Nonfermented milk and other dairy products: associations with all-cause mortality[1,2]

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ABSTRACT

Background: A positive association between nonfermented milk intake and increased all-cause mortality was recently reported, but overall, the association between dairy intake and mortality is inconclusive.

Objective: We studied associations between intake of dairy products and all-cause mortality with an emphasis on nonfermented milk and fat content.

Design: A total of 103,256 adult participants (women: 51.0%) from Northern Sweden were included (7121 deaths; mean follow-up: 13.7 y). Associations between all-cause mortality and reported intakes of nonfermented milk (total or by fat content), fermented milk, cheese, and butter were tested with the use of Cox proportional hazards models that were adjusted for age, sex, body mass index, smoking status, education, energy intake, examination year, and physical activity. To circumvent confounding, Mendelian randomization was applied in a subsample via the lactase *LCT-13910 C/T* single nucleotide polymorphism that is associated with lactose tolerance and milk intake.

Results: High consumers of nonfermented milk (≥2.5 times/d) had a 32% increased hazard (HR: 1.32; 95% CI: 1.18, 1.48) for all-cause mortality compared with that of subjects who consumed milk ≤1 time/wk. The corresponding value for butter was 11% (HR: 1.11; 95% CI: 1.07, 1.21). All nonfermented milk-fat types were independently associated with increased HRs, but compared with full-fat milk, HRs were lower in consumers of medium- and low-fat milk. Fermented milk intake (HR: 0.90; 95% CI: 0.86, 0.94) and cheese intake (HR: 0.93; 95% CI: 0.91, 0.96) were negatively associated with mortality. Results were slightly attenuated by lifestyle adjustments but were robust in sensitivity analyses. Mortality was not significantly associated with the *LCT-13910 C/T* genotype in the smaller subsample. The amount and type of milk intake was associated with lifestyle variables.

Conclusions: In the present Swedish cohort study, intakes of nonfermented milk and butter are associated with higher all-cause mortality, and fermented milk and cheese intakes are associated with lower all-cause mortality. Residual confounding by lifestyle cannot be excluded, and Mendelian randomization needs to be examined in a larger sample. *Am J Clin Nutr* 2017;105:1502–11.

Keywords: all-cause mortality, butter, cheese, dairy products, fermented dairy products, fermented milk, milk, nonfermented milk

INTRODUCTION

Milk and other dairy products constitute important sources of energy as well as macronutrients and micronutrients in most Western countries, but intakes vary largely between populations (1). Associations between dairy intake and different disease outcomes have been evaluated in several studies, but reported associations remain contradictory (2–10). The inconclusive evidence regarding the association between nonfermented milk, specifically, and mortality has been highlighted in a recent systematic review and meta-analysis by Larsson et al. (3). The authors concluded that "large prospective studies assessing the relation between milk consumption and mortality are warranted."

In Sweden, intake of dairy products is among the highest in the world (11, 12) and is concurrent with a low prevalence of lactose intolerance (13). According to 2011 food-balance sheets by the FAO, the average per-capita milk supply in Sweden was the third highest worldwide after that of Finland and the Netherlands (14). Traditionally, low-fat milk and dairy products have been promoted as healthy and nutritious food choices by the Nordic Nutrition Recommendations (15) and international authorities (16). In line with the recommendations, a marked drop in intake of high-fat nonfermented milk in favor of medium-fat alternatives was observed in Sweden between 1986 and 1991 (17). In recent years, fat intake from dairy products has increased in Sweden (17),

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[2] Supplemental Tables 1–4 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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likely reflecting a strong promotion of low-carbohydrate, high-fat diets in the Swedish media (18). On the basis of the high consumption and wide range of intake of dairy products, Sweden offers a unique setting for studying the association of dairy intake with human health. Recently, a Swedish study by Michaëlsson et al. (19) presented a significant positive dose-response association between nonfermented milk intake and all-cause mortality for women and men, whereas an inverse association was observed for fermented dairy products. However, the study did not report the associations for nonfermented milk stratified by the fat content.

Observational nutritional studies are prone to confounding, reverse causality, and bias. To overcome confounding in observed associations between nonfermented dairy intake and all-cause mortality, the single nucleotide polymorphism (SNP)[11] *LCT-13910 C/T* (20) that predisposes individuals to lactose intolerance can be used as an instrumental variable for milk intake within the Mendelian randomization framework (21). Individuals with the CC genotype are lactose intolerant (lactase nonpersistent) with less ability to tolerate milk than are individuals with the lactase-persistent TT/TC genotypes, making this SNP an unbiased proxy exposure for milk consumption.

In the current article, we aimed to extend the analysis by Michaëlsson et al. (19) and study the association between intake of dairy products and all-cause mortality with special emphasis on reported intake of nonfermented milk in total and by fat content in >100,000 men and women in a large population-based cohort from Northern Sweden [The Northern Sweden Health and Disease Study (NSHDS)] and to apply Mendelian randomization in an attempt to reduce the effect of confounding.

METHODS

Study population and design

Participants in the Västerbotten Intervention Program (VIP) and the Northern Sweden Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study (both within the NSHDS) with available dietary information were eligible for the current study.

The VIP, which was initiated in 1985 and is still ongoing, runs in the county of Västerbotten in Northern Sweden with ~260,000 inhabitants of whom ~121,000 individuals live in the main city of Umeå. In the VIP, residents of the county are invited to a health examination when they turn 40, 50, and 60 y of age, and some communities have also invited 30-y-olds. Approximately 30% of individuals have a 10-y follow-up visit. Participants undergo an extensive health examination including measurements of anthropometric measures, blood pressure, and blood lipid profiles, an oral-glucose-tolerance test, and an extensive questionnaire on diet, lifestyle, and health conditions. The mean recruitment rate has been ~60% of available participants, and only limited evidence of selection bias in relation to income, age, and unemployment has been reported (22). No difference was observed in cancer incidence in the VIP cohort compared with in the population of Västerbotten at large, thereby providing further evidence that the VIP is a representative population cohort (23).

