Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort[1–3]

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ABSTRACT

Background: Some observational studies have shown a beneficial effect of dairy consumption on blood pressure, especially in overweight and relatively young (<40 y) persons. However, no results from prospective studies conducted in a free-living population exist that show this association in middle-aged adults.

Objective: The aim of the present study was to assess whether total, low-fat, and whole-fat dairy consumption was associated prospectively with the risk of hypertension.

Design: This was a prospective study conducted in 5880 university graduates in Spain, aged >20 y in 2000 ($\bar{x}$ age: 37 y), free of hypertension and cardiovascular disease at baseline, and followed-up with mailed questionnaires for a median of 27 mo. Dairy consumption was assessed with a previously validated semiquantitative food-frequency questionnaire.

Results: One hundred eighty new cases of hypertension were identified. The hazard ratio of hypertension between extreme quintiles of low-fat dairy product consumption was 0.46 (95% CI: 0.26, 0.84; *P* for trend = 0.02) after adjustment for the main known risk factors for hypertension and several dietary factors. No significant association between whole-fat dairy products or total calcium intake and incident hypertension was seen.

Conclusion: In this Mediterranean cohort, low-fat dairy consumption, but not whole-fat dairy consumption, was associated with a lower risk of incident hypertension. *Am J Clin Nutr* 2005;82: 972–9.

KEY WORDS Milk, Dietary Approaches to Stop Hypertension diet, high blood pressure, calcium, Mediterranean diet, Spain

INTRODUCTION

Diet has an important role in the primary prevention of hypertension (1). The Dietary Approaches to Stop Hypertension (DASH) trial has shown that a dietary pattern rich in fruit, vegetables, and low-fat dairy products and with reduced total and saturated fat (the DASH diet) can be effective in the prevention of hypertension (2, 3). This pattern was more effective than was a diet rich in fruit and vegetables in which dairy consumption was low. However, the DASH study was conducted in a controlled setting with a short follow-up (8 wk), and it was not specifically designed to assess the individual effects of each element of the protective dietary pattern.

Nonetheless, substantial epidemiologic and clinical data exist that show that a long-term high consumption of fruit and vegetables, one of the main components of the DASH diet, is inversely associated with blood pressure (BP) levels independent of other dietary factors (4–7). However, the relation between dairy consumption, another important building block of the DASH diet, and BP is not so clear. Some prospective studies have found a beneficial relation between dairy consumption and the incidence of hypertension or a change in BP, but this association was only evidenced in young adults (8) and in children (9). On the other hand, dairy consumption has been associated with a higher cardiovascular disease mortality risk in postmenopausal women (10), whereas the nutritional intervention in the Oslo study, which was mainly focused on reducing whole-fat dairy consumption, was associated with a lower risk of coronary events (11). In addition to this apparent inconsistency in epidemiologic results, no prospective studies have assessed the relation between dairy consumption and the incidence of hypertension in persons in Mediterranean countries where intake of fat, particularly monounsaturated fatty acids, is high and where, perhaps, results from the DASH trial could not be directly applied (12). The objective of the present study was to prospectively assess the potential association between dairy consumption, particularly low-fat dairy products, and the risk of hypertension in a Mediterranean population.

SUBJECTS AND METHODS

Study population

The University of Navarra Follow-up Study (Seguimiento Universidad de Navarra) is composed of a dynamic cohort of university graduates. A detailed description of the study methods was published elsewhere (13). Briefly, beginning in December

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[2] Supported by the Spanish Ministry of Health (grants PI040233 and G03-140), the Navarra Regional Government (PI41-2005), and the University of Navarra (línea especial Nutrición, Obesidad y Salud, Navarra University, LE-97). AA was supported partially by a Fulbright fellowship and an MMA Foundation grant.

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Received May 27, 2005.

Accepted for publication August 8, 2005.

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1999, all former students of the University of Navarra, registered nurses from some Spanish provinces, and university graduates from other associations received a mailed questionnaire and a letter of invitation to participate in the Seguimiento Universidad de Navarra Study. From December 1999 to January 2002, 9907 of them answered the questionnaire. Subsequently, the follow-up of initial responders was made through biennial mailed questionnaires; persons who did not reply were sent ≤5 additional mailings. On 25 July 2004, 8646 (87%) of the participants had answered the first follow-up questionnaire. The participants were aged between 20 and 90 y at baseline. The Institutional Review Board of the University of Navarra approved the study protocol.

