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# Dietary intake of polyunsaturated fatty acids and risk of hip fracture in men and women

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## Abstract

**Introduction—**Polyunsaturated fatty acids (PUFA) are important in the prevention of chronic diseases, but studies of bone health report inconsistent results. Our aim was to investigate the association between dietary PUFA intake and risk of hip fracture in two large prospective cohorts of men and women with long follow-up times and frequently updated dietary data.

**Methods—**The study population included 75878 women and 46476 men free of osteoporosis at baseline. Dietary intakes were assessed by a food frequency questionnaire at baseline and several times during the follow-up. Multivariable-adjusted Cox proportional hazards models were used to estimate relative risks (RR).

**Results—**During 24 years of follow-up, we identified 1051 hip fracture cases due to low or moderate trauma among the women and 529 cases among the men. In the pooled analyses, no statistically significant associations were found between intakes of total PUFA [RR in the highest vs. lowest quintile: 0.99, 95% confidence interval (CI) 0.69, 1.43; *p* for trend=0.83], total n-3 PUFA (RR 0.89, 95% CI 0.75, 1.06; *p* for trend=0.26), total n-6 PUFA (RR 0.99, 95% CI 0.71, 1.38; *p* for trend=0.82), n-6/n-3 PUFA ratio or individual PUFAs and hip fracture risk. However, in women low intakes of total PUFA, total n-6 PUFA and linoleic acid intakes were associated with higher risk.

**Conclusions—**This study does not support a significant role for PUFA intake in the prevention of hip fractures, although low total PUFA, n-6 PUFA or linoleic acid intakes may increase the risk in women.

### Keywords

fatty acids; fish; hip fracture; population studies; men; women

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## Introduction

In older adults, hip fractures are common and are associated with high morbidity and mortality [1]. Most of the research on dietary factors and bone health has focused on vitamin D and calcium, but polyunsaturated fatty acids (PUFA) may also have a role. Higher total PUFA intake has been associated with greater loss of bone mineral density (BMD) [2] and with both increased [3] and decreased risk [4] of fractures. However, n-3 and n-6 PUFA may have diverse effects on factors affecting bone formation and resorption, such as prostaglandins, cytokines and calcium [5,6]. Serum levels or intake of n-3 PUFA has been associated with greater BMD in some [7–9], but not all studies [10]. In the recent study from the Women's Health Initiative (WHI), higher intake of long-chain n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) was associated with increased fracture risk [4], whereas other studies have found no association with fracture risk for either total n-3 intake [3] or EPA+DHA intake [10,11]. The results from studies investigating the impact of n-6 PUFA on fracture risk have also been inconsistent, with data supporting an increased risk [3] or decreased risk [4] with higher intake. Similarly, although higher dietary n-6/n-3 PUFA ratio has been associated with lower BMD [12], the associations with fracture risk has been mixed [3,4,11]. The results from small intervention trials with fish oil, a source of EPA and DHA, have also varied [13–15].

Therefore, because the existing research data regarding the impact of different PUFA on bone health is inconsistent, the purpose of this study was to investigate the association between PUFA intake and the risk of hip fractures in men in the Health Professionals Follow-up Study (HPFS) and in women in the Nurses' Health Study (NHS), two large cohorts with long follow-up times and frequently updated dietary intake data.

## Methods

### Study populations

The NHS and HPFS cohorts formed the populations for the study. The NHS started in 1976 when 121700 female registered nurses aged 30–55 y responded to a baseline questionnaire. HPFS includes 51529 US male dentists, pharmacists, veterinarians, optometrists, osteopathic physicians, and podiatrists aged 40–75 y when they responded to the baseline questionnaire in 1986. Self-administered questionnaires were mailed to each participant at baseline and then every two years to ascertain lifestyle behaviors and medical conditions. Validated food frequency questionnaires (FFQ) have been sent at least every 4 y to evaluate diet [16]. Responses to the questionnaires constituted written informed consent. The HPFS was approved by the Human Subjects Committee of the Harvard School of Public Health, and the NHS was approved by the Human Research Committee at the Brigham and Women's Hospital.

