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TITLE PAGE

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Summary

Prevention of fractures is a considerable public health challenge. In a population-based cohort of French elderly people, a diet closer to a Mediterranean-type had a borderline significant deleterious effect on the risk of fractures, in part linked to a low consumption of dairy products and a high consumption of fruits.

ABSTRACT

Purpose: Higher adherence to the Mediterranean diet (MeDi) is linked to a lower risk of several chronic diseases, but its association with the risk of fractures is unclear. Our aim was to investigate the association between MeDi adherence and the risk of fractures in older persons.

Methods: The sample consisted of 1,482 individuals aged 67yrs +, from Bordeaux, France, included in the Three-City Study in 2001-2002. Occurrences of hip, vertebral and wrist fractures were self-reported every two years over 8 years and 155 incident fractures were recorded. Adherence to the MeDi was evaluated at baseline by a MeDi score, on a 10-point scale based on a food frequency questionnaire and a 24h recall. Multivariate Cox regression were performed to estimate risk of fractures according to MeDi adherence.

Results: Higher MeDi adherence was associated with a non-significant increased risk of fractures at any site (HR per 1-point increase of MeDi score=1.10, P=0.08) in fully adjusted model. Among MeDi components, higher fruits consumption (>2 servings/day) was significantly associated with an increased risk of hip fractures (HR=1.95, P=0.04), while low intake of dairy products was associated with a doubled risk of wrist fractures (HR=2.03, P=0.007). An inverse U-shaped association between alcohol intake and risk of total fracture was observed (HR high *vs* moderate=0.61, P for trend 0.03).

Conclusions: Greater MeDi adherence was not associated with a decreased risk of fractures in French older persons. The widely recognized beneficial effects of the MeDi do not seem to apply to bone health in these people.

TEXT

INTRODUCTION

Osteoporosis and osteoporotic fractures, the hallmarks of a long-term initiated process, are responsible for a considerable public health challenge since they are associated with an increased risk of disability, morbidity and mortality with a major economical impact [1-2]. The prevalence of fractures among the elderly persons is estimated at 9 million worldwide, amongst which more than one third are European [3-4]. Therefore, effective strategies to prevent osteoporosis and related fractures must be developed.

The prevention of fractures by modifiable factors including falls prevention and lifestyle, such as physical activity and nutrition, has been well documented in older persons [5-6]. Among dietary factors, much attention has been focused on the beneficial effects of calcium and vitamin D on bone metabolism [7-8]. The role of macronutrients (mainly proteins) and other vitamins (A, B, C, E and K) has also been examined, although their ability to reduce the risk of fractures remains controversial [9]. One explanation of these discordant results could rely on potential additive, synergistic or antagonist effects between components of the diet which are ignored by studies based on single nutrient [10]. Thus, considering comprehensive dietary patterns is an appealing approach [11].

In this context, the Mediterranean diet (MeDi) combines several foods and nutrients already proposed as potential protective factors against development and progression of several age-related diseases [12-13]. A limited number of cross-sectional studies have examined the relationship between MeDi adherence and bone health, and they have reported conflicting results. On the one hand, adherence to a traditional MeDi has been associated with higher bone mineral density (BMD) among 100 Spanish postmenopausal women (54 years on average) [14] whereas on the other hand, among 196 Greek women (48 years on average), Kontogianni et al. [15] failed to evidence any association between adherence to the MeDi and indices of bone mass. To our knowledge, the potential protective effect of the MeDi against the risk of hip fractures has been evaluated prospectively only once, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study [16]. In this large cohort of adults (N=188,795, 49 years on average and followed for a median of 9 years), a greater MeDi adherence was associated with a significant 7% reduced risk of hip fractures. This analysis was restricted to the risk of hip fractures, although the risk factors of fractures are site specific [17]. Moreover, the authors were restrained to develop a modified MeDi score, to better take into account the low consumption of olive oil in non-Mediterranean populations [16].

The aim of the present study was to investigate prospectively the relationship between adherence to a MeDi and risk of fractures of the hip, wrist or vertebrae over 8 years, in a large population-based sample of older community-dwellers of both genders living in south-western France.

SUBJECTS AND METHODS

Participants

The data came from the Three-City (3C) study, a prospective cohort study of vascular risk factors of dementia whose methodology has been described elsewhere [18]. The 3C study protocol was approved by the Consultative Committee for the Protection of Persons participating in Biomedical Research at Kremlin-Bicêtre University Hospital (Paris). A sample of 9,294 community dwellers aged 65+ was selected in 1999-2000 from the electoral rolls of three French cities (Bordeaux, Dijon and Montpellier). All participants gave written informed consent. At baseline, data collection included socio-demographic information, lifestyle, symptoms and complaints, medical history, blood pressure, anthropometric data, neuropsychological testing, and blood sampling. Four follow-up examinations were performed, two (wave 1, in 2001-2002), four (wave 2, in 2003-2004), seven (wave 3, in 2006-2007) and ten years (wave 4, in 2009-2010) after baseline examination. The present study extends between the wave 1 (baseline of this study) and wave 4 in Bordeaux, the only centre where the standard data collection was completed with a comprehensive dietary survey at wave 1.

Among the 1,811 individuals from 3C-Bordeaux who accepted to participate at wave 1, 1,774 completed the dietary survey. We first excluded 62 participants who had two missing data or more among dietary items and subsequently excluded 230 participants who were never visited between wave 1 and wave 4 or who never completed history of fractures at visits; leaving 1,482 individuals for the present analyses.

