Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults[1–3]

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ABSTRACT

Background: Few prospective studies have examined dairy fat in relation to cardiovascular disease (CVD).

Objective: We aimed to evaluate the association between dairy fat and incident CVD in US adults.

Design: We followed 43,652 men in the Health Professionals Follow-Up Study (1986–2010), 87,907 women in the Nurses' Health Study (1980–2012), and 90,675 women in the Nurses' Health Study II (1991–2011). Dairy fat and other fat intakes were assessed every 4 y with the use of validated food-frequency questionnaires.

Results: During 5,158,337 person-years of follow-up, we documented 14,815 incident CVD cases including 8974 coronary heart disease cases (nonfatal myocardial infarction or fatal coronary disease) and 5841 stroke cases. In multivariate analyses, compared with an equivalent amount of energy from carbohydrates (excluding fruit and vegetables), dairy fat intake was not significantly related to risk of total CVD (for a 5% increase in energy from dairy fat, the RR was 1.02; 95% CI: 0.98, 1.05), coronary heart disease (RR: 1.03; 95% CI: 0.98, 1.09), or stroke (RR: 0.99; 95% CI: 0.93, 1.05) ($P > 0.05$ for all). In models in which we estimated the effects of exchanging different fat sources, the replacement of 5% of energy intake from dairy fat with equivalent energy intake from polyunsaturated fatty acid (PUFA) or vegetable fat was associated with 24% (RR: 0.76; 95% CI: 0.71, 0.81) and 10% (RR: 0.90; 95% CI: 0.87, 0.93) lower risk of CVD, respectively, whereas the 5% energy intake substitution of other animal fat with dairy fat was associated with 6% increased CVD risk (RR: 1.06; 95% CI: 1.02, 1.09).

Conclusions: The replacement of animal fats, including dairy fat, with vegetable sources of fats and PUFAs may reduce risk of CVD. Whether the food matrix may modify the effect of dairy fat on health outcomes warrants further investigation. *Am J Clin Nutr* doi: 10.3945/ajcn.116.134460.

Keywords: animal fat, cardiovascular disease, dairy fat, prospective, vegetable fat

INTRODUCTION

Dairy fats are predominantly saturated fat, and dairy products are major food sources of saturated fat and contribute to approximately one-fifth of total saturated fat intake in the US diet (1). Saturated fat intake increases LDL cholesterol (2) and may induce chronic inflammation (3), and, thus, may increase risk of cardiovascular disease (CVD)[9] (4). Conversely, specific fatty acids (FAs) in dairy have been associated with lower cardiometabolic risk (2, 5, 6). Prospective cohort studies have shown inconsistent results regarding the association between dairy products and CVD risk regardless of dairy fat contents (7). Few epidemiologic studies have examined the relation between dairy fat intake and CVD. A recent cohort study showed no significant association between circulating biomarkers of dairy fat and stroke (8); however, the relation of dairy fat intake with CVD risk remains unclear and may largely depend on replacement foods and nutrients. A previous meta-analysis showed that the replacement of saturated fat with carbohydrates was not associated with coronary heart disease (CHD) risk, but the replacement of saturated fat with polyunsaturated fat was associated with significantly lower risk (9). Recently, other meta-analyses did not find a significant association between saturated fat and coronary disease risk (10) or butter and CVD risk (11), which has led to a debate over the role of major food sources of saturated fat such as dairy products in a healthy dietary pattern (10). Therefore, in this study, we aimed to investigate the relation between dairy fat intake and risk of CVD in 3 large cohorts of US adults with an emphasis on specific replacement sources of energy.

METHODS

Study population

We used data from the following 3 prospective cohort studies: the HPFS (Health Professionals Follow-Up Study), the NHS (Nurses' Health Study), and the NHS II. The HPFS was composed of 51,529 US male dentists, pharmacists, veterinarians, optometrists, osteopathic physicians, and podiatrists, aged 40–75 y, who returned a baseline questionnaire that inquired about detailed medical histories as well as lifestyles and usual diets in 1986. The NHS was initiated in 1976 when 121,700 female registered nurses, aged 30–55 y, who lived in 1 of 11 states completed a baseline questionnaire about their lifestyle and medical histories. In 1980, 92,468 nurses completed a food-frequency questionnaire (FFQ), which was treated as the baseline for the NHS. The NHS II was established in 1989 and consisted of 116,671 younger female registered nurses, aged 25–42 y, who completed a baseline questionnaire that was similar to the NHS questionnaire, and 97,604 nurses of the NHS II responded to a FFQ in 1991. Detailed descriptions of the 3 cohorts have been published elsewhere (12–14). In all 3 cohorts, questionnaires were administered at baseline and biennially thereafter to collect and update information on lifestyle practice and the occurrence of chronic diseases. The cumulative follow-up of participants in all of these cohorts was >90% of potential person-times.

In the current analysis, we excluded men and women who had diagnoses of diabetes, cancer, CVD, or coronary artery surgery before completion of the baseline dietary questionnaires (15). In addition, we excluded participants who left ≥10 of 131 food items blank on the baseline FFQ (except in the NHS in 1980 when the FFQ had 61 items) or who reported unusual total energy intakes (i.e., daily energy intake <800 or >4200 kcal for men and <500 or >3500 kcal for women). We also excluded participants without baseline information on dairy consumption or follow-up information on the date of CVD diagnosis. After exclusions, data from 43,652 HPFS participants, 87,907 NHS participants, and 90,675 NHS II participants were available for analysis (**Supplemental Figure 1**). The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health.

