Mediterranean Diet and Risk of Hyperuricemia in Elderly Participants at High Cardiovascular Risk

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Background. A Mediterranean-type diet could play a role in decreasing serum uric acid concentrations due to its antioxidant and anti-inflammatory properties. The aim of this study was to evaluate whether better adherence to the Mediterranean diet (MeDiet) reduced or prevented the development of hyperuricemia.

Methods. Cross-sectional and prospective analysis in 4,449 elderly participants at high cardiovascular risk from the PREvención con DIeta MEDiterránea trial randomized to two MeDiet interventions (supplemented with either olive oil or nuts) or a control diet. A validated 14-item questionnaire was used to assess adherence to the MeDiet. Hyperuricemia was considered to be present when serum uric acid was higher than 7 mg/dL in men or higher than 6 mg/dL in women.

Results. After a median follow-up of 5 years, 756 individuals of the 3,037 (24.9%) who did not have hyperuricemia at baseline developed hyperuricemia, whereas 422 of the 964 hyperuricemic individuals at baseline (43.8%) reverted this condition. In cross-sectional analyses, an inverse association was observed between increasing levels of adherence to the 14-item MeDiet score and decreasing hyperuricemia (p_trend < .001). Baseline consumption of red meat, fish and seafood, and wine were associated with a higher prevalence of hyperuricemia. Reversion of hyperuricemia was significantly higher (multivariable-adjusted odds ratio = 1.73; 95% confidence interval: 1.04–2.89) in the highest category of baseline adherence to the MeDiet as compared with the lowest. No association was found between baseline adherence to MeDiet and the incidence of hyperuricemia. The three intervention diets had similar effects in the reduction of hyperuricemia.

Conclusions. Higher baseline adherence to the MeDiet is associated with lower risk of hyperuricemia.

Key Words: Hyperuricemia—Serum uric acid—Mediterranean diet—PREDIMED study.

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The overproduction or the underexcretion of uric acid, or often the combination of both, results in hyperuricemia (1). Hyperuricemia, defined as serum uric acid (SUA) concentration higher than 7 mg/dL in men and higher than 6 mg/dL in women, has been strongly associated with metabolic syndrome, hypertension, type 2 diabetes mellitus, and chronic kidney disease (2–5) and also with cardiovascular morbidity and mortality (6). It has been shown that concentrations of SUA increased with age (7,8). Hyperuricemia has also been regarded as the precursor of gout; an inflammatory arthritis triggered by the crystallization of uric acid within the joints, decreasing life quality (9,10).

Some dietary factors can modulate the risk of hyperuricemia and gout through inflammation, oxidative stress, and insulin resistance mechanisms (11). Purine-rich foods, such as meat or seafood, have been associated with higher SUA concentrations and increased risk of incident gout.
However, no associations have been found with total protein intake or purine-rich vegetables (12,13). Some evidence suggests that high intake of alcohol, particularly beer and liquor, and also sweetened beverages is associated with higher SUA levels (13,14). On the contrary, other dietary factors, such as low-fat dairy food, vegetables, or soya food can have a protective effect (15–17). Finally, drinking regular or decaffeinated coffee has been inversely associated with SUA concentrations in women (18).

However, it is not only important to analyze the effect of isolated nutrients and food on disease; in recent years, interest has been growing in evaluating the effect of the overall diet through dietary patterns (19). Although the relationship between some dietary factors and hyperuricemia has been studied, the association between dietary patterns and hyperuricemia remains unknown.

One of the best-known healthy dietary patterns is the traditional Mediterranean diet (MeDiet). MeDiet is characterized by a high consumption of fruits, vegetables, legumes, olive oil, nuts, and whole grain; a moderate consumption of wine, dairy products, and poultry; and a low consumption of red meat, sweet beverages, creams, and pastries. Due to its antioxidant and anti-inflammatory properties (20), the MeDiet might play a role in decreasing SUA concentrations; this is especially interesting because SUA appears to be a significant independent predictor of cardiovascular disease (CVD) in individuals at high cardiovascular risk (6,21). As far as we know, the prospective association between adherence to the MeDiet and hyperuricemia has never been evaluated before.