Participants were excluded at baseline if they reported a history of cardiovascular disease, cancer, or diabetes or if they had prevalent hypertension. Participants with extreme total energy intakes (<400 or >3500 kcal/d for women and <600 or >4200 kcal/d for men) or those who had missing values for any of the variables that were included in the analyses were also excluded. Of the initial 9907 persons who responded to the baseline questionnaire, 1045 were excluded because they had hypertension; 813 because they had previous cardiovascular disease, cancer, or diabetes; 1018 because they had extreme energy intakes; and 784 because they had missing values for a covariate. Some participants were included in more than one of these categories. This left 6686 participants available for the baseline analyses.

Dietary assessment

The baseline questionnaire included a semiquantitative food-frequency questionnaire that was previously validated in Spain, with 136 items and open-label questions for information about use of dietary supplements (14). The questionnaire was based on typical portion sizes and had 9 options for the frequency of intake in the previous year for each food item (ranging from never or almost never to ≥6 times/d). Dairy consumption was assessed in 15 of these items (whole-fat milk, partially skim milk, skim milk, condensed milk, whipped cream, yogurt, skim yogurt, milkshake, cottage cheese or junket, petit Suisse cheese, spreadable cheese wedges, soft unripened cheese, other cheese, custard, and ice cream). Skim and partially skim milk were the major contributors to low-fat dairy consumption and accounted for 92% of the total low-fat dairy consumption. The follow-up questionnaire included some questions about changes in the participant's habitual diet. A dietitian updated the nutrient data bank using the latest available information that was included in the food-composition tables for Spain (15, 16).

Assessment of other covariates

Information about the main known risk factors for hypertension was reported in baseline questionnaires. Body mass index (BMI), defined as weight (in kg) divided by height^2 (in m), was ascertained in the baseline questionnaire. The validity of self-reported weight was assessed in a subsample of the cohort (n = 144). The mean relative error in self-reported weight was 1%. The correlation coefficient (r) between measured and self-reported weight was 0.99 (95% CI: 0.98, 0.99) (17). We calculated an activity metabolic equivalent (MET) index for each participant to quantify the volume and intensity of leisure-time physical activity as previously described (18). We assessed each participant's involvement and time spent in 17 different activities. We assigned a multiple of the resting metabolic rate (MET score) to each of these activities using previously published guidelines to quantify the average intensity of physical activity (18). The MET index of each activity was multiplied by the weekly time spent in each activity and a value of overall weekly MET-hours was obtained. In the validation study (19), a significant correlation between objectively measured physical activity with an accelerometer and the overall weekly MET-hours assessed with our questionnaire was observed (r = 0.51, P < 0.001). Information about any previous diagnosis of cardiovascular disease, cancer, diabetes, hypercholesterolemia, or other conditions and the participant's family history of hypertension was also obtained in the baseline questionnaire.

Hypertension ascertainment

The participants reported whether they had received a medical diagnosis of hypertension in the baseline and follow-up questionnaires. Additionally, the most recent systolic and diastolic BP values were reported in the baseline questionnaire. The date of hypertension diagnosis (if applicable) and BP measurements in the time elapsed since the baseline questionnaire were also reported in follow-up questionnaires.

A participant was considered to have hypertension at baseline if they reported a medical diagnosis of hypertension, were receiving antihypertensive medication, or reported a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg (20). New cases of hypertension were defined as those participants who reported a physician diagnosis of hypertension in the follow-up questionnaire and did not have hypertension at baseline.

A validation study that was conducted in a random sample of participants (n = 127) in the metropolitan area of Pamplona (Navarra, Spain) showed an adequate validity of the self-reported diagnosis of hypertension in this highly educated cohort (positive predictive value: 82%; negative predictive value: 85%) when a repeated direct measured value of BP was used as the gold standard. When the cutoff for hypertension in the validation study was set at 160/95 mm Hg instead of 140/90 mm Hg, the negative predictive value of self-reporting was 98% instead of 85%, which suggests that the participants that were considered to have false-negative results in the validation study had BP values near the cutoff.

Statistical analysis

Food and nutrient intakes were adjusted for total energy intake with the residuals method, and separate regression models were performed to obtain the residuals for women and men (21). Energy-adjusted food or nutrient intakes were categorized in quintiles. For each participant, we computed person-time of follow-up from the date the baseline questionnaire was returned to the date the follow-up questionnaire was returned or to the date of a new hypertension diagnosis.