Assessment of dairy fat

In 1980, a 61-item FFQ was administered to NHS participants to collect information on their usual intakes of foods and beverages in the previous year. In 1984, 1986, 1990, 1994, 1998, 2002, 2006, and 2010, similar but expanded FFQs with ∼131 items were sent to these participants to update their diet records. Dietary data were collected with the use of similar expanded FFQs in 1986, 1990, 1994, 1998, 2002, and 2006 from the HPFS participants and in 1991, 1995, 1999, 2003, and 2007 from NHS II participants.

In all FFQs, we asked participants how often, on average, they consumed a specified amount of each food. There were 9 possible responses, which ranged from never or <1 time/mo to ≥6 times/d. Nutrient intake was calculated with the use of food-composition databases primarily from USDA sources (16). Questionnaire items on dairy products included skim and low fat milk, whole milk, ice cream, yogurt, cottage and ricotta cheese, cream cheese,

other cheese, and cream. From 1994 in the NHS and HPFS and from 1995 in the NHS II, yogurt consumption was separated into 2 items of plain yogurt (plain or with NutraSweet) and flavored yogurt (without NutraSweet). Standard serving sizes were an 80-oz glass (240 mL) for skim milk, low-fat milk, and whole milk, 1 tbsp (20 g) for cream and sour cream, 0.5 cups (122.5 g) for sherbet or frozen yogurt, ice cream, cottage, and ricotta cheese, and 1 oz (30 g) for cream cheese and other cheese. The reproducibility and validity of these FFQs have been described in detail elsewhere (17–21). Correlation coefficients between FFQs and multiple dietary records were 0.62 both for low-fat dairy and high-fat dairy foods (21), and correlation coefficients for specific dairy foods ranged from 0.57 for hard cheese to 0.97 for yogurt (17).

Dairy fat intake as well as intakes of other fats were summed across food sources and converted to nutrient densities that reflected intake as a percentage of total energy consumed. Values for the amounts of dietary fats and other nutrients in the foods were obtained from the Harvard University Food Composition Database, which is derived from USDA sources (22), and supplemented with information from manufacturers. In a validation study (20), the specific types of fat intake were ascertained reasonably well compared with four 1-wk dietary records collected over 1 y. Correlation coefficients between dairy fat intake (percentage of total fat) and 2 dairy plasma biomarkers, which themselves are highly variable indirect measures of dairy fat, were 0.22 ($P < 0.05$) for plasma pentadecanoic acid (15:0) and 0.16 ($P < 0.05$) for plasma heptadecanoic acid (17:0) in the NHS and HPFS (8).

Assessment of covariates

In the biennial follow-up questionnaires, we inquired about and updated information on risk factors for chronic diseases such as body weight, cigarette smoking, physical activity, medication use, and history of chronic diseases, including diabetes, hypertension, and hypercholesterolemia. In NHS and NHS II participants, we ascertained menopausal status, postmenopausal hormone use, and oral contraceptive use in the questionnaires.

Assessment of study outcome

In the current analysis, CVD outcomes were comprised of CHD, including nonfatal myocardial infarction and fatal CHD, and stroke (nonfatal or fatal). Nonfatal myocardial infarction was classified as confirmed if the criteria of the WHO were met specifically on the basis of symptoms and either electrocardiographic changes or elevated cardiac enzyme concentrations (23). Stroke cases were classified according to the criteria of the National Survey of Stroke (24), which required evidence of a neurologic deficit with a sudden or rapid onset that persisted >24 h. A pathologically confirmed cerebrovascular condition that was due to infection, trauma, or malignancy was excluded. Participants who reported a new diagnosis were asked for permission to access their medical records for the purpose of confirmation. Study physicians, who were blinded to the exposure status of participants, reviewed the medical records. CHD and stroke events for which confirmatory information was obtained by interview or letter but without medical records were designated as probable.

Deaths were identified by reports from next of kin or postal authorities or by searching the National Death Index. At least 98% of deaths in study participants were identified with the use of these methods (25). Fatal CHD was defined as International Classification of Diseases, ninth revision (http://www.cdc.gov/nchs/icd/icd9cm.htm), codes 410–412. Fatal CHD was confirmed via medical records or autopsy reports or if CHD was listed as the cause of death on the death certificate and there was previous evidence of CHD in the medical records. Similarly, we used International Classification of Diseases, ninth revision, codes 430–434 to define fatal stroke and followed the same procedures to classify confirmed or probable fatal stroke cases. Because the exclusion of probable CVD events did not alter the results, we included both confirmed and probable CHD and strokes in the analysis to maximize the statistical power. Unconfirmed CHD and stroke cases were censored in the analysis.