The aim of the present study was to evaluate the cross-sectional and prospective associations between adherence to the MeDiet and the prevalence, incidence, and reversion of hyperuricemia in elderly participants at high cardiovascular risk participating in a primary prevention randomized trial. Also, to assess which of the specific typical components of the MeDiet were associated with hyperuricemia.

**Materials and Methods**

**Study Population**

The present study was conducted within the framework of the PREvención con DIeta MEDiterránea (PREDIMED) study, a large, parallel-group, multicenter, randomized, controlled trial that aims to assess the effects of the MeDiet on the primary prevention of CVD (www.predimed.org and www.predimed.es). The trial was registered at http://www.controlledtrials.com/ISRCTN35739639. The protocol was approved by the Institutional Review Boards at all the study locations, and all participants provided written informed consent. The PREDIMED study was conducted in Spain. Recruitment took place between October 2003 and January 2009. The 7,447 participants were randomly assigned to one of three interventions (two MeDiets enriched with extra virgin olive oil [EVOO] or mixed nuts, or a control low-fat diet). The design and methods used in the PREDIMED study have been described elsewhere (22). In the present study, the main focus was to analyze the association between baseline dietary exposure and hyperuricemia incidence or reversion as an observational cohort of all included participants in the PREDIMED study, regardless of their allocation to the intervention groups. We also assessed the effects of the three intervention groups on these parameters.

In the analysis, 4,449 participants were included, whose concentrations of uric acid at baseline were available (of these, 1,551 were assigned to the MeDiet + EVOO group, 1,407 to the MeDiet + nut group, and 1,491 to the control low-fat diet group). For longitudinal analysis, 4,001 participants were included, whose uric acid concentrations during the follow-up were available. No significant differences were found for the main baseline variables (age, sex, body mass index [BMI], smoking status, and the prevalence of diabetes and hypertension) between PREDIMED participants included in the present analysis and those not included because they did not undergo uric acid determination. Participants were men aged 55–80 years and women aged 60–80 years, who were free of CVD at baseline but who had either type 2 diabetes mellitus or fulfilled at least three or more coronary heart disease risk factors: current smoking, hypertension (blood pressure >140/90 mmHg or treatment with antihypertensive medication), high plasma low-density lipoprotein cholesterol (≥160 mg/dL or lipid-lowering therapy), low plasma high-density lipoprotein cholesterol (≤40 mg/dL in men and ≤50 mg/dL in women), overweight or obesity (BMI ≥ 25 kg/m²), and family history of premature CVD (≤55 years in men and ≤60 years in women). The exclusion criteria were the presence of any severe chronic illness, alcohol or drug abuse, BMI greater than or equal to 40 kg/m², and allergy or intolerance to olive oil or nuts.

**Dietary Assessment**

At baseline and yearly, during the follow-up, trained dieticians completed a validated 137-item semiquantitative food frequency questionnaire in a face-to-face interview with the participant (23). Energy and nutrient intake were estimated using Spanish food composition tables (24,25).

The baseline examination included the administration of a 14-item MeDiet adherence screener, designed to assess the degree of adherence to the traditional MeDiet (26). Participants whose consumption of the “beneficial” foods (olive oil, vegetables, legumes, fruit, nuts, fish and seafood, white meat instead of red meat, sofrito [tomato, onion, spices, garlic, and simmered with olive oil], and red wine) was below a prespecified value were assigned a value of 0 and those above were assigned a value of 1. Participants whose consumption of “detrimental” foods (red meat,
fat-rich dairy products, commercial pastries and snacks, artificially sweetened beverages) was above a prespecified value were assigned a value of 0 and a value of 1 if the values were below the prespecified cutoff point.

Measurements
At baseline, we administered a questionnaire about education, lifestyle variables, history of illnesses, and medication use. Physical activity was assessed using the validated Spanish version of Minnesota Leisure-Time Physical Activity (27). Anthropometric measurements and blood pressure were taken and samples of fasting blood obtained. At baseline and yearly, trained personnel made the following measurements: weight and height (with light clothing and no shoes, calibrated scales and a wall-mounted stadiometer, respectively); waist circumference (midway between the lowest rib and the iliac crest using an anthropometric tape); and blood pressure measured in triplicate (the mean of these values was recorded).

