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## **TITLE PAGE**

### **Title**

**Adherence to a Mediterranean diet and risk of fractures in French older persons**

### **Authors**

Catherine FEART<sup>1,2</sup>, Simon LORRAIN<sup>1,2</sup>, Vanessa GINDER COUPEZ<sup>3</sup>, Cécilia SAMIERI<sup>1,2</sup>, Luc LETENNEUR<sup>1,2</sup>, Damien PAINEAU<sup>3</sup>, Pascale BARBERGER-GATEAU<sup>1,2</sup>

### **Author Affiliations:**

1. Univ. Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France
2. INSERM, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, F-33000 Bordeaux, France
3. Danone Research, Centre Daniel Carasso, Global Nutrition Department, F-91767 Palaiseau Cedex, France

### **Corresponding author:**

Catherine FEART

Address: Equipe Epidémiologie de la nutrition et des comportements alimentaires, INSERM, U897, Université Bordeaux Ségalen, ISPED case 11, 146 rue Léo-Saignat, F-33076 BORDEAUX Cedex – France

Phone: (33) 5 47 304 204; Fax: (33) 5 57 57 14 86

E-mail: [Catherine.Feart@isped.u-bordeaux2.fr](mailto:Catherine.Feart@isped.u-bordeaux2.fr)

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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.

1 **ABSTRACT**

2

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

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

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

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

21 **TEXT**22 **INTRODUCTION**

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

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

37 In this context, the Mediterranean diet (MeDi) combines several foods and nutrients already proposed  
38 as potential protective factors against development and progression of several age-related diseases [12-  
39 13]. A limited number of cross-sectional studies have examined the relationship between MeDi  
40 adherence and bone health, and they have reported conflicting results. On the one hand, adherence to a  
41 traditional MeDi has been associated with higher bone mineral density (BMD) among 100 Spanish  
42 postmenopausal women (54 years on average) [14] whereas on the other hand, among 196 Greek  
43 women (48 years on average), Kontogianni et al. [15] failed to evidence any association between  
44 adherence to the MeDi and indices of bone mass. To our knowledge, the potential protective effect of  
45 the MeDi against the risk of hip fractures has been evaluated prospectively only once, in the European  
46 Prospective Investigation into Cancer and Nutrition (EPIC) study [16]. In this large cohort of adults  
47 (N=188,795, 49 years on average and followed for a median of 9 years), a greater MeDi adherence  
48 was associated with a significant 7% reduced risk of hip fractures. This analysis was restricted to the

49 risk of hip fractures, although the risk factors of fractures are site specific [17]. Moreover, the authors  
50 were restrained to develop a modified MeDi score, to better take into account the low consumption of  
51 olive oil in non-Mediterranean populations [16].

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

## 55 **SUBJECTS AND METHODS**

### 56 **Participants**

57 The data came from the Three-City (3C) study, a prospective cohort study of vascular risk factors of  
58 dementia whose methodology has been described elsewhere [18]. The 3C study protocol was approved  
59 by the Consultative Committee for the Protection of Persons participating in Biomedical Research at  
60 Kremlin-Bicêtre University Hospital (Paris). A sample of 9,294 community dwellers aged 65+ was  
61 selected in 1999-2000 from the electoral rolls of three French cities (Bordeaux, Dijon and  
62 Montpellier). All participants gave written informed consent. At baseline, data collection included  
63 socio-demographic information, lifestyle, symptoms and complaints, medical history, blood pressure,  
64 anthropometric data, neuropsychological testing, and blood sampling. Four follow-up examinations  
65 were performed, two (wave 1, in 2001-2002), four (wave 2, in 2003-2004), seven (wave 3, in 2006-  
66 2007) and ten years (wave 4, in 2009-2010) after baseline examination. The present study extends  
67 between the wave 1 (baseline of this study) and wave 4 in Bordeaux, the only centre where the  
68 standard data collection was completed with a comprehensive dietary survey at wave 1.

