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FULL RESEARCH PAPER

The association between dairy intake and risk of cardiovascular disease and mortality in patients with stable angina pectoris

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Aims The association of dairy products with cardiovascular disease and mortality risk remains heavily debated. We aimed to investigate the association between intake of total dairy and dairy products and the risk of acute myocardial infarction (AMI), stroke, and cardiovascular and all-cause mortality.

Methods and results We included 1929 patients (80% men, mean age 62 years) with stable angina pectoris from the Western Norway B-vitamin Intervention Trial. Dietary data were obtained via a 169-item food frequency questionnaire. Risk associations were estimated using Cox proportional hazard regression models adjusted for relevant covariates. Non-linear associations were explored visually. The mean (±SD) dairy intake in the study population was 169 ± 108 g/1000 kcal. Median follow-up times were 5.2, 7.8, and 14.1 years for stroke, AMI, and mortality, respectively. Higher intake of total dairy and milk were positively associated with stroke risk [HR (95% CI): 1.14 (1.02, 1.27) and 1.13 (1.02, 1.27), cardiovascular mortality 1.06 (1.00, 1.12) and 1.07 (1.01, 1.13)] and all-cause mortality [1.07 (1.03, 1.11) and 1.06 (1.03, 1.10)] per 50 g/1000 kcal. Higher cheese intake was inversely associated with AMI risk [0.92 (0.83, 1.02)] per 10 g/1000 kcal. Butter was associated with increased AMI risk [1.10 (0.97, 1.24)] and all-cause mortality [1.10 (1.00, 1.20) per 5 g/1000 kcal.

Conclusion Higher dairy and milk consumption were associated with increased risk of mortality and stroke. Cheese was associated with decreased, and butter with increased, risk of AMI. Dairy is a heterogenous food group with divergent health effects and dairy products should therefore be investigated individually.

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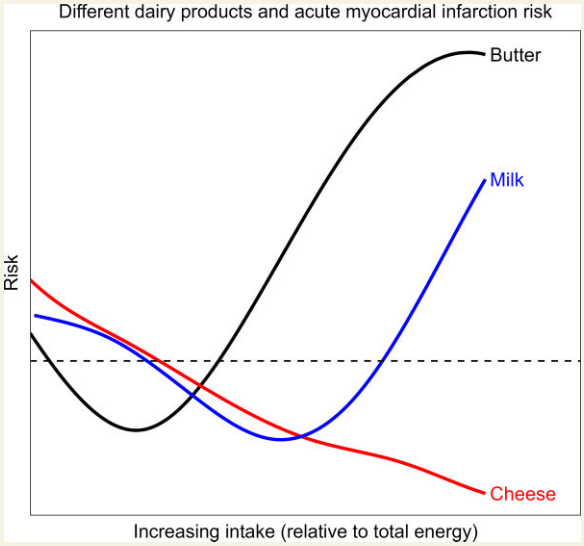
Graphical Abstract



Keywords Acute myocardial infarction • Butter • Cardiovascular disease • Milk • Cheese • Stroke

Introduction

In 2019, cardiovascular disease (CVD) was the leading cause of mortality globally and accounted for 27% of all deaths.[1] One of the most important behavioural risk factors for CVD is an unhealthy diet,[2,3] making dietary intervention a crucial preventive measure. Although there is a widespread agreement that lower intake of red and processed meat and higher intake of fruit, vegetables, and whole grains is protective against CVD, the role of dairy products remains controversial.[4–6] In Western countries, dairy products are a major source of saturated fatty acids (SFAs) and trans fatty acids, which are known to increase circulating concentrations of LDL cholesterol. Accordingly, dietary guidelines have traditionally encouraged consumption of low-fat rather than high-fat dairy products for CVD prevention,[7,8] while also acknowledging dairy as a food group rich in several nutrients including protein, calcium, and iodine. However, conflicting associations have been reported for different food sources of SFAs,[9,10] and prospective studies have failed to show a consistent link between dairy, including high-fat dairy, and CVD risk.[11–14]

Dairy products are a heterogeneous food group supplying multiple nutrients, that are both potentially beneficial (e.g. calcium, vitamin D, iodine, probiotics, and specific amino acids) and harmful (e.g. SFAs and sodium) embedded in a dairy matrix.[15] Hence, the net health effect of whole food dairy products may differ from what would be expected from the nutrient content alone.[16] Thus, the impact on health should not be characterized based on a reductionist view of single nutrient or biomarker but by the individual and collective consumption of a dairy product.[13] Several studies have reported varying effects of individual dairy products with equal amounts of SFAs.[17–21] For instance, some evidence indicates a weak but positive association between butter and total mortality,[22] whereas systematic reviews and meta-analyses have mostly failed to demonstrate consistent associations between total dairy, milk, butter, or yogurt intake and CVD risk.[11–15,23] In contrast, cheese intake has been inversely associated with CVD risk.[12,24]

These studies on the associations of dairy products with CVD risk and mortality are mainly conducted in initially healthy populations, and less is known about these risk associations in patients with established CVD. Considering the importance of dietary advice in secondary prevention, the current study aims to investigate the association between self-reported intake of total dairy products, milk, cheese, and butter, and the subsequent risk of acute myocardial infarction (AMI), stroke, cardiovascular mortality, and all-cause mortality in a cohort of patients with stable angina pectoris (SAP).