Statistical analysis

We calculated each individual's person-years from the date of return of the baseline questionnaire to the date of diagnosis of CVD, death, or the end of the follow-up (31 January 2010 for the HPFS; 30 June 2012 for the NHS; and 30 June 2011 for the NHS II), whichever came first. We used time-dependent Cox proportional hazard regression to estimate the HR for dairy consumption in relation to risk of CVD. Our basic model included age, calendar time with updated information at each 2-y questionnaire cycle, BMI, and total energy intake. We further adjusted for ethnicity, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use (NHS and NHS II participants only), oral contraceptive use (NHS II participants only), baseline diagnosed hypertension, and hypercholesterolemia. In the final model, we further adjusted the dietary factors, including dietary intakes of fruit, vegetables, coffee, protein, vegetable fat, and other animal fat. Coefficients from the final model were interpreted as the estimated effect of substituting a specific percentage of energy from dairy fat for the same percentage of energy from carbohydrates (excluding fruit and vegetables). When the effects of substituting other types of fat for dairy fat were estimated, the difference in the coefficients between fat sources and their covariances were used to calculate RRs and 95% CIs for the substitution effects (26). The same model was used to estimate the effects of substituting different sources of carbohydrates (i.e., from whole grains or refined grains and added sugars) for dairy fat.

We used the cumulative average of fat intakes from baseline to the censoring events to best represent a long-term diet and minimize the within-person variation (15), and we stopped updating dietary information after a self-reported diagnosis of intermediate outcomes including angina, coronary artery surgery or angioplasty, or diabetes during follow-up.

The proportional hazards assumption was tested with the use of a time-dependent interaction variable between dairy intake and months to events ($P > 0.05$ for all tests). To test for linear trend, the median value was assigned to each quintile, and this value was modeled as a continuous variable. All analyses were conducted separately in each cohort, and the results were combined by a meta-analyses approach across the 3 studies. Fixed-effect models were used because no significant heterogeneities were shown. All statistical tests were 2-sided and performed with the use of SAS software (version 9.2 for UNIX; SAS Institute Inc.).

RESULTS

We documented 5825 incident CVD cases including 4422 CHD and 1403 stroke cases during ≤24 y of follow-up in the HPFS, 8018 CVD cases (4055 CHD and 3963 stroke cases) during ≤32 y of follow-up in the NHS, and 972 cases (497 CHD and 475 stroke cases) during ≤20 y of follow-up in the NHS II. For both men and women, at baseline, dairy fat intake was inversely associated with a history of hypertension or hypercholesterolemia, cereal fiber, glycemic load, the ratio of polyunsaturated fat to saturated fat, and intake of fruit and vegetables but positively associated with coffee intake (**Table 1**).

Dairy fat was not associated with risk of CVD in age- and multivariate-adjusted models across the 3 cohorts, as shown in **Table 2**. For a 5% increase in energy from dairy fat compared with an equivalent amount of energy from carbohydrates (excluding fruit and vegetables), RRs were 1.02 (95% CI: 0.98, 1.05) for CVD, 1.03 (95% CI: 0.98, 1.09) for CHD, and 0.99 (95% CI: 0.93, 1.05) for stroke. The findings were similar in participants who did not have hypercholesterolemia and did not report any cholesterol-lowering medications at baseline, with RRs of 1.00 (95% CI: 0.96, 1.05) for CVD, 1.02 (95% CI: 0.96, 1.07) for CHD, and 0.98 (95% CI: 0.92, 1.05) for stroke per 5% increase in energy intake from dairy fat (data not shown).

Compared with 5% of energy intake from dairy fat, the same amount of energy from vegetable fat was significantly associated with a 10% decreased risk of CVD (RR: 0.90; 95% CI: 0.87, 0.93), and 11% decreased risk of CHD (RR: 0.89; 95% CI: 0.85, 0.93), and an 8% lower risk of stroke (RR: 0.92; 95% CI: 0.87, 0.97) (**Figure 1**). Similarly, the replacement of dairy fat with polyunsaturated fat was associated with a significantly lower risk of CVD (RR: 0.76; 95% CI: 0.71, 0.81), CHD (RR: 0.74; 95% CI: 0.68, 0.81), and stroke (RR: 0.78; 95% CI: 0.70, 0.88) (Figure 1). The replacement of 5% of energy from dairy fat with n–6 PUFA was associated with a 25% lower risk of CVD (RR: 0.75; 95% CI: 0.70, 0.81). The replacement of 0.3% of energy from dairy fat with α-linolenic acid and marine n–3 FA was associated with 14% (RR: 0.86; 95% CI: 0.82, 0.90) and 11% (RR: 0.89; 95% CI: 0.84, 0.94) lower risks of CVD, respectively (Figure 1).

In contrast, the substitution of 5% energy intake from other animal fat for dairy fat was significantly associated with a 6% higher risk of CVD (RR: 1.06; 95% CI: 1.02, 1.09), CHD (RR: 1.06; 95% CI: 1.02, 1.10), and stroke (RR: 1.06; 95% CI: 1.00, 1.11) (Figure 1). We did not observe a significant benefit of replacing dairy fat with the same energy intake from refined starch and added sugar ($P > 0.05$ for CVD, CHD, and stroke) (Figure 1), but the substitution of 5% of energy from dairy fat by carbohydrates from whole grains was associated with a significantly lower risk of CVD (RR: 0.72; 95% CI: 0.69, 0.75), CHD (RR: 0.66; 95% CI: 0.62, 0.70), and stroke (RR: 0.84; 95% CI: 0.78, 0.91) (Figure 1). We conducted a sensitivity analysis with further adjustment for total *trans*-fat intake, and the results remained virtually the same (data not shown).