Fractures

Occurrence of new fractures since the previous examination was self-reported at each visit, as previously described [19]. Hip, vertebrae, wrist, upper member (shoulder, collarbone) and lower member (excluding hip) fractures were recorded. The outcome of interest was incidence of a fracture since wave 1. Because the risk factors of fractures are specific to the site of fracture [17], we studied separately the three main sites of osteoporosis-related fractures: hip fractures, wrist fractures and vertebral fractures. We also created a composite endpoint defined as incidence of a fracture whatever the type among the three sites: hip or wrist or vertebrae.

Dietary assessment and MeDi score

Participants were visited at home by a trained dietician who administered a food frequency questionnaire (FFQ), not semi-quantitative, and a 24H dietary recall at wave 1 [20-21]. The 24H recall was used to estimate nutrient intake in g/d, total energy intake in kcal/d and to compute the ratio of monounsaturated to saturated fat (MUFA-to-SFA). Based on the FFQ, frequency of consumption of 40 categories of foods and beverages for each of the 3 main meals and 3 between-meals snacks was recorded in 11 classes (from never to every days). The food items were aggregated into 20 food and beverage groups as described elsewhere [21]. We identified the food groups considered to be part of the MeDi: vegetables, fruits, legumes, cereals including bread, pasta and rice (whole and refined grains), fish and seafood, meat, dairy products including yoghurts, milk and cheese, and alcohol. Intake of each food group was determined in servings/week. Adherence to the traditional Mediterranean-type diet was assessed by the MeDi score, a 10-point Mediterranean-diet scale. The MeDi score was computed as follows: a value of 0 or 1 was assigned to each food group using sex-specific medians of the population as cut-offs, as suggested earlier by Trichopoulou et al. [22]. For presumed beneficial components for health (ie vegetables, fruits, legumes, cereals and fish), individuals whose consumption was above the median were assigned a value of 1, vs 0 for the others. For components presumed to be detrimental for health (ie meat and dairy products), individuals whose consumption was below the median were assigned 1, vs. 0 for the others. For alcohol, 1 point was assigned to men if their consumption was within 7-to-14 glasses/week (10-to-20g/d) and to women if their consumption was within 1-to-4 glasses/week (1.4-to-5.7g/d). These cut-offs, corresponding to the second quartile of distribution of total alcohol intake in this population, were chosen to represent mild-to-moderate consumption. Finally, participants with a MUFA-to-SFA ratio above the sex-specific median were assigned a value of 1, vs. 0 for those below the median. The MeDi score was generated by adding the scores (0 or 1) for each food category. Thus, the MeDi score could range from 0 to 9 for each participant, with higher scores indicating greater adherence [22].

Covariates

Socio-demographic information recorded at baseline included age, gender and education (six educational levels grouped into four classes: no education or primary school only, secondary (middle) school, high school or vocational school and university). Socio-demographic characteristics also included marital status (married, divorced or separated, widowed, single) and income in four categories (< 750 euros, 750 to 1500 euros, 1500 to 2250 euros, > 2250 euros per month). Height (in m) and weight (in kg) were measured by the interviewers at wave 1. BMI was computed as the weight/height² ratio and considered in four categories (< 21 kg/m², 21 to 25 kg/m², 25 to 30 kg/m², > 30 kg/m²). Diabetes was defined as self-reported or as having an anti-diabetic medication at wave 1. Smoking status (never, ex-smoker or current smoker) and regular practice of physical activity (ie doing sport regularly or having at least 1 hour of leisure or household activity per day) were also recorded. Self-reported history of osteoporosis was recorded at each wave. All drugs consumed at least once a week during the last month were collected and prevention or treatment for osteoporosis was recorded, including biphosphonates, raloxifene, strontium ranelate, teriparitide, calcitonine, and supplementation with calcium and/or vitamin D. Long-term corticotherapy was defined as declaring systemic or inhalation corticoid use at both baseline of the 3C study and at wave 1.

Statistical analyses

In a previous report on the same study sample (N=1,482), baseline demographic and clinical characteristics have been compared between individuals who reported an incident fracture (n=155) and those who remained free from fracture during follow-up [19]. In the present study, we also described the demographic, clinical and dietary characteristics of individuals who reported an incident fracture of the hip, the wrist or the vertebrae separately.

The frequency of consumption of each food group composing the MeDi score, expressed as mean number of servings/week, was compared between men and women by Student's t test.

We then explored associations between MeDi score and incidence of fractures using Cox proportional hazards models taking age as the time scale. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated for 1-point increase of the MeDi score considered as a continuous variable.

These analyses were also performed for each individual MeDi component, adjusted for all other components. For these analyses, MeDi components were considered dichotomously, as defined for the computation of the MeDi score, and a three-level variable was generated to better describe the consumption of alcohol. Indeed, a mild-to-moderate consumption of alcohol, corresponding to the second quartile of distribution of total alcohol intake, was defined by a consumption within 7-to-14 glasses/week for men, and within 1-to-4 glasses/week for women and chosen as reference. The first quartile of distribution of total alcohol intake (<7 or 4 glasses/week for men and women respectively) was therefore defined as "no or low consumption", whereas a "high consumption" corresponded to the third and fourth quartiles of distribution (>14 or 4 glasses/week for men and women respectively).