### Dietary assessment

Both cohorts received an FFQ with over 130 food items in 1986, 1990, 1994, 1998 and 2002. In the NHS, an earlier 116-item FFQ in 1984 provided the baseline dietary assessment for this cohort. On each questionnaire, participants were asked to indicate how often, on

average, they had consumed given amounts of various specified foods during the past year. Nutrient intakes were calculated as the frequency of intake multiplied by the nutrient composition of the specified portion size, computed with and without vitamin and mineral supplements. Nutrient estimates were based on US Department of Agriculture [17] and Harvard University food-composition database sources; the latter is continually updated over time to reflect the composition of new foods in the marketplace. We adjusted all nutrient values for total energy intake by separate regression analyses [18,19]. For the present study, we defined the total n-3 PUFA as EPA+DHA+docosapentaenoic acid+alpha-linolenic acid, total n-6 PUFA as linoleic acid+arachidonic acid, and total PUFA as n-3 PUFA+n-6 PUFA. The focus of the paper was on dietary intakes, so only foods contributed to these intakes. Among women, 2.6% in 1990 and 5.7% in 2002 used fish or cod liver oil. Among men, 4.3% in 1990 and 7.5% in 2002 used these supplements. However, inclusion of the PUFAs from supplements in the total amounts or excluding those who used supplements had no appreciable effect on the associations (data not shown). Fish consumption was calculated as the sum of four items on the FFQ: canned tuna, breaded store-bought fish, dark fish, and other fish.

Several validation studies have demonstrated that the FFQ is a suitable instrument for ranking individuals by fat and fish intakes in the NHS and HPFS cohorts [16,20–23]. For example, correlations for alpha-linolenic acid, linoleic acid, EPA and n-6 PUFA as assessed by the FFQ versus the proportion in adipose tissue were 0.34, 0.37, 0.47 and 0.50, respectively [21,24]. In a comparison of the FFQ with multiple 1-week diet records, correlations were 0.37–0.75 for total and types of fat, 0.73 for canned tuna and 0.58 for dark fish, after adjustment for energy and within-person variation [16,22].

### Hip fractures

Participants were asked to report all previous hip fractures (date, exact bone site, and circumstances leading to the fracture) on the baseline questionnaires, and incident fractures were reported on subsequent biennial questionnaires. Cases in this study included only fractures of the proximal femur that were caused by low or moderate trauma (eg, slipping on ice, falling from the height of a chair). Fractures caused by high trauma (eg, skiing, falling down a flight of stairs) were excluded from analysis. During the 24 y of follow-up, we identified 1051 hip fracture cases among the women and 529 cases among the men in the study populations. The median age of hip fracture in women was 68.9 y and in men 75.3 y. We relied on self-reported hip fractures in these cohorts as accurate reporting is expect in these skilled health professionals. In a small validation study in women, all 30 reported hip fractures were confirmed by medical records [25].

### Statistical methods and analyses

The baseline populations from which the study samples were drawn included 81757 women in the Nurses' Health Study cohort who completed the 1984 FFQ and 49934 men from the HSPH cohort who completed the 1986 FFQ. Women who were premenopausal at baseline did not enter analysis until the follow-up cycle in which they became postmenopausal, and men did not enter analysis until they reached age 50 to make the two cohorts more consistent. In total, 75878 women and 46476 men with data on fatty acid and fish intake and

who were not specifically chosen for increased risk for fractures, i.e. did not have a physician-diagnosed osteoporosis at baseline, contributed to the study. Each eligible participant contributed person-time until the occurrence of hip fracture or death, until their last questionnaire response, or until the end of follow-up on 1 June 2006 in NHS and Jan 2008 in HPFS, whichever came first.

We used Cox proportional hazards models with time-varying covariates to evaluate risk in quintiles of fatty acid intake. Fish intake was assessed in categories of <1 serving/mo, 1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, and ≥5 servings/wk. The data from multiple FFQs over time were used to compute cumulative averages of dietary intake to reduce measurement error and provide more accurate estimates of long-term dietary intake [18]. We also compared results using the most recent reported diet in relation to incidence of hip fracture. This did not produce appreciable differences in the findings (data not shown). To assess potential confounding, multivariate models were adjusted for risk factors for hip fracture, including age, body mass index (eight categories), smoking status (never, former, current), physical activity (quintiles), thiazide-type diuretic use, multivitamin use, osteoporosis, CVD and cancer, and intakes of total energy, calcium, protein, vitamin D, vitamin K, retinol, caffeine, and alcohol (all in quintiles), and postmenopausal hormone use in women. All covariates were updated over time. Bisphosphonate use was first reported in the women in 1998 and could potentially modify the association [26]. However, the results were not appreciably different if women who reported bisphosphonate use (3.8%) were excluded from the analyses (data not shown). Tests of linear trend were conducted by assigning the median values for each category of consumption and treating this as a continuous variable. The data from the two cohorts were pooled using a fixed effects model for the log of the RRs [27]. Heterogeneity between the cohorts was assessed by the $Q$ statistic [27]. Interactions were assessed by stratified analyses and by use of a cross-product (multiplicative) term. All probability values were 2-tailed ($p$<0.05). Analyses were performed with SAS 9.0 software (SAS Institute Inc, Cary, NC).