DISCUSSION

In 3 prospective cohorts of US men and women, we showed that, compared with an equivalent amount of energy from carbohydrates (excluding fruit and vegetables), intake of dairy fat was not associated with risk of CVD. However, the replacement of dairy fat with vegetable sources of fat or PUFA was associated

TABLE 1
Baseline age-adjusted characteristics of participants in the 3 cohorts according to quintiles of dairy fat (percentage of energy intake)[1]

	HPFS (1986)			NHS (1980)			NHS II (1991)		
Characteristic	Quintile 1 (n = 8730)	Quintile 3 (n = 8730)	Quintile 5 (n = 8730)	Quintile 1 (n = 17,581)	Quintile 3 (n = 17,581)	Quintile 5 (n = 17,581)	Quintile 1 (n = 18,135)	Quintile 3 (n = 18,135)	Quintile 5 (n = 18,135)
Dairy fat, % of total energy	2.9 (2.3–3.3)[2]	5.4 (5.0–5.7)	9.3 (8.3–11.0)	3.6 (3.0–4.0)	6.1 (5.8–6.4)	9.9 (9.0–11.5)	3.4 (2.9–3.8)	5.9 (5.6–6.2)	9.6 (8.7–11.0)
Age, y	54.1 ± 9.4[3]	52.8 ± 9.6	53.5 ± 9.8	46.7 ± 7.1	46.2 ± 7.2	46.2 ± 7.3	36.9 ± 4.6	36.0 ± 4.7	35.4 ± 4.7
Physical activity, MET-h/wk	22.7 ± 32.5	21.4 ± 28.4	19.4 ± 27.6	14.7 ± 20.1	13.8 ± 19.4	13.0 ± 22.1	20.8 ± 28.6	21.0 ± 27.0	20.7 ± 27.3
BMI, kg/m^2	24.5 ± 5.0	25.0 ± 4.9	25.2 ± 5.0	24.2 ± 4.2	24.4 ± 4.3	24.5 ± 4.7	24.6 ± 5.4	24.7 ± 5.3	24.4 ± 5.2
Race, white, %	91.1	95.7	96.5	94.6	98.3	98.9	92.2	97.5	97.8
Current smoker, %	9.1	8.4	12.3	28.2	27.2	33.5	13.8	11.2	13.4
Hypertension, %	23.3	19.7	17.7	17.6	15.5	15.8	6.8	6.2	5.6
High cholesterol, %	15.6	9.9	6.8	7.7	4.9	4.5	17.3	14.0	12.1
Postmenopausal, %	NA	NA	NA	32.0	31.6	31.9	4.0	2.9	2.7
Current oral conceptive use, %	NA	NA	NA	NA	NA	NA	10.8	11.3	10.7
Total energy, kcal/d	1908 ± 617	2016 ± 603	2051 ± 658	1621 ± 430	1715 ± 426	1734 ± 470	1733 ± 565	1823 ± 542	1784 ± 556
Alcohol, g/d	13.9 ± 18.8	11.1 ± 14.7	9.4 ± 13.3	6.5 ± 10.5	5.8 ± 8.6	5.7 ± 8.7	3.2 ± 6.9	3.1 ± 5.8	3.1 ± 5.9
Cereal fiber, g/d	6.4 ± 4.7	6.0 ± 4.0	5.1 ± 3.1	5.2 ± 2.4	4.9 ± 2.0	4.0 ± 1.8	5.8 ± 3.4	5.7 ± 3.0	5.1 ± 2.6
Glycemic load	130.7 ± 31.6	124.8 ± 23.8	115.7 ± 22.8	106.9 ± 20.3	102.8 ± 15.9	95.1 ± 17.1	130.4 ± 25.7	121.4 ± 19.3	112.7 ± 18.7
Polyunsaturated-to-saturated fat ratio	0.74 ± 0.27	0.56 ± 0.15	0.42 ± 0.13	0.66 ± 0.19	0.56 ± 0.12	0.42 ± 0.11	0.64 ± 0.20	0.52 ± 0.12	0.41 ± 0.10
trans Fat, % of total energy	2.5 ± 1.3	2.9 ± 1.1	3.1 ± 1.0	1.7 ± 0.6	1.7 ± 0.5	1.8 ± 0.5	1.6 ± 0.7	1.6 ± 0.6	1.6 ± 0.6
Fruit and vegetables, servings/d	6.0 ± 3.3	5.5 ± 2.7	4.8 ± 2.4	5.4 ± 2.3	5.2 ± 2.0	4.6 ± 1.9	5.3 ± 3.3	5.2 ± 2.8	4.6 ± 2.6
Red and processed meats, servings/d	1.0 ± 0.9	1.2 ± 0.8	1.2 ± 0.8	1.0 ± 0.7	1.0 ± 0.6	1.1 ± 0.6	1.2 ± 0.8	1.2 ± 0.7	1.0 ± 0.7
Nuts, servings/d	0.5 ± 0.7	0.5 ± 0.6	0.4 ± 0.6	0.2 ± 0.2	0.2 ± 0.2	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2	0.1 ± 0.2
SSBs, servings/d	0.4 ± 0.7	0.4 ± 0.6	0.3 ± 0.6	1.0 ± 0.9	0.9 ± 0.7	0.9 ± 0.8	0.7 ± 1.2	0.4 ± 0.8	0.3 ± 0.6
Coffee, servings/d	1.8 ± 1.7	1.9 ± 1.7	2.1 ± 1.9	1.9 ± 1.5	2.1 ± 1.4	2.2 ± 1.6	1.5 ± 1.7	1.5 ± 1.7	1.7 ± 1.7