Since dairy products constitute a MeDi component of primary interest for bone health, additional Cox proportional hazards analyses were performed considering yoghurts, milk and cheese consumption as individual food categories (1 was assigned to each individual whose consumption of milk, yoghurts or cheese was lower than the respective sex-specific medians of consumption of the sample, otherwise 0). These models were also adjusted for all other dietary components.

Covariates were selected for multivariate models when associated with either incidence of hip or wrist or vertebral fracture at a statistical level $\alpha < 0.20$ in univariate analyses, as described elsewhere [19]. Two models were performed. First, we adjusted for age, gender, physical activity and total energy intake (model 1). Then, we considered additional adjustment for educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, and intake of calcium and/or vitamin D supplements (model 2).

All statistical analyses were performed with SAS Statistical package (Version 9.1 SAS Institute).

RESULTS

At baseline, the mean age of the participants (N=1,482, 550 men, 932 women) was 75.9y (range 67.7-94.9). Over the 8-y follow-up, 155 individuals reported a fracture at any of the three sites, including 57 hip fractures (46 among women), 43 vertebral fractures (37 among women) and 73 wrist fractures (65 among women). Among men (N=550), 23 (4.2%) incident fractures were reported over 8 years: 11 (2.0%) hip fractures, 8 (1.5%) wrist fractures and 6 (1.1%) vertebral fractures. Among 932 women of the study sample, 132 (14.1%) incident fractures were reported over 8 years, divided as 46 (4.9%) of hip fractures, 65 (7.0%) wrist fractures and 37 (4.0%) vertebral fractures. The sociodemographic and health characteristics of all participants are described in Table 1. Regarding MeDi adherence, individuals with an incident fracture at any of the three sites had a higher mean MeDi score at baseline than those who remained free of fracture during follow-up (4.64, (standard deviation (sd) 1.72) vs. 4.35 (sd 1.67), P=0.04).

The sex-specific medians of consumption of food groups used to compute the MeDi score are presented in Table 2. Mean consumption of cheese, meat, legumes and alcohol was significantly lower in women, while mean consumption of yoghurts was significantly higher in women than in men. Mean consumption of vegetables, fruits, fish, milk and of the MUFA-to-SFA ratio was not significantly different between both genders (**Table 2**).

In multivariate analyses adjusted for age, gender, physical activity, total energy intake, educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment, a borderline significant association between MeDi score and an increased risk of fracture at any site (HR = 1.10, 95% CI 0.99-1.21, P=0.08), and, specifically of hip fracture (HR = 1.18, 95% CI 0.99-1.39, P=0.06) was observed (**Table 3**, model 2). Conversely, adherence to the MeDi was not significantly associated with the risk of vertebral or wrist fracture.

In secondary analyses, we examined whether associations between MeDi adherence and risk of fractures were driven by particular food categories (**Table 4**). In fully adjusted models, greater fruit consumption (i.e. >14 servings/week in men and women combined) was significantly associated with a doubled 8-y risk of hip fracture (HR high *vs* low = 1.95, 95% CI 1.04-3.66, P=0.04). Furthermore, lower intake of dairy products (i.e. <17.0 servings/week in men and <17.9 servings/week in women) was significantly associated with an increased risk of fracture at any site (HR low *vs* high = 1.51, 95% CI 1.07-2.11, P=0.02), and, specifically, with a doubled risk of wrist fracture (HR low *vs* high = 2.03, 95% CI 1.22-3.39, P=0.007), but not other sites. Higher levels of alcohol intake (>14 glasses/week in men and >4 glasses/week in women) and marginally, low alcohol intake were associated with a significant reduction (39% for high intake, 33% for low intake, P for trend=0.03) of risk of fracture at any site. A MUFA-to-SFA ratio higher than 0.8 was significantly associated with a reduced risk of vertebral fracture in the model adjusted for age, gender, physical activity, total energy intake and all other dietary components the MeDi score. However, this association was no longer significant in fully adjusted models.

We further analyzed the association between the type of dairy product and the risk of fracture (**Table 5**). Elderly subjects who declared a consumption of yoghurts lower than the median, i.e. <6 servings/week in men and <7 in women, were at increased risk of wrist fracture only (HR low *vs* high = 1.98, 95% CI 1.22-3.21, P=0.005). By contrast, a low consumption of milk or cheese was not associated with the risk of fracture of the hip, the wrist or the vertebrae, in fully adjusted models (**Table 5**). When considering the risk of fracture whatever the type among the three sites, the low consumption of yoghurts, milk or cheese was not associated with the overall risk of fracture.

DISCUSSION

In this longitudinal population-based study of French older adults, a greater adherence to a Mediterranean-type diet was significantly associated with an increased risk of fracture, after adjustment for age, gender, physical activity and total energy intake. Two MeDi components appeared to independently drive this association: a high consumption of fruits (>2 servings/day) and a low consumption of yoghurts (<1 serving/day) were significantly associated with a doubled risk of fracture of the hip and the wrist respectively, in fully adjusted models. Moreover, a consumption of alcohol higher than 14 glasses/week for men or 4 glasses/week for women was significantly associated with a 39% reduced risk of fracture at any site over time.