## Results

The estimated dietary intakes of fatty acids were relatively constant during the follow-up. For example, in 1986, 1990, 1994, 1998 and 2002 the average intakes of total PUFA in men were 13.0, 12.8, 12.9, 13.5 and 13.4 g/d and in women 10.8, 10.3, 9.6, 10.6 and 10.5 g/d. The Table 1 presents the age-standardized baseline characteristics of the two study populations by the total PUFA intake. Both in men and women, those with higher total PUFA intake had lower intakes of calcium, vitamin D, retinol and alcohol. Men and women in the highest total PUFA quintile had a higher intake of both n-3 PUFA and n-6 PUFA. The higher n-3 PUFA intake was explained by the higher intake of alpha-linolenic acid. In both men and women, in 1986 the major food sources of n-3 PUFA were fish, mayonnaise and margarine and the major n-6 PUFA sources mayonnaise, margarine and nuts. In 2002, the major n-3 PUFA sources were fish, walnuts and mayonnaise and the major n-6 PUFA sources mixed nuts, mayonnaise and oil and vinegar salad dressing.

In the final analyses in which results from the men and the women were pooled, no statistically significant associations were found between total PUFA intake or any of the

PUFA subtypes and risk of hip fracture (Table 2). However, statistically significant heterogeneity between the two cohorts was found with intakes of total PUFA ($p$=0.03), total n-6 PUFA ($p$=0.05) and linoleic acid ($p$=0.04), with women having an inverse association with the risk, whereas no statistically significant associations were found in men.

Among women, those in the highest quintile of total PUFA intake had a multivariate-adjusted relative risk (RR) of hip fracture of 0.84 [95% confidence interval (CI) 0.69, 1.02], compared with the lowest quintile (Table 2). Inverse associations of similar magnitude were also observed with intakes of total n-6 PUFAs and linoleic acid, which comprised 88% and 87% of the total PUFA intake, respectively. The RR was 0.85 (95% CI 0.70, 1.03) in the highest vs. lowest n-6 PUFA intake quintile and 0.81 (95% CI 0.67, 0.98) in the highest vs. lowest linoleic acid intake quintile. However, the modest reduction in the risk was evident already in the second quintiles and little or no added benefit was observed with higher intakes. When we compared the lowest quintile to all other quintiles, the multivariate-adjusted RR for total PUFA was 1.18 (95% CI 1.02, 1.36), for total n-6 PUFA 1.21 (95% CI 1.05, 1.40) and for linoleic acid 1.23 (95% CI 1.07, 1.42). Both total n-3 and EPA+DHA intakes in women showed statistically significant inverse trends with hip fracture risk after adjustment for age only, but further multivariate adjustments attenuated the associations. Physical activity and BMI had the greatest impact on the association. No statistically significant associations were found with alpha-linolenic acid intakes.

In contrast to women, the only statistically significant association in men was observed with EPA+DHA intake (Table 2), with an age-adjusted RR of hip fracture of 0.77 (95% CI 0.59, 1.01) in the highest vs. the lowest quintile ($p$ for trend =0.01). The association was slightly attenuated and became statistically insignificant after further adjustments ($p$ for trend =0.09).

The quintile cut points differed between men and women due to higher absolute fatty acid intakes in men, which may explain the heterogeneity in the results. Therefore, we also evaluated the associations with total PUFA, total n-6 PUFA and linoleic acid intakes as percent of energy intake, using the same cut points for both cohorts. However, the results were very similar to those shown in the Table 2. For example, the multivariate-adjusted RRs in women in quintiles of total PUFA as percent of energy were 1, 0.88, 0.85, 0.79 and 0.84 (95% CI 0.69, 1.02), $p$ for trend =0.05. When the lowest quintile (<4.8% of energy) was compared to all other quintiles, the multivariate-adjusted RR was 1.19 (95% CI 1.02, 1.38). Again, no statistically significant associations were found in men (data not shown).

