

**ADHERENCE TO A MEDITERRANEAN DIET IS ASSOCIATED
WITH LOWER PREVALENCE OF OSTEOARTHRITIS:
DATA FROM THE OSTEOARTHRITIS INITIATIVE**

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ABSTRACT

Background & Aims: The Mediterranean diet appears to be beneficial for several medical conditions, but data regarding osteoarthritis (OA) are not available. The aim of this study was to investigate if adherence to the Mediterranean diet is associated with a lower prevalence of OA of the knee in a large cohort from North America.

Methods: 4,358 community-dwelling participants (2,527 females; mean age: 61.2 years) from the Osteoarthritis Initiative were included. Adherence to the Mediterranean diet was evaluated through a validated Mediterranean diet score (aMED) categorized into quartiles (Q). Knee OA was diagnosed both clinically and radiologically. The strength of the association between aMED (divided in quartiles) and knee OA was investigated through a logistic regression analysis and reported as odds ratios (OR) with 95% confidence intervals (CIs), adjusted for potential confounders.

Results: Participants with a higher adherence to Mediterranean diet had a significantly lower prevalence of knee OA compared to those with lower adherence (Q4: 25.2% vs. Q1: 33.8%; $p<0.0001$). Using a logistic regression analysis, adjusting for 10 potential confounders with those in the lowest quartile of aMED as reference, participants with the highest aMED had a significant reduction in presence of knee OA (OR, 0.83; 95% CIs: 0.69-0.99, $p=0.04$). Among the individual components of Mediterranean diet, only higher use of cereals was associated with lower odds of having knee OA (OR: 0.76; 95% CI: 0.60-0.98; $p=0.03$).

Conclusions: Higher adherence to a Mediterranean diet is associated with lower prevalence of knee OA. This remained when adjusting for potential confounders.

Keywords : osteoarthritis; Mediterranean diet; aged; healthy ageing; lifestyle.

INTRODUCTION

The term ‘Mediterranean diet’ encompasses the traditional dietary habits of people from across the Mediterranean region and is usually depicted as a food pyramid[1]. The Mediterranean-style diet is an established healthy-eating diet pattern that has consistently demonstrated to have beneficial effects on musculoskeletal[2], cardiovascular[3], metabolic[4], and cognitive[5] diseases.

Recent global surveys of disease surveys have demonstrated that whilst average life expectancy is increasing[6,7], the number of years people that live with chronic conditions is also rising. One of the most common causes of years lived with disability are chronic musculoskeletal disorders [8,9]. Osteoarthritis (OA) of the knee is the 11th highest contributor to global disability[10]. The worldwide prevalence of OA has been estimated as 10% in men and 20% in women over the age of 60 years [11].

To the best of the author’s knowledge, no analyses have investigated the relationship between Mediterranean diet and OA[12]. The Framingham Osteoarthritis Cohort study previously reported that participants with higher vitamin C and E and β -carotene intake may be less likely to have progressive knee OA[13]. However this is only one of the few studies investigating the effect of diet on OA in humans. In mice, the use of olive oil, an essential component of Mediterranean diet, appears to be associated with a lower articular cartilage degradation[14] suggesting a potential role of diets rich in this component for OA.

Given the potential benefits of the Mediterranean diet on several diseases and the absence of data on OA, this study aimed to investigate whether adherence to a Mediterranean diet is associated with lower prevalence of knee OA in a large cohort of North American people from the Osteoarthritis Initiative dataset. We hypothesized that higher adherence to Mediterranean diet was associated with lower prevalence of knee OA.

MATERIALS AND METHODS

Data source and subjects

Data were gathered from the Osteoarthritis Initiative (OAI) database. The OAI is a publically available database open at <http://www.oai.ucsf.edu/>. Within the OAI, potential participants were recruited across four clinical sites in the United States of America (USA) (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006. People were eligible in the OAI who either: (1) had knee OA with knee pain for a 30-day period in the past 12 months or (2) were at high risk of developing knee OA [15]. For the current paper, we used the data recorded during baseline and screening evaluations (November 2008).

All participants provided informed written consent. The OAI study was given full ethical approval by the institutional review board of the OAI Coordinating Center, at University of California in San Francisco.

Adherence to the Mediterranean diet (exposure)

Dietary pattern was analysed using a validated tool, the Block Brief 2000 food frequency (FFQ) questionnaire during the baseline visit [16]. Seventy items were assessed for checking the usual food and beverage consumption over the past year. The frequency of consumption was reported at nine levels of intake from “never” to “every day”. In addition, were seven dietary behavior questions were available regarding food preparation methods and fat intake, one question on fiber intake, and 13 questions on vitamin and mineral intakes.

