Diet and hip fractures among elderly Europeans in the EPIC cohort

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Background/Objectives: Evidence on the role of diet during adulthood and beyond on fracture occurrence is limited. We investigated diet and hip fracture incidence in a population of elderly Europeans, participants in the European Prospective Investigation into Cancer and nutrition study.
Subjects/Methods: 29 122 volunteers (10 538 men, 18 584 women) aged 60 years and above (mean age: 64.3) from five countries were followed up for a median of 8 years and 275 incident hip fractures (222 women and 53 men) were recorded. Diet was assessed at baseline through validated dietary questionnaires. Data were analyzed through Cox proportional-hazards regression with adjustment for potential confounders.
Results: No food group or nutrient was significantly associated with hip fracture occurrence. There were suggestive inverse associations, however, with vegetable consumption (hazard ratio (HR) per increasing sex-specific quintile: 0.93, 95% confidence interval (CI): 0.85–1.01), fish consumption (HR per increasing sex-specific quintile: 0.93, 95% CI: 0.85–1.02) and polyunsaturated lipid intake (HR per increasing sex-specific quintile: 0.92, 95% CI: 0.82–1.02), whereas saturated lipid intake was positively associated with hip fracture risk (HR per increasing sex-specific quintile: 1.13, 95% CI: 0.99–1.29). Consumption of dairy products did not appear to influence the risk (HR per increasing sex-specific quintile: 1.02, 95% CI: 0.93–1.12).
Conclusions: In a prospective study of the elderly, diet, including consumption of dairy products, alcohol and vitamin D, did not appear to play a major role in hip fracture incidence. There is however, weak and statistically non-significant evidence that vegetable and fish consumption and intake of polyunsaturated lipids may have a beneficial, whereas saturated lipid intake a detrimental effect.

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Introduction

Bone fractures constitute a major public health problem among the elderly worldwide (Cummings and Melton, 2002; Johnell and Kanis, 2006). In the year 2000, there were an estimated 9 million fractures among the elderly, a large fraction of which (35%) were among Europeans (Johnell and Kanis, 2006). Age-related bone fractures represent one of the most important causes of long-standing pain and functional impairment, disability, diminished quality of life and death (Center *et al.*, 1999; Cummings and Melton, 2002; Richmond *et al.*, 2003). In Europe, the estimated disability adjusted life years lost due to osteoporotic fractures exceed those from most common cancers, with the exception of lung cancer (Johnell and Kanis, 2006). Furthermore, bone fractures impose a substantial economic burden to health services and to society (Johnell, 1997). Hip fractures contribute the most to this burden, mainly in terms of severity, functional dependence, social and economic cost and fatality (Kannus *et al.*, 1996; Cummings and Melton, 2002).

The pathogenesis of bone fractures, and hip fracture in particular, is complex (Cummings and Melton, 2002). Impaired bone strength (a parameter depending on density, dimension and quality of the bone) and trauma from falling are the main conditions that usually in combination result in bone fracture among the elderly. Many factors seem to affect bone fracture risk by operating through one of these mechanisms (Kannus *et al.*, 2005; Benetos *et al.*, 2007).

Our knowledge on the role of dietary factors during adulthood and beyond on fracture occurrence is limited (Prentice, 2004). We have examined the potential association of diet with hip fracture incidence in a cohort of elderly European volunteers in the European Prospective Investigation into Cancer and nutrition (EPIC) study.

Subjects and methods

Recruitment

EPIC is a multicentre, prospective cohort study aiming to investigate the role of biological, dietary, lifestyle and environmental factors in the etiology of cancer and other chronic diseases. The study populations are volunteers invited from the general adult population (with few exceptions) as random samples of defined populations were not required; moreover response rates from most centers are not available. The study design and population selection criteria for the EPIC study have been described in detail elsewhere (Riboli *et al.*, 2002). The study protocol has been approved by ethics committees at the individual participating centers, whereas all participants signed informed consent forms before enrollment. All procedures have been in accordance with the Helsinki declaration for human rights.

Data from 30 274 elderly participants from seven centers in five European countries participating in the EPIC-Elderly Network on Ageing and Health project were included in this analysis (for Italy, Varese and Ragusa; for the Netherlands, Utrecht; for Greece, Athens; for Germany, Heidelberg and Potsdam; for Sweden, Umea). EPIC-Elderly Network on Ageing and Health aimed at investigating aspects and predictors of healthy ageing. The source population of EPIC-Elderly Network on Ageing and Health is a cohort consisting of participants aged 60 years and older in the respective EPIC centers (Trichopoulou *et al.*, 2007).