We did not find evidence for an association between n-6 to n-3 PUFA ratio and risk of hip fracture. The ratio ranged from <6.7 in the lowest quintile to >8.9 in the highest quintile in women and from <6.7 to >10.0 in men. The pooled RR in the highest vs. the lowest ratio quintile was 0.96 (95% CI 0.81, 1.15; $p$ for trend =0.64; $p$ for heterogeneity =0.42).

We also evaluated the association between hip fracture and fish consumption, a major source of n-3 PUFAs and especially EPA+DHA (Table 3). The mean intake of fish was 0.3 servings/d (SD 0.3) in men and 0.3 servings/d (SD 0.2) in women. Although higher fish consumption was associated with lower risk of hip fracture in both men and women after adjustment for age ($p$ for trend =0.01 for women and $p$=0.05 for men), further adjustments

attenuated the associations and were no longer significant. Again, physical activity and BMI in women and physical activity in men had the greatest impact on the association. In the pooled analysis, the RR was 0.83 (95% CI 0.56, 1.22) for ≥5 servings/wk of fish compared with <1 serving/month ($p$ for trend =0.16). We also investigated the associations by combining the two highest intake categories because of the low number of events in those consuming fish ≥5 servings/week. However, the associations were not appreciably different (data not shown).

We did not find evidence for effect modification by age, physical activity or alcohol, calcium or vitamin D intakes in men or women, or by postmenopausal hormone use in women ($p$ for interactions >0.05).

## Discussion

Overall, the results from the two large, prospective cohort studies, the NHS and the HPFS, do not support a significant role for PUFA or fish intake in the prevention of hip fractures in older people. However, low intakes of total PUFA, total n-6 PUFA and linoleic acid may increase the risk in women.

Data about PUFA intake and bone health are currently inconsistent. Low BMD increases the risk for fractures; therefore some studies have investigated the impact of PUFA or fish intake on BMD. Interestingly, higher total PUFA intake was associated with greater BMD loss during 5–7 y of follow-up in women aged 45–55 y at baseline [2]. The authors did not differentiate between n-3 and n-6 PUFAs in this study. In a longitudinal study among young men, serum long-chain n-3 PUFA concentration, and especially DHA, was positively associated with peak BMD and bone accrual [8]. In a recent analysis from the Framingham Osteoporosis Study, higher intake of fish in men and women and EPA and DHA in men was associated with lesser loss of BMD over 4 y [9]. In cross-sectional studies, high intake of seafood or total n-3 PUFA has been associated with greater BMD among elderly participants in most [7,28,29], but not all studies [30]. Recently, we did not find strong associations between fish or EPA+DHA intake and BMD among 5045 older men and women from the Cardiovascular Health Study [10]. The small experimental studies that have investigated the effect of fish oil on BMD or biochemical parameters of bone health in post-menopausal women have produced mixed results [13–15].

Although the exact mechanisms by which n-3 and n-6 PUFAs may affect bone health are not currently known, it has been proposed that n-6 and n-3 PUFAs may have opposing effects on factors affecting bone metabolism, such as prostaglandins, cytokines, and calcium [5,6]. For example, the major prostaglandin involved in bone metabolism is prostaglandin $E_2$, which is suggested to stimulate bone formation at low concentrations, but inhibit at high concentrations [31]. The n-6 PUFA are precursors to prostaglandin $E_2$, whereas n-3 PUFA have been shown to inhibit its production [32]. The N-3 PUFA also inhibit production of pro-inflammatory cytokines, such as interleukin 1 and tumor necrosis factor α [32], which have been suggested to be associated with postmenopausal bone loss [33]. In animal models, n-3 PUFA supplementation has been beneficial regarding calcium absorption and balance [6].