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

74

### 75 **Fractures**

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

83

**84 Dietary assessment and MeDi score**

85 Participants were visited at home by a trained dietician who administered a food frequency  
86 questionnaire (FFQ), not semi-quantitative, and a 24H dietary recall at wave 1 [20-21]. The 24H recall  
87 was used to estimate nutrient intake in g/d, total energy intake in kcal/d and to compute the ratio of  
88 monounsaturated to saturated fat (MUFA-to-SFA). Based on the FFQ, frequency of consumption of  
89 40 categories of foods and beverages for each of the 3 main meals and 3 between-meals snacks was  
90 recorded in 11 classes (from never to every days). The food items were aggregated into 20 food and  
91 beverage groups as described elsewhere [21]. We identified the food groups considered to be part of  
92 the MeDi: vegetables, fruits, legumes, cereals including bread, pasta and rice (whole and refined  
93 grains), fish and seafood, meat, dairy products including yoghurts, milk and cheese, and alcohol.  
94 Intake of each food group was determined in servings/week. Adherence to the traditional  
95 Mediterranean-type diet was assessed by the MeDi score, a 10-point Mediterranean-diet scale. The  
96 MeDi score was computed as follows: a value of 0 or 1 was assigned to each food group using sex-  
97 specific medians of the population as cut-offs, as suggested earlier by Trichopoulou et al. [22]. For  
98 presumed beneficial components for health (ie vegetables, fruits, legumes, cereals and fish),  
99 individuals whose consumption was above the median were assigned a value of 1, vs 0 for the others.  
100 For components presumed to be detrimental for health (ie meat and dairy products), individuals whose  
101 consumption was below the median were assigned 1, vs. 0 for the others. For alcohol, 1 point was  
102 assigned to men if their consumption was within 7-to-14 glasses/week (10-to-20g/d) and to women if  
103 their consumption was within 1-to-4 glasses/week (1.4-to-5.7g/d). These cut-offs, corresponding to the  
104 second quartile of distribution of total alcohol intake in this population, were chosen to represent mild-  
105 to-moderate consumption. Finally, participants with a MUFA-to-SFA ratio above the sex-specific  
106 median were assigned a value of 1, vs. 0 for those below the median. The MeDi score was generated  
107 by adding the scores (0 or 1) for each food category. Thus, the MeDi score could range from 0 to 9 for  
108 each participant, with higher scores indicating greater adherence [22].

109

**110 Covariates**



111 Socio-demographic information recorded at baseline included age, gender and education (six  
112 educational levels grouped into four classes: no education or primary school only, secondary (middle  
113 school, high school or vocational school and university). Socio-demographic characteristics also  
114 included marital status (married, divorced or separated, widowed, single) and income in four  
115 categories (< 750 euros, 750 to 1500 euros, 1500 to 2250 euros, > 2250 euros per month). Height (in  
116 m) and weight (in kg) were measured by the interviewers at wave 1. BMI was computed as the  
117 weight/height<sup>2</sup> ratio and considered in four categories (< 21 kg/m<sup>2</sup>, 21 to 25 kg/m<sup>2</sup>, 25 to 30 kg/m<sup>2</sup>, >  
118 30 kg/m<sup>2</sup>). Diabetes was defined as self-reported or as having an anti-diabetic medication at wave 1.  
119 Smoking status (never, ex-smoker or current smoker) and regular practice of physical activity (ie  
120 doing sport regularly or having at least 1 hour of leisure or household activity per day) were also  
121 recorded. Self-reported history of osteoporosis was recorded at each wave. All drugs consumed at least  
122 once a week during the last month were collected and prevention or treatment for osteoporosis was  
123 recorded, including biphosphonates, raloxifene, strontium ranelate, teriparitide, calcitonine, and  
124 supplementation with calcium and/or vitamin D. Long-term corticotherapy was defined as declaring  
125 systemic or inhalation corticoid use at both baseline of the 3C study and at wave 1.

126

### 127 **Statistical analyses**

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

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

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

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

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

153 Covariates were selected for multivariate models when associated with either incidence of hip or  
154 wrist or vertebral fracture at a statistical level  $\alpha < 0.20$  in univariate analyses, as described elsewhere  
155 [19]. Two models were performed. First, we adjusted for age, gender, physical activity and total  
156 energy intake (model 1). Then, we considered additional adjustment for educational level, marital  
157 status, BMI, self-reported osteoporosis, osteoporosis treatment, and intake of calcium and/or vitamin  
158 D supplements (model 2).