Patients and methods

Study population and design

A total of 3090 men and women undergoing coronary angiography due to suspected coronary artery disease or aortic stenosis were enrolled in the Western Norway B-Vitamin Intervention Trial (WENBIT, NCT00354081) between 1999 and 2004. Patients were recruited at Haukeland University Hospital (Bergen, Norway) and Stavanger University Hospital (Stavanger, Norway). The WENBIT study was a randomized, double-blind, placebo-controlled prospective secondary prevention study investigating the effect of vitamin B treatment on mortality and cardiovascular outcomes. Men and women >18 years undergoing coronary angiography for suspected coronary artery disease were eligible for randomization. Exclusion criteria included unavailability for follow-up, known alcohol

abuse, mental illness, or cancer. The study protocol has been described in detail previously.[25]

For this study, only patients from the WENBIT cohort with confirmed SAP were included ($n = 2573$). Patients with a missing or incomplete (at least one blank page) food frequency questionnaire (FFQ) ($n = 565$), with extreme energy intake (>17 500 kJ or <3300 kJ for men and >15 000 kJ or <3000 kJ for women; $n = 27$) or with ≥ 10E% from alcohol ($n = 52$) were excluded, leaving 1929 patients eligible for analyses. The inclusion process is depicted in Supplementary material online, *Figure S1*.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical Health Research Ethics (2010/267). All participants provided written informed consent.

Baseline data

Relevant clinical information regarding patients' lifestyle and medical history was obtained via self-administered questionnaires or interviews and they were verified using hospital records. Diabetes mellitus was defined according to pre-existing diagnosis, HbA1c >6.5%, fasting blood glucose ≥7 mmoL/L, or non-fasting blood glucose ≥11.1 mmoL/L.[26] Smoking was defined based on self-reported smoking habits (current smoking or having quit within the last 4 weeks) or serum concentration of the nicotine metabolite cotinine >85 mmoL/L at baseline.

Study endpoints and follow-up

The clinical endpoints considered were incident AMI (including fatal and non-fatal events, ICD-10 codes I21, I22, I46.1, R96, R98), stroke (including fatal and non-fatal events, ICD-10 codes I60–62, I69), cardiovascular mortality, and all-cause mortality. A coronary event was regarded as fatal if death occurred ≤ 28 days after onset. Information on AMI and stroke were obtained from the Cardiovascular Disease in Norway project (CVDNOR; www.cvdnor.w.uib.no/). Data on AMI were available until October 2015, and stroke data were available until January 2010. Data on cardiovascular and all-cause mortality were obtained from the Cause of Death Registry at Statistics Norway (www.ssb.no) until 1 January 2016.

Dietary assessment

Dietary data were obtained using a 169-item FFQ handed out at the first visit and returned to the study centre by mail or at a follow-up visit 1 month after the baseline visit. The FFQ was an adaptation from an FFQ developed at the Department of Nutrition, University of Oslo, and it was designed to capture the habitual food intake and dietary supplement use of the Norwegian population over the past year. Validation studies have been performed for total energy intake, but not for dairy products.[27,28] Depending on the food item, frequency of consumption was given as times per day, week, month, or never consumed. Food quantity was estimated using units (e.g. slices, pieces, etc.) or household measures. A software system developed at the Department of Nutrition, University of Oslo (Kostberegningssystem, version 3.2, University of Oslo, Norway) was used to calculate energy and nutrient intake.

The 'Milk' variable in this study included high-fat milk, low-fat milk, skimmed milk, and unspecified milk (for porridges, breakfast cereals, etc.). 'Cheese' included brown cheese (Norwegian caramel-like cheese made from whey, milk, and cream), white cheese, cream cheeses (including 'prim', a creamy caramel-like cheese topping), cooked/processed cheeses, and boxed cheeses. Total dairy was calculated as the sum (in grams) of milk, cheese, yogurt, cream, sour cream, ice cream, and butter.

Statistical analyses

Continuous variables are reported as means (SD), whereas categorical variables are reported as counts (percentage). To adjust dietary variables for self-reported energy intake, the density method was used and values are reported as E% or g/1000 kcal.[29] Correlation between dairy intake and intake of other food groups and macronutrients was visually assessed using scatterplots.

The associations between dairy intake and risk of AMI, stroke, cardiovascular mortality, and all-cause mortality were estimated using Cox proportional hazard regression models. Hazard ratios (HRs) are given per increment of 50 g/1000 kcal of total dairy and milk, 10 g/1000 kcal for cheese, and 5 g/1000 kcal for butter. Due to a high prevalence of reported null consumers, and in general low intake of other dairy products in the study population, no analyses were conducted for other specific dairy products. Confounding variables were identified *a priori*, based on current subject matter literature, using a directed acyclic graph approach (*Figure 1*).

To estimate the relative effect of increasing intake of dairy products, self-reported total energy intake was included as a covariate in all models. This implies that the HR should be interpreted as the change in the estimated risk for an increase in dairy intake and with a simultaneous isoenergetic decrease in the intake of other foods.[30] The first and main model was adjusted for reported energy intake, age, and sex. As dietary intake data was collected for the prior year, and body mass index (BMI) was recorded at baseline, the temporal relationship indicated that BMI was considered a mediator in the main model. However, it may also be reasonable to consider BMI as a confounder, i.e. previous BMI is the main predictor of current BMI and a key driver of total food intake. Thus, the second model was additionally adjusted for BMI. Further, the effect of BMI on food intake is not necessarily linear, and hence in the third model we modelled BMI as a penalized spline. For all models, the proportional hazards assumption was tested using the *cox.zph()* function in the *survival* package, and no substantial deviations were observed. Non-linear associations were explored visually by plotting generalized additive models (GAMs), adjusted for Model 1 covariates. Since the average HR depends on the follow-up time as it does not account for the distribution of events during follow-up,[31,32] we calculated a series of average HRs for 1 year increments in follow-up up until 10 years, adjusted for Model 1 covariates. This was done by cropping follow-up times at the yearly intervals, and changing the event status to no event for participants experiencing events at a later point. Further, to assess whether the associations differed by sex, or if the choice of energy-adjustment model influenced the results, GAMs were also plotted stratified by sex and by using the residual method to adjust for self-reported energy intakes.[29]

In accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and statement,[33] we chose not to report *P*-values in the baseline tables. Additionally, in line with the most recent statement from the American Statistical Association on *P*-values,[34] we did not dichotomize the obtained results based on *P*-value cut-offs, but rather reported effect sizes, variation, and uncertainty of the estimates as expressed by confidence intervals (CIs).