To our knowledge, a single study reported an inverse association between adherence to a Mediterranean-type diet and the risk of hip fracture in European older persons [16], which was not in agreement with the present results. Indeed, in this large cohort of adults enrolled in the EPIC study (N=188,795 participants, 802 incident hip fractures), higher adherence to the MeDi was associated with a 7% decrease in hip fracture incidence, notably among participants aged 60y + and among men in the model adjusted only for age [16]. In analyses where the dietary components of the MeDi were mutually adjusted, as in the present study, the components that were significantly associated with the risk of hip fracture in the overall sample were vegetables, meat and ethanol intake. However, several differences between the EPIC study and the present one could explain such discrepancies. First,the statistical power of this French study (only 57 incident hip fractures in the present study) was greatly lower than that of the European study. This may have reduce our chance to evidence stronger or additional associations between MeDi adherence and risk of fracture at any site (or at specific site) among French people. Second, the results from the EPIC study suggested that the prevention of hip fracture might be more challenging in women than in men. Only 11 men (among 57) were identified with an incident hip fracture in the present study which prevented us to stratify our analyses based on gender. Third, country specific characteristics of the dietary patterns may partly explain the discrepancies between the French and the EPIC studies. Indeed, a modified MeDi score has been defined in the EPIC cohort, by substituting the monounsaturated lipids (MUFA) with the sum of mono- and poly- unsaturated fatty acids in the numerator of the lipid ratio, to better take into account the low consumption of olive oil and MUFA in non-Mediterranean populations [16]. Among the eight countries participating in the EPIC study, only three have Mediterranean origins (Greece, Italy and Spain) but there were no data from France. Traditionally, even among Mediterranean countries, distinct dietary habits exist, as already described by Sofi [23]. More importantly, the MeDi score was computed according to sex-specific medians of consumption of only 9 food groups of each study sample, which limited the generalization of the results and prevented definite conclusions. Altogether, these differences could in part explain the lack of homogeneous results of the association between a Mediterranean-type diet and risk of hip fracture among European and French elderly. Finally, adherence to the MeDi may be considered as lifestyle and may reflect specific health concerns and behaviors that may differ between countries, particularly regarding practice of physical exercise or use of supplements, part of lifestyle but not considered in the diet score computation.

Besides, the impact of MeDi adherence on bone health remains unclear. Indeed, of the existing literature, only two cross-sectional studies, including small samples of women, younger than the participants of the present study, were available and yielded mixed results [14-15]. Moreover, a cross-sectional study using another diet quality assessment tool failed to report any significant relation between the Healthy Eating Index (HEI-2005) and several bone turnover markers among post-menopausal women aged 45y + [24].

A posteriori derived dietary patterns, independent of any assumption on the beneficial or harmful effects of food intakes, have also been examined in association with bone health, but less often with fracture risk. For instance, a pattern characterized by a high consumption of fruits, vegetables and whole grains might be an optimal dietary strategy to avoid fractures, particularly in older women, in a Canadian study [25]. However, among Japanese adult women, a pattern characterized by high consumption of vegetables was associated with an increased risk of fractures, and another one characterized by a high consumption of meat was associated with a reduced risk of fractures [26]. Finally, in the 3C study, we previously reported that dietary patterns rich in cheese, milk and charcuteries derived from principal component analysis, were related to a lower risk of hip and wrist fractures over 8-y of follow-up [19].

Among the food groups composing the MeDi score,and unlike most previous studies, we identified an increased risk of hip fractures in participants with a high consumption of fruits, in the fully adjusted model. The association between fruit intake and risk of fractures has scarcely been assessed independently of that of vegetables, which were not associated with the risk of fractures in the present study [27]. A higher fruit consumption was not associated with a significant reduced risk of hip fractures, in the overall sample, in analyses mutually adjusted for the food groups composing the MeDi score in different reports from the EPIC cohort [16][28], suggesting that the relationship between fruit intake and risk of hip fracture remains questionable. The potential benefit of fruits and vegetables is based on their ability to emphasize alkaline status, therefore counterbalancing the acidic load that might lead to osteoporosis [27, 29]; however, conflicting results have also been reported [30]. A meta-analysis, which has called the dietary acid-ash hypothesis on bone loss into question, concluded that there is no evidence that an alkaline diet is protective of bone health [29]. Given the lack of biological plausibility for an adverse effect of fruits on bone health, another explanation might be that older adults consuming high amounts of fruits have specific behaviours or health conditions associated with an increased risk of hip fracture, acting as confounding factors that cannot be totally ruled out here despite multivariate adjustment. Finally, we cannot exclude that our unexpected result may be due to chance finding.

As expected, we found that a low consumption of dairy products was significantly associated with an increased risk of fractures. Less attention has been paid in the literature to specific categories of dairy products. In our study, consuming less than one serving of yoghurt/day was associated with a doubled risk of wrist fracture. Dairy products are the main dietary providers of calcium. In a previous paper, we reported that higher MeDi adherents of the 3C study are those with the lowest calcium intake [31]. Calcium homeostasis and vitamin D status are closely related, particularly with respect to fracture risk [7], although the impact of calcium and/or vitamin D supplementation on the prevention of fracture risk remains questionable [32-33]. Regarding milk consumption, our results are in agreement with those of two meta-analyses in which a low intake of milk was not associated with any marked increase in fracture risk, notably hip fracture risk [34-35].

Alcoholism is known to have negative effects on bone [16, 36], but an inverse U-shaped association between alcohol intake and risk of fracture at any site was observed in the present study. Conversely, a J-shaped relationship between alcohol consumption and hip fracture risk has already been reported [37] and a threshold effect (2 units per day or more) has been defined [38]. . Several explanations for these results could be evoked. A first interpretation would be the relevance of using non-drinkers as a reference group, unlike in the current study. Indeed, present non-drinkers may have given up alcohol for medical reasons and be in poorer health status than drinkers. A second interpretation would be that adjustment for major potential confounders was missing in most studies of the existing literature [37], while our models are fully adjusted, including other food groups composing the MeDi score and energy intake. Finally, high alcohol consumers of the current study, identified as men with a consumption >2 glasses/day and women with a consumption >4 glasses/week, should not be considered as excessive drinkers but as ordinary elderly consumers with French cultural lifestyles including regular alcohol drinking [20].

