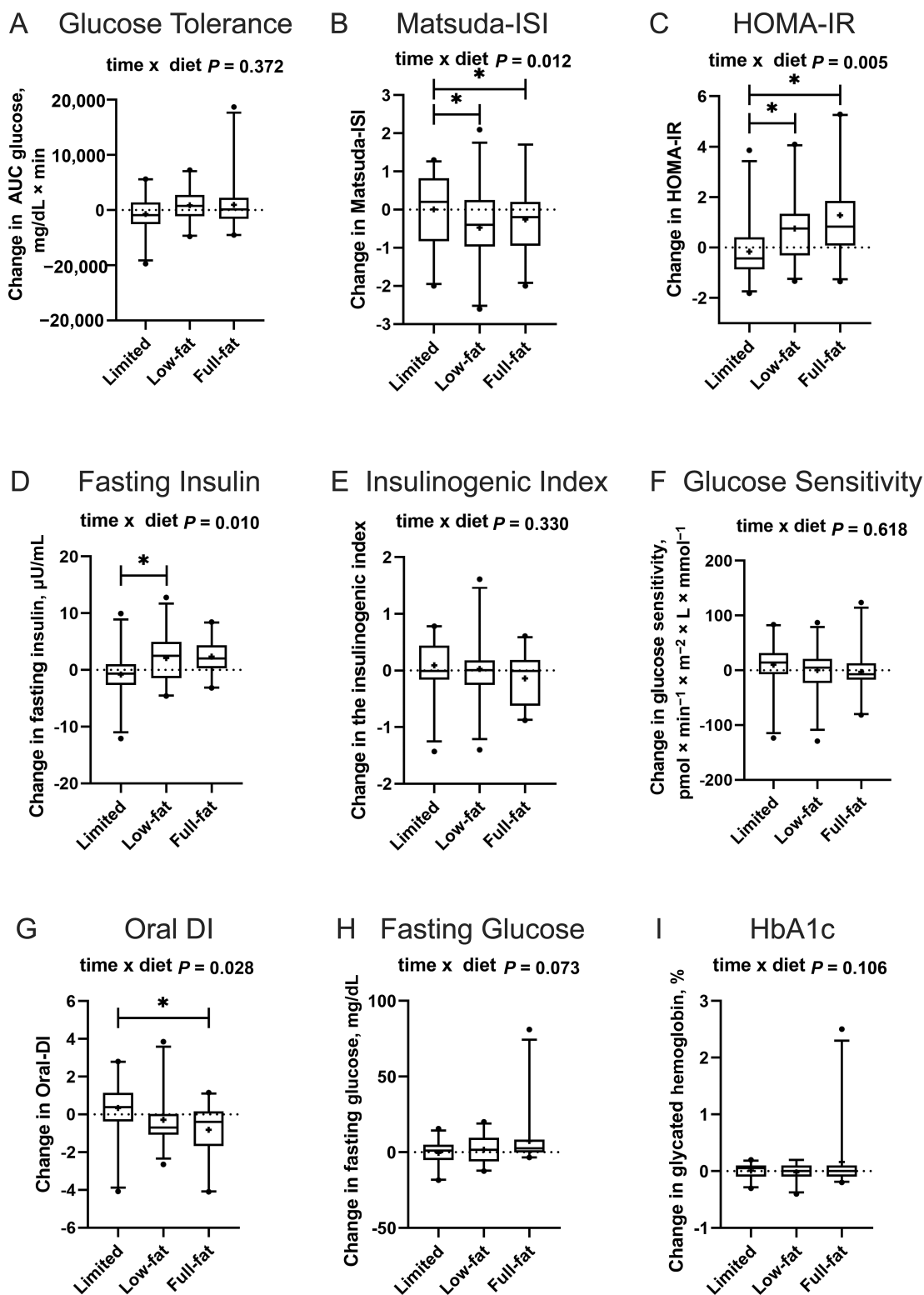
FIGURE 3 Changes in measures of glucose homeostasis, insulin sensitivity, and pancreatic β-cell function during the limited dairy diet ($n = 22$), low-fat dairy diet ($n = 24$) and full-fat dairy diet ($n = 21$) (per-protocol analysis, $n = 67$). Glucose homeostasis and its determinants were assessed by (A) glucose tolerance, i.e., the glucose AUC, (B) the Matsuda ISI, (C) the HOMA-IR index, (D) fasting plasma insulin, (E) the insulinogenic index, (F) glucose sensitivity, (G) the oral DI, (H) fasting plasma glucose, and (I) HbA1c. Outcome variables are represented as the change variable calculated as the value at follow-up minus the value at baseline. Boxes represent IQRs, and whiskers 5th and 95th percentiles, with outliers represented by a solid dot. The medians are represented by horizontal bars across the boxes and the means are represented by crosses. The P values for the time × diet interactions from the overall RM-ANOVA, adjusted for baseline glucose AUC, fasting glucose, and HbA1c, as appropriate, are displayed at the top of each box plot. Bars indicate significant differences between diet groups in post hoc testing (independent-samples t tests or RM-ANOVA with 2 