Adherence to the Mediterranean diet was evaluated using the Mediterranean diet score (aMED) as proposed by Panagiotakos et al.[17]. This score is based on a food frequency questionnaire which was recorded during the baseline OAI visit. The aMED takes into consideration several foods commonly consumed within the Mediterranean diet. Each food has a score from 0 (less adherent)

123 to 5 (better adherence); the total score ranges from 0 to 55, with higher values indicating higher
124 adherence to a Mediterranean diet. Cereals (e.g. bread, pasta, rice), potatoes, fruits, vegetables,
125 legumes (e.g. peas, beans), fish were categorized according to servings/month in: 0=never; 1=1 to 4
126 servings for month; 2=5 to 8; 3=9 to 12; 4=13 to 18; 5= more than 18 servings/month. Since there
127 was no information regarding the consumption of whole cereals vs. refined cereals as this was
128 collected, all types of grains were considered in the present analyses under the same heading. The
129 consumption of red meat, poultry and full fat dairy products (e.g. milk cheese, yogurt) were
130 categorized as: 0=more than 18 servings/month; 1=13 to 17 servings for month; 2=9 to 12; 3=5 to
131 8; 4=1 to 4; 5= never). The use of olive oil was categorised as the times used in a week in: 0=never;
132 1=rare; 2 \leq 1/weekly; 3= 2 times/weekly; 4=3 to 6; 5=daily. Finally, alcoholic beverages were
133 categorised as: 0 \geq 700 ml/day or 0; 1600 to 699 ml/day; 2=500 to 599 ml/day; 3=400 to 499 ml/day;
134 4=300 to 399 ml/day; 5= $<$ 300 ml/day.

135

136 Since there are no agreed cut-offs scores for higher aMED adherence, we divided the population in
137 to quartiles using 25, 28 and 32 points in: aMED $<$ 25, 26-28, 29-32, and $>$ 33.

138

139 ***Outcome***

140 The primary analysis was to determine the presence of knee OA, defined as the combination in the
141 clinical reporting and assessment of pain and stiffness (i.e. pain, aching or stiffness in or around the
142 knee on most days during the last year), and radiographical OA on the baseline fixed flexion
143 radiograph based on the presence of tibiofemoral osteophytes (correspondent to Osteoarthritis
144 Research Society International atlas grades 1-3, clinical center reading). In the OAI, the presence of
145 pain, stiffness, and physical functioning (or disability) due to OA was assessed through the
146 WOMAC (Western Ontario and McMaster Universities Arthritis Index). Briefly, the responses for
147 each subscale (pain, stiffness, disability) are categorized on a five-point Likert scale ranging from

148 none (0 points) to extreme (4 points) [18]. The maximum possible score is 68, and the final score
149 was normalized to 100 (range 0–100), with higher scores reflecting greater activity limitations. [18]

150 *Covariates*

151 We identified 10 potential self-reported confounders that we considered when assessing the
152 relationship between aMED and knee OA. These included body mass index (BMI); physical
153 activity evaluated using the Physical Activity Scale for the Elderly scale (PASE);[19] race; smoking
154 habit, educational attainment level and yearly income ($<$ or \geq \$50,000 and missing data).

155

156 Validated general health measures of self-reported comorbidities were assessed through the
157 modified Charlson comorbidity score[20]. Among the medical morbidities assessed through the
158 Charlson co-morbidity score, we reported descriptively the prevalence of some common diseases in
159 North American people, namely fractures, heart attack and failure, stroke, chronic obstructive
160 pulmonary disease, diabetes and cancer. [21]

161

162 *Statistical analyses*

163 For continuous variables, normal distributed data assumptions were tested using the Kolmogorov-
164 Smirnov test. The data were shown as means \pm standard deviations (SD) for quantitative measures,
165 and frequency and percentages for all discrete variables. For continuous variables, differences
166 between the means of the covariates by aMED quartiles were calculated using an Analysis of
167 Variance (ANOVA); chi-square test was applied for discrete variables. Levene's test was used to
168 test the homoscedasticity of variances and, if its assumption was violated, then Welch's ANOVA
169 was used. Post-hoc analyses and Bonferroni adjustment were applied to compare data.