Analyses were performed with SPSS version 11.0 (SPSS Inc, Chicago, IL). Hazard ratios (HRs) and their 95% CIs were estimated with Cox proportional hazards models, with adjustment for potential confounders. An initial model included only age and sex as covariates. We then included universally accepted risk factors for hypertension (physical activity, BMI, and alcohol and sodium intakes) and variables closely associated with lifestyle and health-related habits (smoking and a history of hypercholesterolemia) in a first multivariate model. Finally, to assess the possibility of confounding by other dietary variables, we ran

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TABLE 1
Distribution of potential confounding variables across quintiles of total dairy product consumption[1]

	Quintile					
	1 (n = 1177)	2 (n = 1174)	3 (n = 1177)	4 (n = 1176)	5 (n = 1176)	P for trend
Dairy consumption (g/d)	155.6 ± 75.3[2]	292.4 ± 27.6	385.9 ± 29.7	530.0 ± 53.0	798.8 ± 215.4	
Whole-fat dairy (g/d)	108.4 ± 84.9	185.9 ± 102.2	237.7 ± 122.0	281.2 ± 208.9	324.4 ± 293.4	
Low-fat dairy (g/d)	47.2 ± 71.7	106.5 ± 101.2	148.2 ± 121.5	248.7 ± 212.8	474.3 ± 337.7	
Age (y)	36.9 ± 11.1	36.0 ± 10.7	35.7 ± 10.6	35.4 ± 10.6	34.7 ± 10.8	< 0.001
Sex (% females)	56.7	58.5	57.3	65.2	68.8	< 0.001
BMI (kg/m^2)	23.2 ± 3.5	23.2 ± 3.3	23.3 ± 3.3	22.9 ± 3.2	22.9 ± 3.1	0.01
Physical activity (MET-hours/wk)	15.8 ± 20.0	15.7 ± 18.6	17.4 ± 22.1	17.2 ± 22.0	17.9 ± 21.5	< 0.001
Smokers (%)						< 0.001
Past	26.2	25.5	26.6	23.3	23.6	
Current	31.4	28.0	26.2	25.9	26.2	
Hypercholesterolemia (%)	13.7	12.5	12.3	11.8	13.9	0.96
Total energy intake (kcal/d)	2553 ± 689	2381 ± 597	2204 ± 590	2463 ± 636	2402 ± 604	< 0.001
Alcohol intake (g/d)	8.7 ± 13.5	6.9 ± 9.0	5.8 ± 8.3	5.2 ± 7.6	4.1 ± 6.3	< 0.001
Sodium intake (g/d)	4.2 ± 3.7	4.2 ± 2.2	4.1 ± 2.0	4.0 ± 2.0	3.9 ± 1.8	< 0.001
Potassium intake (g/d)	4.5 ± 1.4	4.6 ± 1.1	4.6 ± 1.1	4.7 ± 1.1	5.0 ± 1.2	< 0.001
Calcium intake (g/d)	0.9 ± 0.2	1.0 ± 0.2	1.2 ± 0.2	1.4 ± 0.3	1.7 ± 0.4	< 0.001
Magnesium intake (mg/d)	400.0 ± 92.6	400.1 ± 78.1	405.0 ± 73.4	408.7 ± 76.4	435 ± 79.0	< 0.001
Phosphorus intake (g/d)	1.7 ± 0.3	1.8 ± 0.3	1.9 ± 0.3	2.0 ± 0.3	2.3 ± 0.4	< 0.001
Total fat (% of energy intake)	37.4 ± 7.4	37.8 ± 6.3	37.3 ± 6.0	37.7 ± 6.3	36.2 ± 6.4	< 0.001
SFA (% of energy intake)	12.0 ± 3.1	12.8 ± 2.8	13.0 ± 2.9	13.2 ± 3.1	13.2 ± 3.7	< 0.001
MUFA (% of energy intake)	16.7 ± 4.4	16.4 ± 3.6	15.9 ± 3.3	16.0 ± 3.6	15.1 ± 3.4	< 0.001
Total protein intake (g/d)	99.3 ± 19.2	103.5 ± 16.4	105.4 ± 13.9	107.3 ± 15.5	114.6 ± 18.1	< 0.001
Fiber intake (g/d)	28.5 ± 12.2	26.7 ± 9.7	26.5 ± 9.2	26.0 ± 9.6	26.0 ± 10.0	< 0.001
Caffeine intake (mg/d)	44.0 ± 43.4	43.9 ± 39.1	42.5 ± 37.0	44.2 ± 38.6	48.8 ± 44.4	0.008
Vegetable consumption (g/d)	521.9 ± 347.4	504.4 ± 290.1	496.7 ± 277.7	508.9 ± 286.0	517.5 ± 310.9	0.88
Fruit consumption (g/d)	339.4 ± 348.1	309.4 ± 245.9	326.0 ± 258.6	306.6 ± 243.2	334.1 ± 263.0	0.57

[1] MET, metabolic equivalent; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids.
[2] $\bar{x}$ ± SD (all such values).

another multivariate model (multivariate 2), which added several dietary factors that have been related to the risk of hypertension in some studies. In all analyses, the reference group was the lowest intake category. Multivariable tests for linear trends were conducted by assigning the median value to each quintile and modeling these values as a continuous variable. To investigate whether age, sex, or BMI modified the association between dairy consumption and the incidence of hypertension, we used the log-likelihood ratio test to assess statistical interaction with a multiplicative term for dairy consumption and the potentially modifying variable in the models. All P values are 2-tailed. Statistical significance was set at $P < 0.05$.

