Absence of association between inflammatory dietary pattern and low trauma fractures: Results of the French cohort NutriNet-Santé

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Abstract:

Introduction

The aim of our study was to assess the association between the Alternate Dietary Inflammatory Index (ADII) and the risk of fracture in a French cohort of women and men older than 50 years.

Methods

A total of 15,096 participants were included from the French NutriNet-Santé cohort. The ADII score was calculated at inclusion. Incident low trauma fractures were retrospectively self-reported by participants on a specific additional questionnaire. Multivariate hazard ratio obtained from Cox proportional hazard regression models were used to characterize an association between ADII (in quartiles) and incident low trauma fractures.

Results

12,046 participants (7607 (63.2%) women and 4,439 (36.8%) men) were included in our study. For fractures, 806 (10.6%) and 191 (4.3%) low trauma fractures were recorded respectively in women and in men. Mean ADII was -1.23 (+/-3.13) for women and - 0.87 (+/- 3.64) for men. No association was detected between the ADII score and the risk of vertebral fracture ($p = 0.21$), major osteoporotic fracture ($p = 0.93$) and any low trauma fracture ($p = 0.72$) in women nor in men ($p = 0.06$ for major fracture and $p = 0.10$ for low trauma fracture) after adjustment for sociodemographic, lifestyle variables and for bone treatments.

Conclusion

This study in postmenopausal women and men older than 50 years from the general population did not show any association between inflammatory dietary pattern measured using the ADII and the risk of incident low trauma fracture.

Keywords : inflammatory dietary pattern, bone fracture, nutrition, low trauma fracture

Introduction

Chronic inflammation is a well-known risk factor of osteoporosis and fracture [1]. There is a link between high level of serum inflammatory markers, bone loss and low trauma fracture in patients with inflammatory chronic diseases [1,2]. In clinical studies, serum levels of inflammatory cytokines as high levels of IL-6 and anti-tumor necrosis factor (TNF) were associated with a higher risk of hip fracture and any low trauma fractures [3,4]. Even in subjects without chronic diseases, a chronic sub inflammation, as assessed by ultra-sensitive C reactive protein levels has been associated with a higher fracture risk in post-menopausal women and in older women and men [3,5,6]. Macrophage-colony-stimulating factor 1 (M-CSF) and RANKL, a member of the TNF – alpha family are necessary for osteoclastogenesis and are enhanced by pro inflammatory cytokines such as IL-1, IL-6, TNF alpha. Thus, there is a strong biological rationale for the link between inflammation and bone remodeling in the pathogenesis of osteoporosis.

Among causes of sub clinical chronic inflammation, previous studies have shown the role of nutrients and dietary patterns [7]. Nutrients as fiber, fruit and vegetables are associated with anti-inflammatory effects [8,9] while saturated fatty acids have rather pro inflammatory effects [10].

The Dietary Inflammatory Index (DII) was developed to quantify the inflammatory potential of the overall diet. Scientific literature review documented the relationships between various dietary factors and blood inflammatory biomarkers [11]. A higher score of DII represents a high inflammatory diet pattern. In previous studies, a high DII value was associated with a higher level of the interleukin 6 [12], high sensitive C reactive protein [13] and tumor necrosis factor alpha levels [14] in adolescent and adults.

The clinical relevance of a high DII has been assessed in several diseases and has been found to be associated with various conditions including cardiovascular risk, mortality, breast cancer and prostate cancer [15,16,17, 18]. Some studies have reported an association between a high DII and low trauma fracture, with an increased risk of wrist fractures in men and women [19], and an increased risk of incident fractures in women but this association was not found for men [20]. Recent studies showed that low DII scores were significantly associated with a decreased bone loss measured with the bone mineral density (BMD) at the hip over 6 years [21]. However, some studies did not confirm these results [21]. High DII was not associated to fractures in a large cohort of post-menopausal women, the women's health initiative (WHI), but only observed in a sub groups analysis, with an increased risk of hip fractures in younger and white women (age < 63 years) [21]. Finally, few studies assessed the association of a high DII on low trauma fracture in general population.

The Alternate Dietary Inflammatory Index (ADII), a new score assessing inflammatory diet, has been recently developed and validated to calculate the overall inflammatory potential of a diet [13,22] based on the DII but excluding total fat and energy intakes to limit the over-estimation of the inflammatory effect of certain nutrients [22].

The aim of this study was to assess the association of the ADII score and the risk of vertebral fracture, major osteoporotic fracture and any low trauma fracture in postmenopausal women and men 50 years older from the NutriNet-Santé population.

Methods

NutriNet-Santé study and study population

The NutriNet-Santé study is a web-based ongoing French cohort initiated in 2009 [23]. The objectives of this cohort are to assess the relationships between nutrition and health, and also the determinants of dietary behaviors and nutritional status. Participants with an access to internet were recruited via a multimedia campaign to subscribe on a specific secured web-site http://www.etude-nutrinet-sante.fr.