In the Northern Sweden MONICA study, cross-sectional samples of residents in the counties of Västerbotten and Norrbotten have been randomly selected from updated population registers every fourth to fifth year (24). Sampling was stratified to select equal numbers by sex and 10-y age intervals (the age range was 25–64 y in the 1986 and 1990 surveys and, thereafter, 25–74 y). The present study included survey data from the screenings that were performed in 1986, 1990, 1994, 1999, 2004, 2009, and 2014. The participation rate has varied between 62% and 81% over the years. Health-examination and questionnaire procedures are virtually identical to those in the VIP. Evidence of systematic bias across sociodemographic characteristics over time or between participants and nonparticipants has been minimal (25, 26).

The combined VIP-MONICA data set included 112,519 unique participants (women: 50.8%; $n = 57,160$) with ≥1 health examination that included a diet recording. Of these individuals, 9263 participants (8.2%) were excluded from the present analyses on the basis of incomplete food-intake data, extreme (highest and lowest 1%) food intakes (27), extreme energy intakes [lowest 1% and >20.9 MJ (5000 kcal)], and implausible height (<130 or >210 cm) or weight (<35 kg). Overall, 103,256 participants (women: 51.0%; $n = 52,652$) were included in the study of whom 34,677 participants had a 10-y follow-up visit available. The study flowchart for the present study is shown in **Figure 1**.

Ascertainment of mortality

Mortality endpoints until 31 December 2014 were identified by linking the VIP and MONICA databases with the Swedish national cause-of-death registry. The 12-digit Swedish personal identification numbers were used as the linkage variable. After the exclusions that were described previously, the data set included 6892 deaths (women: 41.7%; $n = 2971$) (Figure 1). The mean ± SD follow-up time was 13.7 ± 6.8 y, and the number of person-years at risk was 1,410,233 y.

Dietary assessments

All participants completed a diet and lifestyle questionnaire that included a semiquantitative Northern Sweden food-frequency questionnaire (FFQ) at each screening visit (http://www.biobank.umu.se/biobank/biobank---for-researchers/northern-sweden-diet-database/). For the present study, all MONICA screenings and VIP visits after 1991 were included and, accordingly, VIP follow-up visits were from 2001 and later. Over the study period, the following 2 versions of the FFQ were used: a longer version (84 food items and aggregates) and a shortened version (64–66 food items and aggregates). The longer version, which was used in the VIP until 1996 and in all MONICA screening occasions except the one in 1990, was completed by 41% of the participants, and the shorter version was completed by 59% of the participants. The shorter version, which has been used continuously since 1997 in the VIP, was reduced by deleting some related food items and merging related items. However, the questions

[11] Abbreviations used: FFQ, food-frequency questionnaire; MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; NSHDS, Northern Sweden Health and Disease Study; SNP, single nucleotide polymorphism; VIP, Västerbotten Intervention Program.

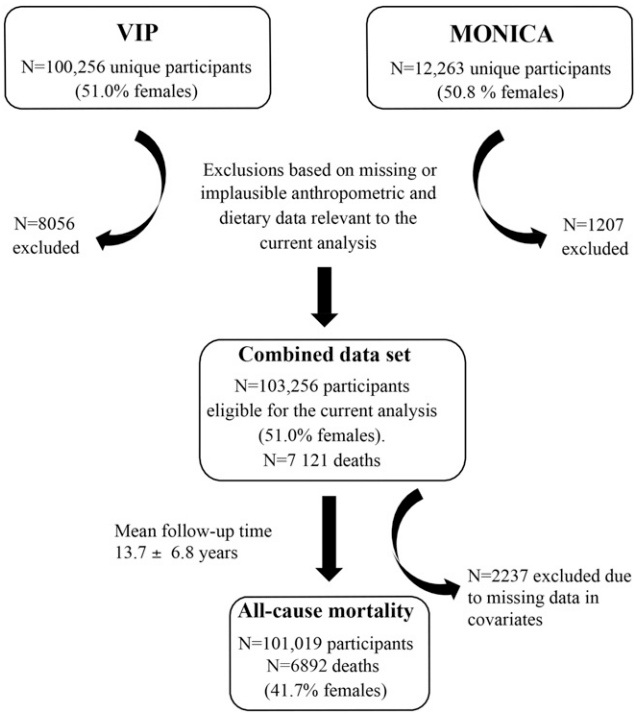

FIGURE 1 Study flowchart illustrating the analysis-specific exclusions that were applied in the VIP and the MONICA study cohorts in setting up the study sample for the current analysis. Intake of dairy products was monitored from 1986 to 2014, and the endpoint for death was 31 December 2014. MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease; VIP, Västerbotten Intervention Program.

about nonfermented milk, fermented milk, and butter products have remained identical over time. Before 1991, the FFQ included only one question on hard-cheese intake, and from 1991 and onward, intakes of high- and low-fat types of hard cheeses were queried separately. In the FFQ, intakes were reported on a fixed 9-level scale (28). Meal-time portion sizes were estimated with the support of 4 color pictures of a plate containing increasing amounts of staple foods (potato, rice, and pasta), main protein sources (meat and fish), and vegetables. For other foods, either sex- and age-specific portion sizes or fixed sizes, such as an apple or egg, were applied (28). Total estimated daily intake of energy and nutrients was calculated by weighting reported intake frequencies by the food composition that is provided by the National Food Agency (http://www.livsmedelsverket.se/en/food-and-content/naringsamnen/livsmedelsdatabasen/). Estimated intakes of energy, nutrients, vitamins, and minerals have been validated against repeated 24-h dietary records and biological markers (28–31).