RESULTS

From the 6686 participants who met the inclusion criteria, 5880 (88%) answered the 2-y follow-up questionnaire. In the baseline comparison, nonresponders were more likely to be young and to have a higher intake of low-fat dairy products than were responders; however, other characteristics were similar.

The characteristics of the participants are shown in **Table 1** and **Table 2** according to the consumption of total dairy products and low-fat dairy products. Women, physically active participants, and younger persons had a higher total dairy and low-fat dairy consumption. Additionally, low-fat dairy consumption was directly associated with fruit and vegetable consumption and with potassium and fiber intake and was inversely associated with alcohol and saturated fatty acid intake. In this population, fat intake accounted for 37% of total energy intake in men and 38% in women.

We observed a significant reduction in the risk of hypertension in the participants in the fourth quintile of dairy consumption when compared with the participants in the lowest quintile, but the inverse linear trend was not consistent (**Table 3**). However, when we separately assessed the effect of low-fat and whole-fat dairy product consumption, we found a 50% reduction in the incidence of hypertension in the participants with the highest consumption compared with the participants with the lowest consumption of low-fat dairy products after adjustment for the main known risk factors of hypertension (multivariate-adjusted HR: 0.44; 95% CI: 0.25, 0.77) and a significant trend that suggested a dose-response relation. This association did not substantially change when we made additional adjustments for other dietary factors (multivariate model 2 in Table 3). In contrast, no clear trend in the association between whole-fat dairy intake and the risk of hypertension was observed. An additional adjustment for total calcium intake did not significantly affect the HR estimates for low-fat dairy products (adjusted HR: 0.38; 95% CI: 0.19, 0.74, in a comparison of the fifth quintile with the lowest quintile of low-fat dairy intake; P for trend = 0.01, data not shown). Additional adjustment for protein intake, phosphorus intake, or total fat intake did not significantly affect our estimates (data not shown).

Calcium from low-fat dairy products, but not total calcium intake or calcium from whole-fat dairy products, was associated

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TABLE 2
Distribution of potential confounding variables across quintiles of low-fat dairy product consumption[1]

	Quintile					
	1 (n = 1176)	2 (n = 1176)	3 (n = 1177)	4 (n = 1175)	5 (n = 1176)	P for trend
Low-fat dairy consumption (g/d)	2.5 ± 4.6[2]	11.3 ± 14.6	140.5 ± 60.8	255.9 ± 55.7	614.7 ± 206.5	
Age (y)	34.6 ± 9.9	36.7 ± 11.0	35.6 ± 10.7	36.3 ± 10.9	35.6 ± 11.2	0.14
Sex (% females)	50.8	49.7	64.0	66.7	75.3	< 0.001
BMI (kg/m^2)	22.8 ± 3.3	23.4 ± 3.5	23.2 ± 3.3	23.3 ± 3.2	22.9 ± 3.1	0.67
Physical activity (MET-hours/wk)	16.5 ± 19.6	15.7 ± 20.3	16.4 ± 21.2	17.3 ± 21.5	18.1 ± 21.8	0.01
Smokers (%)						0.16
Past	23.0	25.3	25.1	26.6	25.3	
Current	27.4	27.3	28.0	28.7	26.3	
Hypercholesterolemia (%)	6.6	12.8	13.3	16.3	15.2	< 0.001
Total energy intake (kcal/d)	2903 ± 448	2078 ± 557	2408 ± 672	2149 ± 549	2466 ± 573	< 0.001
Alcohol intake (g/d)	7.4 ± 11.6	6.3 ± 9.3	6.9 ± 10.1	5.8 ± 7.9	4.6 ± 7.4	< 0.001
Sodium intake (g/d)	4.2 ± 2.6	4.2 ± 2.2	4.0 ± 1.9	4.2 ± 3.4	3.9 ± 1.8	0.03
Potassium intake (g/d)	4.3 ± 1.1	4.5 ± 1.0	4.6 ± 1.1	4.9 ± 1.1	5.2 ± 1.2	< 0.001
Calcium intake (g/d)	1.0 ± 0.4	1.1 ± 0.3	1.1 ± 0.3	1.3 ± 0.3	1.6 ± 0.4	< 0.001
Magnesium intake (mg/d)	381.2 ± 79.5	396.6 ± 71.0	404.1 ± 79.2	423.9 ± 76.0	443.7 ± 85.0	< 0.001
Phosphorus intake (g/d)	1.8 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	2.0 ± 0.3	2.2 ± 0.4	< 0.001
Total fat (% of energy intake)	38.5 ± 5.9	38.6 ± 6.8	37.5 ± 6.6	36.7 ± 6.3	35.1 ± 6.3	< 0.001
SFA (% of energy intake)	13.5 ± 2.9	13.7 ± 3.4	12.6 ± 3.1	12.4 ± 3.0	11.9 ± 3.0	< 0.001
MUFA (% of energy intake)	16.4 ± 3.3	16.5 ± 4.0	16.3 ± 3.9	15.8 ± 3.6	15.0 ± 3.6	< 0.001
Total protein intake (g/d)	101.1 ± 17.7	103.6 ± 16.0	103.4 ± 18.1	108.5 ± 15.6	113.5 ± 17.0	< 0.001
Fiber intake (g/d)	24.2 ± 10.5	26.0 ± 9.4	26.9 ± 10.5	28.5 ± 9.4	28.2 ± 10.7	< 0.001
Caffeine intake (mg/d)	43.5 ± 41.4	41.3 ± 38.3	44.7 ± 41.7	43.3 ± 35.9	50.7 ± 44.9	< 0.001
Vegetable consumption (g/d)	444.1 ± 308.4	481.7 ± 276.5	506.3 ± 292.0	562.7 ± 294.8	554.7 ± 327.4	< 0.001
Fruit consumption (g/d)	260.1 ± 264.4	300.6 ± 242.6	330.1 ± 299.3	358.0 ± 258.6	365.6 ± 291.4	< 0.001