Questionnaires and forms can be filled in online with all security conditions of data and personal information. To be considered as included, participants have to complete a set of five questionnaires related to diet (3 validated random records of 24h food intake during a two weeks period [24,25]), physical activity (with the validated International Physical Activity Questionnaire (IPAQ) [26]), anthropometry (weight, height) [27,28], lifestyle and socio economic conditions (like date of birth, sex, education level, smoking status, number of children, income) [29] and health status (personal and family history of diseases, menopausal status, drug use including oral contraceptive or hormonal replacement treatment (HRT) for menopause). The web-based self-administered anthropometric questionnaire was compared with a traditional paper questionnaire and showed high consistency [27,28]. Web-based questionnaires used to collect baseline characteristics of the participants (eg, sociodemographic and lifestyle data) have been tested against traditional paper questionnaire [29] showing very high consistency between the two methods. Every year, participants are invited to once again fill this whole set of questionnaires (every 6 months for dietary and weight data). Additional questionnaires are regularly published on the web-site, and participants are invited to respond on a voluntary basis. For this study, an additional questionnaire was elaborated for fracture assessment and was available between 15 april 2019 and 15 august 2019 on web-base.

Because of increased of bone loss induced by estrogen deficiency related to menopause, we only used the data of the postmenopausal women and men aged more than 50 years who responded to the questionnaire.

The NutriNet-Santé study is registered at ClinicalTrials.gov as NCT03335644. This study is being conducted according to guidelines laid down in the Declaration of Helsinki and was approved by the International Research Board of the French Institute for Health and Medical Research (IRB Inserm n° 0000388FWA00005831) and the "Comité National Informatique et Liberté" (CNIL n° 908450 and n° 909216). All participants gave their electronic informed consent at inclusion.

Adapted Dietary Inflammatory Index

We used the adaptation of the Dietary Inflammatory Index (ADII) developed by Cavicchia and al. and following the methodology laid down by van Woudenbergh and al. This score has been recently validated to calculate the inflammation of diet pattern [13, 22]. It includes 34 food items and each item is then multiplied by a published coefficient, and all are summed to create the ADII score. A higher range of ADII scores represents a high inflammatory diet pattern [22]. The ADII has been validated in the Supplémentation en Vitamines et Minéraux

Antioxydants french cohort (SU.VI.MAX). Both original DII and ADII were evaluated in the SU.VI.MAX cohort and were strongly correlated [30]. Then ADII has been used in NutriNet-Santé study [31].
In this study, we used dietary data from the first 2 years of follow-up as an estimator of the usual diet to calculate ADII. Daily mean food intake refers to average consumptions based on all available 24-h dietary records during this period, weighted according to the type of day (weekdays or weekend). Average consumptions were based on all available 24-h dietary records during this period. The consumed portions were estimated using validated photographs of portions sizes [32], household measures, or by indicating the exact quantity (grams) or volumes (milliliters). Energy and nutrient intakes were estimated using the NutriNet-Santé composition table.

Fracture assessment

For fractures, data was self-reported by patient on an additional questionnaire published on web-site. The specific questionnaire was developed to collect retrospectively fracture events and the mechanism (low trauma fracture or no). Low trauma fracture was defined as a spontaneous fracture or a fracture occurred after a fall from own height and was explained at the beginning of the questionnaire. Participants had to report all fractures occurred after the age of 18 years with the year of the event, detailed for each location. The following variables: location of the fracture, date of fracture, mechanism of the fracture (low trauma or no), confirmation of the diagnosis (medical imaging and/or surgery), prevalent fracture after the age of 40, presence of osteoporosis at the moment of the fracture, drug-induced bone loss and treatments of osteoporosis were collected. Total fractures included all fracture except fingers, toes, face and cervical vertebrae. Major fractures were defined as the following location: hip, pelvis, proximal humerus, vertebrae, distal femur, proximal tibia and wrist.
Incident fractures were defined as those that occurred after the inclusion in NutriNet-santé. Prevalent fractures at inclusion were defined as those that occurred after the age of 40 and before the inclusion. In order to enhance the quality of this questionnaire, especially for vertebral fractures, we verified the data collected. In patients who declared low trauma vertebral fractures, 90% had had at least a previous fracture or a BMD measurement or an osteoporosis treatment. 21% of them had a prevalent fracture, 87% had had a BMD measurement, and 40% had received a treatment of osteoporosis.

Covariates assessment

Covariates included age, gender, personal and family history of hip fracture, smoking status, all-time use of glucocorticoids (more than 7.5 mg per day during more than 3 years), all-time use of anti-osteoporosis pharmaceutical drugs (as bisphosphonates, teriparatide, raloxifene and denosumab), HRT, total calcium intake at inclusion, vitamin D supplementation (binary criteria) during the follow-up and history of inflammatory diseases. All medication was self-reported in the same questionnaires as fractures. Self-reported rheumatoid arthritis, spondyloarthritis, psoriasic arthritis, Crohn disease and vasculitis were considered as inflammatory disease.
BMI was calculated as the ratio of weight to squared height (kg/m2) at baseline. BMI was classified as 3 classes BMI < 20kg/m^2, BMI between 20kg/m^2 and 25kg/m^2 and BMI > 25kg/m^2. IPAQ was classified as low physical

activity (< 30 min of physical activity), moderate physical activity (≥ 30 min and < 60 min), or high physical activity (≥ 60 min), according to the French guidelines for physical activity [33].