A diet score that reflected healthy eating habits was calculated as previously described (32). Briefly, the daily intake frequency was calculated for 8 food and beverage groups. Favorable food groups included fish, fruit (except juices), vegetables (except potatoes), and whole-grain foods. Unfavorable food and beverage groups included red or processed meats, desserts and sweets, sugar-sweetened beverages, and fried potatoes. Intake frequencies were ranked by sex and 10-y age groups in ascending quartile ranks for favorable food and beverage groups and in descending quartile ranks for unfavorable food and beverage groups. The sum of all quartile ranks represented the Healthy Diet Score with a minimum of 0 and a maximum of 24 and with higher ranks indicating healthier food and beverage choices.

Assessment of potential confounding factors

Body weight (kilograms) and height (meters) were measured with participants wearing light clothes without shoes, and BMI (in kg/m^2) was calculated (body weight divided by the square of height). Participants were categorized as normal weight (BMI <25), overweight (BMI ≥ 25 to <30), and obese (BMI ≥ 30). Information on smoking, the highest obtained level of education, and physical activity was collected from the questionnaires. Smoking was categorized as never smoking, past smoking (having smoked daily or occasionally), and present smoking (daily or occasional smoker). For education, participants were categorized as having a university education or not. The physical activity level was estimated on the basis of the Cambridge Index of Physical Activity (33). This index is a validated index on the basis of information on occupational and leisure-time physical activity, which categorizes participants as inactive, moderately inactive, moderately active, and active, respectively. For the present analyses, the moderately inactive, moderately active, and active categories were combined, thus categorizing participants as inactive or active.

Genotyping

In a subsample of 7404 men and women, DNA was extracted from peripheral white blood cells and diluted to 4 ng/μL as previously described (34). Genotyping of the SNP *LCT-13910 C/T* (rs4988235) was performed with the use of the Sequenom iPLEX platform (Sequenom Inc.) with an SNP call rate $>95\%$. The SNP adhered to Hardy-Weinberg Equilibrium ($P = 0.003$) after adjustment for the total number of SNPs genotyped (i.e., $0.05 \div 32 = 0.001$).

Statistical analyses

Participants were categorized into 4 groups on the basis of reported intakes of nonfermented milk, fermented milk (including soured milk and yogurt), cheese, and butter, respectively [i.e., those reporting intake *1*) never or <1 time/wk, *2*) 1 time/wk to <1 time/d, *3*) 1 to <2.5 times/d, and *4*) ≥ 2.5 times/d]. Participant characteristics by intake category, including frequencies (percentages) and means (95% CIs), were calculated and adjusted for sex and age. Means of nutrient intakes were further adjusted for total energy intake and BMI. Trends in ordinal categories of dairy product intake (order: <1 time/wk, 1 time/wk to <1 time/d, 1 to <2.5 times/d, and ≥ 2.5 times/d) or milk by fat content (order: 3%, 1.5%, and 0.5% fat) were evaluated with the nonparametric Jonckheere-Terpstra trend test. The stability of reported intake of dairy products over time was evaluated in 34,677 participants with FFQ data available from a 10-y follow-up visit in the VIP.

Associations between each of the dairy exposure variables and all-cause mortality were tested in Cox proportional hazards models after the exclusion of individuals with missing data for BMI (0.5%), education (0.7%), and smoking (1.1%), which resulted in 101,019 participants and 6892 deaths (Figure 1). The models were adjusted for an increasing number of potential confounders as follows: sex and age at recruitment (crude model); plus BMI (normal weight, overweight, and obese); plus screening year;

plus smoking status (never, past, or current smoking); plus education (university compared with nonuniversity); plus total energy intake (kilojoules per day) (adjusted model). Models that excluded subjects with missing data on BMI and education were also tested, as these covariates were significantly associated with the all-cause mortality. Missing values for smoking and physical activity were included as separate dummy variables. In subsequent analyses, the Cox proportional hazards models were tested in the 41,676 participants who reported exclusive intake of one type of nonfermented milk (i.e., high-, medium-, or low-fat milk). For these analyses, participants in the lowest category of consumption (i.e., those who reported intake never or <1 time/wk) were excluded because the majority of them were characterized by a preference for another type of nonfermented milk. Dose-response analyses were performed by comparing HRs across the 4 categories of intake (as previously defined). Exclusions were done as previously described. Proportional hazards model assumptions were confirmed with the use of Schoenfeld's test (35). An effect modification by any of the confounders previously mentioned was tested with the use of Wald's test. Heterogeneity was analyzed with the use of chi-square tests. Sensitivity analyses were performed according to the exclusion of participants *1*) with missing data for physical activity (11.0%), *2*) <35 y of age, *3*) reporting intake frequencies greater than the 99th percentile, *4*) of non-Swedish origin by self-report, *5*) who died during the first 2 y of follow-up in line with commonly applied cutoff definitions (36), and *6*) with health examinations before 1991 (i.e., before the question on cheese intake was split into 2 questions and when the major transition from high- to medium-fat nonfermented milk had taken place). Additional adjustment for dairy product–related variables, such as vitamin D, calcium, and lactose (proxy for galactose), and the Healthy Diet Score were done. Furthermore, in an effort to further reduce potential bias from lifestyle variables, analyses were repeated in a restricted more homogeneous group of never and previous smokers with >9 y of education (compulsory school in Sweden) and overall diet pattern assessed by the Healthy Diet Score >12 (median value for the entire cohort).