diet groups), again adjusted for baseline AUC glucose, fasting glucose, and HbA1c, as appropriate (*$P < 0.05$ after adjustment for multiple testing according to Bonferroni). HbA1c, glycated hemoglobin; ISI, insulin sensitivity index; oral DI, oral disposition index; RM-ANOVA, repeated-measures analysis of variance.
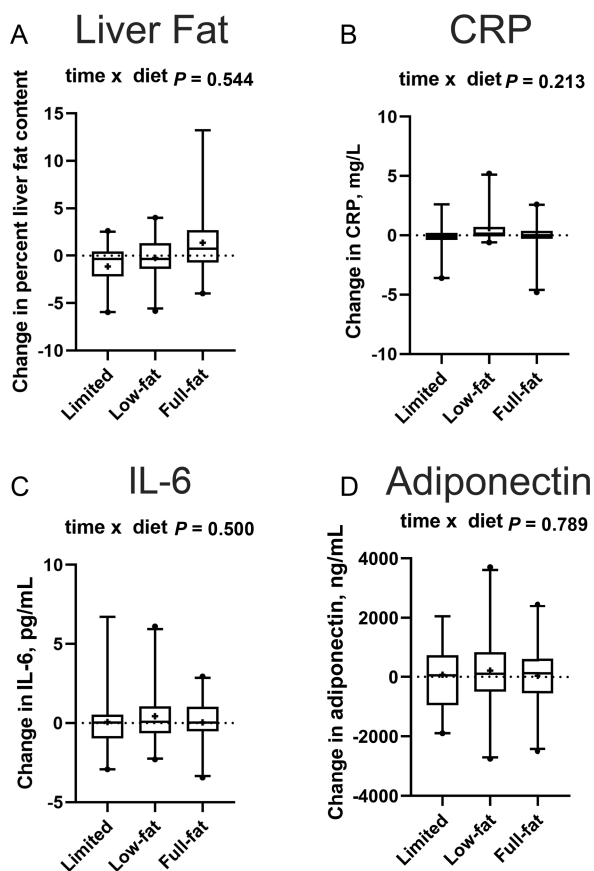
FIGURE 4 Changes in liver fat content (A) and measures of low-grade chronic systemic inflammation (B–D) in the limited dairy diet ($n = 20$ and $n = 19$, respectively), low-fat dairy diet ($n = 22$ and $n = 20$, respectively), and the full-fat dairy diet ($n = 19$ and $n = 20$, respectively) (per-protocol analysis, $n = 61$ for liver fat, $n = 59$ for biomarkers of inflammation). Outcome variables are represented as the change variable calculated as the value at follow-up minus the value at baseline. Boxes represent IQRs, and whiskers 5th and 95th percentiles, with outliers represented by a solid dot. The medians are represented by horizontal bars across the boxes and the means are represented by crosses. The P values for the time × diet interactions from the overall repeated-measures ANOVA are displayed at the top of each box plot. CRP, C-reactive protein.