Samples of fasting serum, plasma, and urine were coded, shipped to central laboratories, and stored at −80°C until analysis. Laboratory technicians were blinded to the interventions. Serum glucose, cholesterol, triglyceride, and uric acid concentrations were measured using standard enzymatic automated methods. High-density lipoprotein cholesterol was measured by enzymatic procedure after precipitation. All examinations were repeated yearly during the follow-up. Hyperuricemia was defined as concentrations of SUA higher than 7 mg/dL in men and higher than 6 mg/dL in women (28). For individuals who did not meet this criteria at baseline, incident hyperuricemia was considered to be present when concentrations of SUA were higher than 7 mg/dL in men or higher than 6 mg/dL in women during the follow-up visits. The proportion of participants who had hyperuricemia at baseline and whose status reverted at the end of the follow-up was also calculated.

Statistical Analysis
Analysis of variance and chi-square tests were used to compare means of quantitative variables and qualitative traits, respectively, across quintiles of the baseline 14-item questionnaire of the adherence to the MeDiet (≤7, 8, 9, 10, ≥11 points).

Logistic regression models were fitted to calculate the prevalence odds ratio (OR) of hyperuricemia according to the quintiles of adherence to the MeDiet at baseline. After the unadjusted model, the first model adjusted for age (continuous, adding a quadratic term), BMI (continuous, adding a quadratic term), and recruitment center was created. The second was additionally adjusted for current smokers (yes/no), former smokers (yes/no), physical activity (continuous), and educational level. And the third (fully adjusted model) was also adjusted for blood pressure (continuous), total energy intake (continuous), caffeine intake (continuous), antihypertensive agents (yes/no), oral hypoglycemic agents (yes/no), allopurinol use (yes/no), and prevalence of diabetes (yes/no). Linear trends were assessed using the median value of each quintile of the adherence to MeDiet as a continuous variable in the different models. Multiple logistic regression models were fitted to evaluate the prevalence of hyperuricemia according to the fulfillment of each item in the 14-item questionnaire. We fitted an unadjusted model and another model adjusted for age (continuous, adding a quadratic term), BMI (continuous, adding a quadratic term), recruitment center (categories), current smokers (yes/no), former smokers (yes/no), physical activity (continuous), educational level (categories), blood pressure (continuous), total energy intake (continuous), caffeine intake (continuous), antihypertensive agents (yes/no), oral hypoglycemic agents (yes/no), allopurinol use (yes/no), prevalence of diabetes (yes/no), and all the other food items.

The OR of the incidence and reversion of hyperuricemia among quintiles of the baseline 14-item questionnaire was assessed by logistic regression analysis. The adjusting variables considered were the same as those used to analyze the prevalence of hyperuricemia, but also adjusted for intervention group and weight changes. Between-group differences in the incidence and reversion of hyperuricemia were also tested by logistic regression models. Moreover, we have analyzed the effect of the intervention on the prevalence, incidence, and reversion of hyperuricemia using the same models as in the previous analyses, considering the low-fat control group as the reference category.

The level of significance for all statistical tests was p < 0.05 for bilateral contrasts. Analyses were performed using SPSS statistical software version 19 (SPSS Inc., Chicago, IL).

Results
Table 1 shows the baseline characteristics of the 4,449 individuals according to their adherence to the MeDiet. Participants in the upper quintiles of baseline adherence to MeDiet had lower weight, BMI, and waist circumference. Adherence to the MeDiet was directly associated with physical activity, total energy intake, consumption of fish and seafood, total protein, vegetable intake, and total alcohol consumption. In contrast, it was inversely associated with total meat intake. The prevalence of diabetes was lower among participants with higher baseline adherence to the MeDiet. This association was also found for hyperuricemia, although no significant differences were apparent between quintiles.