Data on diet and other variables at baseline

Usual dietary intake during the year preceding enrolment was collected with the use of self-administered (in the Netherlands, Germany, Sweden and Varese in Italy) or interviewer-administered (in Greece and Ragusa in Italy) food-frequency questionnaires developed and validated within each country (or center in Italy and Sweden) (Margetts and Pietinen, 1997; Riboli *et al.*, 2002). In addition to baseline dietary questionnaires, highly standardized 24-h dietary recall interviews were conducted, using EPIC-SOFT software International Agency for Research on Cancer (IARC), Lyon, France. (Slimani *et al.*, 1999) on a random sample (5–12%) of each EPIC cohort with the aim to calibrate the measurements across countries (Slimani *et al.*, 2002).

Nutrient intake (in gram/day) and total energy intake (in kcal/day) were calculated for each participant on the basis of the European Prospective Investigation into Cancer and Nutrition Nutrient Database developed in order to harmonize nutrient databases across the 10 European countries participating in EPIC (Slimani *et al.*, 2007).

For the present study, the major food groups (selected from the common EPIC-SOFT classification), the major macronutrients, as well as, selected micronutrients (based on previous knowledge of their association with the outcome of interest) were considered: vegetables, legumes, potatoes, fruits and nuts, dairy products, cereals and cereal products, meat and meat products, fish and shellfish, eggs, sugar and confectionery, as well as, protein, total carbohydrates, total lipids, monounsaturated, polyunsaturated and saturated lipids, ethanol, calcium and vitamin D.

A pre-coded questionnaire was used to collect information on lifestyle, socio-demographic and health characteristics, such as smoking habits, physical activity, education and medical history. Anthropometric measurements (height and weight) were taken in all centers using similar, standardized procedures (Haftenberger *et al.*, 2002). Body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters (in kg/m^2).

Follow-up and information on the primary end point

From the initial cohort of 30 274 elderly participants with reasonable energy intakes (participants in the top and bottom 1% of the ratio of energy intake to estimated energy requirements had already been excluded from the sample), 1152 participants were excluded because of missing values in one or more of the variables used in the analyses. Thus, the final study population consisted of 29 122 elderly, 10 538 men and 18 584 women, with a mean age of 64.3 years at enrolment (min: 60, max: 86). During a median follow-up of 8 years and a total contribution of 243 330 person-years, 275 incident cases of hip fractures (222 women and 53 men) were recorded. When a study participant had more than one hip fracture during follow-up only the first was considered. Information on incident hip fracture was collected through active follow-up methods (telephone interviews or mailed questionnaires eliciting self-reported information) in Germany, Greece and the Netherlands, through record linkage (with hospital discharge records using ICD-10 codes S72.0-S72.2) in Italy and through hip fracture registries (using ICD-10 codes S72.0-S72.2) in Sweden. In a validation exercise conducted in Greece, 79% of self-reported cases of incident hip fractures were medically confirmed, whereas for most of the remaining cases medical records could not be traced.

Statistical analysis

Frequency distributions were used for descriptive purposes. Mean values of intake and standard errors were calculated for each dietary variable investigated, including energy intake.

Cox proportional-hazard regression models were used to quantify the association of intake of selected food groups and nutrients with hip fracture incidence. In all models, length of follow-up was the primary time variable and diagnosis of the first incident hip fracture during follow-up was the outcome event. Subjects with no incident hip fracture were considered as censored at the last date when information on their vital status was assessed or at their date of death. For all dietary variables, sex and country-specific quintiles were computed based on the respective frequency distributions. All models were stratified by center and simultaneously adjusted for sex, age at recruitment (60–64 years, 65–70 years, >70 years; categorically), educational level (⩽6 years, 7–12 years, ⩾13 years, categorically), smoking status (never smokers, former smokers and current smokers, categorically), body mass index (in ordered sex-specific quintiles), height (continuous, in 5 cm increments), physical activity at leisure (per increasing tertile), dietary supplement use, diabetes mellitus at enrolment (yes, no) and total energy intake (per 500 kcal/day).

Data were also analyzed after additive calibration to accommodate for possible systematic differences in estimates of dietary intake from food questionnaires across the centers (Kaaks and Riboli, 1997). Briefly, the differences between the sex and centre-specific means of the values from the food frequency questionnaire and the means of the 24-h recall values were calculated and added to the questionnaire values. The calibrated values and their association to hip fracture incidence were investigated using similar models.

All analyses were performed using the STATA.8 statistical package, Stata Corporation 2003 STATA 8.0 intercooled. College Station, TX, USA (Stata Corp.; 2003).

Results

Baseline characteristics of the total study population and hip fracture cases, by gender are shown in Table 1. Data in this table serve only descriptive purposes as mutual confounding, time to event and country differences are not accounted for. The high mean body mass index values among both men and women and the high percentages of current and former smokers among men are of interest.

In Tables 2 and 3, the mean daily intake of major food groups (Table 2), major energy-generating nutrients and selected micronutrients (Table 3) are shown by country and gender. There is considerable variability among countries with respect to intakes of various food groups with striking examples the higher consumption of vegetables and fruits in Greece and of dairy products in the Netherlands and Sweden.