[1] Data were age standardized except for age and dairy intake. HPFS, Health Professionals Follow-Up Study; MET-h, metabolic equivalent task hours; NA, not available; NHS, Nurses' Health Study; SSB, sugar-sweetened beverage.

[2] Median; IQR in parentheses (all such values).

[3] Mean ± SD (all such values).

TABLE 2
HRs (95% CIs) of CHD, CVD, and stroke risks according to quintiles of dairy fat[1]

	Quintile of dairy fat consumption					*P*-trend	For 5% of energy
	1	2	3	4	5		
CVD							
HPFS							
Daily intake,[2] % of energy	2.9	4.2	5.4	6.7	9.3	—	—
Cases/person-years, *n*	1210/171,104	1119/171,515	1059/171,389	1190/171,079	1247/170,021	—	—
Age, BMI, and energy adjusted	1.00 (—)[3]	0.97 (0.89, 1.05)	0.93 (0.86, 1.01)	1.05 (0.96, 1.13)	1.01 (0.93, 1.09)	0.34	1.03 (0.97, 1.09)
Unadjusted for dietary factors	1.00 (—)	0.98 (0.90, 1.06)	0.94 (0.87, 1.02)	1.05 (0.97, 1.14)	1.00 (0.92, 1.08)	0.47	1.02 (0.96, 1.05)
Adjusted for dietary factors	1.00 (—)	0.97 (0.90, 1.06)	0.94 (0.86, 1.02)	1.05 (0.97, 1.134)	0.99 (0.91, 1.08)	0.63	1.02 (0.96, 1.08)
NHS							
Daily intake,[2] % of energy	3.6	5.0	6.1	7.4	9.9	—	—
Cases/person-years, *n*	1712/503,756	1465/504,675	1482/504,548	1473/504,272	1886/502,351	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.89 (0.83, 0.95)	0.91 (0.85, 0.97)	0.89 (0.83, 0.96)	1.09 (1.02, 1.17)	0.0003	1.10 (1.04, 1.15)
Unadjusted for dietary factors	1.00 (—)	0.92 (0.86, 0.99)	0.93 (0.87, 1.00)	0.91 (0.85, 0.97)	1.02 (0.95, 1.09)	0.24	1.03 (0.98, 1.08)
Adjusted for dietary factors	1.00 (—)	0.93 (0.87, 1.00)	0.94 (0.87, 1.00)	0.91 (0.84, 0.97)	0.99 (0.92, 1.05)	0.94	1.00 (0.95, 1.05)
NHS II							
Daily intake,[2] % of energy	3.4	4.8	5.9	7.2	9.6	—	—
Cases/person-years, *n*	224/356,351	184/357,148	167/357,444	172/356,690	225/355,996	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.86 (0.71, 1.04)	0.81 (0.66, 0.99)	0.86 (0.70, 1.05)	1.18 (0.98, 1.42)	0.04	1.17 (1.01, 1.36)
Unadjusted for dietary factors	1.00 (—)	0.90 (0.74, 1.09)	0.85 (0.70, 1.04)	0.90 (0.74, 1.10)	1.20 (1.00, 1.45)	0.03	1.18 (1.02, 1.37)
Adjusted for dietary factors	1.00 (—)	0.91 (0.75, 1.11)	0.87 (0.71, 1.06)	0.92 (0.75, 1.13)	1.21 (1.00, 1.47)	0.03	1.19 (1.02, 1.38)
Pooled analysis							
Adjusted for dietary factors	1.00 (—)	0.95 (0.90, 1.00)	093 (0.88, 0.98)	0.96 (0.91, 1.01)[4]	1.00 (0.95,1.05)	0.43	1.02 (0.98, 1.05)
CHD							
HPFS							
Cases/person-years, *n*	911/171,104	835/171,515	792/171,389	901/171,079	983/170,021	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.96 (0.87, 1.05)	0.93 (0.84, 1.02)	1.05 (0.95, 1.15)	1.05 (0.96, 1.15)	0.06	1.07 (1.00, 1.14)
Unadjusted for dietary factors	1.00 (—)	0.96 (0.88, 1.06)	0.93 (0.85, 1.03)	1.05 (0.96, 1.16)	1.03 (0.94, 1.13)	0.14	1.05 (0.98, 1.12)
Adjusted for dietary factors	1.00 (—)	0.96 (0.87, 1.05)	0.92 (0.84, 1.02)	1.04 (0.95, 1.15)	1.01 (0.92, 1.11)	0.32	1.04 (0.97, 1.11)
NHS							
Cases/person-years, *n*	829/503,756	736/504,675	762/504,548	732/504,272	996/502,351	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.92 (0.83, 1.01)	0.95 (0.86, 1.05)	0.90 (0.82, 1.00)	1.17 (1.07, 1.29)	<0.001	1.15 (1.07, 1.24)
Unadjusted for dietary factors	1.00 (—)	0.96 (0.87, 1.06)	0.99 (0.89, 1.09)	0.92 (0.83, 1.02)	1.08 (0.98, 1.19)	0.08	1.07 (0.99, 1.14)
Adjusted for dietary factors	1.00 (—)	0.97 (0.87, 1.07)	0.99 (0.89, 1.09)	0.91 (0.82, 1.01)	1.02 (0.93, 1.13)	0.69	1.02 (0.94, 1.09)
NHS II							
Cases/person-years, *n*	109/356,461	99/357,148	96/357,444	82/356,690	111/355,996	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.96 (0.73, 1.26)	0.97 (0.73, 1.27)	0.86 (0.65, 1.15)	1.24 (0.95, 1.61)	0.16	1.16 (0.94 1.43)
Unadjusted for dietary factors	1.00 (—)	1.01 (0.77, 1.33)	1.04 (0.79, 1.37)	0.91 (0.68, 1.22)	1.26 (0.96, 1.65)	0.14	1.17 (0.95, 1.44)
Adjusted for dietary factors	1.00 (—)	1.03 (0.77, 1.33)	1.06 (0.81, 1.41)	0.94 (0.70, 1.26)	1.30 (0.98, 1.71)	0.10	1.20 (0.96, 1.48)
Pooled analysis							
Adjusted for dietary factors	1.00 (—)	0.97 (0.90, 1.03)	0.96 (0.90, 1.03)	0.98 (0.91, 1.05)	1.03 (0.97, 1.10)	0.18	1.03 (0.98, 1.09)
Stroke							
HPFS							
Cases/person-years, *n*	299/171,104	284/171,515	267/171,389	289/171,079	264/170,021		
Age, BMI, and energy adjusted	1.00 (—)	1.01 (0.86, 1.19)	0.96 (0.82, 1.14)	1.04 (0.89, 1.23)	0.88 (0.75, 1.04)	0.17	0.92 (0.82, 1.04)
Unadjusted for dietary factors	1.00 (—)	1.01 (0.85, 1.18)	0.96 (0.81, 1.14)	1.05 (0.89, 1.24)	0.89 (0.75, 1.05)	0.23	0.93 (0.82, 1.04)
Adjusted for dietary factors	1.00 (—)	1.02 (0.86, 1.20)	0.98 (0.83, 1.16)	1.08 (0.91, 1.27)	0.92 (0.77, 1.09)	0.42	0.95 (0.84, 1.08)