Multiple logistic regression models (Table 2) showed an inverse association between baseline adherence to the MeDiet and the prevalence of hyperuricemia (p_trend < 01). After adjustment for potential confounders (fully adjusted model), the OR of having hyperuricemia for individuals in
Table 1. Baseline Characteristics of the Study Participants by Quintiles of Adherence to the Mediterranean Diet

<table>
<thead>
<tr>
<th>n</th>
<th>≤7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>≥11</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67 (6); 67 (62–72)</td>
<td>67 (6); 67 (62–72)</td>
<td>67 (6); 68 (63–72)</td>
<td>66 (6); 66 (62–71)</td>
<td>67 (6); 67 (62–72)</td>
<td>.03</td>
</tr>
<tr>
<td>Men, % (n)</td>
<td>41.9 (486)</td>
<td>42.4 (345)</td>
<td>43.9 (365)</td>
<td>43.3 (363)</td>
<td>47 (378)</td>
<td>.23</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>77.4 (11.7); 76.6</td>
<td>77.4 (11.9); 77.2</td>
<td>76.9 (12.3); 76.1</td>
<td>75.8 (11.5); 75.0</td>
<td>76.8 (11.6); 76.0</td>
<td>.03</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.3 (36); 30.1</td>
<td>30.2 (37); 30.1 (27.4–32.6)</td>
<td>29.3 (37); 29.6</td>
<td>29.6 (38); 29.3 (27.1–31.7)</td>
<td>29.7 (3.6); 29.2 (27.1–31.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>101.1 (97); 101.0</td>
<td>100.7 (98); 101.0</td>
<td>99.5 (10.1); 99.0</td>
<td>98.7 (10.6); 90.0</td>
<td>98.7 (10.3); 99.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>149.3 (20.2); 147.5</td>
<td>149.5 (20.5); 149.0</td>
<td>150.2 (20.4); 149.0</td>
<td>150.7 (20.7); 148.5</td>
<td>148.4 (19.9); 147.5</td>
<td>.19</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>83.0 (10.7); 82.0</td>
<td>83.3 (10.7); 82.5</td>
<td>83.4 (10.6); 83.0</td>
<td>83.6 (10.7); 83.0</td>
<td>82.9 (11.0); 83.0</td>
<td>.65</td>
</tr>
<tr>
<td>Physical activity (METS-h/d)</td>
<td>3.7 (3.9)</td>
<td>3.7 (3.7)</td>
<td>4.1 (4.0)</td>
<td>4.5 (4.7)</td>
<td>4.5 (4.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Current smokers, % (n)</td>
<td>16.4 (190)</td>
<td>15.4 (125)</td>
<td>13.7 (114)</td>
<td>14.4 (121)</td>
<td>12.9 (104)</td>
<td>.23</td>
</tr>
<tr>
<td>Former smokers, % (n)</td>
<td>23.7 (275)</td>
<td>21.9 (178)</td>
<td>26.6 (221)</td>
<td>26.3 (221)</td>
<td>27.1 (218)</td>
<td>.06</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary education or less, % (n)</td>
<td>76 (870)</td>
<td>78 (633)</td>
<td>75 (623)</td>
<td>74 (622)</td>
<td>73 (584)</td>
<td>.36</td>
</tr>
<tr>
<td>Secondary education, % (n)</td>
<td>16 (184)</td>
<td>15 (119)</td>
<td>17 (138)</td>
<td>17 (146)</td>
<td>16 (131)</td>
<td></td>
</tr>
<tr>
<td>Higher education, % (n)</td>
<td>9 (99)</td>
<td>7 (57)</td>
<td>8 (67)</td>
<td>8 (69)</td>
<td>10 (82)</td>
<td></td>
</tr>
<tr>
<td>Total energy intake, kcal/d</td>
<td>2,276 (634); 2,194</td>
<td>2,273 (586); 2,224</td>
<td>2,359 (91); 2,276</td>
<td>2,377 (578); 2,305</td>
<td>2,405 (590); 2,405</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total protein, g/d</td>
<td>90.1 (22.7); 88.6</td>