Among the other food groups composing the MeDi score, we did not observe any association with the risk of fractures, whereas some relationships could have been expected. For instance, fish intake, as main provider of dietary vitamin D, has been suggested to be protective against bone loss if consumption was at or over 3 servings/week, while some opposite results exist as well [39-40], and we previously reported that high MeDi adherents of the 3C study had a mean consumption of 3.7 servings of fish a week [41]. Although still debated, many epidemiological studies, but not the EPIC study, have suggested a positive impact of diets rich in proteins on bone health, especially on the risk of fracture [16, 42-43].

There are nevertheless some potential limitations to our findings. First, the FFQ used in the present study did not allow estimation of portion sizes. The lack of estimation of portion size may lead to consider people with the same frequency of intake of each food group of the MeDi score as comparable, although they may have different quantitative food consumptions [31, 44]. Regarding outcomes, the self-reported history of fractures could induce an information bias which cannot be checked against objective measures of osteoporosis in this cohort. This could be a major issue especially for vertebral fractures which are initially asymptomatic and thus escape to personal and clinical detection. The lack of association between MeDi adherence, or a component of the MeDi score, with vertebral fractures in fully adjusted models could be in part attributed to their underdiagnosis. Third, a selection bias cannot be dismissed and could have limited our ability to find additional or stronger associations. Not included individuals (n=230) were significantly older, with lower BMI, were more often sedentary, and had less often diabetes (data not shown). They took less often calcium and/or vitamin D supplements, and had less often treatment for osteoporosis and long-term corticotherapy. Moreover, not included individuals had a lower mean MeDi score than included participants (4.1 (sd 1.5) vs. 4.4 (sd 1.7), P=0.02). However, the frequency of reported events among participants included in the present study was slightly lower than that expected among European older people [4].

Despite these limitations, the strengths of the present study are the population-based design, including both genders, with long follow-up, the respective account of hip, wrist and vertebrae fracture risk, and the accuracy of food-intake assessment [31]. Moreover, we controlled our analyses for numerous potential confounders including energy intake, BMI, and physical activity. There is a very few vitamin D fortification in most food groups in France, and the calcium and/or vitamin D supplementation and the osteoporosis treatment were also considered as confounders, since they could influence bone health, unlike in the EPIC study.

In conclusion, we found in this large cohort of French elderly community dwellers that a diet closer to a Mediterranean-type diet had a borderline significant deleterious effect on the risk of fractures, in part linked to a low consumption of dairy products and a high consumption of fruits, for which the explanation remains unclear. A high adherence to this French MeDi, as assessed by the MeDi score in the current study, seems not to be beneficial to the prevention of fractures and consequently to bone health in French elderly adults [16]. The present results suggested that the widely recognized beneficial effects of the MeDi on health could be reviewed, although more studies are needed to disentangle these results.

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Conflict of interest

Catherine Féart received fees for conferences from Danone Research. Cécilia Samieri and Simon Lorrain report no conflict of interest. Luc Letenneur receives research support from Danone Research. Vanessa Ginder Coupez and Damien Paineau are members of Danone Research. Pascale Barberger-Gateau served on a scientific advisory board for Caisse Nationale pour la Solidarite et l'Autonomie (CNSA); has received funding for travel and speaker honoraria from Lesieur, Bausch & Lomb, Aprifel, Danone Institute, Canadian Association of Gerontology, and the Jean Mayer Human Nutrition Research Center on Aging, Tufts University; serves on the editorial boards of Disability and Rehabilitation; has received consultancy fees from Vifor Pharma; and receives research support from Lesieur, Danone, Agence Nationale de la Recherche, Conseil Régional d'Aquitaine, Institut Carnot LISA and Groupe Lipides et Nutrition.

Authors' contributions to manuscript

1) designed research (project conception, development of overall research plan, and study oversight): PBG, DP

2) conducted research (hands-on conduct of the experiments and data collection): PBG, LL

3) provided essential reagents or provided essential materials: PBG, LL

4) analyzed data or performed statistical analysis: CF, SL

5) wrote paper: CF, PBG

6) had primary responsibility for final content: CF

7) provided significant advice: PBG, LL,VC, CS, DP

All the authors read the draft critically.