Statistical analysis

In order to examine relationships between different levels of ADII scores and variables of interest, we divided the ADII into sex-specific quartiles. Baseline characteristics of participants were described by baseline ADII quartiles. The lowest quartile represented lowest inflammatory dietary pattern. Baseline characteristics were described in mean and standard deviation for continuous variables using ANOVA and numbers and percent were performed using chi square test for linear trend for categorical variables.

Hazard ratio and 95% confidence intervals (Cis) obtained from Cox proportional hazard regression models and were used to characterize an association between quartile of the ADII and incident low trauma fractures. The p trend values were calculated using the median value of each ADII quartile, as a continuous variable. Hazard ratios with ADII as a continuous variable were also assessed. Several models were examined: unadjusted, BMI and mean energy adjusted and multivariable adjustment model, on previous fracture, familial history of hip fracture, chronic inflammatory disease and using the variables significantly ($p < 0.05$) associated in univariate analysis which included BMI, mean energy, anti-osteoporotic pharmaceutical drugs, previous fracture, parental history of hip fracture, mean alcohol intake per day, tobacco use, dietary calcium intake (dietary only) and vitamin D supplementation (binary response), physical activity, chronic inflammatory diseases, use of glucocorticoids and HRT. Among patients who experienced fracture, follow up was defined as time from inclusion to the first incident low trauma fracture. For patients who did not experience fracture during the follow up, duration was defined as time at the end of the web-site questionnaire availability. Multiple imputations for covariates were performed in order to assess the impact of missing responses. Validity of Cox models was checked using Schoenfeld residuals and Martingale residuals.

Because of the risk of underestimating the number of low trauma fractures declared, sensitivity analysis were performed including all incident fractures reported. We assessed the association between the ADII score and the risk of vertebral fracture, major fracture and any fracture in three analyses: including all incident fractures (high and low trauma), excluding women who received an HRT and those who had a prevalent fracture at inclusion in NutriNet-Santé and excluding only women who had a prevalent fracture.

Analysis were realized on SAS enterprise 9.1 for data management and on R version 3.5.2 for Cox model.

Results

Baseline characteristics

In the NutriNet-Santé cohort, 12,046 participants were included in our study (figure 1), 7607 (63.2%) women and 4439 (36.8%) men. Mean age at inclusion were 59.7(+/- 5.59) and 61.3 (+/- 6.17) years old respectively. Baseline characteristics are described in table 1 and table 2. Mean value of ADII was -1.23 (+/- 3.13) for women and -0.87 (+/- 3.64) for men. Minimal value of ADII was -29.98 and maximal value was 7.52.

The participants with a higher score of ADII compared to those in the lowest quartile were significantly younger ($p < 0.001$), with a higher BMI ($p < 0.001$), a higher number of current smokers (< 0.001), a higher alcohol level (gram per day) ($p<0.001$) and a lower physical activity ($p < 0.001$) in men and women population. Participants with a higher ADII received vitamin D supplementation less frequently ($p < 0.001$) and consumed less total calcium intake at inclusion ($p < 0.001$) among both women and men. Women with a higher ADII were less likely to have received HRT ($p<0.001$).

Assessment of the relationships between ADII and risk of incident low trauma fracture

Mean follow up duration of the participants was 8.24 (+/- 2.07) years. For fractures, 77 (1.0%) vertebral fractures, 596 (7.8%) major osteoporotic fractures and 806 (10.6%) low trauma fractures were recorded in women. In men, 18 (0.4%) vertebral fractures, 153 (3.4%) major osteoporotic fractures and 191 (4.3%) low trauma fractures were recorded. The incidence of low trauma fracture for 1000 persons-year was 13 for women and of 5 for men. Prevalent fractures at inclusion were reported in 751 (9.8%) women and 311 (7.0%) men.

Results of Cox proportional hazard ratio model are presented in table 3 for women and table 4 for men.

In women, we did not find any association between vertebral low trauma fracture (Q4 HR = 0.81, 95% CI 0.44;1.49), major osteoporotic fractures (Q4 HR = 1.05, 95% CI 0.83;1.31) and low trauma fractures (Q4 HR = 1.07, 95% CI 0.80;1.30) and a high ADII after multivariable adjustment for energy intake, BMI, alcohol level and smoking status, osteoporotic treatment, vitamin D and calcium intake, physical activity, previous fracture, glucocorticoids treatment, and HRT.