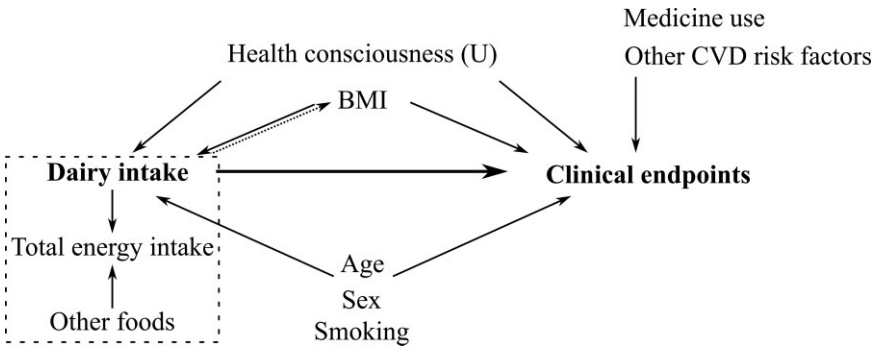


Figure 1 Directed acyclic graph illustrating the causal assumptions made during the model building process. The variables pointing both to dairy intake and clinical endpoints (acute myocardial infarction, stroke, cardiovascular mortality, and all-cause mortality) are considered confounders for this association. BMI can be considered as both a mediator (Model 1) and a confounder (Models 2 and 3). U indicates that the variable is unmeasured, and hence not taken into account. The dashed rectangle indicates that total energy intake is fully determined by dairy and other food intake. Thus, when conditioning on total energy intake, all estimates should be interpreted as isocaloric substitutions of dairy products for other foods. CVD indicates cardiovascular disease.

R version 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria) and the packages within the *tidyverse*[35] and the *survival*[36] package were used for statistical analyses and visualizations.

Results

Baseline characteristics

Baseline characteristics of the patients included in the current analyses ($n = 1929$) are shown in *Table 1*. The cohort consisted of 80% men and the mean (SD) age of the patients was 61.8 (9.7) years. In the total study cohort, 47% were diagnosed with hypertension, 31% with diabetes and 29% were active smokers. All patients had a high medicine use with acetylsalicylic acid (90%), statins (90%), and beta-blockers (77%) being the most commonly prescribed medicines.

Dietary intake

The daily dietary intake of dairy and other food groups (given in g/1000 kcal) and macronutrients (given in E%) are shown in *Table 2*. The mean (SD) reported intake of total dairy was 169 ± 108 g/1000 kcal. The main component of dairy intake was milk [133 (107) g/1000 kcal] followed by cheese [13.3 (11.8) g/1000 kcal], yogurt [11.7 (24.0) g/1000 kcal], cream, sour cream, and ice cream [8.05 (10.81) g/1000 kcal] and butter [2.70 (3.90) g/1000 kcal]. A higher relative total dairy consumption was associated with lower relative consumption of meat, vegetables, fruit and berries, fish, and potatoes (see Supplementary material online, *Figure S2*), as well as a higher proportion of energy derived from protein and a lower proportion from total fat and mono and poly-unsaturated, but not saturated, fatty acids (see Supplementary material online, *Figure S3*).

Dairy intake and association with clinical endpoints

During a median follow-up of 7.8 (25th, 75th percentiles: 6.4, 9.1) years, 309 (16%) incident cases of AMI were observed. For stroke, the median follow-up was 5.2 (3.9, 6.8) years and 52 (3%) cases were reported. Finally, 574 (30%) deaths occurred during a median follow-up of 14.1 (12.8, 15.5) years, whereof 249 (13%) of cardiovascular causes. Average HRs (95% CI) for the endpoints during the full follow-up times are presented for total dairy, milk, cheese, and butter (*Table 3*). Including BMI to Model 2 and 3 did not materially impact the outcomes.

For the association between total dairy or milk intake and AMI risk, the data were completely compatible with the assumption of no association (HR = 1.0) in all models. However, A U-shaped association was observed in the continuous analyses, with the lowest risk observed at reported intakes of ∼200 g/1000 kcal/day. In the main model (Model 1), each 50 g/1000 kcal increment in the intake of total dairy [1.14 (1.02, 1.27)] and milk [1.13 (1.02, 1.27)] was associated with increased risk of stroke. A similar pattern emerged for all-cause mortality [HR 1.07 (1.03, 1.11) and 1.06 (1.03, 1.10) for total dairy and milk, respectively] and CVD mortality [1.06 (1.00, 1.12) and 1.07 (1.01, 1.13), respectively]. These associations were approximately linear across the full intake ranges (*Figure 2E, F, I, J, M*, and *N*).