Studies in animal models showed that diets high in EPA+DHA, compared with diets enriched in n-6 PUFA, can attenuate bone loss [6]. In the Rancho Bernardo Study, a dietary n-6/n-3 PUFA ratio was inversely associated with BMD in older men and women [12]. However, independent associations with n-3 or n-6 PUFA intakes were not reported and use of ratios makes it difficult to interpret whether the associations are due to differences in n-3 or n-6 PUFA intakes or both. Other studies have reported also on the n-6/n-3 PUFA ratio and fracture risk [3,4,11]. In post-menopausal women in the WHI, a modest inverse association was found between n-6/n-3 PUFA ratio and total fracture risk, but no association was found with hip fracture risk [4]. In the WHI, higher n-6 PUFA intake was also modestly associated with decreased risk and higher EPA+DHA intake with increased risk of total fractures, but not with hip fractures [4]. In a Spanish case-control study of older men and women, n-6/n-3 PUFA ratio was not associated with fracture risk, although both the total PUFA and n-6 PUFA intakes were associated with higher risk and no association was observed with n-3 PUFA intake [3]. No association with hip fracture risk was found in older men and women in a recent analysis in the Framingham Osteoporosis Study, either [11]. We did not find associations with n-6/n-3 PUFA ratio and hip fracture risk either in men or women, despite very similar n-6/n-3 ratios in women than in the WHI (>8.9 in the highest quartile in the WHI vs. >8.9 in the highest quintile in the NHS). In our study, women with higher intakes of total PUFA and n-6 PUFA had a lower risk for fracture. The inverse associations were mainly due to the inverse association with linoleic acid intake, which comprised 87% of the total PUFA intake and 98% of the n-6 PUFA intake. However, the lower risk was evident already in the second intake quintile and no dose-response effect was found with higher intakes. The observed higher risk in women in the analysis comparing the lowest total PUFA intake quintile to all other quintiles may indicate that low intake is associated with higher risk, but no benefit is seen with higher intakes. This may explain why no associations were found in men, who had higher average intakes already in the lowest fatty acid quintiles. Women also start out with less dense bones and they go through a greater bone loss at menopause, therefore they are likely more sensitive to risk factors that are too minor to affect men.

In our study, we did not find statistically significant associations between EPA+DHA intake and hip fracture risk. This supports our recent findings from the Cardiovascular Health Study [10] and those form the Framingham Osteoporosis Study [11] and the WHI [4], although in the WHI, higher intake was associated with modestly increased risk of total fractures [4]. We also evaluated the impact of fish consumption on the hip fracture risk, because previously in the NHS, higher consumption of dark meat (oily) fish was associated with a lower risk for hip fracture during 18 y of follow-up ($p$ for trend across the four fish intake groups = 0.03), although there was no statistically significant difference between the extreme intake categories [34]. Fish is a major source of EPA and DHA, and like with the EPA+DHA intake, we did not find any associations with total fish consumption either in women or men after adjustment for confounders. This again corresponds with our recent findings from the Cardiovascular Health Study [10] and with other studies [11,35], even in populations with traditionally high fish consumption, like the Japanese [36].

The major strengths of the study are the inclusion of two well-described cohorts with a large number of both men and women and the 24 y follow-up with a large number of events and

standardized examinations of other risk factors. The dietary data were detailed and serially updated, which allowed evaluation of usual dietary habits over time. The FFQ can be limited by errors in reporting and recall and by incomplete assessment of all sources of fat intake, which can introduce misclassification in dietary intakes and would bias results towards the null. However, the data are suitable for ranking people. The prospective design reduces bias from changes in diet due to known disease. Relatively little loss to follow-up occurred, which minimizes selection bias or missed events. The hip fractures were self-reported and are therefore subject to error. However, the accuracy of self-report has been shown to be good [25,37,38]. In conclusion, although our pooled results do not support a significant role for dietary PUFA or fish intake in the prevention of hip fractures in older men or women, low intakes of total PUFA, n-6 PUFA and linoleic acid may be a risk factor in women.

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**Table 1**

Age and Age-Standardized Characteristics at Baseline in 75878 Women in the NHS and 46476 Men in the HPFS by Quintiles of total polyunsaturated fatty acid intake