A Mann-Whitney *U* test was used to study differences in nonfermented milk intake between individuals with different genotypes of the *LCT-13910 C/T* SNP with the use of a dominant genetic model (TT and TC genotype carriers compared with CC genotype carriers) and a codominant genetic model (TT or TC genotype carriers compared with CC genotype carriers). Logistic regression was used to study association between *LCT-13910 C/T* and mortality with the use of dominant and codominant genetic models including sex and age as covariates. These analyses were restricted to individuals of European descent who reported Sweden as their country of origin (n = 7404). All analyses were based on dairy intake that was reported at the baseline visit. All statistical analyses were performed with the use of SAS version 9.4 software (SAS Institute Inc.) or SPSS version 22 (IBM Analytics Inc.) software.

Ethical considerations

The study protocol and data-handling procedures were approved by the Regional Ethical Review Board of Northern Sweden (registration number: 2013/332/31). All study participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Characteristics of study participants stratified by dairy intake

Characteristics of the study participants stratified by reported intake of nonfermented milk (never or <1 time/wk, 1 time/wk to <1 time/d, 1 to <2.5 times/d, and ≥2.5 times/d) are shown in **Table 1**. Although trends were significant, the mean age (range: 47–48 y) and BMI were similar across the 4 intake categories, whereas the proportions of participants with a university education and who were physical inactive decreased with increasing intake of nonfermented milk. Participants who reported nonfermented milk intake ≥2.5 times/d were most likely to be smokers. In addition, participants who reported nonfermented milk intake ≥2.5 times/d reported slightly higher proportions of energy from saturated and *trans* fatty acids, higher vitamin D and lactose intakes, and lower vitamin C intake than participants did who consumed milk less frequently (**Supplemental Table 1**). Information on the country of origin was available in 73% of the participants, which was mainly due to the fact that this information was not collected in the earliest VIP and MONICA screening years. Of individuals who reported their country of origin, the vast majority were of Swedish origin (94%) with the remaining 6% originating from other European (3.4%) and non-European (2.6%) countries.

Differences in participant characteristics varied in magnitude and direction across reported intakes of fermented milk, cheese, and butter; e.g., high consumers of fermented milk were less likely to be smokers and more likely to have a university education than were low consumers, whereas the opposite trend was seen for high consumers of butter compared with low consumers of butter, and an increasing proportion of participants with university education was observed across categories of cheese intake (Table 1). BMI and physical inactivity decreased across increasing intakes of fermented milk, butter, and cheese (Table 1). The proportion of energy intake from saturated fat increased with higher butter, cheese, and fermented milk intakes (Supplemental Table 1).

A comparison of lifestyle variables between participants who reported exclusive intake of high-, medium-, or low-fat milk is presented in **Supplemental Table 2**. Reported average daily milk intake did not differ between the nonfermented milk-fat types, but in general, participants who reported exclusive intake of high-fat nonfermented milk displayed different levels of some lifestyle-related cardiometabolic risk factors. Specifically, there was a lower proportion of individuals with a university education, and there were more smokers in this group, whereas physical activity and obesity showed the opposite trend.

Associations between reported intakes of dairy products and all-cause mortality

Cox regression analyses between all-cause mortality and intakes of nonfermented milk, fermented milk, cheese, and butter, respectively, were performed. As shown in **Table 2**, models that were adjusted for age and sex (crude model) showed positive associations with all-cause mortality for intake of nonfermented milk and butter, whereas inverse associations were obtained for fermented milk and cheese intakes. The associations for nonfermented milk, cheese, and butter remained significant, although

TABLE 1
Characteristics of study participants by category of reported intakes of various dairy products (n = 103,256)[1]

	Intake category				P-ordinal trend
	<1 time/wk	1 time/wk to <1 time/d	1 to <2.5 times/d	≥2.5 times/d	
Nonfermented milk					
Participants, n (%)	15,788 (15.3)	24,916 (24.1)	34,465 (33.4)	28,087 (27.2)	—
Men/women, %	45/55	50/50	45/55	55/45	<0.001
Age, y	47.4 ± 9.1[2]	46.7 ± 9.5	47.3 ± 9.7	48.0 ± 9.9	<0.001
BMI,[3] kg/m^2	25.8 ± 4.3	26.0 ± 4.2	25.9 ± 4.2	26.0 ± 4.3	0.002
Present smokers,[4] %	21.1	18.4	19.5	24.7	<0.001
University education,[4] %	30.1	30.7	29.5	23.5	<0.001
Physically inactive,[4] %	19.3	18.3	18.0	16.9	<0.001
Fermented milk					
Participants, n (%)	26,419 (25.6)	47,505 (46.0)	27,972 (27.1)	1360 (1.3)	—
Men/women, %	57/43	49/51	43/57	42/58	<0.001
Age, y	46.3 ± 9.6	46.4 ± 9.7	48.0 ± 9.6	46.8 ± 9.4	<0.001
BMI,[3] kg/m^2	26.1 ± 4.3	26.0 ± 4.2	25.7 ± 4.1	25.7 ± 4.4	<0.001
Present smokers,[4] %	25.9	20.7	16.7	19.0	<0.001
University education,[4] %	23.2	27.7	33.6	35.3	<0.001
Physically inactive,[4] %	19.3	17.6	17.5	16.2	<0.001
Butter					
Participants, n (%)	32,907 (31.1)	16,238 (15.7)	17,914 (17.3)	36,197 (35.1)	—
Men/women, %	41/59	52/48	50/50	55/45	<0.001
Age, y	47.2 ± 9.6	46.2 ± 9.5	45.9 ± 9.5	47.2 ± 9.9	<0.001
BMI,[3] kg/m^2	26.2 ± 4.3	26.1 ± 4.2	26.1 ± 4.3	25.5 ± 4.1	<0.001
Present smokers,[4] %	20.6	18.3	20.6	22.5	<0.001
University education,[4] %	27.6	33.9	32.1	24.4	<0.001
Physically inactive,[4] %	18.3	17.9	18.4	17.5	0.008
Cheese					
Participants, n (%)	11,752 (11.4)	43,813 (42.4)	34,512 (33.4)	13,179 (12.8)	—
Men/women, %	52/48	53/47	44/56	46/54	<0.001
Age, y	47.0 ± 9.8	46.6 ± 9.6	47.3 ± 9.7	46.0 ± 9.7	0.322
BMI,[3] kg/m^2	26.3 ± 4.5	26.2 ± 4.3	25.7 ± 4.1	25.3 ± 4.1	<0.001
Present smokers,[4] %	21.9	20.6	21.0	20.8	0.410
University education,[4] %	23.4	27.7	29.4	31.3	<0.001
Physically inactive,[4] %	18.2	18.3	17.9	17.0	0.005