Cheese was associated with a lower risk of AMI [0.92 (0.83, 1.02)] per 10 g/1000 kcal increment, although the data was also compatible with no effect or a small increase in AMI risk. Continuous analyses indicated a linear inverse association with AMI risk (*Figure 2C*). For stroke, CVD mortality, and all-cause mortality risk, the data were compatible with no association, and the continuous analyses did not suggest any particular patterns (*Figure 2G, K, O*).

Butter intake was positively associated with AMI risk [1.10 (0.97, 1.25)], and all-cause mortality [1.10 (1.00, 1.21)] per 5 g/1000 kcal additional intake. However, for both outcomes the data was compatible with no association, and for AMI also a small decrease in risk. The continuous analyses suggested an approximately linear association with AMI risk at reported intakes exceeding about 2 g/1000 kcal/day (*Figure 2D*). For all-cause mortality, the continuous analyses suggested that the increased risk primarily was seen at intakes up to 5 g/1000 kcal/day, before flattening (*Figure 2P*). The associations with stroke and CVD mortality were inconclusive and fully compatible with no association.

Table 1 Key characteristics of included study participants

Variable	Total cohort	Percentiles				
	(*n* = 1929)	10	25	50	75	90
Age, y	61.8 ± 9.7	49.0	55.0	62.0	69.0	75.0
Male, *n* (%)	1539 (80%)	—	—	—	—	—
BMI, kg/m^2	26.4 ± 3.7	22.0	24.0	26.0	28.0	31.0
Hypertension[a], *n* (%)	911 (47%)	—	—	—	—	—
Diabetes[b], *n* (%)	592 (31%)	—	—	—	—	—
Smoking[c], *n* (%)	560 (29%)	—	—	—	—	—
Blood lipids						
Total cholesterol, mmoL/L	5.02 ± 1.2	3.80	4.20	4.90	5.60	6.50
LDL cholesterol, mmoL/L	3.04 ± 1.0	1.93	2.30	2.85	3.60	4.40
HDL cholesterol, mmoL/L	1.26 ± 0.3	0.9	1.00	1.20	1.42	1.70
ApoB, g/L	0.88 ± 0.2	0.61	0.71	0.84	1.01	1.18
ApoA1, g/L	1.28 ± 0.3	0.98	1.10	1.26	1.43	1.60
TG, mmoL/L	1.79 ± 1.2	0.84	1.10	1.54	2.20	2.99
Inflammation and kidney function						
CRP, mg/L	3.26 ± 6.35	0.45	0.81	1.65	3.25	6.69
eGFR, ml/min/1.73m^2	89.7 ± 15.5	69.0	81.0	92.0	100	107
Medicine use, *n* (%)						
Acetylsalicylic acid	1737 (90%)	—	—	—	—	—
Statins	1721 (89%)	—	—	—	—	—
Beta-blockers	1492 (77%)	—	—	—	—	—
ACE inhibitor	384 (20%)	—	—	—	—	—
Calcium blockers	461 (24%)	—	—	—	—	—
Loop diuretics	176 (9%)	—	—	—	—	—

Continuous variables are presented as mean ± standard deviation and specific percentiles. Categorical variables are presented as count (%).
[a]Defined as receiving medical treatment for hypertension.
[b]Defined according to pre-existing diagnosis, HbA1c >6.5%, fasting blood glucose ≥7 mmoL/L or non-fasting blood glucose ≥11.1 mmoL/L.
[c]Defined according to self-reported smoking habits and serum cotinine-levels >85 nmoL/L at baseline.
ACE indicates angiotensin-converting enzyme; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; TG, triglycerides.

Sensitivity analysis

The risk association for all clinical endpoints with increasing intake of dairy products depended on follow-up time (*Figure 3*). The association for total dairy and milk intake with stroke risk was strongest during the first 2 years of follow-up, before approaching the overall estimate (*Figure 3E* and *F*). The inverse associations observed for cheese intake with AMI risk persisted with increasing follow-up (*Figure 3C*). For stroke, CVD mortality and all-cause mortality, an inverse association was observed during the first 3–5 years, before approaching no association (*Figure 3G, K, O*). The association for butter with AMI risk was not observed during the first 4 years of follow-up but was then accentuated with increasing follow-up (*Figure 3D*). The increased all-cause mortality risk was not observed during the first 7 years of follow-up (*Figure 3P*). Sex-stratified analyses demonstrated no major differences between males and females (see Supplementary material online, *Figure S4*). Replacing the density method with the residual method for energy adjustment did not materially influence the shape of the associations (see Supplementary material online, *Figure S5*). Additional adjustments for baseline serum LDL, ApoB, or Statin use at baseline did not influence the results (data not shown).

Discussion

Main findings

In this population of patients with SAP, we observed a positive, linear association between total dairy intake and risk for stroke, cardiovascular mortality, and all-cause mortality. A similar association was observed for milk intake alone. This association was not observed for cheese intake, where a negative, linear relationship was found for AMI risk. Butter intake was associated with increased AMI and all-cause mortality risk. Sensitivity analysis showed that risk estimates were attenuated over time, except for the association between butter and AMI risk which was accentuated.