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

160 **RESULTS**

161 At baseline, the mean age of the participants (N=1,482, 550 men, 932 women) was 75.9y (range  
 162 67.7-94.9). Over the 8-y follow-up, 155 individuals reported a fracture at any of the three sites,  
 163 including 57 hip fractures (46 among women), 43 vertebral fractures (37 among women) and 73 wrist  
 164 fractures (65 among women). Among men (N=550), 23 (4.2%) incident fractures were reported over 8  
 165 years: 11 (2.0%) hip fractures, 8 (1.5%) wrist fractures and 6 (1.1%) vertebral fractures. Among 932  
 166 women of the study sample, 132 (14.1%) incident fractures were reported over 8 years, divided as 46  
 167 (4.9%) of hip fractures, 65 (7.0%) wrist fractures and 37 (4.0%) vertebral fractures. The  
 168 sociodemographic and health characteristics of all participants are described in Table 1. Regarding  
 169 MeDi adherence, individuals with an incident fracture at any of the three sites had a higher mean  
 170 MeDi score at baseline than those who remained free of fracture during follow-up (4.64, (standard  
 171 deviation (sd) 1.72) vs. 4.35 (sd 1.67), P=0.04).

172

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

178

179 In multivariate analyses adjusted for age, gender, physical activity, total energy intake, educational  
 180 level, marital status, BMI, self-reported osteoporosis, osteoporosis treatment, calcium and/or vitamin  
 181 D treatment, a borderline significant association between MeDi score and an increased risk of  
 182 fracture at any site (HR = 1.10, 95% CI 0.99-1.21, P=0.08), and, specifically of hip fracture (HR =  
 183 1.18, 95% CI 0.99-1.39, P=0.06) was observed (**Table 3**, model 2). Conversely, adherence to the  
 184 MeDi was not significantly associated with the risk of vertebral or wrist fracture.

185

186 In secondary analyses, we examined whether associations between MeDi adherence and risk of  
 187 fractures were driven by particular food categories (**Table 4**). In fully adjusted models, greater fruit

188 consumption (i.e. >14 servings/week in men and women combined) was significantly associated with  
189 a doubled 8-y risk of hip fracture (HR high vs low = 1.95, 95% CI 1.04-3.66, P=0.04). Furthermore,  
190 lower intake of dairy products (i.e. <17.0 servings/week in men and <17.9 servings/week in women)  
191 was significantly associated with an increased risk of fracture at any site (HR low vs high = 1.51, 95%  
192 CI 1.07-2.11, P=0.02), and, specifically, with a doubled risk of wrist fracture (HR low vs high = 2.03,  
193 95% CI 1.22-3.39, P=0.007), but not other sites. Higher levels of alcohol intake (>14 glasses/week in  
194 men and >4 glasses/week in women) and marginally, low alcohol intake were associated with a  
195 significant reduction (39% for high intake, 33% for low intake, P for trend=0.03) of risk of fracture at  
196 any site. A MUFA-to-SFA ratio higher than 0.8 was significantly associated with a reduced risk of  
197 vertebral fracture in the model adjusted for age, gender, physical activity, total energy intake and all  
198 other dietary components the MeDi score. However, this association was no longer significant in fully  
199 adjusted models.

200

201 We further analyzed the association between the type of dairy product and the risk of fracture (**Table**  
202 **5**). Elderly subjects who declared a consumption of yoghurts lower than the median, i.e. <6  
203 servings/week in men and <7 in women, were at increased risk of wrist fracture only (HR low vs high  
204 = 1.98, 95% CI 1.22-3.21, P=0.005). By contrast, a low consumption of milk or cheese was not  
205 associated with the risk of fracture of the hip, the wrist or the vertebrae, in fully adjusted models  
206 (**Table 5**). When considering the risk of fracture whatever the type among the three sites, the low  
207 consumption of yoghurts, milk or cheese was not associated with the overall risk of fracture.

208 **DISCUSSION**

209

210 In this longitudinal population-based study of French older adults, a greater adherence to a  
211 Mediterranean-type diet was significantly associated with an increased risk of fracture, after  
212 adjustment for age, gender, physical activity and total energy intake. Two MeDi components appeared  
213 to independently drive this association: a high consumption of fruits (>2 servings/day) and a low  
214 consumption of yoghurts (<1 serving/day) were significantly associated with a doubled risk of fracture  
215 of the hip and the wrist respectively, in fully adjusted models. Moreover, a consumption of alcohol  
216 higher than 14 glasses/week for men or 4 glasses/week for women was significantly associated with a  
217 39% reduced risk of fracture at any site over time.

