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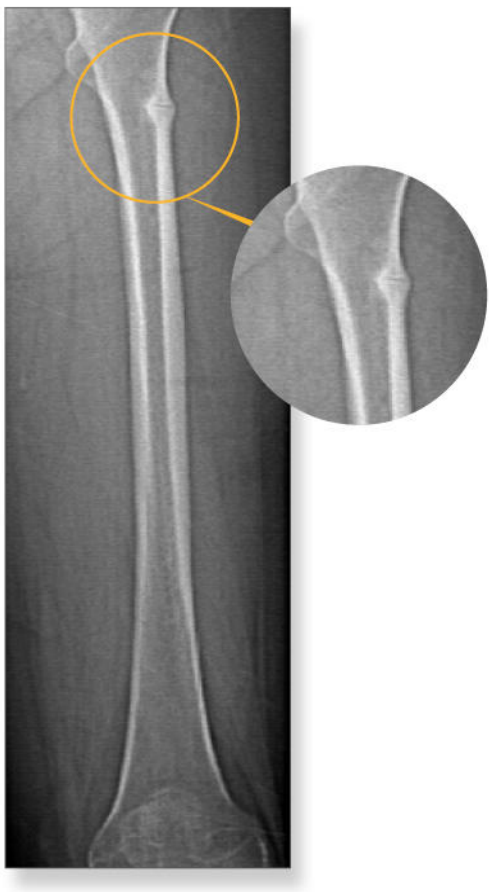

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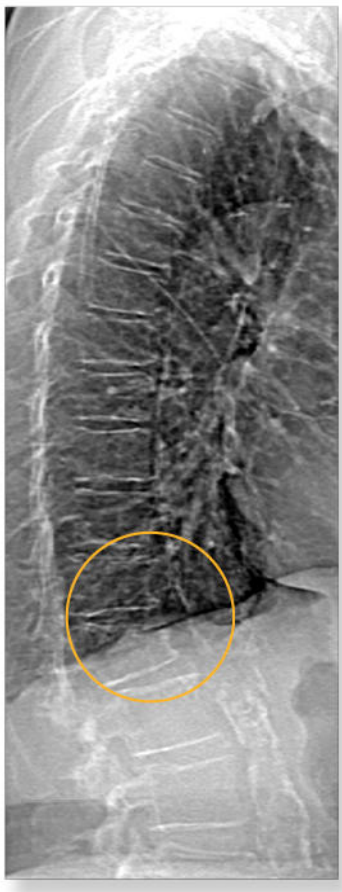

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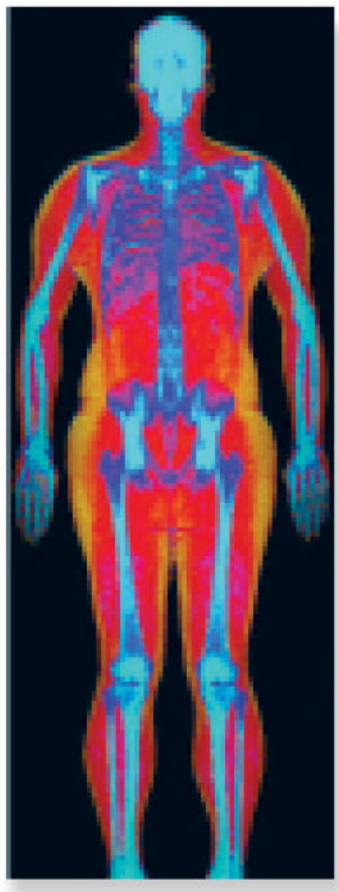

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ORIGINAL ARTICLE

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Intake of Milk or Fermented Milk Combined With Fruit and Vegetable Consumption in Relation to Hip Fracture Rates: A Cohort Study of Swedish Women

Karl Michaëlsson,[1] Alicja Wolk,[1,2] Eva Warensjö Lemming,[1] Håkan Melhus,[3] and Liisa Byberg[1]

[1]Department of Surgical Sciences, Section of Orthopedics, Uppsala University, Uppsala University Hospital, Uppsala, Sweden
[2]National Institute of Environmental Medicine, Division of Nutritional Epidemiology, Karolinska Institutet, Stockholm, Sweden
[3]Department of Medical Sciences, Section of Clinical Pharmacology, Uppsala University, Uppsala University Hospital, Uppsala, Sweden

ABSTRACT

Milk products may differ in pro-oxidant properties and their effects on fracture risk could potentially be modified by the intake of foods with antioxidant activity. In the population-based Swedish Mammography Cohort study, we aimed to determine how milk and fermented milk combined with fruit and vegetable consumption are associated with hip fracture. Women born in 1914–1948 ($n = 61,240$) answered food frequency and lifestyle questionnaires in 1987–1990 and 38,071 women contributed with updated information in 1997. During a mean follow-up of 22 years, 5827 women had a hip fracture (ascertained via official register data). Compared with a low intake of milk (<1 glass/day) and a high intake of fruits and vegetables (≥5 servings/day), a high intake of milk (≥3 glasses/day) with a concomitant low intake of fruits and vegetables (<2 servings/day) resulted in a hazard ratio (HR) of 2.49 (95% CI, 2.03 to 3.05). This higher hip fracture rate among high consumers of milk was only modestly attenuated with a concomitant high consumption of fruit and vegetables (HR, 2.14; 95% CI, 1.69 to 2.71). The combination of fruits and vegetables with fermented milk (yogurt or soured milk) yielded a different pattern with lowest rates of hip fracture in high consumers: HR, 0.81 (95% CI, 0.68 to 0.97) for ≥2 servings/day of fermented milk and ≥5 servings/day of fruits and vegetables compared with low consumption of both fruit and vegetables and fermented milk. We conclude that the amount and type of dairy products as well as fruit and vegetable intake are differentially associated with hip fracture rates in women. © 2017 American Society for Bone and Mineral Research.