(Continued)

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TABLE 2 (*Continued*)

	Quintile of dairy fat consumption					*P*-trend	For 5% of energy
	1	2	3	4	5		
NHS							
Cases/person-years, *n*	883/503,756	729/504,675	720/504,548	741/504,272	890/502,351	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.86 (0.78, 0.95)	0.86 (0.78, 0.95)	0.88 (0.80, 0.97)	1.01 (0.92, 1.11)	0.26	1.04 (0.97, 1.12)
Unadjusted for dietary factors	1.00 (—)	0.89 (0.80, 0.98)	0.88 (0.79, 0.97)	0.89 (0.80, 0.98)	0.96 (0.87, 1.06)	0.87	0.99 (0.93, 1.07)
Adjusted for dietary factors	1.00 (—)	0.90 (0.81, 0.99)	0.89 (0.80, 0.98)	0.90 (0.81, 0.99)	0.95 (0.86, 1.04)	0.56	0.98 (0.91, 1.05)
NHS II							
Cases/person-years, *n*	115/356,351	85/357,148	71/357,444	90/356,690	114/355,996	—	—
Age, BMI, and energy adjusted	1.00 (—)	0.77 (0.58, 1.01)	0.66 (0.49, 0.89)	0.86 (0.65, 1.13)	1.12 (0.86, 1.45)	0.14	1.17 (0.95, 1.45)
Unadjusted for dietary factors	1.00 (—)	0.79 (0.59, 1.04)	0.68 (0.51, 0.92)	0.88 (0.67, 1.17)	1.14 (0.88, 1.48)	0.12	1.19 (0.96, 1.47)
Adjusted for dietary factors	1.00 (—)	0.79 (0.60, 1.05)	0.69 (0.51, 0.93)	0.89 (0.67, 1.18)	1.13 (0.86, 1.48)	0.16	1.17 (0.94, 1.46)
Pooled analysis							
Adjusted for dietary factors	1.00 (—)	0.91 (0.84, 0.99)	0.89 (0.82, 0.97)	0.94 (0.86, 1.02)	0.95 (0.88, 1.04)	0.63	0.99 (0.93, 1.05)

[1]Model 1 was adjusted for age (continuous), BMI (8 categories), and total energy intake (quintiles). Model 2 was adjusted as for model 1 and for race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use (NHS I and II participants only), oral contraceptive use (NHS II participants only), baseline hypertension, and baseline hypercholesterolemia. Model 3 was adjusted as for model 2 and for dietary intakes of fruit, vegetables, coffee, protein, vegetable fat, and animal fat without dairy fat. *P*-trend values were calculated by assigning median values to each quintile and were treated as continuous variables. CHD, coronary heart disease; CVD, cardiovascular disease; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

[2]All values are medians.