Dairy, disease, and mortality

Our results support the suggestion that not all dairy products are alike regarding health and disease. First, some dairy products are fermented (e.g. yogurt and some cheeses) which are suggested to have neutral or positive effects on CVD or mortality risk in observational studies.[37–39] Second, some dairy products are more homogenized which causes fat droplets present in milk fat to become smaller

Table 2 Daily dietary intake of study participants

Variable	Total cohort ($n = 1929$)	Null consumers	Percentiles				
		n (%)	10	25	50	75	90
Dairy products, g/1000 kcal							
Total Dairy	169 ± 108	1 (0.1%)	41.7	84.7	154	233	315
Milk	133 ± 107	10 (0.5%)	11.3	41.1	118	194	275
Whole milk	11 ± 41	636 (33.0%)	0.00	0.00	0.20	0.40	20.6
Low-fat milk	63 ± 88	232 (12.0%)	0.00	1.30	6.60	106	185
Skimmed milk	38 ± 80	1401 (72.6%)	0.00	0.00	0.00	45.8	150
Unspecified milk	21 ± 22	57 (3.0%)	3.20	7.20	15.1	27.0	44.3
Cheese	13 ± 12	149 (7.7%)	1.00	5.10	10.3	18.2	28.9
White cheese	10 ± 10	310 (16.1%)	0.00	2.40	6.70	13.1	22.9
Brown cheese	4 ± 6	835 (43.3%)	0.00	0.00	1.20	5.20	10.5
Yogurt	12 ± 24	936 (48.5%)	0.00	0.00	0.80	12.2	35.2
Cream, Sour Cream and Ice cream	8 ± 11	203 (10.5%)	0.00	1.70	4.70	10.1	18.5
Butter	3 ± 4	71 (3.7%)	0.20	0.50	1.40	3.00	6.50
Other food groups, g/1000 kcal							
Meat	55 ± 23	1 (0.1%)	26.7	39.0	53.3	68.9	85.1
Vegetables	106 ± 75	2 (0.1%)	37.4	57.5	88.7	134	189
Fruit and berries	126 ± 86	3 (0.2%)	40.9	67.9	108	163	230
Grains	108 ± 31	0 (0.0%)	70.3	87.0	106	128	150
Potatoes	65 ± 34	11 (0.6%)	25.1	41.0	60.6	83.4	108
Fish	54 ± 29	5 (0.3%)	21.9	33.6	48.8	68.7	91.6
Egg	8 ± 6	42 (2.2%)	2.00	4.00	7.20	11.0	15.9
Energy intake, kcal	2092 ± 631	—	1320	1653	2033	2478	2953
Macronutrients, E%							
Fat	32.0 ± 5.5	—	24.9	28.4	31.8	35.7	38.9
SFA	11.8 ± 2.6	—	8.60	10.0	11.6	13.3	15.0
MUFA	10.3 ± 2.0	—	7.90	9.00	10.3	11.6	12.8
PUFA	7.22 ± 1.97	—	5.00	5.80	6.90	8.40	9.80
Protein	16.7 ± 2.5	—	13.7	15.0	16.5	18.2	19.9
Carbohydrate	49.1 ± 6.2	—	41.3	45.1	49.3	53.4	56.7

Continuous variables are presented as mean (± standard deviation). Categorical variables are presented as count (%).
MUFA indicates mono-unsaturated fatty acid; PUFA, poly-unsaturated fatty acid; SFA, saturated fatty acid.

and increase in number[40] and leaving only small fragments of the milk fat globule membrane (MFGM) intact. It has been shown that homogenized milk leads to quicker digestion of fat droplets[41] and smaller fat droplets generate more lipolysis compared to bigger ones.[42] Indeed, different dairy products with a similar total fat content caused different post-prandial responses of triglycerides, high-density lipoprotein cholesterol, and insulin in a randomized, controlled cross-over study in healthy volunteers.[21,43] We can speculate that at least part of the differential associations seen for milk, butter, and cheese may be because cheese contains intact MFGM, while milk and butter does not. Finally, dairy products differ regarding nutrient composition (e.g. calcium, fat, and protein) which may cause different effects on blood lipids and thus CVD outcomes. For example, calcium is thought to dampen post-prandial lipaemia, and protein quantity and quality have been shown to affect the post-prandial lipaemia response in high-fat diets.[44,45] All the above-mentioned differences argue for an individual evaluation of dairy products as opposed to a collective one.

Our results are comparable to the risk estimates reported by Michaelsson *et al.*[46] from two large Swedish cohorts, where increased intake of milk was associated with increased all-cause mortality during an average follow-up of 20 years. They additionally reported a slightly reduced mortality risk with increasing intakes of fermented milk, yogurt, and cheese, with stronger associations observed for females.[46] Similar results were observed for AMI risk in the female cohort.[47] In another Swedish cohort, Sonestedt *et al.*[48] observed an increased risk of mortality with intakes >1000 g/day of non-fermented milk but only marginal associations for lower intakes. They further reported lower risk with increasing intake of fermented milk and cheese. However, in a Dutch cohort including 4365 patients with previous AMI, neither total dairy, milk, or hard cheese intake was associated with cardiovascular or all-cause mortality.[49] The findings of the Dutch study agree with the results from a large meta-analysis of cohort studies including healthy volunteers.[50] The authors observed no association between total dairy intake and risk for coronary heart disease (CHD, including AMI) or stroke.