<td>91.6 (22.0); 90.8</td>
<td>94.2 (22.7); 91.7</td>
<td>95.3 (22.7); 92.9</td>
<td>98.9 (23.4); 95.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total fish and seafood, g/d</td>
<td>86.5 (51.3); 80.1</td>
<td>98.4 (492); 93.0</td>
<td>1057 (46.6); 103.5</td>
<td>112.3 (49.7); 107.3</td>
<td>126.8 (58.5); 121.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total meat, g/d</td>
<td>132.5 (60.7); 127.2</td>
<td>131.0 (55.3); 128.2</td>
<td>131.4 (59.0); 125.7</td>
<td>129.8 (59.5); 122.8</td>
<td>123.0 (54.4); 116.1</td>
<td>.007</td>
</tr>
<tr>
<td>Total dairy products, g/d</td>
<td>396.8 (235.1); 335.7</td>
<td>402.0 (223.8); 344.5</td>
<td>402.5 (229.8); 346.4</td>
<td>403.9 (236.7); 346.4</td>
<td>404.6 (228.1); 341.4</td>
<td>.95</td>
</tr>
<tr>
<td>Total vegetables, g/d</td>
<td>286.8 (132.7); 270.5</td>
<td>315.5 (130.7); 295.4</td>
<td>331.0 (150.0); 311.9</td>
<td>358.5 (162.2); 333.6</td>
<td>386.6 (164.5); 359.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Alcohol intake, g/d</td>
<td>7.7 (14.7); 7.0 (9.0)</td>
<td>8.9 (16.0); 1.5 (10.0–14.4)</td>
<td>9.9 (16.1); 2.1 (0.0–11.8)</td>
<td>10.2 (16.1); 2.1 (0.0–11.8)</td>
<td>11.3 (15.1); 5.1 (0.0–15.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Serum uric acid, mg/dL</td>
<td>5.7 (1.5); 5.6 (4.6–6.6)</td>
<td>5.7 (1.5); 5.6 (4.7–6.6)</td>
<td>5.7 (1.5); 5.6 (4.7–6.5)</td>
<td>5.6 (1.5); 5.5 (4.6–6.5)</td>
<td>5.6 (1.5); 5.4 (6.6–7.5)</td>
<td>.35</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>124.0 (44.4); 110.0</td>
<td>122.4 (43.3); 109.0</td>
<td>1216 (40.1); 108.5</td>
<td>119.9 (39.8); 107.0</td>
<td>119.4 (39.9); 106.0</td>
<td>.11</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>142.8 (75.7); 126.0</td>
<td>140.2 (92.7); 120.0</td>
<td>137.3 (73.7); 121.0</td>
<td>136.8 (75.4); 119.0</td>
<td>127.3 (63.5); 113.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>211.1 (38.3); 209.8</td>
<td>210.9 (37.4); 209.0</td>
<td>212.2 (38.3); 211.0</td>
<td>214.8 (38.0); 212.0</td>
<td>213.0 (37.9); 211.0</td>
<td>.18</td>
</tr>
<tr>
<td>Hyperuricemia, % (n)</td>
<td>26.5 (307)</td>
<td>24.7 (201)</td>
<td>24.3 (202)</td>
<td>24.4 (205)</td>
<td>21.0 (169)</td>
<td>.09</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>49.6 (575)</td>
<td>49.1 (400)</td>
<td>49.7 (413)</td>
<td>43.9 (368)</td>
<td>43.5 (330)</td>
<td>.007</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>83.4 (967)</td>
<td>82.6 (672)</td>
<td>83.3 (692)</td>
<td>81.4 (683)</td>
<td>81.4 (655)</td>
<td>.59</td>
</tr>
<tr>
<td>Use of antihypertensive agents, % (n)</td>
<td>74.6 (865)</td>
<td>77.1 (627)</td>
<td>75.6 (628)</td>
<td>72.1 (601)</td>
<td>74.1 (596)</td>
<td>.19</td>
</tr>
<tr>
<td>Use of oral hypoglycemic agents, % (n)</td>
<td>33.3 (386)</td>
<td>32.6 (265)</td>
<td>33.3 (277)</td>
<td>27.8 (232)</td>
<td>27.4 (223)</td>
<td>.005</td>
</tr>
<tr>
<td>Use of allopurinol medication, % (n)</td>
<td>1.5 (17)</td>
<td>2.2 (18)</td>
<td>1.0 (8)</td>
<td>1.1 (9)</td>
<td>1.7 (14)</td>
<td>.21</td>
</tr>
</tbody>
</table>