[1] MET, metabolic equivalent; SFA, saturated fatty acids; MUFA, monounsaturated fatty acids.
[2] $\bar{x}$ ± SD (all such values).

with a lower risk of hypertension (**Table 4**). Neither total vitamin D nor lactose intake was significantly associated with the risk of hypertension (data not shown). Low-fat dairy products accounted for 39% of the calcium intake in our cohort. Whole-fat dairy products contributed 26% and nondairy sources contributed 35% to the total calcium intake.

When we restricted the analysis to the participants who reported a BP measurement in the period between the baseline and first follow-up questionnaire or when we excluded participants with hypercholesterolemia, the results were not significantly changed (data not shown). These results did not vary significantly by sex, BMI (<25 and ≥25), age (<40 and ≥40 y), total fat or protein intake, or the ratio of calcium to phosphorus in the diet.

DISCUSSION

In this highly educated Mediterranean cohort, low-fat dairy intake was associated with a lower risk of incident hypertension, even after control for several potential confounders such as age, sex, physical activity, BMI, and major dietary factors related to hypertension. This association was not statistically different between men and women, younger and older persons, and lean and obese persons.

The observed risk reduction was high. Two reasons, however, support that a substantial protective association actually exists. First, the reported results are consistent with the findings of the Coronary Artery Risk Development in Young Adults Study (8) and with findings of clinical trials that included low-fat dairy products in the intervention diet (2, 22). For instance, in the DASH trial (2), systolic and diastolic BP reductions were −5.5 and −3.0 mm Hg, respectively, for the combination (DASH) diet, whereas respective decreases of only −2.8 and −1.1 mm Hg were observed with the fruit-and-vegetables diet. These results also represent an important difference in the magnitude of the effect of each diet, which had clear-cut differences in the amount of low-fat dairy products provided (2.0 servings/d in the combination diet compared with 0 servings/d in the fruit-and-vegetables diet). Second, our cohort provided a unique opportunity to capture an impressive between-subject variability in the consumption of low-fat dairy products, which ranged from 3 g/d in the lowest quintile to 615 g/d in the top quintile; a large between-subject variation in the consumption of a nutrient or food within a cohort results in a better ability to ascertain diet-disease associations and to obtain stronger estimates for the relative risk.

To our knowledge, this is the first study that showed an inverse association between the consumption of low-fat dairy products and incident hypertension independent of other dietary factors in a prospectively followed-up population, which included subjects aged >40 y. Nonetheless, previous epidemiologic studies have assessed the relation between dairy consumption and BP or hypertension. Thus, some cross-sectional studies have shown a beneficial association between dairy consumption and BP (7, 23). Also, 2 prospective studies reported an independent beneficial effect of dairy consumption on BP, but they were conducted in either young adults or children. One of the studies, the Coronary Artery Risk Development in Young Adults Study, followed up >3000 persons aged 18-30 y in the United States for 10 y (8). In that