KEY WORDS: MILK; DAIRY; FRUIT; VEGETABLES; HIP FRACTURE

Introduction

Hip fracture is a major public health problem and cause of disability, dependency, and excess mortality in older populations.[1,2] Consumption of milk has long been promoted to strengthen bone and reduce the likelihood of fragility fractures, but this effect has been difficult to demonstrate.[3,4] In contrast to previously dominating beliefs,[5,6] we recently showed that a high consumption of milk was associated with an increased hip fracture risk, as well as with augmented concentrations of oxidative stress and inflammation markers, especially in women.[7] Oxidative stress is a suggested pathogenic mechanism of age-related bone loss and sarcopenia,[8,9] factors known to increase the risk of hip fracture.

A diet rich in antioxidants reduces oxidative stress,[10–13] which could potentially improve health[14,15] and lower hip fracture rates as previously shown by us and several other independent cohort studies.[16–18] Because of the antioxidant properties of vegetables and fruits and pro-oxidant properties of milk that may be induced by galactose,[7] we hypothesized that a high intake of fruits and vegetables[19,20] may partially counteract the observed association between a high milk intake and increased risk of hip fracture.

Separating milk intake from the consumption of fermented milk is theoretically important. A blunted induction of oxidative stress and inflammation in humans is expected with fermented dairy products because of their possible probiotic antioxidant and anti-inflammatory effects,[21–23] effects on gut microbiota,[24–26] and their lower content of lactose and galactose.[27,28] We previously showed that those with higher fermented milk intake also have lower concentrations of oxidative stress and inflammation markers.[7]

The main objective of the present cohort study in Swedish women was to determine whether combinations of milk and fruit and vegetable intake have a different hip fracture risk pattern compared with combinations of fermented milk, such as yogurt and soured milk, and fruit and vegetable intake.

Materials and Methods

We used the previously described[7] population-based Swedish Mammography Cohort (SMC) with a longer follow-up and

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Address correspondence to: Liisa Byberg, PhD, Department of Surgical Sciences, Uppsala University, SE-751 85 Uppsala, Sweden. E-mail: liisa.byberg@surgsci.uu.se
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additional hip fracture cases. The SMC started in 1987–1990 when 74% of all 90,303 women aged 39 to 74 years residing in two Swedish counties completed a lifestyle and a food frequency questionnaire (FFQ). In 1997, a subsequent expanded questionnaire was sent to the 56,030 women still living in the study area (response rate 70%). In the present study we included 61,240 women without a prevalent cancer diagnosis at baseline (ie, 1987–1990). Of these, 38,071 contributed with updated information from 1997 (38,331 women provided information and 260 of those suffered a hip fracture before 1997). The Regional Ethical Review Boards in Uppsala and Stockholm, Sweden, approved the study.

Exposures

The participants reported via a valid and reproducible FFQ their average frequency of consumption of up to 96 foods and beverages during the past year, including milk, soured milk and yogurt, fruits, and vegetables.[29–31] There were eight possible frequency categories in increasing order from zero times/month to more than three times/day.

Milk intake and fermented milk intakes were specified according to fat content (skim milk $\leq$0.5%, reduced-fat milk 1.5%, regular milk 3%, and low-fat soured milk or yogurt 0.5%, regular soured milk or yogurt 3%) and summed into a single measure representing total nonfermented milk and fermented milk intake, respectively. In the 1997 questionnaire, the daily or weekly intake of milk and fermented milk (yogurt and soured milk) was reported using open questions. Instructions in the FFQ stated that one serving of milk or fermented milk corresponds to 200 mL. The usual means of intake in Sweden is by the glass for milk and with spoon from a bowl for yogurt and Swedish soured milk; we therefore present the intakes as glasses/day for milk and servings/day for fermented milk. Missing values for individual dairy products were interpreted as no intake of that particular product.[32] The small fraction (0.3%) of missing data reported on all single items, which were regarded as zero consumption, is unlikely to represent a bias for the observed findings.[32]

The combined daily intake of fruits and vegetables (servings/day) was calculated by adding the daily reported intakes of fruits, vegetables, and juice from the FFQs. In the 1987–1990 FFQ there were three categories of fruit (apple/pear; orange/citrus fruit; banana), five categories of vegetables (root vegetables [beetroots, carrots, etc.]; cabbage; tomatoes; lettuce, Chinese cabbage, and cucumber; spinach and kale), and one item for juice. In the 1997 FFQ there were five categories of fruit (apple/pears; orange/citrus fruit; banana; berries; other fruit), 14 categories of vegetables (carrots; beet root; broccoli; cabbage; cauliflower; lettuce; onion; garlic; peas; pea soup; peppers; spinach; tomatoes; mixed vegetables), and one item for orange/grapefruit juice. The fruit and vegetable items in the FFQs represent the consumption patterns in Sweden at the time of each investigation. A maximum of one glass of juice was included in the daily intake, even if the reported intake was higher, in accordance with national dietary guidelines (before 2015).[33] A nonresponse was considered as no intake of that item. However, those with missing data on all fruit and vegetable items were excluded. One serving of fruits and vegetables is on average 101 g (one serving of fruit 121 g, one serving of vegetables 82 g).[17]