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Table 1. Baseline demographic, health and dietary characteristics of the participants at baseline according to 8-year incidence of a fracture, in the Bordeaux sample of the Three-City study (2001-2009) (N=1482)

	Hip fracture (n=57)		**Vertebral fracture (n=43)**		**Wrist fracture (n=73)**		**Fracture at any site* (N=155)**		**No incident fracture (N=1327)**	
Sociodemographic characteristics										
Age, y, mean (SD)	78.1	(4.6)	76.6	(4.5)	76.0	(4.7)	76.9	(4.6)	75.9	(4.9)
Male sex, n (%)	11	(19.3)	6	(14.0)	8	(11.0)	23	(14.8)	527	(39.7)
Education, n (%)										
None or primary	20	(35.1)	13	(30.2)	23	(31.5)	50	(32.3)	441	(33.2)
Secondary	16	(28.1)	11	(25.6)	19	(26.0)	41	(26.5)	358	(27.0)
High school	11	(19.3)	11	(25.6)	25	(34.3)	42	(27.1)	273	(20.6)
University	9	(15.8)	8	(18.6)	5	(6.9)	21	(13.6)	247	(18.6)
Refused to answer	1	(1.8)	0	(0.0)	1	(1.4)	1	(0.7)	8	(0.6)
Income, n (%)										
<750 €	7	(12.3)	3	(7.0)	5	(6.9)	13	(8.4)	92	(6.9)
[750-1500[€	12	(21.)	15	(34.9)	27	(37.0)	47	(30.3)	392	(29.5)
[1500-2250] €	15	(26.3)	13	(30.2)	18	(24.7)	42	(27.1)	334	(25.2)
> 2250 €	19	(33.3)	8	(18.6)	14	(19.2)	38	(24.5)	412	(31.1)
Refused to answer	4	(7.0)	4	(9.3)	9	(12.3)	15	(9.7)	97	(7.3)
Marital status, n (%)										
Married	30	(52.6)	15	(34.9)	28	(38.4)	69	(44.5)	732	(55.2)
Divorced / separated	3	(5.3)	3	(7.0)	3	(4.1)	9	(5.8)	105	(7.9)
Widowed	21	(36.8)	18	(42.0)	33	(45.2)	63	(40.7)	408	(30.7)
Single	3	(5.3)	7	(16.3)	9	(12.3)	14	(9.0)	82	(6.2)
Health indicators										
BMI, n (%)										
< 21	4	(7.0)	7	(16.3)	10	(13.7)	17	(11.0)	82	(6.2)
[21- 25[	23	(40.4)	10	(23.3)	25	(34.3)	53	(34.2)	389	(29.3)
[25-30]	22	(38.6)	21	(48.8)	24	(32.9)	61	(39.4)	590	(44.5)
> 30	6	(10.5)	3	(7.0)	13	(17.8)	21	(13.6)	232	(17.5)
Refused to answer	2	(3.5)	2	(4.7)	1	(1.4)	3	(1.9)	34	(2.6)

	Hip fracture (n=57)		**Vertebral fracture (n=43)**		**Wrist fracture (n=73)**		**Fracture at any site* (N=155)**		**No incident fracture (N=1327)**	
Diabetes, n (%)	5	(8.8)	4	(9.3)	4	(5.5)	13	(8.4)	138	(10.4)
Smoking, n (%)										
Never	34	(59.7)	26	(60.5)	59	(80.8)	108	(69.7)	812	(61.2)
Former	18	(31.6)	10	(23.3)	11	(15.1)	37	(23.9)	429	(32.3)
Current	5	(8.8)	6	(14.0)	2	(2.7)	9	(5.8)	85	(6.4)
Physical activity, n (%)										
Yes	12	(21.1)	10	(23.3)	17	(23.3)	38	(24.5)	375	(28.3)
No	27	(47.4)	23	(53.5)	44	(60.3)	82	(52.9)	731	(55.1)
Refused to answer	18	(31.6)	10	(23.3)	12	(16.4)	35	(22.6)	221	(16.6)
Calcium and/or vitamin D treatment, n (%)	8	(14.0)	11	(25.3)	11	(15.1)	27	(17.4)	104	(7.8)
Osteoporosis treatment, n (%)	5	(8.8)	8	(18.6)	2	(2.7)	11	(7.1)	47	(3.5)
Long-term corticotherapy[a], n (%)	1	(1.8)	0	(0.0)	3	(4.1)	4	(2.6)	35	(2.6)
Dietary characteristic										
MeDi score, mean (SD)	4.72	(1.51)	4.49	(1.72)	4.66	(1.80)	4.64	(1.72)	4.35	(1.67)

Abbreviations: BMI: Body Mass Index.

[a] systemic or inhalation corticoid use both at baseline of the 3C study and at wave 1

* Fracture at any sites among the hip, the wrist and the vertebrae

Table 2. Baseline median and mean number of servings per week for individual MeDi components and mean MUFA-to-SFA ratio by gender, among older persons living in Bordeaux, The Three-City study (2001-2002) (N=1482)

	Men n=550			Women n=932			
Food categories, servings per week	Median	Mean	SD	Median	Mean	SD	P*
Dairy products	17.0	18.0	7.8	17.9	18.6	7.8	0.15
Yoghurt	6.0	5.8	4.9	7.0	8.0	5.2	<0.0001
Milk	0.25	3.7	4.4	0.25	3.4	4.5	0.13
Cheese	7.0	8.4	4.7	7.0	7.2	4.5	<0.0001
Meat	5.0	5.3	2.6	4.0	4.5	2.3	<0.0001
Vegetables	19.1	19.6	7.3	18.0	19.0	7.2	0.13
Fruits	14.0	13.2	6.7	14.0	13.7	7.0	0.17
Legumes	0.5	0.8	0.8	0.5	0.5	0.5	<0.0001
Cereals [a]	23.6	23.2	5.2	23.0	21.3	6.5	<0.0001
Fish	2.8	2.9	1.7	2.5	2.8	1.8	0.35
MUFA-to-SFA ratio [b]	0.8	0.9	0.3	0.8	0.9	0.3	0.99
Alcohol [c]		16.9	14.6		5.9	6.8	<0.0001
No or low		1.8	1.8		0.0	0.0	<0.0001
Mild-to-moderate		9.7	3.0		2.0	1.1	<0.0001
High		27.9	12.9		11.2	6.4	<0.0001