[3]HR; 95% CI in parentheses (all such values).

[4]*P*-heterogeneity < 0.05.

with significantly lower risk of CVD, whereas the replacement of dairy fat with other animal sources of fat was associated with slightly higher risk of CVD. These associations were similar for CHD and stroke. The results suggest that, compared with dairy fat, vegetable sources of fat and PUFA are a better choice for reducing risks of CHD, stroke, and total CVD, although other animal fat (e.g., from meats) may be a less healthy choice than dairy fat. In addition, we showed that types of carbohydrates made a difference; the replacement of dairy fat with high-quality carbohydrates such as whole grains was associated with lower risk of CVD, but the replacement with refined starch and added sugar did not appear beneficial.

To our knowledge, this is the first large-scale prospective study to examine dairy fat intake and its replacement with other types of fat in relation to CVD risk. Other smaller prospective cohort studies have examined associations between dairy intake and CVD risk, and findings have been conflicting (27–30). Some studies that stratified dairy intake by the fat content showed a positive association of high-fat dairy with CHD (31, 32) and inverse associations of low-fat dairy consumption with CHD (31) and stroke (33). A meta-analysis suggested a modest inverse association between milk and overall CVD risk but no significant associations between high-fat and low-fat dairy intakes and CHD (27). Another meta-analysis suggested minimal associations between butter intake and risks of diabetes, CHD, and mortality (11). This result was not surprising because butter was largely compared with calories from refined starch, sugar, potatoes, and meats. In the current study, we were able to make comparisons with specific sources of calories and confirmed that the replacement of dairy fat with vegetable fats or high quality

carbohydrates such as whole grains was associated with reduced risk of CVD.

Dairy fat consists of ~60% SFAs (34, 35), which are mostly long-chain SFAs including lauric acid, myristic acid, palmitic acid, and stearic acid. Compared with unsaturated FAs, myristic acid, palmitic acid, and stearic acid increase LDL cholesterol and apolipoprotein B concentrations and the LDL-to-HDL ratio (36, 37). Compared with other SFAs, stearic acid tended to lower LDL cholesterol (2, 37). Besides SFAs, dairy fat consists of 5% *trans* FAs, which are naturally occurring in the milk of ruminant animals. These *trans* FAs can be biomarkers of dairy fat intake because *trans* FAs cannot be synthesized by humans (38). Although *trans* 18:1n–7 (vaccenic acid) is the major *trans* isomer in dairy fat, its correlation with dairy fat intake is weak probably because this *trans* isomer not only exists in dairy products but also in partially hydrogenated oils (39). A study by Sun et al. (38) suggested that *trans* palmitoleic acid (*trans* 16:1n–7) might be a more-robust biomarker for dairy fat intake, and its circulating concentration was associated with higher LDL cholesterol but also with lower triglycerides and blood pressure. However, no association was shown between circulating *trans* palmitoleate and risk of ischemic heart disease (38) or stroke (8). For other health outcomes such as diabetes, *trans* palmitoleic acid was associated with a lower fasting insulin concentration and incident diabetes in a multiethnic US cohort (40). Furthermore, circulating concentrations of the 2 odd-chain FAs pentadecanoic acid and heptadecanoic acid have reasonable correlations with dairy fat intake and, thus, may be considered as weak biomarkers of dairy fat (8, 38). In a large prospective cohort, pentadecanoic acid was associated with higher risk of

ischemic heart disease (38), but neither pentadecanoic acid nor heptadecanoic acid were significantly associated with risk of stroke in 2 large prospective cohorts (8). On the basis of a meta-analysis of 4 studies, circulating heptadecanoic acid was associated with significantly lower risk of coronary outcomes (10). However, it is unclear whether this inverse association represents the effects of dairy products, human metabolism, or unknown confounding factors.

Saturated fat, which is a major content of dairy fat, could affect the blood lipid profile and promote atherosclerosis and CVD. In a meta-analysis, saturated fat was not significantly associated with risk of CHD compared with the effect of carbohydrates (41). In contrast, the replacement of saturated fat with polyunsaturated fat was associated with lower risk (9). Our results on dairy fat are consistent with the overall findings for saturated fat, whereby the replacement of dairy fat with vegetable fat or PUFA was associated with lower risk of CVD. Future studies regarding different food sources of vegetable fat or PUFA are warranted. Ramsden

et al. (42) observed that the replacement of saturated fat with vegetable oils that were rich in linoleic acid significantly reduced serum cholesterol by 13.8% (compared with a 1% reduction in the control), but the reduction in serum cholesterol did not lead to an expected reduction in CVD mortality. However, the study was hampered by a short duration of intervention (average: 1 y), extremely high rates of dropouts, and potential confounding by the *trans*-fat content in the vegetable oils.