Nutrients were estimated by multiplying the consumption frequency of each food item by the nutrient content of age-specific portion sizes (reference data obtained from the Swedish National Food Agency database[34]) and were adjusted for total energy intake using the residual method.[35] We excluded those with an implausible value for total energy intake ($\geq$3 SDs below or above the log-transformed mean energy intake).[36] The Spearman correlation between self-reported milk intake from the FFQs in the cohort and four 7-day food records every third month was 0.7.[37] Corresponding correlation coefficients ranged from 0.4 to 0.7 for individual fruit and vegetable items. The reported intake of dairy was directly correlated ($r = 0.6$) with the fat tissue content of pentadecanoic acid, a biological marker reflecting average long-term intake of milk fat, present in both milk and fermented milk products.[38]

Hip fracture identification

We considered outcomes registered between study entry (in 1987–1990) and December 31, 2014. Almost complete information on all incident hip fracture events (International Classification of Diseases, Ninth Revision [ICD9] code 820 in 1987–1996 and International Classification of Diseases and Related Health Problems, 10th Revision [ICD-10] codes S720, S721, and S722 from 1997 and onward) was obtained through linkage to the Swedish National Patient Registry. Hip fractures occurring before baseline (between 1964 and baseline in 1987–1990; identified through ICD7–ICD9 code 820) were defined as previous hip fractures. Incident hip fractures were separated from readmissions of a previous fracture by use of a previously validated and accurate method.[39] Suspected high-impact trauma fractures, <1% of all hip fractures,[40] were retained in the analysis because comparable increases in the risks of low-trauma and high-trauma fractures are seen with decreasing bone density in the elderly.[41]

Statistical analysis

We calculated time at risk for each participant from study entry (in 1987–1990) until date of hip fracture, date of death, or the end of the study period, whichever occurred first. Exposures and covariates were updated with information from the 1997 questionnaire. First, we separately evaluated trends of hip fracture rates by time-updated milk, fermented milk (yogurt and soured milk), and fruit and vegetable intake using restricted cubic-spline Cox regression with three knots placed at the 10th, 50th and 90th percentiles of the exposures.[42] As a sensitivity analysis, we examined the linear associations of time-updated intakes of milk, fermented milk, and fruit and vegetables stratified by dichotomous categories of year of birth, and baseline body mass index, healthy diet score,[7] education, marital status, and ever use of estrogen replacement therapy. Next, we calculated age-standardized hip fracture rates, age-adjusted and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for time-updated categories of milk (<1, 1 to <2, 2 to <3, $\geq$3 glasses/day) and fermented milk (0, <1, 1 to <2, $\geq$2 servings/day) across three categories of fruit and vegetable consumption (<2, $\geq$2 to <5, $\geq$5 servings/day). These a priori determined categories were chosen both to reflect extreme intakes and to be reasonably large with respect to number of hip fracture outcomes. The distributions of the intakes are shown in Supporting Fig. 1. The rates were directly standardized to the age distribution of the total population (based on the rate in the age groups 38–64 years, 65–74 years, and 75–83 years) using the "distrate" command in Stata version 13.1 (Stata Corporation, Inc., College Station, TX, USA). HRs were

calculated using Cox regression. We thereafter assessed hip fracture rates and HRs for the combined categories of milk or fermented milk and fruit and vegetable intake. The proportional hazard assumptions were confirmed graphically by log-log plots.

To select suitable covariates for the multivariable model we used present knowledge and directed acyclic graphs.[43] The simplest model considered age. The main model (model 2) for the total effect included age, body mass index (BMI, kg/m^2), height, energy intake, intake of alcohol, milk, fermented milk, cheese, red and processed meat (all continuous), educational level ($\leq$9, 10-12, $>$12 years, other), cohabiting status (living alone/living with someone), ever use of antioxidant supplements (yes/no), physical activity (metabolic equivalents, continuous), smoking status (never, former, current), and Charlson comorbidity index (continuous). To avoid loss of efficiency and limit the introduction of bias by restricting the analysis to individuals with complete data alone missing data on covariates were imputed using multiple imputation.[44] We also imputed covariates not assessed at baseline in 1987–1990 (eg, smoking status, physical activity, and supplement use).[7] In model 3 we added use of calcium-containing supplements (prescribed or over-the-counter preparations), ever use of oral cortisone, and estrogen replacement therapy. In a fourth model, to address whether major nutrients in dairy products affected our estimates, we included energy-adjusted dietary intake of calcium, vitamin D, retinol, phosphorous, protein, and total and saturated fat as covariates. We further examined how much covariates measured in 1997 only influenced estimates during follow-up from baseline 1997 by adding these (ever use of antioxidant supplements, physical activity, and smoking status) to a model with age, body mass index, height, energy intake, intake of alcohol, milk, fermented milk, cheese, red and processed meat, educational level, cohabiting status, and Charlson comorbidity index. Additional sensitivity analyses included exclusion of the first 2 years of follow-up, exclusion of second hip fracture cases and additional adjustment for supplemental vitamin D intake (prescribed or over-the-counter preparations). All statistical analyses were performed with Stata version 13.1 (StataCorp).