Table 3 Associations between dairy intake and clinical endpoints

Exposure	Model 1[a]	*P*	Model 2[b]	*P*	Model 3[c]	*P*
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
AMI						
n = 309 (16%), follow-up = 7.8 (6.4, 9.1)						
Total dairy	1.00 (0.95, 1.05)	0.993	1.00 (0.95, 1.05)	0.946	1.00 (0.95, 1.05)	0.990
Milk	1.00 (0.95, 1.06)	0.899	1.00 (0.95, 1.06)	0.856	1.00 (0.95, 1.06)	0.906
Cheese	0.92 (0.83, 1.02)	0.121	0.92 (0.83, 1.02)	0.126	0.92 (0.83, 1.03)	0.137
Butter	1.10 (0.97, 1.25)	0.130	1.10 (0.97, 1.24)	0.141	1.10 (0.97, 1.25)	0.143
Stroke						
n = 52 (3%), follow-up = 5.2 (3.9, 6.8)						
Total dairy	1.14 (1.02, 1.27)	0.025	1.14 (1.02, 1.27)	0.025	1.13 (1.01, 1.27)	0.027
Milk	1.13 (1.02, 1.27)	0.025	1.13 (1.02, 1.27)	0.025	1.13 (1.01, 1.26)	0.029
Cheese	1.01 (0.80, 1.27)	0.934	1.01 (0.80, 1.27)	0.931	1.02 (0.81, 1.29)	0.859
Butter	1.00 (0.70, 1.42)	0.986	1.00 (0.70, 1.43)	0.991	0.99 (0.69, 1.42)	0.939
Cardiovascular mortality						
n = 249 (13%), follow-up = 14.1 (12.8, 15.5)						
Total dairy	1.06 (1.00, 1.12)	0.041	1.06 (1.00, 1.12)	0.036	1.06 (1.00, 1.11)	0.055
Milk	1.07 (1.01, 1.13)	0.019	1.07 (1.01, 1.13)	0.017	1.06 (1.01, 1.12)	0.028
Cheese	1.00 (0.90, 1.11)	0.975	1.00 (0.90, 1.11)	0.957	1.01 (0.91, 1.12)	0.849
Butter	1.04 (0.89, 1.21)	0.608	1.04 (0.89, 1.21)	0.629	1.03 (0.88, 1.20)	0.728
All-cause mortality						
n = 574 (30%), follow-up = 14.1 (12.8, 15.5)						
Total dairy	1.07 (1.03, 1.11)	< 0.001	1.07 (1.03, 1.11)	<0.001	1.06 (1.02, 1.10)	0.001
Milk	1.06 (1.03, 1.10)	0.001	1.06 (1.03, 1.10)	0.001	1.06 (1.02, 1.10)	0.002
Cheese	0.97 (0.91, 1.05)	0.471	0.97 (0.91, 1.05)	0.478	0.98 (0.91, 1.05)	0.550
Butter	1.10 (1.00, 1.21)	0.055	1.10 (1.10, 1.20)	0.059	1.09 (0.99, 1.20)	0.076

HRs (95% CI) are given per 50 g/1000 kcal increment for total dairy and milk, per 10 g/1000 kcal for cheese, and per 5 g/1000 kcal for butter.
The follow-up time in years is presented as the median (25th, 75th percentile) follow-up time for the respective clinical endpoints.
[a]Adjusted for energy intake, sex, age, and smoking.
[b]Adjusted for energy intake, sex, age, smoking, and BMI.
[c]Adjusted for energy intake, sex, age, smoking, and BMI (spline).
AMI indicates acute myocardial infarction; HR, hazard ratio; CI, confidence interval.

However, they did observe an increased stroke risk when comparing high vs. low milk consumers. Consistent with our findings, they reported a decreased CHD risk with increasing cheese intake. However, published results are somewhat inconsistent. In the Prospective Urban Rural Epidemiology (PURE) study, a large multinational cohort study including volunteers from 21 countries across five continents, total dairy intake was inversely associated with CVD and all-cause mortality. The authors additionally reported an inverse association between milk consumption and all-cause mortality and major CVD outcomes (including AMI, stroke, and cardiovascular death). No association was observed with cheese consumption.[51] It should, however, be pointed out that other findings from PURE have also directionally conflicted with what have been observed in Western cohorts, such as the associations for carbohydrate and fats with CVD.[52]

Associations seen with different intakes of dairy may be a result of substitution effects, as changing dairy intake inevitably must be followed by an altered intake of other foods and/or total energy intake.[53] Whether our observations represent an effect of dairy *per se*, or whether the altered intake of other foods is the main driver, cannot be answered directly and is often overlooked when drawing conclusions, especially from observational studies. We adjusted for total energy intake, meaning the results must be interpreted as isocaloric substitutions of dairy for other foods. We observed lower intake of vegetables, fruit, and berries, fish, meat, and potatoes with increasing intake of total dairy (see Supplementary material online, *Figure S2*). Lower intake of vegetables, fruit and berries, and fish is in discordance with the current dietary recommendations and food-based dietary guidelines made to reduce the risk of chronic diseases including CVD,[7,8] and could partially explain the increased risk of CVD and mortality observed in our study cohort. Our observations may also be affected by the healthy consumer bias, where low intake of dairy could be regarded as a proxy marker of a health-conscious lifestyle.[54]

The literature covering associations between dairy intake and CVD, or mortality has grown largely over the past years with increasing numbers of meta-analyses and systematic reviews. However, the reported results are often contradicting. This can be attributed to the large heterogeneity between studies but also due to the differences in study design, study quality, dietary assessment method, and heterogeneity of populations.[15] Indeed, different background diets and different underlying food substitutions may have a large impact on the observed associations.[55] Further, a distinction is often