| | Total PUFA quintile (g/d), women | | | | | Total PUFA quintile (g/d), men | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Q1 (<8.6)** | **Q2 (8.6–10.2)** | **Q3 (10.3–11.6)** | **Q4 (11.7–13.4)** | **Q5 (>13.4)** | **Q1 (<10.5)** | **Q2 (10.5–12.0)** | **Q3 (12.1–13.4)** | **Q4 (13.5–15.2)** | **Q5 (>15.2)** |
| Age (y) | 63.6 | 63.3 | 63.2 | 63.1 | 63.1 | 65.0 | 65.1 | 65.0 | 64.9 | 64.5 |
| Dietary intakes | | | | | | | | | | |
| Total n-3 PUFA (g/d) | 1.0 | 1.2 | 1.3 | 1.5 | 1.8 | 1.2 | 1.3 | 1.4 | 1.5 | 1.7 |
| EPA+DHA (g/d) | 0.21 | 0.19 | 0.19 | 0.18 | 0.18 | 0.32 | 0.32 | 0.32 | 0.30 | 0.29 |
| ALA (g/d) | 0.8 | 1.0 | 1.0 | 1.1 | 1.4 | 0.8 | 1.0 | 1.1 | 1.2 | 1.4 |
| Total n-6 PUFA (g/d) | 6.8 | 8.7 | 10.0 | 11.4 | 14.2 | 8.0 | 10.0 | 11.3 | 12.8 | 15.9 |
| Linoleic acid (g/d) | 6.5 | 8.5 | 9.9 | 11.3 | 14.4 | 8.0 | 10.1 | 11.4 | 12.8 | 15.9 |
| Fish (servings/wk) | 2.1 | 2.0 | 2.0 | 1.9 | 1.9 | 2.5 | 2.6 | 2.5 | 2.5 | 2.3 |
| Energy (kcal/d) | 1686 | 1756 | 1783 | 1761 | 1688 | 1968 | 1987 | 1997 | 2007 | 1979 |
| Calcium (mg/d) | 999 | 920 | 881 | 857 | 822 | 985 | 927 | 894 | 873 | 849 |
| Vitamin D (IU/d) | 359 | 330 | 311 | 302 | 300 | 440 | 417 | 409 | 401 | 387 |
| Vitamin K (μg/d) | 185 | 181 | 183 | 187 | 196 | 191 | 191 | 190 | 187 | 187 |
| Retinol (IU/d) | 5101 | 4724 | 4371 | 4296 | 4350 | 5813 | 5568 | 5467 | 5395 | 5230 |
| Protein (g/d) | 74 | 73 | 72 | 71 | 69 | 92 | 93 | 93 | 93 | 91 |
| Caffeine (mg/d) | 301 | 316 | 325 | 330 | 343 | 218 | 229 | 230 | 232 | 238 |
| Alcohol (g/d) | 9 | 7 | 7 | 6 | 6 | 16 | 13 | 11 | 10 | 9 |
| Body mass index (kg/m$^2$) | 24.9 | 25.0 | 25.1 | 25.1 | 25.2 | 24.8 | 25.0 | 25.0 | 25.0 | 25.0 |
| Physical activity[a] | 3.1 | 3.0 | 2.8 | 2.8 | 2.7 | 21.9 | 21.3 | 20.3 | 19.8 | 18.5 |
| Current smoker (%) | 26 | 23 | 23 | 22 | 24 | 9 | 8 | 8 | 9 | 9 |
| CVD (%) | 1 | 1 | 1 | 1 | 1 | 7 | 6 | 6 | 6 | 6 |
| Cancer (%) | 3 | 3 | 2 | 3 | 2 | 3 | 3 | 3 | 3 | 4 |
| Postmenopausal hormone use (%) | 29 | 27 | 27 | 27 | 28 | NA | NA | NA | NA | NA |
| Thiazide diuretic use (%) | 26 | 25 | 24 | 24 | 25 | 10 | 9 | 9 | 8 | 9 |
| Multivitamin use (%) | 40 | 38 | 36 | 36 | 35 | 43 | 42 | 42 | 41 | 41 |

All values are means or percentages. ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids. Most of the variables in the table had a significant *p* value for differences across quintiles of PUFA due to the large size of the study populations.

[a] Physical activity reported as h/wk in women and MET-h/wk in men. MET-h is a measure of energy expenditure.

**Table 2**

Relative risks of hip fracture in quintiles of cumulatively updated polyunsaturated fatty acid intake in 75878 women in the NHS (1984–2006) and in 46476 men in the HPFS (1986–2008)