Results

Reflecting population changes in dairy consumption by time, about 9% of the women reported a milk consumption of $\geq$3 glasses/day in 1987–1990 (Table 1, Supporting Table 1), whereas in 1997 only 2% reported such intake (Supporting Table 2). During the same period, the proportion of women in the highest category of fermented milk changed from 2% to 13%. With increasing categories of milk and fermented milk intake, the estimated energy and several nutrient intakes also increased, although alcohol intake tended to decrease (Table 1, Supporting Table 1). There were generally small differences between categories of dairy intake in body stature, intake of fruits and vegetables, comorbidity, educational level, use of nutritional supplements, marital status, smoking status, and physical activity level.

During a mean follow-up of 22 years and a total time at risk of 1,375,900 person-years, 5827 women presented with a hip fracture. The median age at the hip fracture event was 80.4 years. With a longer follow-up compared to our previous analysis,[7] we confirm a dose-response pattern of hip fracture risk with milk intake (Supporting Fig. 1A), with a multivariable-adjusted HR of 1.07 (95% CI, 1.04 to 1.10) per a 200-mL glass of milk. Lower rates of hip fracture were found in women with a higher consumption of fermented milk (multivariable-adjusted HR, 0.89 (95% CI, 0.86 to 0.92) per 200 mL/day; Supporting Fig. 1B). Hip fracture rates decreased with a higher consumption of fruits and vegetables, up to approximately five servings/day (Supporting Fig. 1C).[17] Above these intake levels, hip fracture rates differed only modestly.

The rates of hip fracture in four categories of milk and fermented were evaluated across three categories of fruit and vegetable consumption. Absolute rates are presented in Table 2 and HRs in strata of fruit and vegetable intake are shown in Fig. 1*A*, *B* (and in Supporting Table 3). Within each stratum and irrespective of whether the women were low or high consumers of fruits and vegetables, we found higher hip fracture rates with increasing consumption of milk. In contrast, increasing consumption of fermented milk was associated with a lower rates of hip fracture in every category of fruit and vegetable intake.

We further combined the intake of different dairy products with fruit and vegetable consumption using a common reference category. Figure 2*A* (Supporting Table 4) shows the multivariable-adjusted HRs of hip fracture by milk and fruit and vegetable intake using the group with the lowest intake of milk ($<$1 glass/day) and the highest intake of fruits and vegetables ($\geq$5 servings/day) as reference. A high intake of milk ($\geq$3 glasses/day) with a concomitant low intake of fruits and vegetables ($<$2 servings/day) led to a multivariable-adjusted HR of 2.49 (95% CI, 2.03 to 3.05). When a high milk intake was combined with a high intake of fruits and vegetables ($\geq$5 servings/day), the HR was still elevated: HR, 2.14 (95% CI, 1.69 to 2.71). A larger contrast, dependent on low or high fruit and vegetable intake, was observed with lower milk consumption. With the same reference category, women who reported 1 to $<$2 glasses/day of milk had an HR of 2.02 (95% CI, 1.79 to 2.29) if they also reported a low intake of fruits and vegetables ($<$2 servings/day) and 1.16 (95% CI, 1.03 to 1.31) if they reported a high intake of fruits and vegetables ($\geq$5 servings/day).

When intakes of fermented milk were combined with intake of fruits and vegetables, a different pattern for the association with hip fracture was observed (Fig. 2*B*, Supporting Table 4). The highest rates of hip fracture were found in low consumers of soured milk and yogurt, particularly in those who had a concomitant low consumption of fruits and vegetables. Compared with the joint category of low intake of both fermented milk and fruit and vegetables, women in the highest consumption category of fruits and vegetables in combination with the highest soured milk and yogurt intake had an HR of hip fracture of 0.81 (95% CI, 0.68 to 0.97).

Sensitivity analyses

The dose-response associations of milk, fermented milk, and fruit and vegetables intakes with hip fracture rate were evident in all strata of baseline BMI, healthy diet score, socioeconomic status and ever use of estrogen replacement therapy (Fig. 3).

The higher HRs for hip fracture in those with a high consumption of milk were increased after additional adjustment for vitamin and mineral nutrients common in milk, whereas the inverse association found with a high consumption of fermented milk disappeared after adjustment for mineral, vitamin, protein, and fat constituents of dairy (Model 4, Supporting Table 4), an attenuation mainly driven by calcium

Table 1. Characteristics of the Swedish Mammography Cohort at Baseline, 1987–1990 ($n = 61{,}240$)