[1] Ordinal left-to-right differences between categories were calculated with the use of a nonparametric Jonckheere-Terpstra trend test.
[2] Mean ± SD (all such values).
[3] Standardized for sex and age.
[4] Proportion (percentage) in each intake category.

slightly attenuated, after additional adjustments for BMI, screening year, smoking, education, and total energy intake (adjusted model). Additional adjustment for physical activity did not change overall associations. The inverse association between intake of fermented milk and all-cause mortality disappeared when additionally adjusting for potential confounding lifestyle factors (Table 2). The results were similar (P-heterogeneity > 0.05) in men and women, but in men, the associations of nonfermented and fermented milk with all-cause mortality were no longer significant in the adjusted model, and the same relation was true for fermented milk and butter in women (data not shown).

Association of nonfermented milk with all-cause mortality stratified by fat content

We compared the HRs for all-cause mortality for the 3 types of nonfermented milk that were available on the market [i.e., high-fat milk (3%), medium-fat milk (1.5%), and low-fat milk (0.5%)] in separate models. As shown in **Table 3**, intakes of all 3 types of nonfermented milk showed significant, positive associations with all-cause mortality, and similar results were obtained when the analyses were restricted to participants who reported exclusive intake of one nonfermented milk type. However, the models that included all participants showed slightly higher HRs in subjects who reported intake of high-fat milk than in participants who consumed medium- or low-fat milk, whereas the HRs were more similar in the models that were restricted to exclusive consumers. Overall, adjustment of the models for putative confounding factors slightly reduced the magnitude and significance of the results.

HRs were also compared in exclusive nonfermented milk–type consumers in a Cox proportional model that was based on the fat content with high-fat milk as reference. As shown in **Table 4**, compared with high-fat nonfermented milk, significantly lower HRs were observed for both medium-fat milk and low-fat milk, although the HRs were attenuated in the adjusted models and were nonsignificant for low-fat milk. In line with this, all-cause mortality was significantly higher in exclusive high-fat–milk consumers (11.5%) than in participants who exclusively reported

TABLE 2
HRs (95% CIs) for intakes of dairy products and all-cause mortality calculated from Cox proportional hazard models adjusted for potential confounders[1]

	HR by dairy product			
	Nonfermented milk	Fermented milk	Cheese	Butter
Subjects in analyses,[2] *n*	101,019	101,019	101,019	101,019
Mortality cases, *n*	6892	6892	6892	6892
Person-years, *n*	1,377,035	1,377,035	1,377,035	1,377,035
HR (95% CI)[3]				
Crude model	1.05 (1.03, 1.07)***	0.90 (0.86, 0.94)***	0.93 (0.91, 0.96)***	1.03 (1.01, 1.05)***
Adjusted model	1.02 (1.00, 1.05)*	0.96 (0.92, 1.01)	0.94 (0.91, 0.97)***	1.02 (1.00, 1.04)*

[1] Crude models were adjusted for age and sex, adjusted models were further adjusted for BMI, screening year, smoking, education, and energy intake, and participants with missing values for these covariates were excluded in all models. *$P < 0.05$, ***$P < 0.001$.

[2] Exclusion of participants with missing values for covariates in the adjusted model reduced the number of observations from 103,256 to 101,019 and the number of deaths from 7121 to 6892. Additional adjustment for physical activity (excluding those with missing information) did not affect HRs but reduced the number of subjects in the analyses by another 11,187 persons because Cambridge Index of Physical Activity questions were not included in the initial version of the screening questionnaire.

[3] Energy and dairy intakes were included as reported intakes per day as continuous variables.

intake of medium-fat–milk (6.3%) or low-fat–milk (8.7%) alternatives ($P < 0.001$; chi-square test).

Dose-response analyses

To further explore a dose-response association between intake of nonfermented milk and all-cause mortality, HRs were calculated for increasing categories of intake with adjustment for potential confounders. The reference category was set to participants who reported intake <1 time/d when total nonfermented milk intake was the exposure and 1 time/wk to 1 time/d when the analysis was stratified by the fat content of nonfermented milk. These analyses revealed significant, positive dose-response associations between nonfermented milk intake and mortality (both total intake and by fat content). High consumers of nonfermented milk (≥2.5 times/d) had a 32% increased hazard (HR: 1.32; 95% CI: 1.18, 1.48) for all-cause mortality compared with that of individuals who consumed milk ≤1 time/wk (**Table 5**). The corresponding value for butter was 11% (HR: 1.11; 95% CI: 1.07, 1.21).