170

171 Next, in order to consider the relationship between knee OA and aMED scores, a logistic regression
172 was conducted with the presence of knee OA considered as the outcome and the aMED as the
173 exposure and categorized in quartiles and taking in Q1 (=lowest aMED) as the reference group. The

174 basic model was not adjusted for any confounders, whilst the fully adjusted model included the
175 following adjustments: age (as continuous); sex; race (whites vs. others); BMI (as continuous);
176 education (degree vs. others); smoking habits (current and previous vs. others); yearly income
177 (categorized as \geq or $<$ 50,000\$ and missing data); Charlson comorbidity index; PASE score (as
178 continuous), total energy intake (as continuous). Multi-collinearity among covariates was assessed
179 through variance inflation factor (VIF), taking a cut-off of two as reason of exclusion, but no
180 covariate was excluded for this reason. Adjusted odds ratios (OR) and 95% confidence intervals
181 (CI) were finally calculated to estimate the strength of the associations between aMED (categorised
182 as quartiles) and knee OA. Similarly, we performed the same analyses taking individual
183 components of Mediterranean diet as exposure and dividing the adherence in low (score 0-1-2
184 points over 5 available) and high (4-5).

185 The analyses for the paper were undertaken with the SPSS software version 21.0 for Windows
186 (SPSS Inc., Chicago, Illinois). All of the statistical tests were two-tailed and a level of <0.05 was
187 considered as significant. .

RESULTS

Sample selection

The OAI dataset includes a total of 4,796 North American participants. After excluding 109 participants with hip or knee replacement, 175 participants due to missing aMED data and 62 with unreliable caloric intake (<500 or >5000 Kcal/day), 4,358 participants were finally included in the current analyses.

Descriptive characteristics

Among the final sample of 4,358 participants, 1,831 were males and 2,527 females. Mean age was 61.2 years (± 9.1 years; range: 45-79). Mean aMED score was 28.1 points (5.1 points; range: 5-44). The prevalence of OA (diagnosed according to the presence of pain, stiffness and radiographical tibiofemoral osteophytes) in this cohort was 29.1%.

Table 1 illustrates the baseline characteristics by aMED quartiles. Those in the highest quartile (reflecting higher adherence to Mediterranean diet) were older, more likely to be female, white, with higher educational level and income than those within the other quartiles. Those in the highest quartile of aMED had a lower BMI values) and had fewer medical morbidities, even if these participants reported a higher prevalence of cancer (**Table 1**).

Adherence to Mediterranean diet and osteoarthritis

As shown in **Table 2**, there was a significant lower presence of knee OA in those with higher aMED scores compared to other quartiles (Q4: 25.2% vs. Q1: 33.8%; $p < 0.0001$). Using a logistic regression analysis adjusting for 10 potential confounders, and taking those with the lowest adherence to Mediterranean diet as reference (=Q1), participants with the highest adherence to Mediterranean diet had a significantly reduced probability of knee OA (OR=0.83; 95% CI: 0.69-0.99, $p=0.04$; **Table 2**). Other factors significantly associated with knee OA in the multivariate

214 analysis were: BMI (for each increase in one Kg/m²: OR=1.08; 95%CI: 1.06-1.10, p<0.0001), non-
215 white ethnicity (OR=1.60, 95%CI: 1.35-1.90, p<0.0001) and below college level education
216 (OR=1.23; 95%CI: 1.04-1.44; p=0.03), while age was marginally significant (for each year:
217 OR=1.008; 95%CI: 1.00-1.02, p=0.05).

218

219 **Table 3** illustrates the effect of individual components of Mediterranean diet and their association
220 with the presence of knee OA. After adjusting for potential confounders, only higher use of cereals
221 was associated with a significantly reduced probability of knee OA (OR=0.76; 95%CI: 0.60-0.98;
222 p=0.03).

DISCUSSION

In this large cross-sectional study, we found evidence to suggest that North American people who are more adherent to a Mediterranean diet had a significantly lower presence of knee OA. After adjusting for 10 potential confounders, those with the highest aMED score (i.e. more adherent to the Mediterranean diet) had a significant lower prevalence of knee OA by approximately 17%.

Participants with a higher adherence to a Mediterranean diet had significantly lower BMI values and fewer medical morbidities (particularly diabetes), higher education level and greater income than other participants. This suggests that these factors may also influence the prevalence of knee OA in individuals with higher adherence to Mediterranean diet. At the same time, such participants had a significantly higher presence of two important risk factors for knee OA, namely being female and older in age [22]. The apparent paradox of higher prevalence of cancer among those with higher aMED score could be due to a change toward a healthier diet among those diagnosed with cancer.[23] This discrepancy, however, indirectly confirmed a significant and independent association between higher adherence to this dietary pattern and lower prevalence of knee OA. After adjusting for potential confounders (including severity of comorbidity and social and economic factors), the association between aMED and knee OA remained statistically significant. The multivariate analysis suggests that obesity, education and race are associated with prevalent OA, also taking in account other potential confounders. Thus, since our research suggests that Mediterranean diet is associated with a lower risk of knee OA, obese, less educated and non-white people should be monitored in order to encourage them to follow a healthier diet.