	Daily servings					
	Milk		Fermented milk		Fruit and vegetables	
	<1	≥3	0	≥2	<2	≥5
n (%)	16869 (27.5)	5581 (9.1)	13411 (21.9)	1190 (1.9)	13779 (22.5)	10529 (17.2)
Age at entry (years), mean ± SD	53.2 ± 9.5	52.8 ± 9.6	55.1 ± 9.9	53.7 ± 9.7	54.7 ± 10.1	53.3 ± 9.4
Body mass index (kg/m^2), mean ± SD[a]	24.4 ± 3.9	24.9 ± 4.2	25.0 ± 4.1	24.7 ± 3.9	24.9 ± 4.1	24.9 ± 4.1
Height (m), mean ± SD[b]	1.64 ± 0.06	1.64 ± 0.06	1.64 ± 0.06	1.64 ± 0.06	1.63 ± 0.06	1.64 ± 0.06
Dietary intake, mean ± SD						
Milk (mL/day)	17.3 ± 37.3	676.8 ± 151.9	238.3 ± 212.9	229.7 ± 234.4	268.5 ± 216.7	227.6 ± 196.5
Fermented milk (yogurt and soured milk) (mL/day)	102.7 ± 117.3	87.2 ± 113.1	0.0 ± 0.0	542.3 ± 137.8	67.8 ± 95.7	128.5 ± 125.5
Fruit (g/day)[c]	201.0 ± 143.4	183.0 ± 147.1	167.7 ± 136.2	255.2 ± 181.1	68.3 ± 45.2	380.5 ± 163.7
Vegetables (g/day)[d]	92.5 ± 67.5	81.7 ± 63.9	78.9 ± 64.8	116.0 ± 102.9	37.5 ± 20.2	169.3 ± 92.5
Fruits and vegetables (servings/day)	3.6 ± 2.1	3.2 ± 2.1	3.0 ± 2.0	4.6 ± 3.0	1.3 ± 0.5	6.8 ± 2.0
Cheese (g/day)	26.8 ± 21.2	27.7 ± 22.0	24.1 ± 20.5	30.4 ± 24.4	23.5 ± 20.3	28.5 ± 20.7
Red and processed meat (g/day)	70.2 ± 42.2	85.4 ± 44.8	73.4 ± 45.2	79.2 ± 54.8	68.9 ± 39.4	82.0 ± 50.9
Energy intake (kcal/day), mean ± SD	1414 ± 433	1967 ± 525	1470 ± 472	1960 ± 560	1468 ± 467	1738 ± 491
Metabolic equivalents (kcal/kg and hour), mean ± SD[e]	42.2 ± 4.8	42.8 ± 5.0	42.3 ± 4.9	42.7 ± 4.9	42.3 ± 4.9	42.8 ± 4.8
Education, %[f]						
≤9 years	78.9	79.3	83.7	80.5	84.4	77.1
10–12 years	7.6	6.7	5.8	6.6	5.4	8.1
>12 years	5.3	4.6	3.4	4.6	2.7	6.1
Other[g]	8.3	9.5	7.0	8.3	7.5	8.6
Smoking status, %[e]						
Never	48.6	46.5	48.2	50.2	47.1	52.5
Former	31.5	29.5	30.3	31.0	29.6	30.4
Current	19.8	24.0	21.5	18.8	23.3	17.1
Marital status; living alone, %	23.4	25.6	24.6	28.8	27.3	22.1
Charlson's comorbidity, %						
0 comorbidity	89.8	87.9	88.0	88.0	88.3	89.9
1 comorbidity	8.3	9.5	9.2	8.7	9.1	7.8
≥2 comorbidities	1.9	2.6	2.8	3.4	2.6	2.3
Calcium containing supplement use, %[e]	17.3	14.4	11.9	20.8	10.9	19.9
Vitamin D containing supplement use, %[e]	15.0	12.8	10.0	18.2	9.5	17.5
Ever antioxidant-containing supplement use, %[e]	29.8	24.2	21.6	33.7	20.4	33.5
Ever estrogen replacement use, %[e]	20.7	26.1	18.6	28.4	18.1	26.6
Ever use of oral cortisone, %[e]	5.3	4.6	4.3	4.5	4.5	5.3

The characteristics in the intermediate categories of milk, fermented milk, and fruit and vegetable intake are presented in Supporting Table 1.
One glass of milk corresponds to 200 mL and one serving of fermented milk (yogurt and soured milk) corresponds to 200 mL.
[a] $n = 58{,}960$.
[b] $n = 59{,}685$.
[c] $n = 61{,}031$.
[d] $n = 61{,}104$.
[e] Values imputed from the 1997 questionnaire.
[f] $n = 60{,}158$.
[g] Such as vocational.

Table 2. Number of Hip Fractures and Age-Standardized Rate of Hip Fracture by Milk or Fermented Milk and Fruit and Vegetable Intake

Fruit and vegetable intake	Hip fractures	Glasses of milk per day			
		<1	≥1 to <2	≥2 to <3	≥3
<2 servings per day	Number of hip fractures	440	375	261	110
	Age-adjusted rate per 1000 person-years	5.0 (4.6–5.5)	5.1 (4.6–5.7)	5.2 (4.5–5.9)	6.1 (4.7–7.7)
≥2 to <5 servings per day	Number of hip fractures	1430	931	524	141
	Age-adjusted rate per 1000 person-years	4.2 (3.9–4.4)	4.2 (4.0–4.5)	4.7 (4.3–5.2)	4.2 (3.5–5.1)
≥5 servings per day	Number of hip fractures	939	390	209	77
	Age-adjusted rate per 1000 person-years	3.4 (3.2–3.6)	3.5 (3.2–3.9)	4.8 (4.1–5.5)	5.7 (4.5–7.2)
		Servings of fermented milk (yogurt and soured milk) per day			
		0	<1	≥1 to <2	≥2
<2 servings per day	Number of hip fractures	517	426	184	59
	Age-adjusted rate per 1000 person-years	6.1 (5.6–6.7)	4.6 (4.1–5.1)	4.7 (4.0–5.4)	4.4 (3.2–6.0)
≥2 to <5 servings per day	Number of hip fractures	873	1182	734	237
	Age-adjusted rate per 1000 person-years	5.0 (4.7–5.4)	4.0 (3.7–4.2)	4.0 (3.7–4.3)	4.0 (3.4–4.6)
≥5 servings per day	Number of hip fractures	343	489	571	212
	Age-adjusted rate per 1000 person-years	3.9 (3.5–4.4)	3.5 (3.2–3.8)	3.7 (3.4–4.0)	3.1 (2.7–3.6)

Age-standardized rates were directly standardized to the age distribution of the total population.