Mendelian randomization based on lactase-persistence–associated gene

To investigate if the relation between nonfermented milk intake and all-cause mortality was causal rather than driven by confounding factors, the association between all-cause mortality

TABLE 3
HRs (95% CIs) for nonfermented milk by fat content and all-cause mortality in all participants and consumers reporting intake of one milk type exclusively calculated from Cox proportional hazard models adjusted for potential confounders[1]

	HR by milk fat content		
	High fat (3%)	Medium fat (1.5%)	Low fat (0.5%)
All subjects			
Participants (reported intake ≥1 time/wk),[2] *n*	16,183	62,856	24,699
Mortality cases, *n* (%)	1551 (9.6)	3875 (6.2)	1829 (7.4)
HR (95% CI)[3]			
Crude model	1.13 (1.08, 1.18)***	1.05 (1.01, 1.08)**	1.05 (1.01, 1.10)*
Adjusted model	1.08 (1.03, 1.14)**	1.01 (0.98, 1.05)	1.03 (0.98, 1.08)
Subjects with exclusive milk-type preference[2]			
Participants (reported intake ≥1 time/wk), *n*	6177	27,966	6566
Mortality cases, *n* (%)[2]	710 (11.5)	1769 (6.3)	569 (8.7)
HR (95% CI)[3]			
Crude model	1.12 (1.05, 1.19)***	1.13 (1.08, 1.19)***	1.09 (1.01, 1.18)*
Adjusted model	1.06 (0.99, 1.13)	1.08 (1.03, 1.14)**	1.07 (0.98, 1.16)

[1] Crude models were adjusted for age and sex and adjusted models were further adjusted for BMI, screening year, smoking, education, and energy intake. Participants with missing values for these covariates were excluded in all models. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[2] Additional adjustment for physical activity with exclusions made for missing information did not affect any HR. Models including all subjects and missing values as a dummy category only affected the HR (95% CI) by 1 unit of the second decimal.

[3] Energy and dairy intakes were included as reported intakes per day as continuous variables.

TABLE 4
Relative associations of nonfermented milk intake by fat content and all-cause mortality in consumers reporting intake of one milk type exclusively calculated from Cox proportional hazard models adjusted for potential confounders[1]

	HR between milk type[2]			
	High fat (3%)	Medium fat (1.5%)	Low fat (0.5%)	*P*-trend
Participants (reporting intake ≥1 time/wk), *n*	6177	27,966	6566	—
Mortality cases, *n* (%)	710 (11.5)	1769 (6.3)	569 (8.7)	—
HR (95% CI)[2]				
Crude model	Reference	0.78 (0.71, 0.85)***	0.84 (0.75, 0.94)**	0.002
Adjusted model	Reference	0.90 (0.82, 0.98)*	0.94 (0.84, 1.05)	0.101

[1] Crude model was adjusted for age and sex, and the adjusted model was further adjusted for BMI, screening year, smoking, education, and energy intake. Participants with missing values for these covariates were excluded in all models. *P*-trend values were calculated by treating categories of milk as a continuous variable (i.e., high fat = 1, medium fat = 2, and low fat = 3). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

[2] Milk type was included in the model as a categorical variable, and high-fat nonfermented milk intake is the reference. The analyses were restricted to consumers reporting exclusive intake of high-, medium-, or low-fat nonfermented milk ≥1 time/wk. Energy was included as reported intake per day as a continuous variable. Additional adjustment for physical activity with exclusions made for missing information did not affect any HR. Models including all subjects and missing values as dummy categories only affected the HR and 95% CI by 1 unit of the second decimal.

and the *LCT-13910 C/T* variant was tested. Of 7404 participants of European origin (who reported Sweden as their country of origin) with available genotype data, 484 individuals (6.5%) had the CC lactase-nonpersistent genotype, whereas 2630 individuals (35.5%) and 4290 individuals (58.0%) had either TC or TT lactase-persistent genotypes, respectively.

Nonfermented milk intake was significantly lower in participants with the CC genotype than in participants with the TC genotype ($P = 2.91 \times 10^{-5}$; Mann–Whitney *U* test) or TT genotype ($P = 1.21 \times 10^{-6}$; Mann–Whitney *U* test) under a co-dominant genetic model (**Table 6**). Similar results were observed for the CC-genotype group compared with the TC- and TT-genotype groups combined under a dominant genetic model ($P = 2.14 \times 10^{-6}$; Mann–Whitney *U* test). The numbers of study participants by genotype and nonfermented milk–intake category are presented in Table 6.

Compared with CC lactase-nonpersistent participants, mortality ORs in a co-dominant model were 1.08 (95% CI: 0.80, 1.46) for TC lactase-persistent participants and 1.06 (95% CI: 0.79, 1.43) for TT lactase-persistent participants. For the dominant model, the mortality OR was 1.07 (95% CI: 0.80, 1.43) for TC and TT lactase-persistent participants compared with CC lactase-nonpersistent participants (Table 6).

Stability of intakes from baseline to follow-up

Of 103,256 participants, 34,677 VIP participants with a baseline visit in 1991 or later had a 10-y follow-up and were administered a second FFQ that allowed for an evaluation of the stability of dairy intake over time. Overall, the proportion of participants who reported intakes of various dairy products including nonfermented milk in total and by fat content were similar over the 10-y period, and similar results were observed for participants who reported exclusive intake of 1 type of nonfermented milk by fat content at baseline ($n = 13,856$ persons) (**Supplemental Table 3**).