| | Fatty acid quintile | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **95% CI** | ***p* for trend** |
| Total PUFA | | | | | | | |
| Women | | | | | | | |
| Intake (g/d) | 7.9 | 9.4 | 10.5 | 11.8 | 13.9 | | |
| N of cases | 271 | 212 | 195 | 181 | 192 | | |
| Model 1[a] | 1 | 0.86 | 0.82 | 0.78 | 0.85 | (0.70, 1.04) | 0.05 |
| Model 2[b] | 1 | 0.89 | 0.85 | 0.81 | 0.84 | (0.69, 1.02) | 0.05 |
| Men | | | | | | | |
| Intake (g/d) | 9.4 | 11.3 | 12.7 | 14.2 | 16.8 | | |
| N of cases | 105 | 113 | 91 | 108 | 112 | | |
| Model 1[a] | 1 | 1.08 | 0.87 | 1.07 | 1.21 | (0.92, 1.60) | 0.18 |
| Model 2[b] | 1 | 1.13 | 0.94 | 1.09 | 1.21 | (0.91, 1.61) | 0.24 |
| Pooled | 1 | 0.95 | 0.87 | 0.89 | 0.94 | (0.80, 1.10) | 0.45[c] |
| Total n-3 | | | | | | | |
| Women | | | | | | | |
| Intake (g/d) | 0.9 | 1.1 | 1.2 | 1.4 | 1.6 | | |
| N of cases | 260 | 213 | 188 | 210 | 180 | | |
| Model 1[a] | 1 | 0.86 | 0.76 | 0.86 | 0.78 | (0.64, 0.94) | 0.02 |
| Model 2[b] | 1 | 0.93 | 0.84 | 0.98 | 0.86 | (0.70, 1.06) | 0.26 |
| Men | | | | | | | |
| Intake (g/d) | 1.0 | 1.2 | 1.4 | 1.6 | 1.9 | | |
| N of cases | 112 | 107 | 103 | 103 | 104 | | |
| Model 1[a] | 1 | 0.90 | 0.86 | 0.88 | 0.87 | (0.66, 1.14) | 0.36 |
| Model 2[b] | 1 | 0.95 | 0.95 | 0.99 | 0.96 | (0.71, 1.31) | 0.92 |
| Pooled | 1 | 0.94 | 0.87 | 0.98 | 0.89 | (0.75, 1.06) | 0.35 |
| EPA+DHA | | | | | | | |

| | Fatty acid quintile | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 95% CI | *p* for trend |
| Women | | | | | | | |
| Intake (g/d) | 0.07 | 0.12 | 0.18 | 0.24 | 0.37 | | |
| N of cases | 214 | 238 | 213 | 185 | 201 | | |
| Model 1[a] | 1 | 1.08 | 0.93 | 0.81 | 0.88 | (0.72, 1.07) | 0.02 |
| Model 2[b] | 1 | 1.16 | 1.03 | 0.94 | 1.06 | (0.84, 1.34) | 0.82 |
| Men | | | | | | | |
| Intake (g/d) | 0.09 | 0.18 | 0.26 | 0.36 | 0.57 | | |
| N of cases | 115 | 124 | 109 | 75 | 106 | | |
| Model 1[a] | 1 | 0.96 | 0.85 | 0.60 | 0.77 | (0.59, 1.01) | 0.01 |
| Model 2[b] | 1 | 1.05 | 0.94 | 0.67 | 0.83 | (0.60, 1.15) | 0.09 |
| Pooled | 1 | 1.12 | 1.00 | 0.84 | 0.98 | (0.81, 1.19) | 0.16 |
| α-linolenic acid | | | | | | | |
| Women | | | | | | | |
| Intake (g/d) | 0.7 | 0.8 | 0.9 | 1.0 | 1.2 | | |
| N of cases | 249 | 208 | 193 | 199 | 202 | | |
| Model 1[a] | 1 | 0.88 | 0.84 | 0.88 | 0.89 | (0.74, 1.07) | 0.28 |
| Model 2[b] | 1 | 0.94 | 0.91 | 0.96 | 0.95 | (0.78, 1.15) | 0.70 |
| Men | | | | | | | |
| Intake (g/d) | 0.8 | 0.9 | 1.1 | 1.2 | 1.5 | | |
| N of cases | 105 | 117 | 115 | 78 | 114 | | |
| Model 1[a] | 1 | 1.12 | 1.04 | 0.94 | 1.23 | (0.93, 1.62) | 0.33 |
| Model 2[b] | 1 | 1.20 | 1.13 | 1.03 | 1.29 | (0.96, 1.72) | 0.22 |
| Pooled | 1 | 1.01 | 0.96 | 0.97 | 1.04 | (0.88, 1.22) | 0.63 |
| Total n-6 | | | | | | | |
| Women | | | | | | | |
| Intake (g/d) | 6.9 | 8.3 | 9.3 | 10.4 | 12.4 | | |
| N of cases | 274 | 205 | 195 | 177 | 200 | | |
| Model 1[a] | 1 | 0.82 | 0.81 | 0.75 | 0.87 | (0.72, 1.05) | 0.09 |