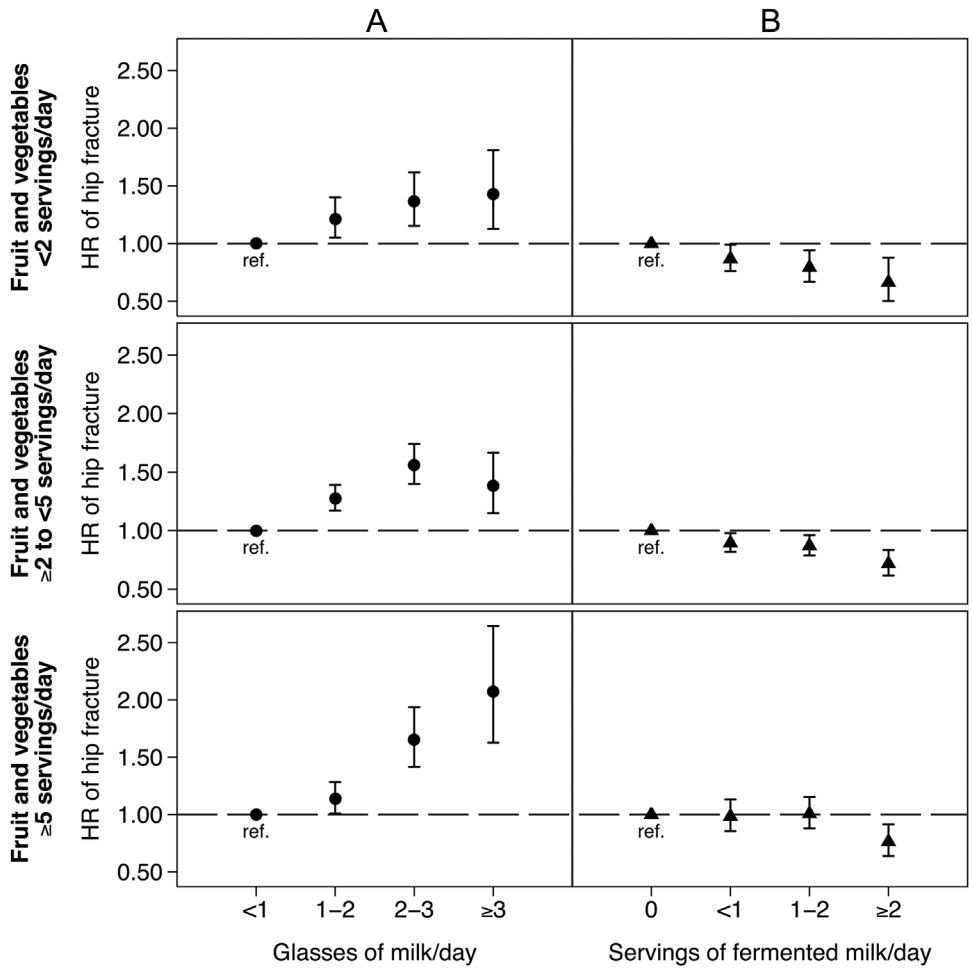

Fig. 1. HRs and 95% confidence intervals of hip fracture by intake of milk (*A*) or fermented milk (yogurt and soured milk; *B*) in strata of fruit and vegetable intake. The reference category in each stratum of fruit and vegetable intake is indicated by "ref." HRs were adjusted for age, body mass index, height, energy intake, alcohol intake, cheese intake, intake of red and processed meat, education, cohabiting status (living alone versus not), smoking, physical activity (metabolic equivalents), ever use of antioxidant-containing supplements, and Charlson weighted comorbidity index. The HRs were also mutually adjusted for intake of the other dairy exposure. HR = hazard ratio.