TABLE 3
Hazard ratios (HRs) and 95% CIs of hypertension according to quintiles of dairy product consumption in the Seguimiento Universidad de Navarra cohort

	Quintile					
	1	2	3	4	5	*P* for trend
Total dairy consumption						
New cases of hypertension	49	38	39	24	30	
Person-years	2709.3	2708.3	2708.5	2705.4	2694.4	
Incidence (cases per 1000 person-years)	18.1	14.0	14.4	8.9	11.1	
Age- and sex-adjusted HR (95% CI)	1	0.85 (0.56, 1.30)	0.89 (0.58, 1.35)	0.59 (0.36, 0.97)	0.79 (0.50, 1.25)	0.14
Multivariate 1 HR (95% CI)[1]	1	0.85 (0.55, 1.29)	0.84 (0.54, 1.29)	0.58 (0.35, 0.95)	0.75 (0.47, 1.20)	0.10
Multivariate 2 HR (95% CI)[2]	1	0.84 (0.54, 1.29)	0.85 (0.54, 1.32)	0.57 (0.34, 0.95)	0.75 (0.45, 1.27)	0.12
Low-fat dairy consumption						
New cases of hypertension	40	45	35	39	21	
Person-years	2735.1	2706.1	2722.9	2657.7	2704.2	
Incidence (cases per 1000 person-years)	14.6	16.6	12.9	14.7	7.8	
Age- and sex-adjusted HR (95% CI)	1	0.94 (0.62, 1.45)	0.84 (0.53, 1.33)	0.96 (0.62, 1.50)	0.55 (0.32, 0.94)	0.03
Multivariate 1 HR (95% CI)[1]	1	0.76 (0.47, 1.23)	0.65 (0.41, 1.06)	0.74 (0.45, 1.21)	0.44 (0.25, 0.77)	0.009
Multivariate 2 HR (95% CI)[2]	1	0.77 (0.47, 1.27)	0.65 (0.40, 1.06)	0.77 (0.46, 1.28)	0.46 (0.26, 0.84)	0.02
Whole-fat dairy consumption						
New cases of hypertension	30	25	54	40	31	
Person-years	2710.0	2696.0	2680.9	2712.5	2726.5	
Incidence (cases per 1000 person-years)	11.1	9.3	20.1	14.7	11.4	
Age- and sex-adjusted HR (95% CI)	1	0.92 (0.54, 1.57)	1.88 (1.20, 2.94)	1.42 (0.88, 2.30)	1.21 (0.73, 2.01)	0.48
Multivariate 1 HR (95% CI)[1]	1	0.96 (0.56, 1.67)	1.99 (1.23, 3.20)	1.52 (0.92, 2.51)	1.35 (0.80, 2.27)	0.30
Multivariate 2 HR (95% CI)[2]	1	1.02 (0.58, 1.77)	1.98 (1.20, 3.25)	1.48 (0.88, 2.51)	1.37 (0.77, 2.42)	0.44

[1] Cox regression model adjusted for age (continuous variable), sex, BMI (lineal and quadratic term), physical activity, alcohol consumption, sodium intake, total energy intake, smoking (never, former, or current), and hypercholesterolemia (yes or no).

[2] Cox regression model with additional adjustment for quintiles of fruit, vegetable, fiber, caffeine, magnesium, potassium, monosaturated fatty acid, and saturated fatty acid intakes.

population, total dairy consumption (including both whole and low-fat products) was significantly associated with a lower risk of hypertension only in obese subjects but not in normal-weight subjects, although the trend in subjects with a BMI < 25 was marginally significant ($P = 0.06$) and suggests a protective effect in that group also. However, that study did not evaluate this question in persons aged >30 y, in whom the incidence of hypertension is much higher and preventive efforts are more needed. Similarly, in the Framingham Children's Study, children who consumed ≥2 servings/d of dairy products during their preschool years had smaller increments in systolic BP during childhood, but the association with diastolic BP was not clear (9).

Calcium could partly account for the observed inverse association between dairy consumption and the risk of hypertension. However, calcium intake has only a small effect on BP and cannot fully explain the important reduction in hypertension risk that was observed (24). In fact, studies that assessed the relation between calcium intake and coronary artery disease or stroke, which are 2 major consequences of hypertension, could not find any association (25) or the association was present only for calcium from dairy products but not from other sources (26, 27). In our study, several facts suggest an effect of low-fat dairy products beyond their calcium content. First, only calcium from low-fat dairy products was associated with a lower risk of hypertension. Second, although a high protein intake, an optimal dietary phosphorus to calcium balance, and a relatively high fat intake all improve calcium absorption (25, 26), stratified analyses for these factors did not show clear evidence of a modification in the relation between calcium and hypertension. Finally, when we adjusted for total calcium intake, the risk estimates for the association between low-fat dairy products and hypertension did not materially change, which suggests that calcium is not the only nutrient responsible for this inverse association.