Notes: Data are expressed as means (SD) and medians (P25–P75) or percentage (n). p Value for comparisons across quintiles of adherence to the Mediterranean diet (Pearson chi-square test for categorical variables or one-way analysis of variance for continuous variable). METS = metabolic equivalents.
the upper quintile was 0.77 (95% confidence interval [CI]: 0.62–0.97). These results were similar in Models 1 and 2.

Table 3 shows the ORs for the prevalence of hyperuricemia according to the fulfillment of each item in the questionnaire of adherence to the Mediterranean diet. In the unadjusted model, the odds of having hyperuricemia was 23% lower in the individuals who consumed little red or processed meat. The results also showed a positive association between high consumption of fish or seafood and the risk of hyperuricemia (OR: 1.20; 95% CI: 1.04–1.38). Conversely, the consumption of greater than or equal to 3 servings a week of legumes was associated with lower odds of having hyperuricemia (OR: 0.74; 95% CI: 0.63–0.87).

The use of sofrito sauce also showed an inverse association with hyperuricemia (OR: 0.74; 95% CI: 0.63–0.87). When it was adjusted for additional potential confounders, these associations remained significant. Besides, wine intake (≥7 glasses/wk) was associated with an increased risk of hyperuricemia in the fully adjusted model (OR: 1.21; 95% CI: 1.02–1.43).

After a median follow-up of 5 years, 756 individuals (24.9%) of the total 3,037 who did not have hyperuricemia at baseline developed new-onset hyperuricemia. Of the 964 participants who had hyperuricemia at baseline, a reversion in 422 (43.8%) by the end of follow-up was observed. A total of 74 participants (49%) who were classified in the highest quintile of adherence to Mediterranean diet (McDiet) reverted hyperuricemia (Table 4). A similar effect of the three intervention diets on hyperuricemia was found with 26.0%, 25.4%, and 23.2% participants developing hyperuricemia in the EVOO, nuts, or control group. The respective percentages of hyperuricemia reversion were 40.1%, 47.9%, and 44.3%. Therefore, the prevalence of hyperuricemia was similarly reduced in the three groups. No significant effect
of the intervention (vs control) on the prevalence of hyperuricemia was observed (OR = 1.00 [95% CI: 0.85–1.19] for the MeDiet + EVOO and 0.89 [95% CI: 0.74–1.06] for the MeDiet + nuts group). The ORs for the incidence of hyperuricemia were 0.97 (95% CI: 0.79–1.29) for the MeDiet + EVOO and 0.85 (95% CI: 0.69–1.06) for the MeDiet + nuts group. For the reversion, the OR was 0.81 (95% CI: 0.59–1.12) in the MeDiet + EVOO and 1.13 (95% CI: 0.81–1.58) in the MeDiet + nuts.

No associations were found between the incidence of hyperuricemia and the baseline adherence to MeDiet. Logistic regression analyses confirmed that a greater MeDiet adherence at baseline was associated with hyperuricemia reversion among individuals who had hyperuricemia at baseline (Table 4). At the highest quintile, the crude ORs for hyperuricemia reversion was 1.68 times higher than at the lowest quintile (95% CI: 1.03–2.74). Similar results were found in Models 1 and 2. After adjusting for potential confounders, the OR for the highest quintile was 1.73 (95% CI: 1.04–2.89) in Model 3. The test for linear trend across successive quintiles of adherence to the MeDiet was significant for the fully adjusted model.

Because the consumption of dairy foods and vitamin C has also been associated with lower uric acid levels in previous studies, we conducted an additional analysis adjusting the different fully adjusted models for these covariates. The OR of having hyperuricemia for individuals in the upper category of adherence to MeDiet was 0.80 (95% CI: 0.64–1.00). The association between MeDiet adherence and the incidence of hyperuricemia remained nonsignificant after adjusting for dairy products and vitamin C. Finally, the OR of hyperuricemia reversion in the highest category of adherence was 1.71 (95% CI: 1.02–2.86; data not shown).

**Discussion**

In this large prospective cohort study involving elderly participants at high cardiovascular risk, an inverse association between adherence to the MeDiet and the prevalence of hyperuricemia was observed. Moreover, rates of reversion were higher among hyperuricemic participants at baseline who had greater adherence to the MeDiet. These associations were independent of other purported risk factors for hyperuricemia, such as age, BMI, smoking, physical activity, hypertension, and diabetes. Conversely, in the present study, no significant association was found between the MeDiet and incident hyperuricemia.