In men, we did not find any association between major osteoporotic fractures (Q4 HR = 0.59, 95% CI 0.37; 0.94) and low trauma fractures (Q4 HR = 0.65, 95% CI 0.43;0.99) and a high ADII after multivariate adjustment for mean energy, BMI, alcohol and smoking status, osteoporotic treatment, calcium and vitamin D intake, physical activity, previous fracture, parental history of hip fracture, chronic inflammatory disease, secondary osteoporosis and glucocorticoids treatment.

According to factors associated with incident fractures, a low dietary calcium intake was independently associated with a low number of incident fracture ($p < 0.001$) in the cox model.

Sensitivity analysis

We included all incident fractures in our sensitivity analysis. In women,110 (1.0%) vertebral fracture, 843 (11.1%) major osteoporotic fractures and 1140 (15%) low trauma fractures were recorded. In men, 45 (1.0%) vertebral fractures, 271 (6.1%) major osteoporotic fractures and 350 (7.9%) total fractures were recorded.

In women, we did not find any association between incident vertebral fracture, major osteoporotic fractures and total fractures and a high ADII after multivariable adjustment (p non significant for all locations). In men, we did not find any association between major osteoporotic fractures ($p=0.06$) and total fracture (p non significant) and a high ADII after multivariate adjustment.

Excluding women who received an HRT and those who had experienced a fracture before inclusion in NutriNet-Santé, we did not find any association between inflammatory diet and risk of vertebral low trauma fracture, major osteoporotic fracture and low trauma fracture (p non significant for all locations). Similar results were observed after only exclusion of women with prevalent fracture (data not shown).

Dietary calcium intake was not associated with a low number of incident fracture in this population.

Assessment of incident fractures risk factors

Participants had reported 997 (8.3%) incident low trauma fracture, among a majority of women (N=806, 80.6%). Baseline characteristics were in table 5.

Multivariate analysis showed a significant association between an incident low trauma fracture and female gender (< 0.001), an older population (<0.05), a previous fracture (< 0.001) and a glucocorticoids treatment (< 0.001).

Discussion

In this French cohort study from the general population, high inflammatory dietary pattern was not associated with vertebral, major osteoporotic and any low trauma fractures over a mean follow up period of 8 years in both men and women. Inflammatory dietary pattern was measured with the ADII. The mean value of ADII score in our study were lower than other studies in women and in men [20,21]. This suggests that participants in NutriNet-Santé were somewhat healthier than population in other studies, as confirmed for example by the lower prevalence of the diabetes in our study and a low prevalence of fractures.

Participants with a higher ADII were younger, with a higher BMI, had also higher tobacco use, a higher alcohol level and did lower physical activity, as found in others studies [20,21].

We did not find any association between this index and the risk of incident fractures over a mean follow up period of 8 years, in both women and men, suggesting that the inflammatory diet status may have a none-to-limited impact on bone fragility in general population. Our results are in agreement with another large cohort study of American women, including 160,106 post-menopausal women aged of 63 years, they did not find an association between a high DII and hip, lower-arm and any fractures after a mean follow up of nine years.

In contrast, two studies have shown that higher DII significantly was associated with fractures. Mazidi and al. have found a link between DII scores and wrist fractures in younger women and men (mean age of 48 years) than in our study (mean age of 60 years) from the National Health and Nutrition Examination Surveys (NHANES). A second study showed a higher risk of fracture (hip, wrist and vertebral fractures taken together) with a higher pro inflammatory diet [20] in knee osteoarthritis population. The mean follow up was similar than those in our study (8 years) but the mean DII score value (3.16) was much higher compared to our study (-1.14) and 15.4% individuals developed a fracture (versus 10% in our population) limiting the comparison with our study.

The comparison of our results with others studies could be due to the somewhat low rates of incident fractures (10% for any low trauma fracture) compared with the WHI study (27.7%) [21] and the study of Veronese and al. (15.5%) [20]. Moreover, in our principal analysis we selected only women and men who declared incident low trauma fractures on self-questionnaire retrospective report (removing 30% of fractures) and underestimating the number of low trauma fractures. For vertebral fracture, only 77 occurred in women and no association was found

with a high ADII. To our knowledge, no study has found an association between clinical vertebral fractures and a high inflammatory diet pattern in women. Studies showed an association between inflammatory markers and the risk of fracture with a higher risk of hip fracture and total fractures but not with clinical vertebral fracture [3,4,34], although inflammatory markers have been associated with BMD loss in both spine and hip sites in healthy postmenopausal women [35,36]. A sub-group analysis of the WHI study showed an increased risk of hip fractures in young white women (age < 63 years) [21], confirmed in a case control study which found an association between hip fracture and a high DII in both women and men population 50 years older (age between 52 and 83 years) [37]. We could not assess the link between ADII and hip fracture because of the low number of events.