given that the gut microbiome is an emerging determinant of insulin sensitivity (47).

Another key finding from our trial was that there were no differential effects of our diets on liver fat content or biomarkers of systemic inflammation. The only additional endpoints with intervention effects were body weight, waist circumference, and fat mass. Both body weight and waist circumference were more strongly increased in participants consuming full-fat dairy foods and had intermediate effects in participants consuming low-fat dairy foods. This increase in weight and waist circumference was associated with higher total energy intake, suggesting that participants did not reduce their ad libitum energy intake from nondairy foods enough to fully compensate for the energy consumed in the form of mandatory dairy foods. Energy intake increased in the full-fat dairy group as measured both during the 5-d controlled ad libitum feeding period and through multiple unannounced 24-h dietary recalls, suggesting that the inability to compensate for the caloric content of mandatory dairy foods was sustained throughout the intervention period. This indicates that

dairy consumption, and particularly full-fat dairy consumption, in the context of an ad libitum diet, increases energy intake resulting in increased adiposity. This conclusion is in alignment with the result of a recent meta-analysis that showed that dairy intake consistently increased weight in ad libitum studies (48). Our study adds to this literature by providing evidence that full-fat dairy foods increase adiposity to a larger extent than their low-fat counterparts.

Our finding that neither the low-fat nor the full-fat dairy diet had an effect on glucose tolerance is consistent with previous RCTs (16–19). Our data provide additional assurance that null findings in prior trials were not due to the fact that these trials included mostly low-fat unfermented dairy foods. Our finding of decreased insulin sensitivity in participants consuming dairy is also consistent with several prior trials (49–51). At the same time, the majority of previous studies found no effect of dairy consumption on insulin resistance (16–27, 52) and several trials found improvements in insulin sensitivity in participants increasing their dairy intake (52–56). One factor that may explain the differential effects on insulin sensitivity is the duration of the interventions: all studies that showed a reduction in insulin sensitivity were 12 wk in duration or shorter (49–51), whereas almost all studies that showed an improvement in insulin sensitivity were 12 wk in duration or longer (52–54, 56). Another potential factor is that our study was conducted in individuals with the metabolic syndrome, whereas most of the previous studies used comparatively healthier participants, or a population with a less homogeneous metabolic health profile (16–20, 23–25, 27, 49, 50, 52, 53, 55).

The results of our study are greatly at odds with data from observational cohort studies. Five meta-analyses evaluating the effect of dairy foods on T2D concluded that there is a significant inverse relation between dairy consumption and risk of T2D (4–8), with particularly consistent data linking low-fat dairy, yogurt, and plasma biomarkers of dairy fat intake to reduced T2D incidence (11, 14, 15, 57). One possible explanation for the discrepancy between the observational data and findings from trials is that residual confounding may have contributed to the associations in observational studies. It is also possible that effects of increasing dairy consumption on glucose homeostasis were less beneficial in trials given that individuals who are interested and invested in their health are more likely to participate, creating a healthy participant bias. With regards to the data utilizing dairy fat biomarkers, a potential explanation may be that early metabolic changes not commonly measured in observational studies that eventually lead to T2D, such as an increase in liver fat content, affect the concentration of dairy fat biomarkers in plasma phospholipids, thereby confounding the observed association.