Abbreviations: MUFA-to-SFA Monounsaturated fatty acid-to-saturated fatty acid ratio

[a] Cereals included consumption of cereals, bread, pasta and rice (whole and refined grains)

[b] The 24H recall was used to compute the MUFA-to-SFA ratio (intake g/d)

[c] Number of glasses per week. For the computation of the MeDi score, we attributed a value of 1 for people whose consumption was mild-to moderate, corresponding to the second quartile of distribution of total alcohol intake. One point was given to men if their consumption was within 7-to-14 glasses per week (10-to-20g/d) (N=150) and to women if consumption was within 1-to-4 (1.4-to-5.7g/d) glasses per week (N=238). "No or low consumption" corresponded to the first quartile of distribution of total alcohol intake (less than 7 or 4 glasses per week for men (N=126) and women (N=244) respectively). "High consumption" corresponded to the third and fourth quartiles of distribution (over 14 or 4 glasses per week for men (N=274) and women (N=450) respectively).

* *P*-value for Student’s t test comparing mean consumption of individual food intake or ratios between men and women.

Table 3. Multivariate associations between adherence to a Mediterranean diet, as assessed by the MeDi Score (continuous) at baseline, and incidence of fracture among older persons living in Bordeaux, The Three-City study (2001-2009)

	Hip fracture		**Vertebral fracture**		**Wrist fracture**		**Fracture at any site***	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Model 1 (N=1,482)								
MeDi Score	1.18 (1.00-1.39)	0.05	1.06 (0.88-1.28)	0.54	1.12 (0.97-1.29)	0.13	1.12 (1.02-1.24)	0.02
Model 2 (N=1,435)								
MeDi Score	1.18 (0.99 -1.39)	0.06	1.06 (0.87-1.29)	0.55	1.09 (0.94-1.26)	0.25	1.10 (0.99-1.21)	0.08

Abbreviations: MeDi Mediterranean diet; HR Hazard ratio; CI Confidence Intervals
Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated for 1-unit increase of the MeDi score

P -value for Cox proportional hazard models

* Fracture at any sites among the hip, the wrist and the vertebrae
Model 1 was adjusted for age, gender, physical activity and total energy intake
Model 2 as Model 1 plus additional adjustment for educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment

Table 4. Multivariate associations between individual food groups component of the Mediterranean diet score at baseline and incidence of fracture among older persons living in Bordeaux, The Three-City study (2001-2009)

	Hip fracture		**Vertebral fracture**		**Wrist fracture**		**Fracture at any site***	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Model 1 (N=1,482)†								
Low dairy products	1.03 (0.60-1.76)	0.92	1.73 (0.91-3.27)	0.09	**1.97 (1.20-3.24)**	**0.008**	**1.58 (1.13-2.20)**	**0.007**
Low meats	0.96 (0.55-1.68)	0.88	0.71 (0.37-1.39)	0.32	0.74 (0.44-1.22)	0.23	0.78 (0.56-1.10)	0.16
High vegetables	1.51 (0.86-2.68)	0.15	1.45 (0.75-2.77)	0.27	0.69 (0.43-1.11)	0.12	1.01 (0.72-1.40)	0.97
High fruits	1.74 (0.96-3.16)	0.07	0.75 (0.40-1.39)	0.36	1.15 (0.71-1.85)	0.58	1.16 (0.83-1.62)	0.38
High legumes	0.93 (0.54-1.59)	0.78	1.06 (0.56-2.00)	0.85	0.93 (0.58-1.50)	0.76	0.96 (0.69-1.33)	0.78
High cereals [a]	1.09 (0.62-1.90)	0.77	0.95 (0.51-1.80)	0.88	1.41 (0.86-2.31)	0.18	1.11 (0.79-1.55)	0.56
High fish	1.07 (0.62-1.85)	0.81	1.54 (0.82-2.91)	0.18	1.05 (0.65-1.70)	0.83	1.33 (0.95-1.85)	0.10
High MUFA-to-SFA ratio	0.98 (0.57-1.67)	0.94	**0.48 (0.25-0.91)**	**0.02**	1.47 (0.90-2.38)	0.12	0.94 (0.68-1.31)	0.73
Alcohol [b]								
No or low	0.48 (0.23-1.03)	0.15	0.46 (0.19-1.13)	0.17	0.94 (0.52-1.69)	0.13	**0.66 (0.43-1.02)**	**0.03**
Mild-to-moderate	1		1		1		**1**	
High	0.69 (0.38-1.25)		0.60 (0.31-1.18)		0.59 (0.34-1.03)		**0.63 (0.43-0.90)**	
Model 2 (N=1,435) †								
Low dairy products	0.95 (0.54-1.68)	0.86	1.53 (0.79-2.95)	0.21	**2.03 (1.22-3.39)**	**0.007**	**1.51 (1.07-2.11)**	**0.02**
Low meats	0.99 (0.55-1.78)	0.96	0.70 (0.35-1.40)	0.31	0.62 (0.36-1.05)	0.08	0.74 (0.52-1.06)	0.10
High vegetables	1.52 (0.84-2.74)	0.17	1.40 (0.70-2.79)	0.34	0.70 (0.42-1.14)	0.15	1.00 (0.71-1.41)	0.99
High fruits	**1.95 (1.04-3.66)**	**0.04**	0.70 (0.36-1.36)	0.29	1.13 (0.69-1.86)	0.63	1.15 (0.82-1.63)	0.42
High legumes	0.84 (0.47-1.48)	0.54	0.92 (0.47-1.80)	0.80	1.02 (0.62-1.70)	0.93	0.92 (0.65-1.29)	0.62
High cereals [a]	0.98 (0.55-1.75)	0.94	1.05 (0.54-2.06)	0.88	1.25 (0.76-2.07)	0.39	1.04 (0.74-1.47)	0.81
High fish	1.18 (0.67-2.09)	0.57	1.58 (0.81-3.08)	0.18	0.98 (0.60-1.61)	0.94	1.29 (0.92-1.81)	0.14
High MUFA-to-SFA ratio	1.00 (0.57-1.75)	0.99	0.61 (0.31-1.18)	0.14	1.40 (0.85-2.31)	0.19	0.94 (0.67-1.31)	0.72
Alcohol [b]								**0.03**
No or low	0.45 (0.20-1.00)	0.12	0.46 (0.18-1.22)	0.24	1.01 (0.55-1.86)	0.07	**0.67 (0.43-1.05)**	
Mild-to-moderate	1		1		1		**1**	
High	0.64 (0.35-1.18)		0.64 (0.32-1.30)		0.55 (0.31-0.98)		**0.61 (0.42-0.88)**	