Table 1 Baseline characteristics of 29 122 participants and 275 incident HF cases during follow-up by gender

Characteristics	*Men*		*Women*	
	Cohort (N = *10 538)*	*HF Cases* (N = *53)*	*Cohort* (N = *18 584)*	*HF Cases* (N = *222)*
Country				
Italy	693	0	1687	6
the Netherlands	—	—	5725	86
Greece	3656	21	5443	91
Germany	4679	5	4758	10
Sweden	1510	27	971	29
Age (years)				
Mean (s.d.)	64.0 (4.1)	64.9 (6.1)	64.5 (3.7)	65.9 (4.7)
Education				
⩽6 years	7902 (75%)	42 (80%)	14 489 (79%)	162 (73%)
7–2 years	548 (5%)	4 (7%)	2509 (13%)	38 (17%)
⩾13 years	2088 (20%)	7 (13%)	1589 (8%)	22 (10%)
Height (in cm)				
Mean (s.d.)	170.6 (7.3)	170.9 (8.2)	158.8 (7.2)	159.6 (7.6)
Body Mass Index (in kg/m^2)				
Mean (s.d.)	27.5 (3.8)	25.7 (3.4)	27.7 (7.7)	26.7 (4.5)
Physical activity at leisure[a]				
Minimal (first tertile)	2851 (27%)	16 (30%)	5736 (31%)	90 (41%)
Moderate (second tertile)	3388 (32%)	13 (24%)	6264 (34%)	74 (33%)
Intense (third tertile)	4299 (41%)	24 (45%)	6584 (35%)	58 (26%)
Smoking status				
Never	3747 (36%)	24 (45%)	13 204 (71%)	156 (70%)
Former	4666 (44%)	17 (32%)	3411 (18%)	38 (17%)
Current	2125 (20%)	12 (23%)	1969 (10%)	28 (13%)
History of diabetes mellitus				
No	9364 (89%)	43 (81%)	17126 (92%)	201 (91%)
Yes	1174 (11%)	10 (19%)	1458 (8%)	21 (9%)
Supplement use				
No	9259 (88%)	31 (68%)	14 950 (80%)	170 (77%)
Yes	1282 (12%)	17 (32%)	3634 (20%)	52 (23%)

Abbreviation: HF, hip fracture.
[a]Incorporates recreational and household physical activity in sex and center specific tertiles.
The EPIC-Elderly Network on Ageing and Health study.

Table 2 Mean daily intake in grams (and standard error) of selected food groups in 29 122 EPIC-Elderly-NAH participants by country and gender

Food groups	*Italy*		*The Netherlands*		*Greece*		*Germany*		*Sweden*	
	M (N = *693*)	*F* (N = *1687*)	*M* (–)	*F* (N = *5725*)	*M* (N = *3656*)	*F* (N = *5443*)	*M* (N = *4679*)	*F* (N = *4758*)	*M* (N = *1510*)	*F* (N = *971*)
Vegetables	139.4 (3.2)	142.2 (2.1)		136.2 (0.7)	437.9 (2.7)	389.9 (2.2)	121.9 (0.8)	131.9 (0.8)	66.4 (1.7)	102.0 (2.9)
Legumes	5.7 (0.3)	5.8 (0.2)		9.3 (0.1)	20.9 (0.2)	16.6 (0.2)	6.4 (0.1)	3.6 (0.1)	4.7 (0.2)	2.9 (0.1)
Potatoes	27.1 (0.9)	22.8 (0.6)		90.4 (0.8)	54.8 (0.5)	45.5 (0.4)	116.6 (0.8)	98.9 (0.6)	191.3 (3.4)	153.0 (3.4)
Fruits—including nuts	377.2 (9.3)	343.2 (5.3)		141.9 (1.9)	352.1 (2.9)	330.5 (162.3)	136.4 (1.3)	163.6 (1.4)	137.9 (2.9)	199.5 (4.3)
Dairy products	211.8 (6.6)	250.8 (4.5)		450.7 (3.3)	199.1 (2.2)	186.0 (1.8)	231.4 (3.3)	213.3 (3.1)	458.1 (6.4)	363.6 (6.0)
Cereals and cereal products	398.1 (5.9)	239.8 (2.6)		141.2 (0.7)	219.6 (1.3)	180.8 (0.9)	209.9 (1.1)	169.5 (0.9)	215.9 (2.7)	180.9 (2.9)
Meat and meat products	103.2 (1.9)	83.4 (1.0)		83.5 (0.6)	81.6 (0.6)	63.3 (0.4)	120.4 (0.9)	85.1 (0.7)	77.2 (1.1)	52.4 (0.9)
Fish and shellfish	26.6 (0.8)	23.3 (0.5)		10.4 (0.2)	23.1 (0.3)	19.7 (0.2)	26.2 (0.4)	20.8 (0.3)	19.7 (0.7)	18.9 (0.6)
Eggs	14.3 (0.4)	12.7 (0.3)		15.3 (0.2)	12.0 (0.2)	9.3 (0.1)	14.3 (0.2)	11.5 (0.2)	2.3 (0.1)	1.5 (0.0)
Sugar and confectionary	41.9 (1.2)	38.5 (0.8)		36.5 (0.3)	20.7 (0.3)	18.0 (0.2)	35.9 (0.4)	32.1 (0.4)	43.1 (0.9)	18.7 (0.5)

Abbreviations: EPIC-Elderly-NAH, EPIC-Elderly Network on Ageing and Health; F, females; M, males.
The EPIC-Elderly Network on Ageing and Health study.