Sensitivity analyses

Several sensitivity analyses were performed including additional adjustment for a Healthy Diet Score and intakes of lactose (also a proxy for galactose), vitamin D, and calcium, respectively. Separate analyses were also performed with the exclusion of participants who *1*) had an incomplete set of physical activity questions for the Cambridge Index of Physical Activity, *2*) were <35 y of age, *3*) were characterized by extreme dairy intakes ($n = 878$), *4*) reported a non-Swedish origin, *5*) had died during the first 2 y of follow-up ($n = 9834$), or *6*) were recruited before 1991 (before the major transition from high-fat to medium-fat nonfermented milk occurred). None of the sensitivity analyses materially changed the results. Finally, none of the covariates included in our models showed evidence of acting as an effect modifier of the association between each dairy exposure and all-cause mortality.

Overall, the HRs (95% CIs) for intakes of various dairy products and all-cause mortality in the restricted more homogeneous sample ($n = 33,486$) (**Supplemental Table 4**) were in line with those seen in all participants (Table 2), although significance was no longer reached. Thus, for nonfermented milk, the HR in the restricted group was 1.04 (95% CI: 0.98, 1.11; $P = 0.186$).

DISCUSSION

The present study investigated the association between intake of dairy products and all-cause mortality in adults within the VIP and MONICA study, both of which are population-based cohorts from Northern Sweden and parts of the NSHDS. The Northern Sweden population is characterized by high nonfermented milk consumption and lactase persistence. Thus, average intake of nonfermented and fermented milk in Swedes has been estimated to be 83 kg/y (95th percentile: 195 kg/y) of which 50 kg/y (95th percentile: 83 kg/y) constituted nonfermented milk (37). We were able to confirm the positive association between nonfermented milk intake and all-cause mortality that was previously reported by Michaëlsson et al. (19) in another Swedish population and further extended this finding to show that the association with all-cause mortality was present regardless of the fat content of nonfermented milk, albeit it was most pronounced for high-fat nonfermented milk. In addition, butter intake was positively associated with all-cause mortality, whereas intake of fermented dairy products [i.e., cheese and fermented milk (soured

TABLE 5
HRs (95% CIs) by reported intake category of nonfermented milk stratified by fat content and all-cause mortality calculated from Cox proportional hazard models adjusted for potential confounders[1]

		HR (95% CI) with increasing number of potential confounders in the model	
Intake categy[2]	*n*	Crude model	Adjusted model
Total milk			
<1 time/wk	7616	Reference	Reference
1 time/wk to <1 time/d	8729	0.97 (0.86, 1.10)	0.97 (0.86, 1.10)
1 to <2.5 times/d	13,418	1.15 (1.03, 1.29)	1.12 (1.00, 1.25)*
≥2.5 times/d	10,946	1.32 (1.18, 1.48)***	1.18 (1.06, 1.33)**
P-trend		0.052	0.157
High-fat milk			
1 time/wk to <1 time/d	1698	Reference	Reference
1 to <2.5 times/d	1686	1.18 (0.96, 1.45)	1.12 (0.91, 1.39)
≥2.5 times/d	1881	1.28 (1.05, 1.56)*	1.10 (0.89, 1.35)
P-trend		0.011	0.368
Medium-fat milk			
1 time/wk to <1 time/d	8274	Reference	Reference
1 to <2.5 times/d	9478	1.18 (1.04, 1.33)*	1.14 (1.00, 1.29)*
≥2.5 times/d	7200	1.38 (1.21, 1.57)***	1.24 (1.09, 1.42)**
P-trend		<0.001	0.002
Low-fat milk			
1 time/wk to <1 time/d	1647	Reference	Reference
1 to <2.5 times/d	2254	1.19 (0.94, 1.48)	1.16 (0.92, 1.46)
≥2.5 times/d	1865	1.28 (0.99, 1.56)	1.18 (0.93, 1.49)
P-trend		0.041	0.155

[1] Crude models were adjusted for age and sex and adjusted models were further adjusted for BMI, screening year, smoking, education, and energy intake. Participants with missing values for these covariates were excluded in all models. *P*-trend values were calculated by treating categories of milk intake as continuous measures. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

[2] For total milk, all 4 categories of intake (compare with Table 1) were included, and for the nonfermented milk by fat content, the analysis was restricted to participants reporting intake ≥1 time/wk with the exclusive consumption of 1 milk type. Energy intake was included as reported intake per day as continuous variables. Additional adjustment for physical activity with exclusions made for missing information did not affect any HR. Models including all subjects and missing values as a dummy category affected the HRs (95% CI) by only 1 unit of the second decimal.

milk and yogurt)] were associated with lower risk of all-cause mortality in this study. Therefore, our results support a difference in the relation between nonfermented dairy products (regular milk and butter) and fermented dairy products (fermented milk and cheese) and all-cause mortality. Although we were not able to test soured milk and yogurt separately, similar traits and fermentation processes with added bacteria, combined with soured milk being the commonly consumed product in the study region, argue for similar biological effects of soured milk and yogurt. Calcium, vitamin D, and lactose intakes could not explain the observed associations between dairy exposures and all-cause mortality.

Studies that have investigated dairy intake as a primary or secondary exposure in relation to all-cause mortality have been either conflicting (5, 6, 19, 38, 39) or did not study the effects of single dairy foods (4, 9, 40). Therefore, we believe that our results contribute to the understanding of the different associations of single dairy-food products and health. Intake of nonfermented milk and a preference for high-fat–containing nonfermented milk were associated with a lower educational level, whereas the opposite association was true for cheese. We were not able to exclude residual confounding by socioeconomic or lifestyle factors, which was further supported by all HRs being attenuated after adjustment for the potential confounding lifestyle factors. It is difficult to draw conclusions from observational studies as to whether identified associations are causal or due to confounding by other related factors, which calls for less bias-sensitive methods or intervention studies. Because genotypes are assigned randomly at conception, the results obtained from analyses including genetic variants are not prone to confounding by lifestyle factors.