Whilst our data is cross sectional and causality cannot be determined, there may be a number of mechanisms that might explain the relationship we observed. Firstly, a higher adherence to a Mediterranean diet is linked to a decrease in inflammation.[24] Inflammation is acknowledged as an important pathway in the development of knee OA.[25] Therefore the anti-inflammatory properties

249 derived from the phytochemicals in a Mediterranean diet may modify this pathway.[14] Secondly,
250 a Mediterranean diet may influence a reduction in oxidative stress markers.[26] These have been
251 purported to influence the onset of OA though providing increasing levels of collagen type II and
252 aggrecan expression whilst inhibiting apoptosis-related proteins expression, providing a
253 chondroprotective effect.[27,28] Finally, Mediterranean diet could play a role in the remodeling of
254 extracellular matrix (ECM)[29] promoting effective repair of the ECM which is frequently
255 defective in those who develop and present with OA. All factors could play an important role in the
256 development of knee OA, and provide a physiological rationale for these findings.[30]

257

258 Previous literature on Mediterranean diet and rheumatic diseases has largely focused on population
259 with rheumatoid arthritis. In this case, several observational[31–34] and interventional[35–37]
260 studies suggest a protective role for some components of Mediterranean diet on rheumatoid arthritis
261 indirectly suggesting a potential role also for OA. However the pathogenesis of this condition is
262 very different to OA, thereby making these finding important. Whilst a subset of people with OA
263 may present with an inflammatory phenotype to their disease process, this is not uniform[38].
264 Accordingly, these results suggest that the protective mechanism which a Mediterranean diet is
265 suggestive to confer may not be solely attributed to the inflammatory pathway[37], but to some
266 other pathophysiological or epigenetic mechanism.

267

268 Previously there had been limited investigating into the impact of Mediterranean diet on knee OA.
269 Animal models have shown that the supplementation of olive oil, an essential component of
270 Mediterranean diet, may preserve the articular cartilage, particularly when prescribed in
271 combination with physical activity[14]. From our analyses, there was no independent association
272 between the use of olive oil and knee OA. Conversely, on assessing the individual components of a
273 Mediterranean diet, only higher use of cereals was associated with lower probability of knee OA.
274 There is limited evidence around the consumption of cereals and the relationship to knee OA.

275 However it could hypothesized that a higher intake of cereals could contribute to a lower prevalence
276 of knee OA through anti-inflammatory and anti-oxidative stress action, but also due to these being
277 good sources of vitamins and minerals (such as magnesium[39,40]) which may play a role in lower
278 prevalence of knee OA. However it should be noted that pasta and rice are often consumed in
279 association with olive oil and vegetables and, as supported in previous studies[1,41], not the single
280 components, but the combination of the different ingredients of the Mediterranean diet is
281 responsible for the protective effect and the health benefit observed with this dietary pattern.

282

283 The analysis suggests a negative association between Mediterranean diet and knee OA, suggesting a
284 possible a protective effect on knee OA. Clinically, these findings indicate that for those at higher
285 risk of developing knee OA, recommendation and promotion of such a diet may be warranted.
286 Further investigation to identify which types of individuals are most to benefit from this
287 recommendation and what the mechanisms and contexts should be in which to implement such
288 dietary advice, should be undertaken.

289

290 The findings of our research should be considered within its limitations. The main is the cross-
291 sectional nature of our research therefore precluding any consideration of a potential causal
292 relationship between Mediterranean diet and knee OA, making residual confounding very likely.
293 Second, we were not able to see the influence of bio-humoral markers (e.g. inflammation) in the
294 association between Mediterranean diet and knee OA, but these markers could be of importance. A
295 third limitation is that the medical conditions are self-reported and this could introduce a bias.
296 Finally, we have used a slight modified version of a previous Mediterranean diet adherence[17] and
297 also this choice could introduce another bias. On the contrary, among the strengths of our work, we
298 could say the large sample size included and the fact this is the first epidemiological study reporting
299 data on the impact of this dietary pattern on a frequent condition, like knee OA.

300

301 To conclude, the results from our paper indicate that a higher adherence to a Mediterranean diet is
302 associated with lower prevalence of knee OA, even after adjusting for several important
303 confounders. Further longitudinal research is required to confirm/ refute our findings and explore
304 potential pathophysiological mechanisms.

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