The ADII has been developed in European population and the variation in the ADII was not only driven by components with a large range in intake. Indeed, Woudenbergh and al. have excluded total fat and energy to limit over-estimation of the inflammatory effect of certain nutrients. The ADII score has been validated in the SU.VI.MAX cohort and currently used in NutriNet-Santé study [30]. Moreover, the ADII was positively associated with CRP in younger participants to the long term in SU.VI.MAX cohort [30].

We only used the ADII of the 2 first years after the inclusion in the cohort to have a prospective design as some data suggests a stability of dietary patterns over time, indicating stable behaviors [38]. One study assessed the stability of the DII over time (6 years), showing that the percent change was never greater than 2%, witnessing a relative stability of the DII over time [39].

Sensitivity analyses showed similar results, especially in subgroups of patients with less severe bone fragility (without any prevalent fracture and both without any HRT and without any prevalent fracture).

If ADII was not associated with an increased risk of fractures, we found a significant association between classical risk of factors (gender, age, glucocorticoids treatment and previous fracture) and incident fractures, suggesting the relevance of this population.

Our study had strengths, including its large sample of participants. We checked in the databasis the association between reporting a low trauma vertebral fracture and a BMD measurement, a previous fracture or an antiosteoporosis treatment. This study had some limitations. Limitations due to the definition of low trauma fracture; first, fractures were self-reported and were retrospectively reported, this can underestimate the incidence of some osteoporotic fractures, such as vertebral fractures and introducing a possible recall bias. Secondly, the population was rather healthy, for instance, only a small proportion of Nutri-Netters were diabetics (2% in women and 5.5% in men). The data of this study are for a rather healthy population but are of interest, although they are not generalizable to other populations. Data on bone mineral density and markers of bone remodelling are unfortunately not available.

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None of the authors has any conflicts of interest to declare