A validated 14-item questionnaire evaluating adherence to the MeDiet was used to analyze which specific component of the MeDiet was related to hyperuricemia. These findings suggest that the consumption of less than 1 serving a day of red meat compared with higher intake is associated with 23% reduced risk of hyperuricemia. The reason for this may be the high saturated fatty acid content of red meat, which has been associated with inflammation and insulin resistance (29). Another interesting aspect of the findings is the positive association between

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**Table 4. Incidence and Reversion of Hyperuricemia During Follow-up Across Quintiles of Adherence to Mediterranean Diet at Baseline**

<table>
<thead>
<tr>
<th>n</th>
<th>Incidence, n (%)</th>
<th>Person-years, n</th>
<th>Unadjusted model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>n</th>
<th>Reversion, n (%)</th>
<th>Person-years, n</th>
<th>Unadjusted model</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>775</td>
<td>184 (23.7)</td>
<td>2,984</td>
<td>1</td>
<td>1.02 (0.79–1.32)</td>
<td>1.18 (0.92–1.51)</td>
<td>1.01 (0.78–1.30)</td>
<td>1.14 (0.89–1.46)</td>
<td>.36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>552</td>
<td>133 (24.1)</td>
<td>2,130</td>
<td>1</td>
<td>0.99 (0.77–1.29)</td>
<td>1.18 (0.92–1.52)</td>
<td>1.02 (0.78–1.32)</td>
<td>1.10 (0.85–1.42)</td>
<td>.44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>569</td>
<td>153 (26.9)</td>
<td>2,241</td>
<td>1</td>
<td>1.00 (0.77–1.29)</td>
<td>1.17 (0.91–1.51)</td>
<td>1.01 (0.78–1.31)</td>
<td>1.11 (0.86–1.44)</td>
<td>.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>564</td>
<td>135 (23.9)</td>
<td>2,270</td>
<td>1</td>
<td>0.99 (0.76–1.29)</td>
<td>1.14 (0.88–1.48)</td>
<td>0.95 (0.72–1.24)</td>
<td>1.07 (0.82–1.39)</td>
<td>.74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>577</td>
<td>151 (26.2)</td>
<td>2,304</td>
<td>1</td>
<td>0.97 (0.79–1.19)</td>
<td>1.10 (0.85–1.42)</td>
<td>1.03 (0.78–1.32)</td>
<td>1.06 (0.80–1.40)</td>
<td>.90</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Notes:** Multiple logistic regressions were used to assess the association between adherence to the Mediterranean diet (quintiles) at baseline and the incidence of hyperuricemia among participants who did not have hyperuricemia at baseline (top) and reversion of hyperuricemia among participants who had hyperuricemia at baseline (bottom). Multiple logistic regressions with polynomial contrast were used to generate p for trend. Data are expressed as odds ratio (95% confidence interval). Hyperuricemia was defined as uric acid level >7 mg/dL for men or >6 mg/dL for women. Model 1: adjusted for intervention group, age (continuous, adding a quadratic term), body mass index (continuous, adding a quadratic term), and recruitment center; Model 2: additionally adjusted for current smokers (yes/no), former smokers (yes/no), physical activity (continuous), and educational level; Model 3: additionally adjusted for blood pressure (continuous), total energy intake (continuous), caffeine intake (continuous), antihypertensive agents (yes/no), oral hypoglycemic agents (yes/no), allopurinol use (yes/no), prevalence of diabetes (yes/no), and weight changes.
the amount of fish and seafood consumed and the prevalence of hyperuricemia, which is probably due to its high purine content (15). These results are in agreement with a previous study, which has reported that a higher intake of meat and seafood is associated with higher SUA concentrations, in a representative sample of U.S. adults (12), and the higher intake of meat and seafood is also related to a future risk of gout in men (15). In contrast, in a cross-sectional study conducted in the framework of the Shanghai Men’s Health Study, no association was shown between meat consumption and hyperuricemia (30).