218

219 To our knowledge, a single study reported an inverse association between adherence to a  
220 Mediterranean-type diet and the risk of hip fracture in European older persons [16], which was not in  
221 agreement with the present results. Indeed, in this large cohort of adults enrolled in the EPIC study  
222 (N=188,795 participants, 802 incident hip fractures), higher adherence to the MeDi was associated  
223 with a 7% decrease in hip fracture incidence, notably among participants aged 60y + and among men  
224 in the model adjusted only for age [16]. In analyses where the dietary components of the MeDi were  
225 mutually adjusted, as in the present study, the components that were significantly associated with the  
226 risk of hip fracture in the overall sample were vegetables, meat and ethanol intake. However, several  
227 differences between the EPIC study and the present one could explain such discrepancies. First, the  
228 statistical power of this French study (only 57 incident hip fractures in the present study) was greatly  
229 lower than that of the European study. This may have reduce our chance to evidence stronger or  
230 additional associations between MeDi adherence and risk of fracture at any site (or at specific site)  
231 among French people. Second, the results from the EPIC study suggested that the prevention of hip  
232 fracture might be more challenging in women than in men. Only 11 men (among 57) were identified  
233 with an incident hip fracture in the present study which prevented us to stratify our analyses based on  
234 gender. Third, country specific characteristics of the dietary patterns may partly explain the  
235 discrepancies between the French and the EPIC studies. Indeed, a modified MeDi score has been

236 defined in the EPIC cohort, by substituting the monounsaturated lipids (MUFA) with the sum of  
237 mono- and poly- unsaturated fatty acids in the numerator of the lipid ratio, to better take into account  
238 the low consumption of olive oil and MUFA in non-Mediterranean populations [16]. Among the eight  
239 countries participating in the EPIC study, only three have Mediterranean origins (Greece, Italy and  
240 Spain) but there were no data from France. Traditionally, even among Mediterranean countries,  
241 distinct dietary habits exist, as already described by Sofi [23]. More importantly, the MeDi score was  
242 computed according to sex-specific medians of consumption of only 9 food groups of each study  
243 sample, which limited the generalization of the results and prevented definite conclusions. Altogether,  
244 these differences could in part explain the lack of homogeneous results of the association between a  
245 Mediterranean-type diet and risk of hip fracture among European and French elderly. Finally,  
246 adherence to the MeDi may be considered as lifestyle and may reflect specific health concerns and  
247 behaviors that may differ between countries, particularly regarding practice of physical exercise or use  
248 of supplements, part of lifestyle but not considered in the diet score computation.

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

255

256 *A posteriori* derived dietary patterns, independent of any assumption on the beneficial or harmful  
257 effects of food intakes, have also been examined in association with bone health, but less often with  
258 fracture risk. For instance, a pattern characterized by a high consumption of fruits, vegetables and  
259 whole grains might be an optimal dietary strategy to avoid fractures, particularly in older women, in a  
260 Canadian study [25]. However, among Japanese adult women, a pattern characterized by high  
261 consumption of vegetables was associated with an increased risk of fractures, and another one  
262 characterized by a high consumption of meat was associated with a reduced risk of fractures [26].  
263 Finally, in the 3C study, we previously reported that dietary patterns rich in cheese, milk and

264 charcuteries derived from principal component analysis, were related to a lower risk of hip and wrist  
265 fractures over 8-y of follow-up [19].

266

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

284

285 As expected, we found that a low consumption of dairy products was significantly associated with an  
286 increased risk of fractures. Less attention has been paid in the literature to specific categories of dairy  
287 products. In our study, consuming less than one serving of yoghurt/day was associated with a doubled  
288 risk of wrist fracture. Dairy products are the main dietary providers of calcium. In a previous paper,  
289 we reported that higher MeDi adherents of the 3C study are those with the lowest calcium intake [31].  
290 Calcium homeostasis and vitamin D status are closely related, particularly with respect to fracture risk  
291 [7], although the impact of calcium and/or vitamin D supplementation on the prevention of fracture

292 risk remains questionable [32-33]. Regarding milk consumption, our results are in agreement with  
293 those of two meta-analyses in which a low intake of milk was not associated with any marked increase  
294 in fracture risk, notably hip fracture risk [34-35].

295

296 Alcoholism is known to have negative effects on bone [16, 36], but an inverse U-shaped association  
297 between alcohol intake and risk of fracture at any site was observed in the present study. Conversely, a  
298 J-shaped relationship between alcohol consumption and hip fracture risk has already been reported  
299 [37] and a threshold effect (2 units per day or more) has been defined [38]. . Several explanations for  
300 these results could be evoked. A first interpretation would be the relevance of using non-drinkers as a  
301 reference group, unlike in the current study. Indeed, present non-drinkers may have given up alcohol  
302 for medical reasons and be in poorer health status than drinkers. A second interpretation would be that  
303 adjustment for major potential confounders was missing in most studies of the existing literature [37],  
304 while our models are fully adjusted, including other food groups composing the MeDi score and  
305 energy intake. Finally, high alcohol consumers of the current study, identified as men with a  
306 consumption >2 glasses/day and women with a consumption >4 glasses/week, should not be  
307 considered as excessive drinkers but as ordinary elderly consumers with French cultural lifestyles  
308 including regular alcohol drinking [20].