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Figure 1: flow chart

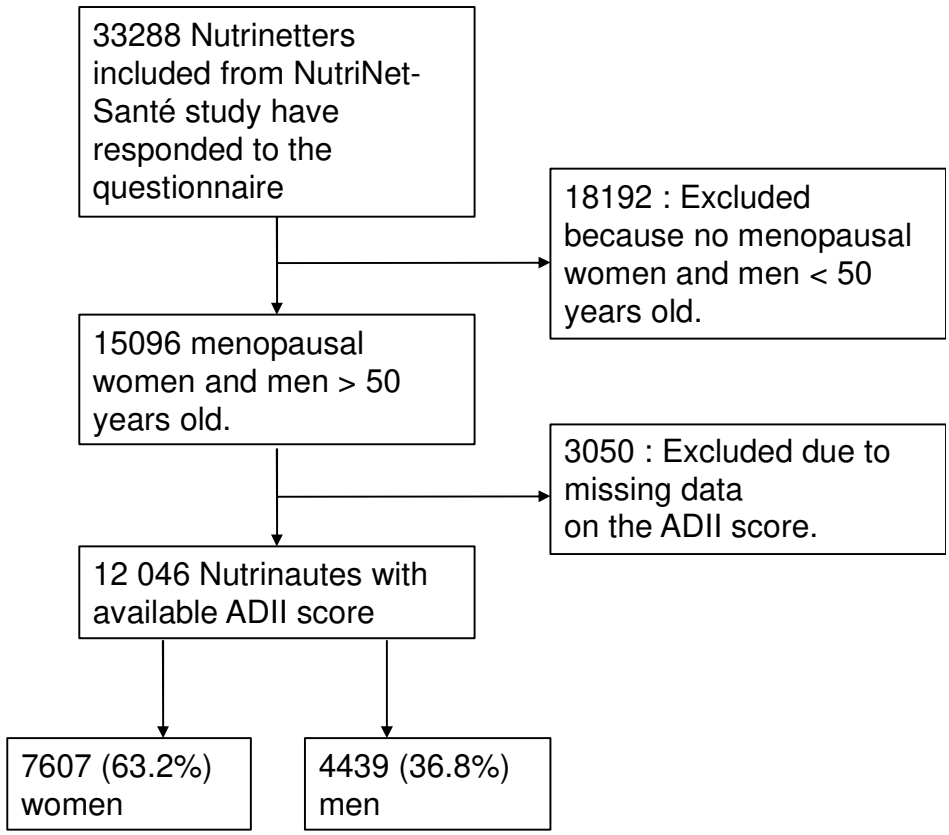

Table 1 : Baseline characteristics in women

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Characteristics					
Participants (N, %)	7607	1902 (25%)	1902 (25%)	1901 (25%)	1902 (25%)
Age (means, SD)	59.7 (5.59)	60.3 (5.48)	59.7 (5.55)	59.6 (5.59)	59.3 (5.68)*
BMI (kg/m^2) (means, SD)	24.1 (4.29)	23.7 (4.38)	24.1 (4.09)	24.2 (4.14)	24.2 (4.51)*
Smoking status (N,%) *					
Current smoker		86 (4.5%)	95 (5%)	98 (5.2%)	149 (7.8%)
Alcohol (g per day) (means, SD)	7.1 (9.61%)	6.2 (8.58)	7.3 (9.82)	7.6 (9.71)	7.4 (10.2)*
Physical activity (N,%) *					
Low		230 (13.4%)	274 (16%)	295 (17.4%)	370 (21.9%)
Moderate		686 (40%)	703 (41.1%)	686 (40.4%)	699 (40.9%)
High		799 (46.6%)	734 (42.9%)	716 (42.2%)	642 (37.5%)
Yearly income (< 45500 euros/years)	3209 (42.2%)	819 (43.1%)	801 (42.1%)	777 (41..0%)	812 (42.7%)
Inflammatory diet pattern					
ADII (means, SD)	-1.23 (3.13)	-5.34 (2.79)	-1.73 (0.56)	0.04 (0.48)	2.10 (0.98)*
Mean energy (means, SD)	1786.9 (352.82)	1839.4 (366.64)	1764.6 (337.20)	1756.6 (335.87)	1787.1 (364.72)*
History of fractures					
History of parental hip fracture (N, %)	1407 (18.5%)	351 (18.4%)	346 (18.2%)	363 (19.1%)	347 (18.2%)
Prevalent fractures (N, %)	751 (9.8%)	198 (10.4%)	196 (10.3%)	183 (9.6%)	174 (9.1%)
Diseases					
Diabetes (N,%)	145 (1.9%)	32 (1.7%)	39 (2.0%)	39 (2.0%)	35 (1.8%)
Inflammatory disease (N,%)	214 (2.8%)	55 (2.9%)	52 (2.7%)	52 (2.7%)	55 (2.9%)
Secondary osteoporosis (N,%)	342 (4.5%)	82 (4.3%)	88 (4.6%)	83 (4.4%)	89 (4.7%)
Treatments					
HRT (N,%)	2790 (36.2%)	732 (38.5%)	714 (37.5%)	677 (35.6%)	628 (33%)*
Osteoporotic treatment (N,%)	821 (10.8%)	229 (12.0%)	189 (9.9%)	201 (10.6%)	202 (10.6%)
Calcium intake (means, SD)	929.9 (287.3)	970.9 (296.8)	940.4 (288.2)	904.9 (270.5)	902.9 (287.7)*
Calcium class (mg per day) (N,%)*					
Calcium < 800	2442 (34.8%)	541 (30.5%)	585 (33.5%)	656 (37.4%)	660 (38%)
Calcium between 800 and 1200	3464 (49.4%)	874 (49.2%)	879 (50.3%)	878 (50%)	833 (48%)
Calcium > 1200	1107 (15.8%)	360 (20.3%)	282 (16.2%)	221 (12.6%)	244 (14%)
Vitamin D treatment (N,%)	4832 (63%)	713 (37.5%)	750 (39.4%)	699 (36.8%)	628 (33.0%)**
Glucocorticoids (N,%)	175 (2.3%)	45 (2.4%)	28 (1.5%)	47 (2.5%)	55 (2.9%)
Anti-aromatases (N,%)	121 (1.6%)	32 (1.7%)	39 (2.0%)	28 (1.5%)	22 (1.1%)

ADII: Alternate Dietary Inflammatory Index, BMI: Body Mass Index, HRT: hormonal replacement treatment; *p<0.001; **p<0.01.