Adjustment for other dietary factors such as potassium, magnesium, phosphorus, protein, or total fat did not significantly modify the results. It could be that other components that occur in low-fat dairy products or an interaction between some different nutrients may have caused the observed reduction in the risk of hypertension. For example, milk proteins—both caseins and whey proteins—are a rich source of angiotensin converting enzyme inhibitory peptides. In animal models, these proteins (casokinins and lactokinins) have been shown to significantly reduce blood pressure (28).

Although no definitive explanation exists for the inverse association found for only low-fat dairy products and not for full-fat dairy products, it is plausible that saturated fats in whole-fat dairy products somehow neutralize the beneficial effect of dairy consumption. The capacity of calcium to form soaps is much higher when fat intake is increased. Therefore, foods that are high in fat, such as whole-fat dairy foods, might hinder calcium absorption, thereby reducing the bioavalability of calcium (29, 30). This interpretation has some support from epidemiologic studies; for example, although dairy consumption reduced the incidence of the metabolic syndrome in the Coronary Artery Risk Development in Young Adults Study, the consumption of whole-fat dairy products was associated with an increase in LDL cholesterol. This association was not observed for low-fat dairy products (31). Low-fat, but not whole-fat, dairy consumption

TABLE 4
Hazard ratios (HRs) and 95% CIs of hypertension according to quintiles of calcium intake in the Seguimiento Universidad de Navarra cohort

	Quintile					
	1	2	3	4	5	*P* for trend
Total calcium intake						
New cases of hypertension	39	39	35	30	37	
Person-years	2734.2	2725.5	2706.1	2668.2	2691.8	
Incidence (cases per 1000 person-years)	14.3	14.3	12.9	11.2	13.7	
Age- and sex-adjusted HR (95% CI)	1	0.94 (0.60, 1.47)	0.84 (0.53, 1.33)	0.78 (0.48, 1.26)	1.00 (0.63, 1.57)	0.85
Multivariate 1 HR (95% CI)[1]	1	0.98 (0.62, 1.54)	0.82 (0.51, 1.30)	0.73 (0.45, 1.19)	0.97 (0.61, 1.54)	0.67
Multivariate 2 HR (95% CI)[2]	1	0.99 (0.62, 1.59)	0.83 (0.51, 1.36)	0.69 (0.40, 1.18)	0.99 (0.57, 1.73)	0.71
Calcium from low-fat dairy products						
New cases of hypertension	41	46	33	39	21	
Person-years	2739.8	2709.8	2723.0	2651.7	2701.8	
Incidence (cases per 1000 person-years)	15.0	17.0	12.1	14.7	7.8	
Age- and sex-adjusted HR (95% CI)	1	0.95 (0.62, 1.46)	0.77 (0.49, 1.22)	0.95 (0.61, 1.48)	0.54 (0.32, 0.92)	0.03
Multivariate 1 HR (95% CI)[1]	1	0.76 (0.47, 1.24)	0.62 (0.38, 1.01)	0.74 (0.46, 1.20)	0.44 (0.25, 0.76)	0.007
Multivariate 2 HR (95% CI)[2]	1	0.77 (0.47, 1.26)	0.61 (0.37, 1.00)	0.76 (0.46, 1.26)	0.46 (0.25, 0.82)	0.02
Calcium from other dietary sources						
New cases of hypertension	33	28	37	38	44	
Person-years	2731.3	2707.8	2695.9	2700.1	2690.8	
Incidence (cases per 1000 person-years)	12.1	10.3	13.7	14.1	16.4	
Age- and sex-adjusted HR (95% CI)	1	0.85 (0.52, 1.41)	1.01 (0.63, 1.62)	1.06 (0.67, 1.69)	1.28 (0.81, 2.01)	0.15
Multivariate 1 HR (95% CI)[1]	1	0.81 (0.48, 1.36)	1.04 (0.64, 1.69)	1.10 (0.68, 1.76)	1.31 (0.83, 2.08)	0.10
Multivariate 2 HR (95% CI)[2]	1	0.82 (0.49, 1.39)	1.09 (0.65, 1.83)	1.11 (0.66, 1.87)	1.34 (0.77, 2.32)	0.16

[1] Cox regression model adjusted for age (continuous variable), sex, BMI (lineal and quadratic term), physical activity, alcohol consumption, sodium intake, total energy intake, smoking (never, former, or current), and hypercholesterolemia (yes or no).