Table 3 Mean daily intake in grams (and standard error) of selected nutrients in 29 122 EPIC-elderly-NAH participants by country and gender

Nutrients	*Italy*		*The Netherlands*		*Greece*		*Germany*		*Sweden*	
	M (N = *693*)	*F* (N = *1687*)	*M* (–)	*F* (N = *5725*)	*M* (N = *3656*)	*F* (N = *5443*)	*M* (N = *4679*)	*F* (N = *4758*)	*M* (N = *1510*)	*F* (N = *971*)
Protein	98.9 (1.2)	79.2 (0.6)		76.9 (0.2)	77.2 (0.4)	63.6 (0.3)	81.6 (0.3)	67.9 (0.3)	68.0 (0.6)	53.3 (0.5)
Total carbohydrates	282.6 (3.25)	213.0 (1.7)		198.9 (0.7)	54.3 (0.90)	164.5 (0.6)	73.7 (1.1)	207.5 (1.0)	241.9 (2.0)	187.8 (1.9)
Total lipids	83.2 (1.0)	72.8 (0.6)		64.8 (0.3)	95.0 (0.5)	80.4 (0.4)	82.8 (0.4)	69.4 (0.4)	70.6 (0.7)	47.4 (0.5)
Saturated lipids	28.5 (0.4)	25.6 (0.3)		27.0 (0.1)	26.7 (0.2)	22.8 (0.1)	33.8 (0.2)	28.8 (0.2)	31.5 (0.3)	21.3 (0.3)
Polyunsaturated lipids	10.8 (0.2)	9.3 (0.1)		11.8 (0.6)	14.6 (0.2)	12.3 (0.1)	14.3 (0.1)	11.9 (0.1)	9.3 (0.1)	6.3 (0.1)
Monounsaturated lipids	39.0 (0.5)	33.4 (0.3)		19.1 (0.1)	47.2 (0.3)	40.3 (0.2)	28.8 (0.2)	23.6 (0.1)	24.5 (0.2)	16.0 (0.2)
Alcohol	25.8 (0.8)	8.3 (0.3)		7.4 (0.2)	16.1 (0.4)	2.6 (0.1)	23.2 (0.4)	7.9 (0.2)	4.4 (0.1)	1.4 (0.1)
Calcium[a]	1032.8 (17.0)	952.0 (9.6)		1082.9 (4.9)	942.8 (5.3)	804.1 (4.1)	851.2 (5.3)	877.0 (5.0)	912.4 (9.6)	736.6 (9.0)
Vitamin D[b]	2.5 (0.1)	2.2 (0.0)		2.7 (0.0)	1.59 (0.0)	1.30 (0.0)	4.4 (0.1)	3.4 (0.0)	5.7 (0.1)	3.9 (0.1)
Energy[c]	2454 (23.7)	1882 (13.2)		1738 (5.0)	2039 (9.2)	1654 (6.4)	2197 (8.8)	1781 (7.2)	1906 (15.1)	1398 (12.8)

Abbreviations: EPIC-Elderly-NAH, EPIC-Elderly Network on Ageing and Health; F, female; M, male.
[a]In mg/day.
[b]In μg/day.
[c]In kcal/day.
The EPIC-Elderly Network on Ageing and Health study.

Table 4 shows Cox-regression-derived hazard ratios (HRs) for incident hip fractures with respect to the dietary variables of interest, alternatively evaluated, controlling for potential confounders as shown in the footnote of the table.

No significant associations are evident with respect to any of the nutritional variables. Higher vegetable consumption is non-significantly associated with lower hip fracture incidence (HR per increasing quintile = 0.93 with 95% confidence interval (CI): 0.85–1.01). The same applies for fish and shellfish consumption (HR per increasing quintile = 0.93 with 95% CI: 0.85–1.02). Consumption of dairy products was not related to hip fracture incidence. With respect to intake of energy-generating nutrients, hip fracture incidence was positively associated with saturated lipids (HR per increasing quintile 1.13 with 95% CI: 0.99–1.29) and inversely associated with polyunsaturated lipids and total carbohydrates (HR per increasing quintile 0.92 with 95% CI: 0.82–1.02 and 0.91 with 95% CI from 0.79 to 1.06, respectively). Lastly, we found no evidence that calcium and vitamin D, or ethanol is associated with hip fracture occurrence. It is interesting to note that intake of dietary supplements was positively, albeit not significantly, associated with risk of hip fracture.