Table 2: Baseline characteristics in men

	Total	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Characteristics					
Participants (N, %)	4439	1110 (25%)	1110 (25%)	1109 (25%)	1110 (25%)
Age (means, SD)	61.3 (6.17)	61.6 (6.24)	61.7 (6.24)	61.2 (5.97)	60.9 (6.18)**
BMI (kg/m^2) (means, SD)	25.4 (3.47)	24.9 (3.50)	25.3 (3.43)	25.5 (3.35)	25.7 (3.56)*
Smoking status (N,%) *					
Current smoker		42 (3.8%)	45 (4.1%)	79 (7.1%)	77 (6.9%)
Alcohol (g per day) (means, SD)	16.5 (16.44)	14.1 (14.73)	16.5 (16.05)	17.5 (16.84)	18.0 (17.74)*
Physical activity (N,%) *					
Low		112 (11%)	154 (15.2%)	170 (17.0%)	229 (22.6%)
Moderate		371 (36.3%)	355 (35.1%)	371 (37.1%)	312 (30.8%)
High		538 (52.7%)	502 (49.7%)	459 (45.9%)	472 (46.6%)
Yearly income (< 45500 euros/years)	1450 (32.7%)	362 (32.6%)	346 (31.2%)	350 (31.6%)	392 (35.3%)
Inflammatory diet pattern					
ADII (means, SD)	-0.87 (3.64)	-5.68 (3.39)	-1.29 (0.66)	0.63 (0.49)	2.87 (1.08)*
Mean NEJ (kcal per day)	2287.6 (451.9)	2332.9 (454.57)	2255.4 (440.48)	2264.8 (454.33)	2297.4 (454.45)*
History of fractures					
History of parental hip fracture (N, %)	666 (15%)	179 (16.1%)	157 (14.1%)	172 (15.5%)	158 (14.2%)
Prevalent fractures (N,%)	311 (7.0%)	70 (6.3%)	86 (7.7%)	73 (6.6%)	82 (7.4%)
Diseases					
Diabetes (N,%)	230 (5.2%)	55 (5.0%)	64 (5.8%)	60 (5.4%)	51 (4.6%)
Inflammatory disease (N,%)	102 (2.3%)	14 (1.3%)	34 (3.1%)	27 (2.4%)	27 (2.4%)
Secondary osteoporosis (N,%)	124 (2.8%)	36 (3.2%)	37 (3.3%)	23 (2.1%)	28 (2.5%)
Treatments					
Osteoporotic treatment (N,%)	60 (1.4%)	15 (1.3%)	12 (1.1%)	15 (1.3%)	18 (1.6%)
Calcium intake (means, SD)	1049.3 (337.75)	1103.5 (353.51)	1044.5 (333.81)	1025.2 (320.59)	1022.8 (336.01)*
Calcium class (mg per day) (N,%)*					
Calcium < 800		211 (20.2%)	246 (23.8%)	254 (24.9%)	261 (25.7%)
Calcium between 800 and 1200		473 (45.3%)	500 (48.4%)	493 (48.4%)	493 (48.5%)
Calcium > 1200		359 (34.4%)	286 (27.7%)	272 (26.7%)	262 (25.8%)
Vitamin D treatment (N,%)	678 (15.3%)	206 (18.6%)	188 (16.9%)	149 (13.4%)	135 (12.2%)*
Glucocorticoids (N,%)	54 (1.2%)	18 (1.6%)	15 (1.4%)	8(0.7%)	13 (1.2%)

ADII: Alternate Dietary Inflammatory Index, BMI: Body Mass Index. *p<0.001; **p<0.01.

Table 3: Cox proportional Hazard Ratios (HR) between ADII and risk of fractures in women

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR [IC95%] continuous variable ADII
Median	-5.34 [-33.18;-2.75]	--1.73 [-2.75; -0.80]	0.04 [-0.80;0.86]	2.10 [0.86;7.52]	
Person-time	15491	15612	15319	15109	
Vertebral fracture					
Vertebral fracture	26 (1.4%)	16 (0.8%)	16 (0.8%)	19 (1%)	
Unadjusted HR, 95% CI[a]	Ref	0.63 (0.34;1.18)	0.65 (0.35;1.21)	0.80 (0.44;1.44)	0.95 (0.90;1.02)
BMI and energy intake-adjusted HR, 95% CI[b]	Ref	0.59 (0.31;1.10)	0.60 (0.32;1.12)	0.75 (0.42;1.37)	0.94 (0.88;1.01)
Multivariate-adjusted HR, 95% CI[c]	ref	0.62 (0.33;1.16)	0.59 (0.31;1.11)	0.81 (0.44;1.49)	0.94 (0.88;1.01)
Any low trauma fracture					
Total fracture	216 (11.3%)	187 (9.8%)	200 (10.5%)	203 (10.7%)	
Unadjusted HR, 95% CI[a]	Ref	0.88 (0.72 ;1.07)	0.96 (0.79;1.17)	1.00 (0.83;1.21)	0.99 (0.97;1.01)
BMI and energy intake-adjusted HR, 95% CI[b]	Ref	0.87 (0.72;1.06)	0.96 (0.79;1.16)	1.00 (0.83;1.22)	0.99 (0.97;1.01)
Multivariate-adjusted HR, 95% CI[c]	Ref	0.89 (0.73;1.08)	0.97 (0.80;1.18)	1.07 (0.80;1.30)	0.99 (0.97;1.02)
Major fracture					
Major Fracture	165 (8.7%)	137 (7.2%)	145 (7.6%)	149 (7.8%)	
Unadjusted HR, 95% CI[a]	Ref	0.85 (0.68;1.06)	0.92 (0.74;1.15)	0.97 (0.78;1.22)	0.99 (0.96;1.01)
BMI and energy intake-adjusted HR, 95% CI[b]	Ref	0.86 (0.68;1.08)	0.93 (0.75;1.17)	0.99 (0.79;1.23)	0.99 (0.96;1.01)
Multivariate-adjusted HR, 95% CI[c]	ref	0.88 (0.70;1.11)	0.95 (0.76;1.19)	1.05 (0.83;1.31)	0.99 (0.96;1.02)

Baseline Alternate Dietary Inflammatory Index Score : quartile 1, least inflammatory, quartile 4, most inflammatory.

BMI: Body Mass Index

[a]Unadjusted

[b]Included BMI and mean energy

[c]Included BMI, mean energy, anti-osteoporotic pharmaceutical drugs, previous fracture, parental history of hip fracture, mean alcohol intake per day, tobacco use, dietary calcium intake (dietary only) and vitamin D supplementation (binary response), physical activity, chronic inflammatory diseases, use of glucocorticoids and HRT.