[2] Cox regression model with additional adjustment for quintiles of fruit, vegetable, fiber, caffeine, magnesium, potassium, monosaturated fatty acid, and saturated fatty acid intakes.

was reported to be associated with a lower risk of type 2 diabetes in a large cohort (32). Although diabetes is a different outcome, both hypertension and diabetes share common risk factors and are more frequently present in persons who have the metabolic syndrome.

More recently, the WELL trial (a moderate-sodium, high-potassium, high-calcium, low-fat DASH diet; 22) found that a diet rich in low-fat dairy products resulted in a greater decrease in BP than did a low-fat comparison diet, which supports the beneficial effect of low-fat dairy consumption for the prevention of hypertension. In fact, compared with the control group, the only striking dietary changes in the intervention group were a significant increase (1.5 servings/d) in the consumption of dairy products and a significantly greater reduction in saturated fat intake. This is likely explained because participants were offered low-fat dairy products of their choice and were given specific amounts for low-fat dairy consumption (22). This trial also found a large difference between the 2 diets in the magnitude of the effect, which is consistent with our results. Therefore, several findings provide additional support for our results (22, 31, 32).

Even though the DASH Study has shown a beneficial effect of a dietary pattern rich in low-fat dairy products, its design did not allow the assessment of the separate effects of each component in that diet. Moreover, assessment of the long-term effects of diet on BP was not planned (2). Our results complement those of the DASH trial because we showed how long-term consumption of low-fat dairy products is inversely associated with the risk of hypertension.

Our study has some important strengths. First, its prospective design implies that information about diet and other risk factors for hypertension was obtained before the diagnosis of the disease. All participants in the cohort were university graduates, which suggests that the self-reported information was of good quality, as was previously reported in other similar cohorts (33, 34). Furthermore, the dietary questionnaire used in the present study was previously validated (14) and was used successfully in another study by our group (35). With regard to the validity of outcome ascertainment, abundant evidence indicates that self-reported information about a hypertension diagnosis is valid for epidemiologic studies (36), particularly in highly educated populations (37). In a validation study that was conducted in a randomly selected subsample of our cohort, we observed acceptable positive and negative predictive values for self-reported medical diagnoses of hypertension, even when our gold standard, which was a repeated direct measurement, missed true cases of hypertension. In addition, the results were the same when we included only those participants who reported a BP measurement in the period between both questionnaires in the analysis.

Cohort participants with higher low-fat dairy consumption had a healthier lifestyle than did cohort participants with a lower low-fat dairy consumption. Thus, residual confounding or some unmeasured factor could explain the observed association, particularly if we consider that the strongest risk reduction was evident for the participants in the highest quintile of low-fat dairy consumption. These participants could be different from the rest of the cohort. However, although we cannot rule out the existence of unmeasured confounders, we adjusted our analyses for the main important known risk factors for hypertension, including alcohol use and other lifestyle variables such as smoking, which could act as markers of a general healthier lifestyle. It is difficult

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to think of an unknown risk factor that could produce a reduction in risk such as we observed. Although we validated most of the information in the questionnaires (14, 17, 19), sodium intake is not easily measured with food-frequency questionnaires and could partially explain the observed inverse association. We acknowledge that adjustment for an imperfectly measured confounder could still lead to residual confounding. However, when we adjusted for the relevant set of confounders, the estimates for low-fat dairy products were away from the null value. If residual confounding explained our results, then the expected change in estimates after adjustment would be toward the null, not away from the null. This shift in adjusted estimates can be explained by a positive association between BMI and low-fat dairy product consumption, which was not apparent in the crude analysis. When we fitted a linear regression model with low-fat dairy consumption as the outcome and age, sex, and BMI as predictors, the coefficient for BMI was positive and showed a P value $<$ 0.001. A similar positive relation was observed between hypercholesterolemia and low-fat dairy product consumption ($P <$ 0.001; *see* Table 2). That is, although low-fat dairy consumption was associated with a healthier dietary pattern, important risk factors for hypertension were also positively associated with low-fat dairy consumption in our participants.

In conclusion, our results add new information about the role of dairy products, especially those with a low-fat content, in the prevention of hypertension. Particularly, we showed that the possible beneficial effect of low-fat dairy consumption is not restricted to young adults and obese persons. Additionally, our study provided evidence to support a possible role of low-fat dairy products in the primary prevention of hypertension, even in a population with a high total fat intake.

We thank the participants in the Seguimiento Universidad de Navarra Study and María Seguí-Gomez and Carmen de la Fuente for expert advice.

MAM-G, MD-R, and JAM helped design the study, collect the data, and obtain the funding. AA analyzed the data, drafted the manuscript, and helped obtain the funding. JJB helped design the study and collect the data. All authors edited and critically reviewed the manuscript. None of the authors had any conflicts of interest.

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