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

317

318 There are nevertheless some potential limitations to our findings. First, the FFQ used in the present  
319 study did not allow estimation of portion sizes. The lack of estimation of portion size may lead to



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

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

342

343 In conclusion, we found in this large cohort of French elderly community dwellers that a diet closer  
344 to a Mediterranean-type diet had a borderline significant deleterious effect on the risk of fractures, in  
345 part linked to a low consumption of dairy products and a high consumption of fruits, for which the  
346 explanation remains unclear. A high adherence to this French MeDi, as assessed by the MeDi score in  
347 the current study, seems not to be beneficial to the prevention of fractures and consequently to bone

348 health in French elderly adults [16]. The present results suggested that the widely recognized  
349 beneficial effects of the MeDi on health could be reviewed, although more studies are needed to  
350 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 Solidarité 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**

*I*) 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)	
<b>Sociodemographic characteristics</b>										
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)
<b>Health indicators</b>										
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 <sup>a</sup> , n (%)	1	(1.8)	0	(0.0)	3	(4.1)	4	(2.6)	35	(2.6)
<b>Dietary characteristic</b>										
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.

<sup>a</sup> 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)

Food categories, servings per week	Men n=550			Women n=932			P*
	Median	Mean	SD	Median	Mean	SD	
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 <sup>a</sup>	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 <sup>b</sup>	0.8	0.9	0.3	0.8	0.9	0.3	0.99
Alcohol <sup>c</sup>		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

<sup>a</sup> Cereals included consumption of cereals, bread, pasta and rice (whole and refined grains)

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

<sup>c</sup> 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
<b>Model 1</b> (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
<b>Model 2</b> (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)

	<b>Hip fracture</b>		<b>Vertebral fracture</b>		<b>Wrist fracture</b>		<b>Fracture at any site*</b>		
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	
<b>Model 1 (N=1,482)†</b>									
Low dairy products	1.03 (0.60-1.76)	0.92	1.73 (0.91-3.27)	0.09	<b>1.97 (1.20-3.24)</b>	<b>0.008</b>	<b>1.58 (1.13-2.20)</b>	<b>0.007</b>	
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 <sup>a</sup>	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	<b>0.48 (0.25-0.91)</b>	<b>0.02</b>	1.47 (0.90-2.38)	0.12	0.94 (0.68-1.31)	0.73	
Alcohol <sup>b</sup>									
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	<b>0.66 (0.43-1.02)</b>	<b>0.03</b>	
Mild-to-moderate	1		1		1		<b>1</b>		
High	0.69 (0.38-1.25)		0.60 (0.31-1.18)		0.59 (0.34-1.03)		<b>0.63 (0.43-0.90)</b>		
<b>Model 2 (N=1,435) †</b>									
Low dairy products	0.95 (0.54-1.68)	0.86	1.53 (0.79-2.95)	0.21	<b>2.03 (1.22-3.39)</b>	<b>0.007</b>	<b>1.51 (1.07-2.11)</b>	<b>0.02</b>	
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	<b>1.95 (1.04-3.66)</b>	<b>0.04</b>	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 <sup>a</sup>	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 <sup>b</sup>								<b>0.03</b>	
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	<b>0.67 (0.43-1.05)</b>		
Mild-to-moderate	1		1		1		<b>1</b>		
High	0.64 (0.35-1.18)		0.64 (0.32-1.30)		0.55 (0.31-0.98)		<b>0.61 (0.42-0.88)</b>		

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.

<sup>a</sup> Cereals included consumption of cereals, bread, pasta and rice (whole and refined grains)

<sup>b</sup> 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
<b>Model 1 (N=1,482) †</b>								
Low yoghurts	1.06 (0.61-1.87)	0.82	0.87 (0.45-1.70)	0.68	<b>1.85 (1.16-2.94)</b>	<b>0.01</b>	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
<b>Model 2 (N=1,435) †</b>								
Low yoghurts	1.11 (0.62-1.99)	0.72	0.85 (0.42-1.70)	0.64	<b>1.98 (1.22-3.21)</b>	<b>0.005</b>	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