Table 4: Cox proportional Hazard Ratios (HR) between ADII and risk of fractures in men

Variables	Quartile 1	Quartile 2	Quartile 3	Quartile 4	HR continuous variable ADII
Median Person-time	-4.57 [-29.98;-2.50] 9401	-1.240 [-2.50;-0.23] 9482	0.633 [-0.23;1.51] 9407	2.648 [1.51;7.17] 9459	
Any low trauma fracture					
Non-cases					
Total fracture	52 (4.7%)	44 (4.0%)	56 (5.0%)	39 (3.5%)	
Unadjusted HR, 95% CI[a]	Ref	0.84 (0.56;1.25)	1.09 (0.75 ;1.59)	0.76 (0.50;1.15)	1.01 (0.97;1.05)
BMI and energy intake-adjusted HR, 95% CI[b]	Ref	0.82 (0.55;1.23)	1.08 (0.74;1.58)	0.75 (0.49;1.13)	1.00 (0.96;1.05)
Multivariate-adjusted HR, 95% CI[c]	Ref	0.76 (0.51;1.14)	1.01 (0.69;1.49)	0.65 (0.43;0.99)	0.99 (0.95;1.04)
Major fracture					
Non-cases					
Major Fracture	45 (4.1%)	33 (3.0%)	44 (4.0%)	31 (2.8%)	
Unadjusted HR, 95% CI[a]	Ref	0.72 (0.46;1.14)	0.99 (0.66;1.51)	070 (0.44;1.10)	0.99 (0.95;1.04)
BMI and energy intake-adjusted HR, 95% CI[b]	Ref	0.71 (0.45;1.12)	0.98 (0.65;1.49)	0.68 (0.43;1.08)	0.99 (0.95;1.04)
Multivariate-adjusted HR, 95% CI[c]	Ref	0.65 (0.41;1.03)	0.92 (0.60;1.40)	0.59 (0.37;0.94)	0.98 (0.94;1.03)

Baseline Alternate Dietary Inflammatory Index Score : quartile 1, least inflammatory, quartile 4, most inflammatory.

BMI: Body Mass Index

[a]Unadjusted

[b]Included BMI and mean energy

[c]Included BMI, mean energy, anti-osteoporotic pharmaceutical drugs, previous fracture, parental history of hip fracture, mean alcohol intake per day, tobacco use, dietary calcium intake (dietary only) and vitamin D supplementation (binary response), physical activity, chronic inflammatory diseases and use of glucocorticoids.

Table 5: Baseline characteristics between participants with incident fractures occurred.

Variables	No Fractures (N = 11049, 91.7%)	Fractures (N = 997, 8.3%)	OR [IC 95%]
Characteristics			
Age (mean, SD)	60.3 (5.87)	60.3 (5.77)	1.01 (0.99 ;1.02)****
Sex (women) (N, %)	6801 (61.5%)	806 (80.8%)	2.64 (2.25 ;3.11)*
BMI (mean, SD)	24.5 (4.05)	24.4 (4.04)	0.99 (0.98 ;1.01)
Alcohol (g per day) (mean, SD)	10.6 (13.46)	9.6 (12.19)	0.99 (0.98;0.99)***
Tobacco (current smoker and past smoker) (N, %)	5854 (53.0%)	528 (52.9%)	0.997 (0.875;1.135)
Physical activities (mean, SD)			
Low	1696 (16.9%)	138 (15.8%)	
Moderate	3832 (38.3%)	351 (40.3%)	1.07 (0.92 ;1.25)
High	4479 (44.8%)	383 (43.9%)	0.95 (0.77 ;1.16)
Yearly income (< 45500 €) (N, %)	4252 (38.5%)	407 (40.8%)	1.10 (0.96 ;1.26)
History of fractures			
Familial history of fractures (N, %)	1900 (17.1%)	173 (17.3%)	1.01 (0.85 ;1.20)
Previous fracture (N, %)	889 (8.0%)	173 (17.3%)	2.40 (2.00 ;2.86)*,*****
Diseases			
Secondary osteoporosis (N, %)	423 (3.8%)	43 (4.3%)	1.13 (0.81 ;1.54)
Diabetes (N, %)	357 (3.2%)	18 (1.8%)	0.55 (0.33 ;0.86)***
Inflammatory disease (N, %)	277 (2.5%)	39 (3.9%)	1.58 (1.11 ;2.20)**
Dietary			
ADII (mean, SD)	-1.08 (3.32)	-1.26 (3.37)	0.98 (0.97 ;1.00)
Mean energy (mean, SD)	1978.47 (463.21)	1893.7 (423.68)	0.9995 (0.9994 ;0.9997)*

ADII: Alternate Dietary Inflammatory Index, BMI: Body Mass Index, HRT: hormonal replacement treatment.
P univariate : *p<0.001; **p<0.01; ***p<0.05. P multivariate: ****p<0.05; *****p<0.001.