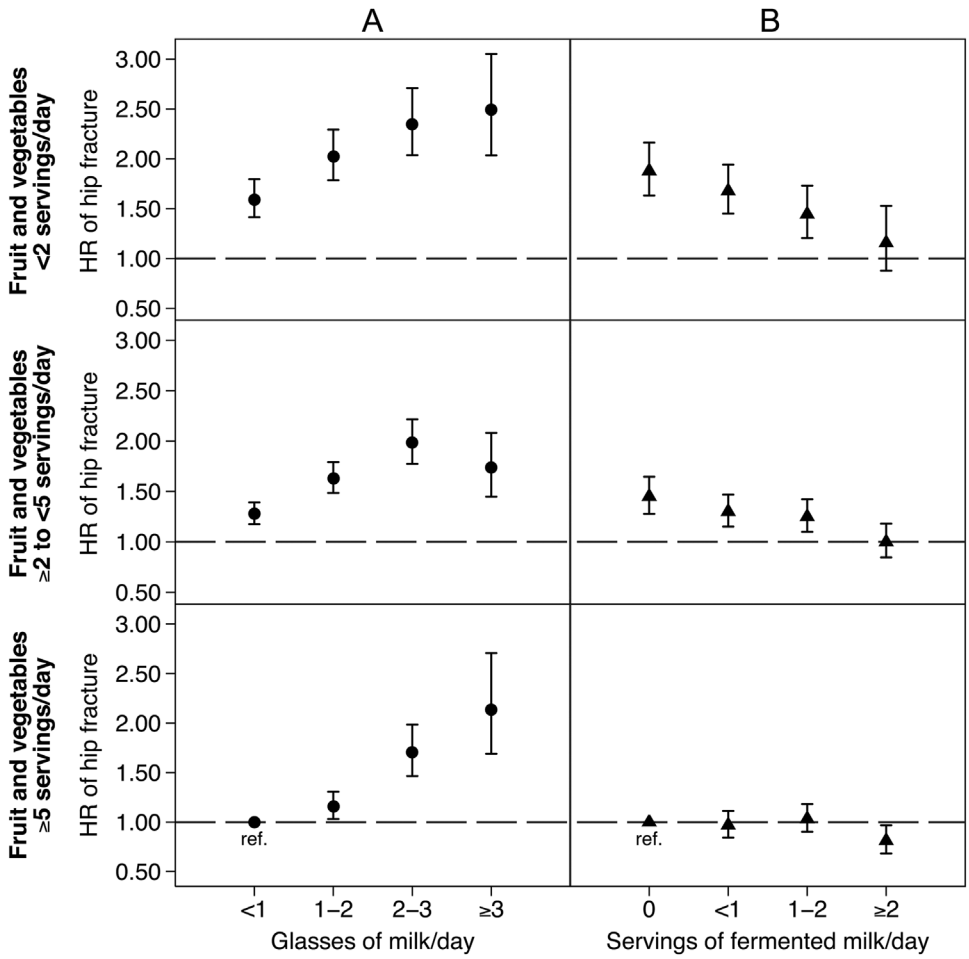

Fig. 2. Combined intake of fruits and vegetables and milk (*A*) and fermented milk (yogurt and soured milk; *B*) and HRs of hip fracture using a joint reference (indicated by "ref"). HRs were adjusted for age, body mass index, height, energy intake, alcohol intake, cheese intake, intake of red and processed meat, education, cohabiting status (living alone versus not), smoking, physical activity (metabolic equivalents), ever use of antioxidant-containing supplements, and Charlson weighted comorbidity index. The HRs were also mutually adjusted for intake of the other dairy exposure. HR = hazard ratio.

intake (data not shown). Additional adjustment for vitamin D supplement use only marginally changed our estimates (data not shown).

Adjustment for smoking, physical activity, and use of antioxidant supplements only marginally altered the estimates when added to a model adjusted for other main confounders using the questionnaire in 1997 as baseline (Supporting Table 5).

We examined the influence of potential reverse causation by running all analyses in two subsets: exclusion of the first 2 years of follow-up (134 hip fractures excluded) and exclusion of those with a hip fracture before baseline (351 women excluded). Estimates were similar to those obtained from the total cohort (data not shown).

Discussion

In this large population-based investigation of middle-aged and elderly Swedish women we evaluated combinations of dairy products and fruit and vegetable intake and their associations with hip fracture risk. This has previously not been done. Hip fracture rates were highest in those with a high consumption of milk combined with a low consumption of fruits and vegetables, whereas hip fracture rates were lowest among women with a high intake of fermented milk in combination with high intakes of fruits and vegetables.

Our analysis was made possible by a unique cohort with a large number of hip fracture outcomes,[7] and the comprehensive time-updated FFQ in a setting with a wide variety of dairy products and antioxidant foods. Given changes in dairy habits with a decreased intake of milk and an increased intake of fermented products in the population during the past decades[7] and the annual 10% exchange of the skeleton,[8,9] time-updated exposure information is crucial to lessen misclassification. Nonetheless, misclassification of our exposure will lead to conservatively biased estimates. Loss to follow-up is negligible and close to complete hip fracture identification was possible because of the unique personal identification numbers.

We have a well-suited design and setting but nevertheless our observational study should be evaluated by ordinary cautionary measures. Our results might not apply to people of