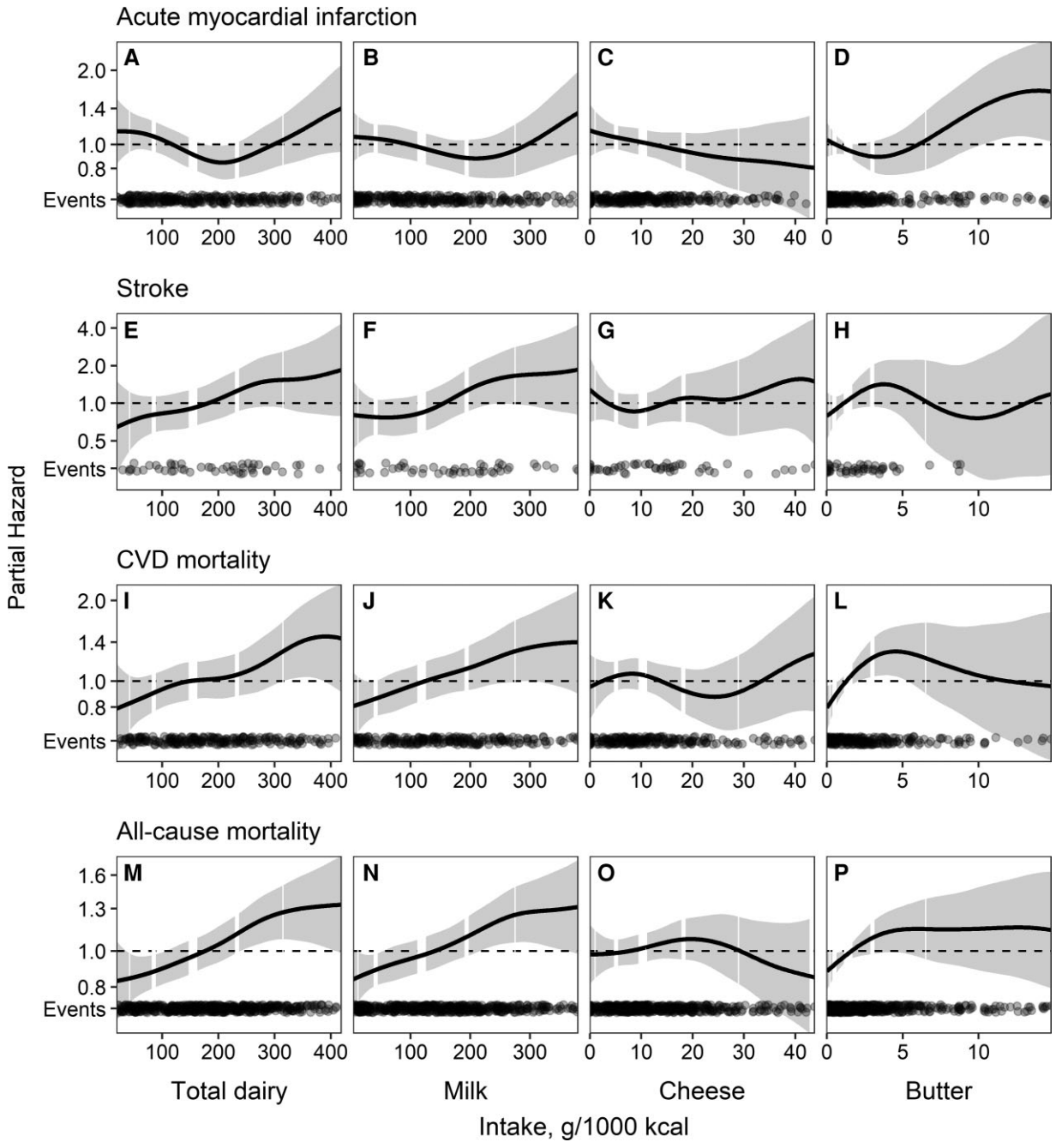


Figure 2 Generalized additive cox regression models with penalized splines representing the continuous association between the intake of total dairy, milk, cheese, and butter with the risk of acute myocardial infarction (Panels *A–D*), stroke (*E–H*), cardiovascular (*I–L*) and all-cause (*M–P*) mortality, adjusted for energy intake, age, sex, and smoking status. The solid line represents the observed association and the dark grey areas around it the 95% confidence intervals. White vertical lines indicate the 10th, 25th, 50th, 75th, and 90th percentile of intake. The distribution of clinical events across intake is plotted as dots.

made between high and low-fat dairy, but not between the individual dairy products.

Strengths and limitations

Among the strengths of the current study are the large, well-characterized, population with comprehensive information on baseline clinical characteristics. The prospective design and long-term follow-up with complete data on clinical endpoints and no loss to follow-up, due to linkage to CVDNOR and the Cause of Death Registry, additionally contribute to the strength of the study. The FFQ used for dietary assessment allows us to rank individuals according to both total dairy intake and the different dairy products. Moreover, using an FFQ avoids day-to-day variations and represents usual long-term intake. This allowed data collection from less frequently