We repeated the analysis after exclusion of data from Italy and Greece in order to examine whether dietary vitamin D could have an inverse association with risk of hip fracture in countries in which limited sunshine does not

Table 4 Hazard ratios[a] for incident hip fracture, 95% CI and *P*-values associated with consumption of selected food groups and nutrients

Food groups and nutrients	*Hazard ratio and 95% CI per sex and country-specific quintile (trend test)*[a]		*P-value*
Vegetables	0.93	0.85–1.01	0.10
Legumes	0.95	0.87–1.04	0.27
Potatoes	0.96	0.88–1.05	0.40
Fruits—including nuts	0.98	0.89–1.07	0.64
Dairy products	1.02	0.93–1.12	0.62
Cereals and cereal products	0.99	0.89–1.09	0.78
Meat and meat products	1.01	0.91–1.11	0.89
Fish and shellfish	0.93	0.85–1.02	0.09
Eggs	1.05	0.96–1.15	0.31
Sugar and confectionary	1.06	0.96–1.16	0.26
Protein	1.03	0.89–1.18	0.71
Total carbohydrates	0.91	0.79–1.06	0.23
Total fat	1.13	0.97–1.32	0.12
Saturated lipids	1.13	0.99–1.29	0.07
Polyunsaturated lipids	0.92	0.82–1.02	0.12
Monounsaturated lipids	1.02	0.89–1.15	0.61
Alcohol	0.97	0.88–1.05	0.44
Calcium	1.02	0.91–1.13	0.80
vitamin D	0.99	0.90–1.11	0.94

Abbreviation: CI, confidence intervals.
[a]The hazard ratios for each food group or nutrient were adjusted for sex, age (60–64 years, 65–70 years, >70 years; categorically), body mass index (in ordered sex-specific quintiles), height (continuous, per 5 cm increment), educational level (⩽6 years, 7–12 years, ⩾13 years, categorically), smoking status (never smokers, former smokers and current smokers, categorically), physical activity at leisure (in ordered tertiles), supplement use, history of diabetes at enrolment (yes, no) and total energy intake. No mutual adjustment among food groups or nutrients. All models were stratified by center.
The EPIC-Elderly Network on Ageing and Health study.

allow generation of abundant endogenous vitamin D. There was no such evidence; in fact the HR changed from 0.99 to 1.04.

We also repeated the analysis after calibration, but the results were very similar; the largest difference was with respect to total carbohydrates for which the HR changed from 0.91 (95% CI: 0.79–1.06) to 0.94 (95% CI: 0.81–1.09) and the corresponding *P*-value from $P=0.23$ to $P=0.40$.

Furthermore, we ran the same models using sex-specific quintiles across the total EPIC cohort for all dietary variables. Minor, yet notable, changes were evident with respect to saturated lipids for which the HR increased from 1.13 (*P*-value = 0.07) to 1.20 (*P*-value = 0.01) and to fish intake for which the HR decreased from 0.93 (*P*-value = 0.09) to 0.91 (*P*-value = 0.06).

A secondary analysis looking for a possible threshold effect was also conducted but no deviation from log-linearity for any of the food groups and nutrients examined was found.

Discussion

In a prospective study of elderly Europeans diet including consumption of dairy products did not appear to have a major role in the incidence of hip fractures. There is, however, weak and statistically non-significant evidence that vegetable and fish consumption and intake of polyunsaturated lipids may have a beneficial effect, whereas saturated lipid intake may have a detrimental effect.

Our knowledge on the role of diet during adulthood and beyond on fracture occurrence is limited (Prentice, 2004). Adequate calcium intake is thought to be essential in all stages of life, for achieving the maximum of bone mass during childhood and early adult years, and for minimizing bone loss thereafter (WHO, 2003). Nevertheless, the association between calcium intake from usual diet, mainly in the form of dairy products, and fracture risk among middle aged and elderly populations remains inconclusive (Weinsier and Krumdieck, 2000; Prentice, 2004). Observational epidemiological studies have shown that in countries with average mean calcium intakes, no association between calcium intake and hip fracture risk is apparent in older men and women (Kato *et al.*, 2000; Weinsier and Krumdieck, 2000; Feskanich *et al.*, 2003; WHO, 2003; Bischoff-Ferrari *et al.*, 2007), whereas in populations with low mean calcium intakes, an increased risk of hip fractures with declining calcium intake (below around 400–500 mg of calcium/day) has been reported. On the other hand, the beneficial effect of combined calcium and vitamin D supplementation for fracture prevention in the frail elderly population is considered as documented and constitutes a recommended intervention against bone loss (Kannus *et al.*, 2005). Nevertheless, results from randomized controlled trials concerning the antifracture efficacy of calcium and/or vitamin D intake are not in agreement (Jackson *et al.*, 2006; Bischoff-Ferrari *et al.*, 2007; Tang *et al.*, 2007). In this population of elderly Europeans, no association between hip fracture risk and consumption of dairy products or intake of calcium or vitamin D was observed.