Abbreviations: HR Hazard ratio; CI Confidence Intervals
Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated for 1-unit increase of the MeDi score

P -value for Cox proportional hazard models

* Fracture at any sites among the hip, the wrist and the vertebrae
† These consumptions corresponded to one point attributed in the computation of the Mediterranean diet score. A low consumption of dairy products corresponded to less than 17.0 servings/week for men and 17.9 for women. A low consumption of meats corresponded to less than 5.0 servings/week for men and 4.0 for women. A high consumption of vegetables corresponded to more than 19.1 servings/week for men and 18.0 for women. A high consumption of fruits corresponded to more than 14.0 servings/week for men and women. A high consumption of legumes corresponded to more than 0.5 serving/week for men and women. A high consumption of cereals corresponded to more than 23.6 servings/week for men and 23.0 for women. A high consumption of fish corresponded to more than 2.8 servings/week for men and 2.5 for women. A high MUFA-to-SFA ratio corresponded to a ratio higher than 0.8 for men and women.

[a] Cereals included consumption of cereals, bread, pasta and rice (whole and refined grains)
[b] For the computation of the MeDi score, we attributed a value of 1 for people whose consumption was mild-to moderate, corresponding to the second quartile of distribution of total alcohol intake. One point was given to men if their consumption was within 7-to-14 glasses per week and to women if consumption was within 1-to-4 glasses per week. This category was chosen as reference in this analysis. "No or low consumption" corresponded to the first quartile of distribution of total alcohol intake (less than 7 or 4 glasses per week for men and women respectively). "High consumption" corresponded to the third and fourth quartiles of distribution (over 14 or 4 glasses per week for men and women respectively).

Model 1 was adjusted for each individual food group component of the Mediterranean diet score, age, gender, physical activity and total energy intake
Model 2 as Model 1 plus additional adjustment for educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment

Table 5. Multivariate association between dairy products consumption at baseline and incidence of fracture among older persons living in Bordeaux, The Three-City study (2001-2009)

	Hip fracture		Vertebral fracture		Wrist fracture		Fracture at any site *	
	HR (95%CI)	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
Model 1 (N=1,482) †								
Low yoghurts	1.06 (0.61-1.87)	0.82	0.87 (0.45-1.70)	0.68	**1.85 (1.16-2.94)**	**0.01**	1.25 (0.90-1.75)	0.18
Low milk	1.23 (0.72-2.10)	0.45	1.26 (0.68-2.36)	0.46	0.99 (0.62-1.58)	0.95	1.16 (0.84-1.60)	0.38
Low cheese	1.44 (0.84-2.49)	0.19	1.49 (0.80-2.78)	0.21	1.08 (0.67-1.76)	0.75	1.23 (0.88-1.71)	0.23
Model 2 (N=1,435) †								
Low yoghurts	1.11 (0.62-1.99)	0.72	0.85 (0.42-1.70)	0.64	**1.98 (1.22-3.21)**	**0.005**	1.29 (0.92-1.81)	0.15
Low milk	1.16 (0.67-2.02)	0.60	1.15 (0.60-2.20)	0.68	0.96 (0.59-1.56)	0.88	1.10 (0.79-1.53)	0.57
Low cheese	1.28 (0.72-2.28)	0.40	1.55 (0.80-2.99)	0.19	0.98 (0.59-1.62)	0.93	1.14 (0.81-1.61)	0.46

Abbreviations: HR Hazard ratio; CI Confidence Intervals

Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated for 1-unit increase of the MeDi score

* Fracture at any sites among the hip, the wrist and the vertebrae

† These consumptions corresponded to one point attributed for the considered food group in the computation of the Mediterranean diet score. Participants received 1 point if their intake of yoghurts was lower than 6 servings/week for men and 7 servings/week for women; if their intake of milk was lower than 0.25 serving/week for men and women; and if their intake of cheese was lower than 7 servings/week for men and women.

Model 1 was adjusted for each individual food group component of the Mediterranean diet score, age, gender, physical activity and total energy intake

Model 2 as Model 1 plus additional adjustment for educational level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin D treatment