This study had multiple strengths that increase our confidence in the results: it is the only study to date to our knowledge that directly compared a variety of low-fat with full-fat dairy foods on glucose tolerance; it assessed glucose homeostasis through dynamic testing; results were basically identical for per-protocol and ITT analyses; we controlled for changes in body weight and fat mass statistically; and participant compliance was excellent. Limitations of this study include a lack of generalizability of the results to populations other than those with metabolic syndrome, and the duration of our dairy intervention, which, even at 12 wk, may have been insufficient
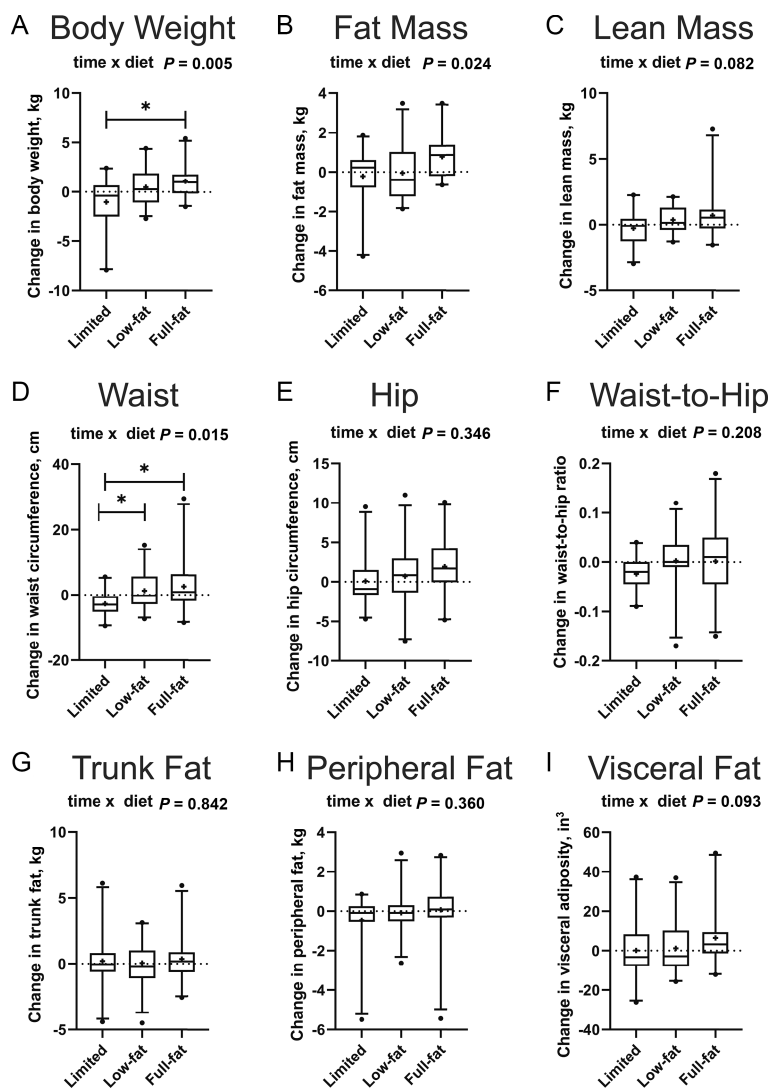
FIGURE 5 Changes in measures of body weight, anthropometrics, and body composition in the limited dairy diet ($n = 21$), low-fat dairy diet ($n = 24$), and the full-fat dairy diet ($n = 21$) (per-protocol analysis, $n = 66$). (A) Body weight, (B) total fat mass, (C) lean mass, (D) waist circumference, (E) hip circumference, (F) waist-to-hip ratio, (G) trunk fat mass, (H) peripheral fat mass, and (I) visceral fat area. Outcome variables are represented as the change variable calculated as the value at follow-up minus the value at baseline. Boxes represent IQRs, and whiskers 5th and 95th percentiles, with outliers represented by a solid dot. The medians are represented by horizontal bars across the boxes and the means are represented by crosses. The P values for the time × diet interaction from the overall RM-ANOVA are displayed at the top of each box plot. Bars indicate significant differences between diet groups in post hoc (independent-samples t tests or RM-ANOVA with 2 diet groups) testing (*$P < 0.05$ after adjustment for multiple testing according to Bonferroni). RM-ANOVA, repeated-measures analysis of variance.

to fully capture the long-term implications of habitual dairy consumption.

In conclusion, our study indicates that consuming 3 servings of milk, yogurt, and cheese per day, regardless of fat content, did not affect glucose tolerance in men and women with metabolic syndrome. However, both low-fat and full-fat dairy consumption resulted in a modest decrease in insulin sensitivity. It is unclear whether these changes would persist with prolonged exposure and would affect glucose tolerance and increase the risk of T2D over time. The effect of the dairy diets on insulin sensitivity was not explained by changes in systemic inflammation, liver fat content, body weight, or fat mass. Consuming 3 servings of dairy, particularly full-fat dairy, per day also resulted in an increase in ad libitum energy intake, body weight, and waist circumference.

Future studies should investigate potential mechanisms by which dairy consumption may reduce insulin sensitivity and assess whether similar effects are seen in healthy populations. Although results from a single study are insufficient to revise guidelines, the findings from the present study suggest that lower dairy intake may be beneficial in individuals with the metabolic syndrome.

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