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| | Fatty acid quintile | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **95% CI** | ***p* for trend** |
| Model 2[b] | 1 | 0.84 | 0.83 | 0.77 | 0.85 | (0.70, 1.03) | 0.07 |
| Men | | | | | | | |
| Intake (g/d) | 8.2 | 10.0 | 11.3 | 12.7 | 15.2 | | |
| N of cases | 107 | 108 | 98 | 104 | 112 | | |
| Model 1[a] | 1 | 1.03 | 0.94 | 1.02 | 1.21 | (0.92, 1.59) | 0.19 |
| Model 2[b] | 1 | 1.07 | 1.00 | 1.03 | 1.19 | (0.90, 1.58) | 0.28 |
| Pooled | 1 | 0.90 | 0.88 | 0.84 | 0.94 | (0.81, 1.10) | 0.51[c] |
| Linoleic acid | | | | | | | |
| Women | | | | | | | |
| Intake (g/d) | 6.8 | 8.1 | 9.1 | 10.2 | 12.1 | | |
| N of cases | 272 | 200 | 196 | 188 | 195 | | |
| Model 1[a] | 1 | 0.79 | 0.80 | 0.79 | 0.83 | (0.69, 1.00) | 0.06 |
| Model 2[b] | 1 | 0.81 | 0.82 | 0.81 | 0.81 | (0.67, 0.98) | 0.04 |
| Men | | | | | | | |
| Intake (g/d) | 8.2 | 10.0 | 11.3 | 12.7 | 15.2 | | |
| N of cases | 107 | 113 | 95 | 109 | 105 | | |
| Model 1[a] | 1 | 1.09 | 0.93 | 1.09 | 1.18 | (0.89, 1.56) | 0.27 |
| Model 2[b] | 1 | 1.13 | 0.98 | 1.10 | 1.15 | (0.86, 1.53) | 0.42 |
| Pooled | 1 | 0.90 | 0.87 | 0.89 | 0.90 | (0.77, 1.06) | 0.33[c] |

Intakes reported represent median intakes in each quintile.

[a] Model 1 was adjusted for age.

[b] Model 2 was adjusted for age, body mass index, smoking status (never, former, current), physical activity (quintiles), thiazide-type diuretic use, multivitamin use, osteoporosis, CVD and cancer, and intakes of total energy, calcium, protein, vitamin D, vitamin K, retinol, caffeine, and alcohol (all in quintiles), and postmenopausal hormone use in women.

[c] Statistically significant heterogeneity was observed between men and women: $p$=0.03 for total PUFA, $p$=0.05 for total n-6 PUFA and $p$=0.04 for linoleic acid.

**Table 3**

Relative risks of hip fracture in categories of fish intake in 75878 women in the NHS (1984–2006) and in 46476 men in the HPFS (1986–2008)

| | Fish intake, servings | | | | | | |
|---|---|---|---|---|---|---|---|
| | **<1/mo** | **1–3/mo** | **1/wk** | **2–4/wk** | **≥5/wk** | **95% CI** | ***p* for rend** |
| Women | | | | | | | |
| N of cases | 71 | 149 | 669 | 143 | 19 | | |
| Model 1[a] | 1 | 1.14 | 1.02 | 0.85 | 0.79 | (0.47, 1.31) | 0.01 |
| Model 2[b] | 1 | 1.20 | 1.14 | 1.01 | 0.95 | (0.55, 1.63) | 0.31 |
| Men | | | | | | | |
| N of cases | 43 | 64 | 288 | 108 | 26 | | |
| Model 1[a] | 1 | 0.85 | 0.67 | 0.65 | 0.60 | (0.36, 0.99) | 0.05 |
| Model 2[b] | 1 | 0.93 | 0.79 | 0.78 | 0.72 | (0.42, 1.25) | 0.32 |
| Pooled | 1 | 1.10 | 1.00 | 0.92 | 0.83 | (0.56, 1.22) | 0.16 |

[a]Model 1 was adjusted for age.

[b]Model 2 was adjusted for age, body mass index, smoking status (never, former, current), physical activity (quintiles), thiazide-type diuretic use, multivitamin use, osteoporosis, CVD and cancer, and intakes of total energy, calcium, protein, vitamin D, vitamin K, retinol, caffeine, and alcohol (all in quintiles), and postmenopausal hormone use in women.