Fruits and vegetables have been linked with decreased risk of fractures (WHO, 2003). Several components in these foods, such as vitamins K and C, phytoestrogens, potassium and magnesium, as well as, the promotion of an alkaline environment, have been associated with the preservation of bone health (Tucker *et al.*, 1999; Burns *et al.*, 2003). In our study, vegetable consumption appears to be inversely, although statistically not significant, associated with hip fracture risk ($P=0.10$).

Fish consumption was weakly and inversely associated with hip fracture risk in this study. This finding is consistent with those of other investigations (Suzuki *et al.*, 1997; Feskanich *et al.*, 2003) even though, null associations have also been reported (Appleby *et al.*, 2007). Fish (especially dark meat fish) constitute good sources of calcium (especially when edible bones are consumed) and vitamin D. Moreover, they are rich in ω-3 fatty acids. Recent studies have provided evidence for a beneficial role of ω-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid, on bone health and the prevention of bone/joint diseases (Watkins *et al.*, 2001; Manek and Connor, 2007). The evidence points to an attenuation of bone loss through inhibition of cytokine formation and consequently suppression of osteoclast activation (Sun *et al.*, 2003). Moreover, a positive association of ω-3 fatty acids and bone mineral density (BMD) in healthy men has been reported (Högström *et al.*, 2007). Nevertheless, further studies of the physiologic effects of ω-3 fatty acids and fish intake on bone health are needed.

No association between protein intake and hip fracture risk was apparent in our population. Dietary protein is important for the growth, development and maintenance of bones. High dietary protein intake has been positively associated with BMD (Promislow *et al.*, 2002), whereas low intake with increased bone loss (Hannan *et al.*, 2000). Nevertheless, epidemiological findings concerning protein intake and hip fracture risk are inconsistent (Feskanich *et al.*, 1996; Heaney, 2001; Wengreen *et al.*, 2004).

There is emerging evidence from human and animal studies that dietary lipids have an important role in skeletal biology and bone health (Corwin, 2003). Total lipid intake may increase the risk of bone fractures, especially among postmenopausal women (Kato *et al.*, 2000) and decrease BMD (Cooper *et al.*, 1996; Corwin *et al.*, 2006). Moreover, there are indications that the type of lipids consumed is important (Macdonald *et al.*, 2004; Weiss *et al.*, 2005; Corwin *et al.*, 2006; Manek and Connor, 2007). Saturated lipids were found to be inversely associated with BMD in the National Health and Nutrition Examination Survey (NHANES) III (Corwin *et al.*, 2006). Monounsaturated lipids were found to be positively associated with BMD in a study of Greek adults (Trichopoulou *et al.*, 1997), although other investigations have not reproduced that finding (Macdonald *et al.*, 2004). Polyunsaturated lipids have been associated with increased bone loss and reduced calcium absorption attributed to the formation of calcium-fatty acid soaps (Macdonald *et al.*, 2004). In line with the existing evidence, in our study saturated lipid intake tended to increase hip fractures risk (HR per increasing quintile = 1.13 with 95% CI: 0.99–1.29), whereas polyunsaturated lipid intake to reduced this risk (HR per increasing quintile = 0.92 with 95% CI: 0.82–1.02) although neither association was statistically significant.

Little is known on the relation of carbohydrates with bone health and fracture risk. Monosaccharides and disaccharides have been reported to increase fracture risk (Trichopoulou *et al.*, 1997). High alcohol consumption over a long period of time, as well as, alcoholism, appears to increase hip fracture risk (Høidrup *et al.*, 1999; Holberg *et al.*, 2005). There are conflicting reports, however, with respect to moderate alcohol consumption (Hernandez-Avila *et al.*, 1991; Baron *et al.*, 2001). In our study, neither carbohydrates nor alcohol were found to be significantly or suggestively related to hip fracture risk.

Strengths of our investigation are its prospective design, the relatively long follow-up and the employment of validated research instruments (Margetts and Pietinen, 1997; Riboli *et al.*, 2002). A limitation is that fractures, even though as important as hip fractures, may not be always reported particularly in centers that rely on active follow-up. This would create underestimation of the incidence of fractures and of the incidence attributable to various exposures. However, the ratio of the incidence rates among exposed and unexposed will not be affected unless underreporting is associated with a particular exposure, something that could not happen with the specific study design (MacMahon and Trichopoulos, 1996). It is also possible that underreporting would be different among centers and this could create confounding bias. In our analysis, however, we have stratified for center and this controls for any possible confounding. Other limitations are the relatively small number of outcomes and the different sources of information on hip fracture incidence between the centers. In some of the centers, hip fracture cases were only self-reported. Nevertheless, the accuracy of self-reported hip fractures is considered high and more reliable compared to other fracture sites (Chen *et al.*, 2004).