The strengths of the current study include a large sample size, a high rate of follow-up, and repeated assessments of dietary and lifestyle variables. The current study is also subject to limitations. First, our study populations primarily consisted of health professionals with European ancestry. Therefore, the observed associations may not be generalizable to other populations. However, previous findings from our cohorts were generally similar to those observed in other populations. Also, the high educational level of our subjects was an advantage because high-quality and reliable data could be collected from our study participants. In addition, the relative homogeneity of socioeconomic status helped reduce confounding. Second, the measurement error of a dairy fat assessment is inevitable. However, the FFQs used in these studies were validated against multiple diet records, and reasonable correlation coefficients between these assessments of dairy intake were observed. Moreover, we calculated cumulative averages from many repeated questionnaires for dietary variables to minimize random-measurement errors that might have been caused by the within-person variation and to accommodate diet changes over time. Third, we were unable to evaluate the impact of the food matrix on the association between dairy fat intake and CVD in the current analysis. Previous clinical trials that examined dairy foods with known fat contents have shown effects of the food matrix on blood lipids independent of the dairy fat content. For example, the LDL-cholesterol–raising effect of dairy fat in cheese was less than that of butter at comparable intakes of total fat and saturated fat (43), which was confirmed by the meta-analysis of clinical trials that the consumption of hard cheese lowers LDL cholesterol and HDL cholesterol compared with the consumption of butter (44). A detailed analysis of our cohorts and an updated meta-analysis showed that the regular consumption of yogurt was associated with lower risk of type 2 diabetes independent of BMI and other diabetes risk (45). Therefore, whether the food matrix may modify the effect of dairy fat on health outcomes warrants further investigation. Last, because of the observational nature of our cohorts, although we adjusted for established and potential risk factors for CVD, unmeasured and residual confounding was still possible.

In conclusion, we showed that, compared with carbohydrates in the diet, dairy fat is not associated with risk of CVD. However, the substitution of dairy fat with vegetable or polyunsaturated fats is associated with lower risk of CVD, whereas the replacement of dairy fat with other animal fat is associated with slightly higher CVD risk. In addition, the replacement of dairy fat with high-quality carbohydrates from whole grains is associated with lower risk of CVD. These results support current recommendations to replace animal fats, including dairy fat, with vegetable sources of fats and polyunsaturated fat (both n–6 and n–3) in the prevention of CVD.
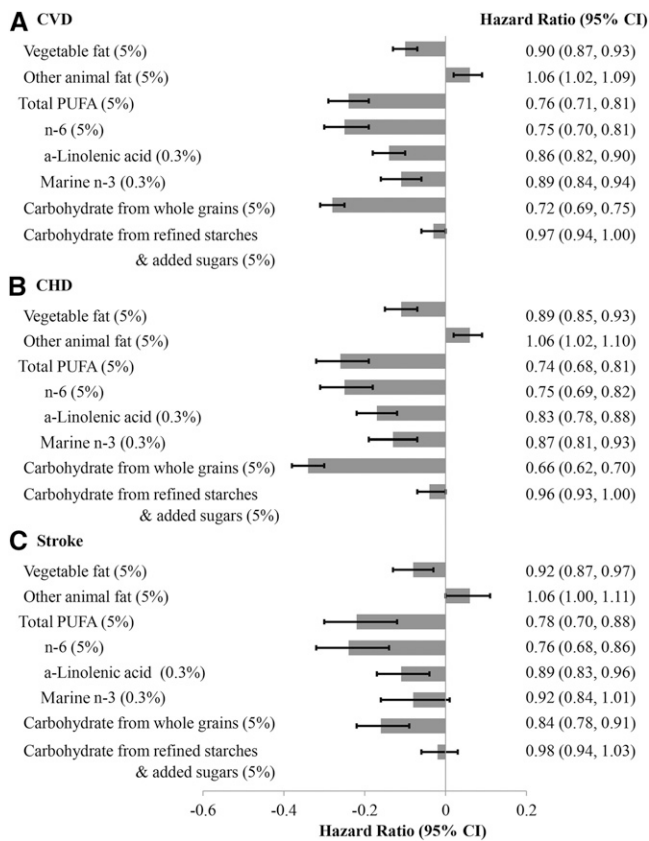

FIGURE 1 RR (95% CIs) for CVD (A), CHD (B), and stroke (C) associated with isocaloric substitutions of vegetable fat, other animal fat, PUFA, and carbohydrate for dairy fat. The 95% CIs are represented by horizontal lines, and gray bars represent overall estimates. The total sample size was 222,234 men and women at baseline with 5,158,337 person-years of follow-up. Substitution effects of substituting dairy fat with other sources of energy were estimated by the difference in the coefficients between fat sources and their covariances with the use of a time-dependent Cox proportional hazard regression model adjusted for age (continuous), BMI (8 categories), total energy intake (quintiles), race, smoking, physical activity, alcohol consumption, menopausal status and menopausal hormone use (NHS and NHS II participants only), oral contraceptive use (NHS II participants only), baseline hypertension, and baseline hypercholesterolemia, and dietary intakes of fruit, vegetables, coffee, and protein. CHD, coronary heart disease; CVD, cardiovascular disease; NHS, Nurses' Health Study.

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