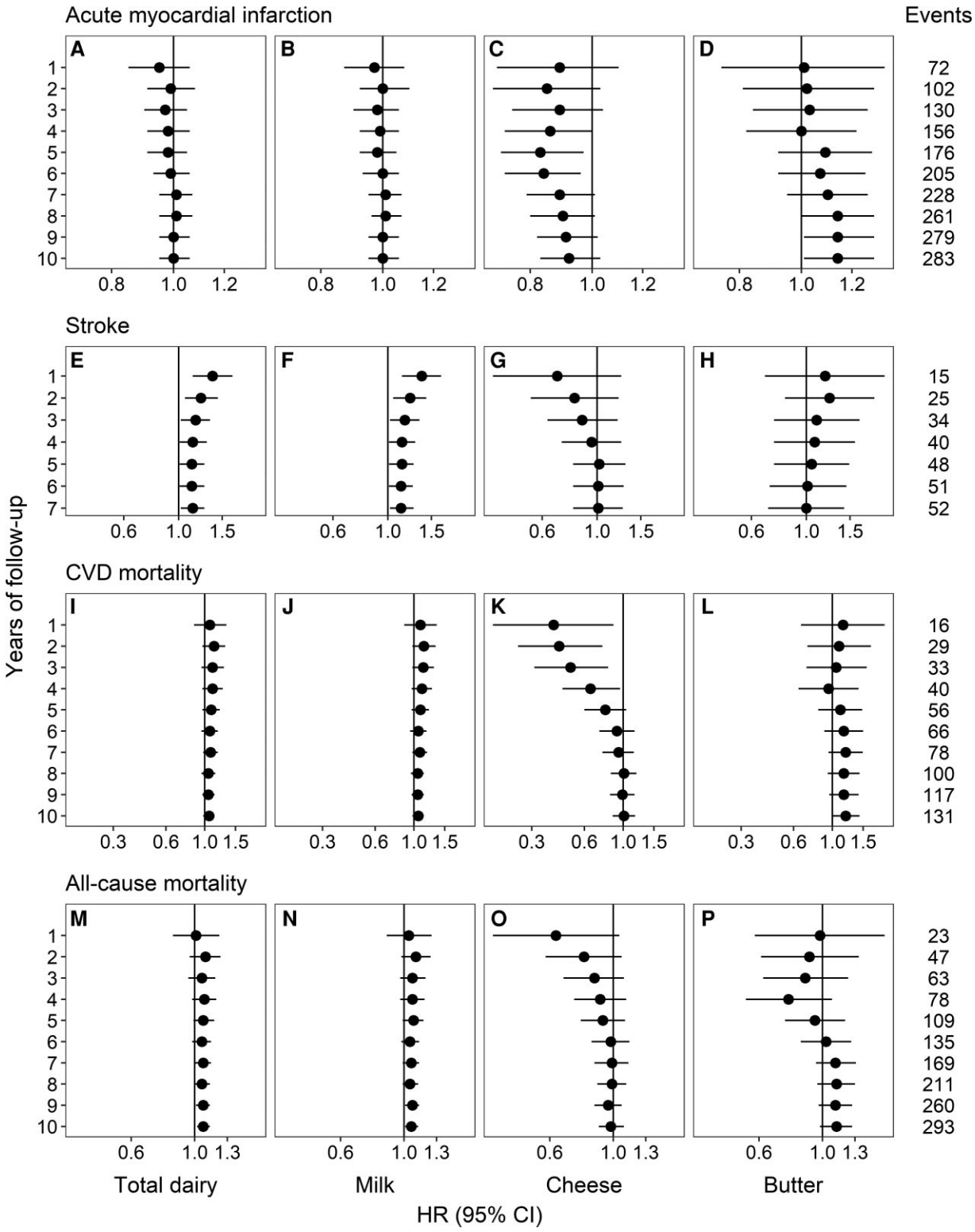


Figure 3 Associations between dairy intake and the risk of acute myocardial infarction (Panels *A–D*), stroke (*E–H*), cardiovascular (*I–L*) and all-cause (*M–P*) mortality for 1-year increments in follow-up time up to 10 years. The Cox regression model was adjusted for energy intake, age, sex, and smoking status. AMI indicates acute myocardial infarction; CI, confidence interval; HR, hazard ratio.

consumed food items. Finally, the dietary data analyses were all energy-adjusted which helps attenuate the measurement error and improves the precision when estimating diet–disease relationships.[29,56]

Some limitations also merit attention. First, the observational design limits our ability to draw causal inferences. Albeit using directed acyclic graphs, a widely used tool for causal inference, to inform our models, the presence of residual confounding cannot be excluded. Second, the study population consists of mainly, older, male cardiovascular patients. While this can be considered a strength with regard to internal validity, as the population has been shown to be representative of a general CVD disease population,[25] it limits the external validity and thereby the generalizability towards the general population. Third, as the used FFQ is not validated for the food groups included in the study, we do not have any estimates of the extent of bias in the dietary data and are not able to address the measurement further by recommended methods such as de-attenuation or regression calibration.[57] In general, the observed effect estimates are rather modest, and although we may assume an attenuation towards the null due to nondifferential measurement error, this does not necessarily apply to individual studies.[58] Fourth, diet was only measured at baseline, which prohibits us from evaluating whether the diet changed during follow-up. The patients' diagnosis may have influenced their reported dietary intake at baseline and their dietary habits during follow-up may have changed as they may have received dietary advice. Especially consumption of full-fat dairy products is discouraged for these patients due to their high SFA content and could have led to both reduced intake and underreporting.[8] Fifth, we were unable to distinguish between fermented and non-fermented, or low- and high-fat dairy products, which have been previously suggested to partly explain the varying diet-health associations observed for different dairy products. Finally, FFQ derived dietary data is well known to be affected by systematic errors, meaning that caution is warranted when interpreting the absolute intakes at face value.[59]

Conclusion

In conclusion, in a cohort of patients with established SAP, total dairy consumption was associated with increased risk for stroke, cardiovascular mortality, and all-cause mortality. Similar findings were observed for milk intake, but not cheese intake, which showed an inverse relationship with AMI risk. The diverging risk associations observed for different dairy products provide further support for the investigation of individual dairy products, rather than total dairy, in future studies.

Author contributions

V.L. and O.K.N. contributed to the conception or design of the work. A.V.P., J.S., N.G.P., and V.L. drafted the manuscript. A.V.P. and V.L. performed the statistical analyses. J.S., N.G.P., Å.M.F., T.K., T.O., T.R.H., K.J.V., K.B.H., J.D., and O.K.N. contributed to the interpretation of data and critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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