In conclusion, in a sample of elderly Europeans from five countries followed up for approximately 8 years we have found suggestive evidence that intake of vegetables, fish and polyunsaturated lipids may decrease hip fracture risk, whereas intake of saturated lipids may increase that risk. Dairy products, calcium, vitamin D and ethanol were not found to be associated with hip fracture occurrence.

Conflict of interest

The authors declare no conflict of interest.

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References

Appleby P, Roddam A, Allen N, Key T (2007). Comparative fracture risk in vegetarians and nonvegetarians in EPIC-Oxford. *Eur J Clin Nutr* **61**, 1400–1406.

Baron JA, Farahmand BY, Weiderpass E, Michaëlsson K, Alberts A, Persson I *et al.* (2001). Cigarette smoking, alcohol consumption, and risk of hip fracture in women. *Arch Intern Med* **161**, 983–988.

Benetos IS, Babis GC, Zoubos AB, Benetou V, Soucacos PN (2007). Factors affecting the risk of hip fractures. *Injury* **38**, 735–744.

Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D *et al.* (2007). Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* **86**, 1780–1790.

Burns L, Ashwell M, Berry J, Bolton-Smith C, Cassidy A, Dunnigan M *et al.* (2003). UK Food Standards Agency Optimal Nutrition Status Workshop: environmental factors that affect bone health throughout life. *Br J Nutr* **89**, 835–840.

Center JR, Nguyeen TV, Schneider D, Sambrook PN, Eisman JR (1999). Mortality after all types of osteoporotic fracture in men and women: an observational study. *Lancet* **353**, 878–882.

Chen Z, Kooperberg C, Pettinger MB, Bassford T, Cauley JA, LaCroix AZ *et al.* (2004). Validity of self-report for fractures among a multi-ethnic cohort of postmenopausal women: results from the Women' health Initiative observational study and clinical trials. *Menopause* **11**, 264–274.

Cooper C, Atkinson EJ, Hensrud DD, Wahner HW, O'Fallon WM, Riggs BL *et al.* (1996). Dietary protein intake and bone mass in women. *Calcif Tissue Int* **58**, 320–325.

Corwin R, Hartman T, Maczuga S, Graubard B (2006). Dietary saturated fat intake is inversely associated with bone density in humans: Analysis of NHANES III. *J Nutr* **136**, 159–165.

Corwin RL (2003). Effects of dietary fats on bone health in advanced age. *Prostaglandins Leukot Essent Fatty Acids* **68**, 379–386.

Cummings SR, Melton LJ (2002). Epidemiology and outcomes of osteoporotic fractures. *Lancet* **359**, 1761–1767.

Feskanich D, Willett WC, Colditz GA (2003). Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women. *Am J Clin Nutr* **77**, 504–511.

Feskanich D, Willet W, Stampfer M, Colditz G (1996). Protein consumption and bone fractures in women. *Am J Epidemiol* **143**, 472–479.

Haftenberger M, Lahmann PH, Panico S, Gonzalez CA, Seidell JC, Boeing H *et al.* (2002). Overweight, obesity and fat distribution in 50-to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Public Health Nutr* **5**, 1147–1162.

Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP (2000). Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. *J Bone Miner Res* **15**, 2504–2512.

Heaney RP (2001). Protein intake and bone health: the influence of belief systems on the conduct of nutritional science. *Am J Clin Nutr* **73**, 5–6.

Hernandez-Avila M, Colditz GA, Stampfer MJ, Rosner B, Speizer FE, Willett WC (1991). Caffeine, moderate alcohol intake, and risk of fractures of the hip and forearm in middle-aged women. *Am J Clin Nutr* **54**, 157–163.

Högström M, Nordström P, Nordström A (2007). N-3 Fatty acids are positively associated with peak bone mineral density and bone accrual in healthy men: the NO2 Study. *Am J Clin Nutr* **85**, 803–807.

Høidrup S, Grønbaek M, Gottschau A, Lauritzen JB, Schroll M (1999). Alcohol intake, beverage preference, and risk of hip fracture in men and women. Copenhagen Centre for Prospective Population Studies. *Am J Epidemiol* **149**, 993–1001.

Holberg A, Johnell O, Nilsson P, Nilsson JA, Berglung G, Akesson K (2005). Risk factors for hip fractures in a middle-aged population: a study of 33 000 men and women. *Osteoporos Int* **16**, 2185–2194.

Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE *et al.* (2006). Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* **354**, 669–683.

Johnell O (1997). The socioeconomic burden of fractures: today and in the 21th century. *Am J Med* **103**, S20–S25.

Johnell O, Kanis JA (2006). An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* **17**, 1726–1733.

Kaaks R, Riboli E (1997). Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol* **26**(Suppl1), S15–S25.

Kannus P, Parkkari J, Sievanen H, Heinonen A, Vuori I, Järvinen M (1996). Epidemiology of hip fractures. *Bone* **18**, 57S–63S.

Kannus P, Uusi-Rasi K, Palvanen M, Parkkari J (2005). Non-pharmacological means to prevent fractures among older adults. *Ann Med* **37**, 303–310.