Here, we used the *LCT-13910 C/T* SNP in the framework of Mendelian randomization and showed mortality ORs pointing toward a potential causal association. However, the 95% CIs were wide and included zero, which indicated that we did not have sufficient statistical power in these analyses to accept or reject the support for a causal association. Therefore, the Mendelian randomization analyses should be repeated in a considerably larger study sample, and the presented results might be an incentive for a larger meta-analysis effort.

To our knowledge, this is the second study that shows a positive association between nonfermented milk intake and all-cause mortality in a Swedish population (19). As previously stated, dairy intakes in Sweden are among the highest worldwide (11) and are dominated by milk, with an average of 60% of milk being nonfermented (37). Thus, the positive association between intake of nonfermented milk and mortality might only be observable in countries with such a high total and wide variation in exposure as in Sweden. This may, at least in part, explain some of the discrepancies between previous studies.

There are several plausible biological explanations that could explain the opposite results for fermented and nonfermented dairy products. One possible explanation involves dairy fatty acids. However, our results do not support a simple detrimental effect of dairy fat. Although butter intake was positively associated with all-cause mortality, hard cheese, which is dominated by high-fat alternatives (>28% weight) in Sweden, was an inverse predictor. Indeed, cheese has been reported to increase LDL-cholesterol concentrations less strongly than butter at an equal fat content, thereby suggesting potential beneficial effects of cheese (including bacterial fermentation and proteolysis during ageing) over butter (41). The production of cheese curd from nonfermented milk is essentially a process in which both fat and casein are concentrated ~10-fold, whereas whey proteins, lactose, and soluble salts and enzymes are removed (42). Therefore, a possible hypothesis to explain the opposite associations of nonfermented milk compared with cheese is that production and bacterial fermentation reduce the galactose content in hard cheese. A detrimental effect of galactose is a hypothesis that has been suggested and seemingly supported by Michaëlsson et al. (19). However, the fact that adjustment for lactose intake (as a proxy for galactose intake) did not attenuate our observed associations suggests that other biological explanations may be involved. A second potential mechanism relates to the presence of bioactive peptides and host-receptor mimicking epitopes in fermented dairy products that can influence the gut microbe–host interaction with subsequent effects on immune function, cell signaling,

TABLE 6
Intake frequency of nonfermented milk and mortality ORs by *LCT-13910* genotypes (rs4988235) (n = 7404)[1]

Genotype	Intake category of nonfermented milk				P^2		Total, n	Dead, n (%)	OR (95% CI) [P][2]	
	<1 time/wk	1 time/wk to <1 time/d	1 to <2.5 times/d	≥2.5 times/d	Mann-Whitney, codominant model	Mann-Whitney, dominant model			Codominant model	Dominant model
CC (lactase nonpersistent)	114	120	160	90	Reference	Reference	484	60 (12.4)	Reference	Reference
TC (lactase persistent)	435	602	939	654	2.9×10^{-5}	2.1×10^{-6}	2630	352 (13.4)	1.08 (0.80, 1.46) [0.621]	1.07 (0.80, 1.43) [0.651]
TT (lactase persistent)	670	968	1544	1108	1.2×10^{-6}		4290	581 (13.5)	1.06 (0.79, 1.43) [0.685]	

[1] Analyses were restricted to individuals of European descent (reporting Sweden as their country of origin) per self-report.
[2] Models were adjusted for age and sex.

and overall bacteria attachment and colonization (43, 44). A different stimulation of gut-bacteria activity after intake of either milk or cheese was suggested in a recent metabolomics study that showed that the microbiota-related metabolite hippurate was significantly higher in participants who ate cheese than in milk consumers and control participants (45). In the same study, cheese consumption was associated with an increased concentration of short-chain fatty acids in the gut, which was possibly induced by gut-microbiota modulation. Finally, it should be underscored that both lifestyle and causal factors are likely to interact in an individual-determined fashion.

The strengths of the present study are the large sample size, the possibility to stratify the analyses of nonfermented milk by fat content, and the possibility to adjust for several potential confounders. Nonetheless, there are weaknesses that need to be taken into account. We are not able to exclude potential residual confounding by lifestyle variables, we are not able to adjust for galactose exposure directly but use lactose intake as a proxy, and our Mendelian randomization analyses are underpowered. Finally, although we confirm that rankings of dairy product intake are similar for a large portion of the participants with 10-y follow-up recordings, we believe that the analyses in participants with repeated measures are not justified. This is because the reduced number of observations, compared with the main analyses, would have caused a reduction in statistical power and a lack of information.

In conclusion, the positive association between total nonfermented milk intake and all-cause mortality can now be confirmed, and fermentation is likely to counteract the association of milk with all-cause mortality in the current study. Furthermore, all nonfermented milk fat types are independently associated with increased HRs, but compared with full-fat milk, the HRs are lower in consumers of medium- and low-fat milk. However, the question of whether the observed associations are due to confounding lifestyle factors cannot be answered by our Mendelian randomization substudy and needs to be further explored in larger samples.

The authors' responsibilities were as follows—GT, LMN, DS, FR, AW, and IJ: designed the study; FR, IJ, and LL: provided essential materials; GT, LMN, DS, and IJ: analyzed the data; GT and IJ: wrote the manuscript and had primary responsibility for the final content of the manuscript; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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