The results suggest that the intake of greater than or equal to 7 glasses/wk of wine is directly associated with a higher prevalence of hyperuricemia. Although it is recognized that moderate alcohol consumption is associated with reduced risk of CVD, and polyphenols in wine have beneficial endothelial and anti-inflammatory properties (31), it is not surprising that the present data suggest that alcohol consumption might increase the risk of hyperuricemia, as it decreases urate excretion and increases urate production (32). The findings are consistent with a recent prospective study showing a direct relationship between alcohol consumption and the risk of hyperuricemia (33). In contrast, drinking beer and spirits was associated with an increased risk of gout incidence, whereas a moderate intake of wine was not (34).

An inverse association between the consumption of legumes and sofrito sauce and the prevalence of hyperuricemia was found. Legumes are an excellent source of protein, fiber, vitamins, and minerals. Legume consumption was associated with such health benefits as improving lipid profile, glucose metabolism, and inflammation (35). Sofrito is a traditional component of the MeDiet. It is made with tomato, onion, spices, garlic, and simmered with olive oil, and its high content in antioxidants makes it anti-inflammatory, thus reducing oxidative damage (20).

Even though this study is unique in prospectively evaluating the adherence to the MeDiet and hyperuricemia, a previous cross-sectional study examined the impact of the MeDiet on SUA levels. Adherence to the MeDiet was found to be associated with lower SUA levels in elderly individuals free of known CVD. However, the study was conducted in relatively few individuals and because of its cross-sectional design, causal relationships cannot be assumed (36).

The present findings provide evidence of the benefits of healthy dietary patterns on the reversion of hyperuricemia. What is more, reversion was achieved by the MeDiet alone, without weight loss or physical activity counseling. The role that the MeDiet plays in decreasing the risk of hyperuricemia could be explained by the effect of MeDiet on improving insulin resistance (20) related to the reduction of renal excretion of urate (29). Hyperuricemia has been associated with higher concentrations of several inflammatory markers (37). Because the MeDiet has antioxidant and anti-inflammatory properties, it may play an important role decreasing SUA levels. High concentration of SUA may contribute to high morbidity and mortality through direct injury to the endothelium and to alteration of cardiovascular function (21). Nevertheless, some of the evidence regarding the effects of uric acid is controversial. SUA is a major antioxidant in human plasma; but under ischemic conditions, its antioxidant activity is overcome by the prooxidant and proinflammatory effects of reactive oxygen species accumulation (38). Although SUA concentration is a very weak predictor of CVD in populations at low risk of CVD, it is a significant independent predictor among participants at high risk, such as the population studied in the present study (6).

In the PREDIMED trial, the hyperuricemia reversion rate was almost double that of the incidence rate, which shows that the condition improved during the follow-up for the three intervention groups. There are two reasons explaining the similar effect of the three diets on the reduction of hyperuricemia. First, baseline adherence to the MeDiet (probably a proxy of lifetime exposure) may have a greater effect on risk of hyperuricemia than the implementation of a nutritional intervention during only for 5 years. Second, the control diet, which is low in fat, could have similar beneficial effects on hyperuricemia than the MeDiet.

Several strengths and potential limitations of the study deserve comment. First, this study is the first to have assessed the adherence to the MeDiet and its effect on hyperuricemia. Moreover, the sample was sufficiently large to provide adequate power to detect important associations. However, the main limitation of the findings is that the analyses were conducted in a sample of Spanish elderly participants at high cardiovascular risk, so they cannot be generalized to the general population and to other racial and ethnic groups. Another major drawback is the possibility of reverse causation bias, as high risk patients might be more likely to change their food habits as a consequence of these conditions being diagnosed. Finally, we cannot rule out the possibility that unmeasured factors might contribute to the associations observed.

In summary, the findings provide prospective evidence that a greater baseline adherence to the MeDiet is associated with a lower risk of hyperuricemia in elderly Mediterranean participants at high cardiovascular risk. Further prospective and clinical trials may be useful to confirm these findings in other populations and to extend these to determine the possible effects of the MeDiet on gout.

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CONFLICT OF INTEREST

None of the authors have any potential conflicts of interest relevant to this article.

REFERENCES