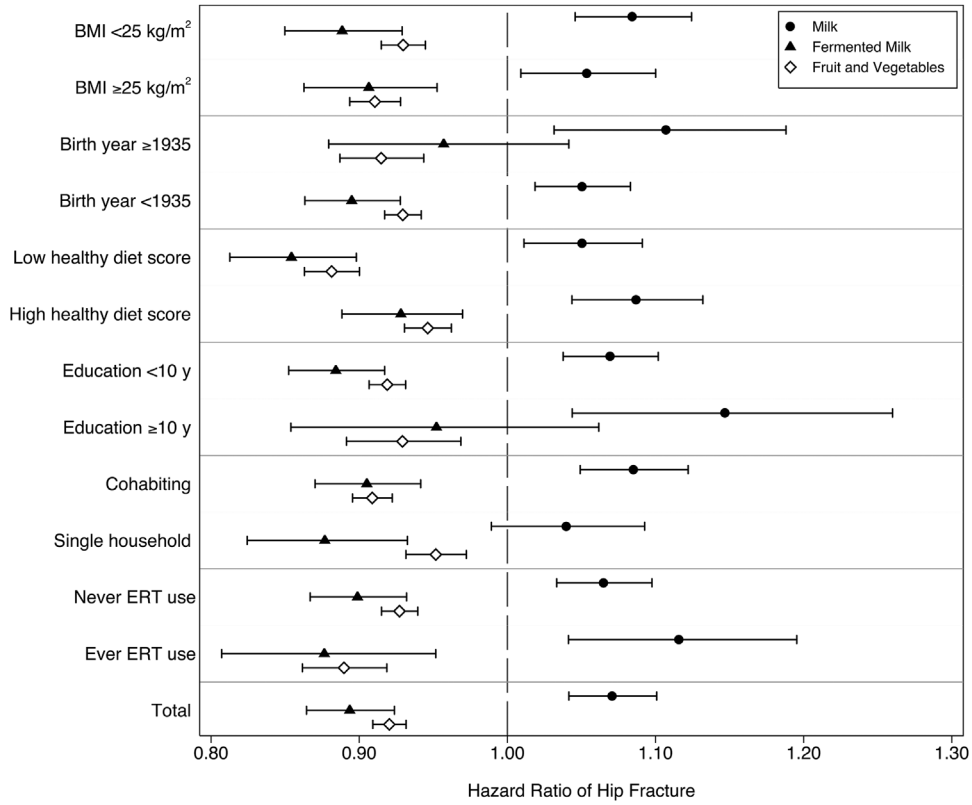

Fig. 3. HRs of hip fracture per time-updated serving of milk, fermented milk (yogurt and soured milk), and fruits and vegetables stratified by baseline characteristics. HRs and 95% confidence intervals for hip fracture per serving of milk (circles), fermented milk (yogurt and soured milk, triangles), and fruits and vegetables (diamonds) stratified by body mass index (BMI; <25 kg/m^2, ≥ 25 kg/m^2), year of birth (≥ 1935, <1935), adherence to a healthy diet score (low, high),[7] educational level (<10 years, ≥ 10 years of education), cohabiting status (cohabiting, living alone) and ever use of ERT (ever use, never use). Total estimates are also shown for reference. HRs were adjusted for age, body mass index, height, energy intake, alcohol intake, cheese intake, intake of red and processed meat, education, cohabiting status (living alone versus not), physical activity (metabolic equivalents), smoking habits (never/former/current smoker), ever use of antioxidant-containing supplements, and Charlson weighted comorbidity index. Associations were also mutually adjusted for the other exposures (additional covariates for milk intake were intake of fermented milk and fruits and vegetables). One glass of milk corresponds to 200 mL and one serving of fermented milk (yogurt and soured milk) corresponds to 200 mL. HR = hazard ratio; ERT = estrogen replacement therapy.

other ethnic origins, such as those with a high prevalence of lactose intolerance, to children, or to men, why replication in other populations would be of importance. Theoretically, women with a higher predisposition of fractures may have deliberately increased their milk intake, and in addition have a low intake of antioxidants leading to reverse causation. However, we investigated time to an incident hip fracture event, an approach that reduces the likelihood of biased estimates. The possibility of a reverse causation theory is also contradicted in that neither personal nor family history of fracture was associated with a change to higher milk intake levels.[7] Furthermore, in contrast to milk, fermented milk intake was inversely associated with fracture risk. Finally, residual confounding is a possibility but such unmeasured confounding factors ought to be strong (at least an HR of 4.4) to explain the milk and fruit/vegetable association[45] and we did consider covariates known to be of importance. Specifically, the patterns of hip fracture risk with dairy products and fruits and vegetables were observed in every stratum of socioeconomic status.

Milk is the main dietary source of D-galactose, one component of the disaccharide lactose (milk sugar). D-galactose exposure in animals, with a dose corresponding to one to two glasses of milk in humans,[7,46] induces oxidative stress damage and chronic inflammation, which shortens lifespan.[46–49] Female animals are especially vulnerable.[50–52] Specifically, the enzyme galactose-1-phosphate uridylyltransferase in the Leloir pathway of galactose metabolism has a higher activity in male than in female animals.[51,53,54] Consequently, the elimination capacity of circulating galactose is higher in men and declines in both sexes with increasing age.[55–57] Our analysis therefore focused on women because of the lower capacity than men to degrade galactose by the main Leloir degradation pathway, leading to an alternative degradation route of galactose (polyol pathway) that may cause free radical formation.[58,59] In addition, excess of galactose reacts non-enzymatically with amino groups in proteins and peptides forming advanced glycation end-products (AGEs).[49] Genetic lactase persistence as a proxy for higher milk intake in a Mendelian randomization study has recently been shown to be related to higher mortality and cardiovascular disease rates in women but not in men, although pleiotropy of the gene variant cannot be

excluded.[60] Nonetheless, we have also found similar sex differences in mortality rates in relation to milk intake.[7,61]

Thus, our postulated mechanism is that high milk consumption is acting as a pro-oxidant via the galactose component of lactose, and in contrast to fermented milk products that may exhibit antioxidant and anti-inflammatory effects by their probiotic content.[7] In addition, Swedish fermented milk products such as yogurt and soured milk have, dependent on type and storage time, 10% to 50% lower total galactose content compared with ordinary nonfermented milk.[27] The pro-oxidant mechanism of milk is indirectly supported by our analysis with additional adjustment for nutrients found in dairy products. For milk the HRs were increased and for fermented milk, the association was attenuated in all categories of fruit and vegetable intake. Further, using the main model, we found lower risk estimates with high fruit and vegetable intake within all dairy consumption categories. Short-term intervention studies display that increased intake of fermented dairy products may reduce inflammation load[22,62] but long-term trials are lacking.

Experimental evidence in animals indicates that galactose-induced aging can be prevented by a higher consumption of fruits and vegetables.[63–66] Although there was in our study a general tendency of lower hip fracture rates in high consumers of fruits and vegetables, there was still a persistent elevated rate of hip fracture in women consuming high amounts of milk. Therefore, the hypothesized antioxidant capacity from the intake of fruits and vegetables appears not to fully counterbalance the postulated oxidant activity by milk, if consumed in large quantities (several servings per day).

Our observational results in this population of Swedish women question the value of recommending high consumption of milk in the prevention of fragility fractures. However, the results show that moderate intakes of fermented milk in combination with a high intake of fruits and vegetables are associated with lower hip fracture rates.

Disclosures

All authors state that they have no conflicts of interest.

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