Kato I, Toniolo P, Zeleniuch-Jacquatte A, Shore RE, Koening KL, Akhmedkhanov A *et al.* (2000). Diet, smoking and anthropometric indices and postmenopausal bone fractures: a prospective study. *Int J Epidemiol* **29**, 85–92.

MacMahon B, Trichopoulos D (1996). Cohort studies. In: MacMahon B, Trichopoulos D (eds). *Epidemiology: principles and methods*, 2nd ed. Little Brown and Company: Boston. pp 184–185.

Manek C, Connor WE (2007). Do n-3 fatty acids prevent osteoporosis? *Am J Clin Nutr* **85**, 647–648.

Margetts BM, Pietinen P (1997). European Prospective Investigation into Cancer and Nutrition: validity studies on dietary assessment methods. *Int J Epidemiol* **26**(Suppl 1), S1–S5.

Macdonald H, New S, Golden M, Cambell M, Reid D (2004). Nutritional associations with bone loss during the menopausal transition: evidence of beneficial effect of calcium, alcohol, and fruit and vegetable nutrients and of detrimental effect of fatty acids. *Am J Clin Nutr* **79**, 155–165.

Prentice A (2004). Diet, nutrition and the prevention of osteoporosis. *Public Health Nutr* **7**, 227–243.

Promislow JH, Goodman-Gruen D, Slymen DJ, Barrett-Connor E (2002). Protein consumption and bone mineral density in the elderly: the Rancho Bernardo Study. *Am J Epidemiol* **155**, 636–644.

Richmond J, Aharonoff GB, Zucherman JD, Koval KJ (2003). Mortality risk after hip fracture. *J Orthop Trauma* **17**, 53–56.

Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M *et al.* (2002). European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* **5**, 1113–1124.

Slimani N, Deharveng G, Charrondière RU, van Kappel AL, Ocké MC, Welch A *et al.* (1999). Structure of the standardized computerized 24-h diet recall interview used as reference method in the 22 centers participating in the EPIC project. European Prospective Investigation into Cancer and Nutrition. *Comput Methods Programs Biomed* **58** (3), 251–266.

Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G *et al.* (2007). The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr* **61**, 1037–1056.

Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G *et al.* (2002). European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. *Public Health Nutr* **5**, 1125–1145.

STATA Corporation. Stata/SE 8.0 for Windows. Stata Corp: College Station, TX, USA, 2003.

Sun D, Krishnan A, Zaman K, Lawrence R, Bhattacharya A, Fernandes G (2003). Dietary n-3 fatty acids decrease osteoclastogenesis and loss of bone mass in ovariectomized mice. *J Bone Miner Res* **18**, 1206–1216.

Suzuki T, Yoshida H, Hashimoto T, Yoshimura N, Fujiwara S, Fukunaga M *et al.* (1997). Case-control study of risk factors for hip fractures in the Japanese elderly by a Mediterranean osteoporosis study (MEDOS) questionnaire. *Bone* **21**, 461–467.

Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A (2007). Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* **370**, 657–666.

Tucker KL, Hannan MT, Chen H, Cupples LA, Wilson PW, Kiel DP (1999). Potassium, magnesium, and fruit and vegetable intakes are associated with greater bone mineral density in elderly men and women. *Am J Clin Nutr* **69**, 727–736.

Trichopoulou A, Bamia C, Norat T, Overvad K, Schmidt EB, Tjønneland A *et al.* (2007). Modified Mediterranean diet and survival after myocardial infarction: the EPIC-Elderly study. *Eur J Epidemiol* **22**, 871–881.

Trichopoulou A, Georgiou E, Bassiakos Y, Lipworth L, Lagiou P, Proukakis C *et al.* (1997). Energy intake and monounsaturated fat in relation to bone mineral density among women and men in Greece. *Prev Med* **26**, 395–400.

Watkins BA, Li Y, Lippman HE, Seifert MF (2001). Omega-3 polyunsaturated fatty acids and skeletal health. *Exp Biol Med (Maywood)* **226**, 485–497.

Weinsier RL, Krumdieck CL (2000). Dairy foods and bone health: examination of the evidence. *Am J Clin Nutr* **72**, 681–689.

Weiss L, Barrett-Connor E, Muhlen D (2005). Ratio of n-6 to n-3 fatty acids and bone mineral density in older adults: the Rancho Bernardo Study. *Am J Clin Nutr* **81**, 934–938.

Wengreen H, Munger GR, West NA, Cutler DR, Corcoran C, Zhang J *et al.* (2004). Dietary Protein Intake and risk of osteoporotic hip fracture in elderly residents of Utah. *J Bone Miner Res* **19**, 537–545.

WHO. *Diet, Nutrition and the Prevention of Chronic Diseases. Report of a Joint WHO/FAO Expert Consultation*. World Health Organization, Geneva. (WHO Technical Report Series, No. 916) Geneva, (2003).