Adherence to a Mediterranean-type diet and reduced prevalence of clustered cardiovascular risk factors in a cohort of 3204 high-risk subjects

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Running head: Mediterranean diet & cardiovascular risk

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ABSTRACT

Background: the Mediterranean food pattern (MeDiet) has been suggested to have beneficial effects on cardiovascular risk factors. However there is scarcity of assessment of this effect on large samples of subjects at high risk. Our objective was to estimate the association between adherence to MeDiet and the prevalence of risk factors in 3204 asymptomatic high-risk patients.

Design: cross-sectional assessment of baseline characteristics of participants in a primary prevention trial (PREDIMED).

Methods: Participants were assessed by their usual primary care physicians to ascertain the prevalence of diet-related cardiovascular risk factors (diabetes, hypertension, dyslipidemia or obesity) using standard diagnostic criteria. A dietitian interviewed each participant to obtain a 14-point score measuring the degree of adherence to MeDiet.

Results: Adherence to MeDiet was inversely associated with individual risk factors and, above all, with the clustering of them. The multivariate adjusted odds ratio (OR) to present simultaneously the four risk factors for those above the median value of the MeDiet score was 0.67 (95% confidence interval: 0.53-0.85). The multivariate ORs for successive categories of adherence to MeDiet were 1 (ref.), 1.03, 0.85, 0.70 and 0.54 (p for trend < 0.001).

Conclusions: Following a Mediterranean-type dietary pattern was inversely associated with the clustering of hypertension, diabetes, obesity, and hypercholesterolemia among high-risk patients.

Key words: Mediterranean food pattern; diabetes; hypertension; obesity; dyslipidemia
INTRODUCTION

The major causal risk factors for cardiovascular disease (CVD) are well known and include smoking, an atherogenic lipid profile, hypertension, obesity, and diabetes [1]. It has become apparent that more than one risk factor is often present in the same individual. The clustering of risk factors most frequently observed together includes obesity, type 2 diabetes, hyperlipidaemia, and hypertension [2-5]. The prevalence of each combination of these entities is higher than what would be expected by chance [6] and they are included as criteria for different definitions of the metabolic syndrome [7-8]. The dramatic rise in the prevalence of these 4 entities threatens to reverse the reductions in CVD risk observed in most Western countries. Therefore, effective preventive approaches are needed to combat these cardiovascular risk factors.

A Mediterranean-type dietary pattern (MeDiet) has attracted considerable interest because of its potential advantages in the prevention of CVD. The American Heart Association gave attention to the MeDiet as potentially useful for the prevention of CVD, but a cautious recommendation was issued emphasizing that more studies were needed before advising people to follow a MeDiet [9]. Specially, studies assessing this association conducted on large samples of high-risk individuals are needed. We assessed the association between adherence to a MeDiet and the prevalence of hypertension, dyslipidemia, diabetes and obesity or their clustering in a large sample of high-risk asymptomatic individuals.
METHODS

The present study represents a cross-sectional assessment of baseline characteristics of the first participants consecutively recruited for the PREDIMED (Prevention with MeDiet) trial, a parallel-group, randomized, single-blinded clinical trial (www.predimed.org). The protocol has been described elsewhere [10-11].

Participants and recruitment

All participants are recruited in primary care centers in eight Spanish cities. Eligible participants are community-dwelling men, 55 to 80 years of age, and women, 60 to 80 years of age, who meet at least 3 or more CVD risk factors [10].

Exclusion criteria were previous history of CVD, any severe chronic illness, drug or alcohol addiction, and history of allergy or intolerance to olive oil or nuts.

Measurements and outcomes

Trained personnel made the following measurements: weight and height with calibrated scales and a wall-mounted stadiometer, respectively; blood pressure in triplicate with a validated semi-automatic oscillometer (Omron HEM-705CP, The Netherlands). Each subject underwent testing for diabetes, hypertension, and hypercholesterolemia. Standardized criteria for the diagnosis of diabetes were used [12]. A patient was considered to be hypertensive if the average of the two last measurements of blood pressure was ≥140 mmHg for systolic or ≥90 mmHg for diastolic blood pressure, and was classified in the obesity category when his/her BMI was ≥30 kg/m².

Hypercholesterolemia was defined as total cholesterol ≥240 mg/dL (≥6.20 mmol/L) [5].
**Dietary assessment**

A trained dietitian administered a 14-item questionnaire [10] (available at www.unav.es/preventiva/pagina_11.html) specifically designed to assess adherence to the traditional MeDiet. We assigned values of 0 or 1 to each item, so a score of 14 points meant the maximum adherence to MeDiet. The dietitian also administered a 137-item validated food frequency questionnaire (FFQ) [13].

**Statistical analyses**

Descriptive statistics (means and standard deviation (SDs) or percentages) were compared for characteristics of the participants across levels of MeDiet adherence. We dichotomized the score of MeDiet adherence using the median and used this dichotomous variable as the exposure in logistic regression models. We fitted several logistic models using each of the 4 metabolic disorders as the outcome (hypertension, diabetes, hypercholesterolemia and obesity). Because, by design, most participants exhibited one or more of these risk factors, we did logistic analyses using as the outcome a binary variable representing the simultaneous presence of all risk factors as the outcome. To assess linear trends we categorized the 14-point score in categories roughly approaching quintiles and introduced the median value of each category as a continuous variable in the fully adjusted models. Ten-year risk of fatal coronary disease was calculated using the SCORE model [14] across these five categories of adherence to the Mediterranean diet. Sex- and age-adjusted mean risks for each category were computed using analysis of covariance (ANCOVA).

All P values presented are 2-tailed; P< 0.05 was considered statistically significant.
RESULTS

Table 1 describes the characteristics of participants according to their adherence to the MeDiet. We observed a very high prevalence of the four risk factors (and their combinations) in the 3204 participants assessed, being 79.8 % of them hypertensive, 49.9 % diabetic, 45.4 % obese and 67.9 % hypercholesterolemic. More than 85 % of the sample showed at least two of the four risk factors and 10% presented all of them.

We found a higher adherence to the MeDiet inversely and significantly associated with the prevalence of each of the four conditions with the exception of hypercholesterolemia (table 2). These inverse associations tended to be stronger among women than among men, but no significant differences were observed when we formally tested them by means of an interaction product-term (P>0.30 for all tests).

An even stronger inverse association between MeDiet adherence and risk factors was found when we considered as the outcome the coexistence of at least two of them together (adjusted OR = 0.69 [95% CI: 0.56-0.86], P<0.001). A similar, highly significant, inverse association was found when the outcome was presenting together the clustering of all the four risk factors (adjusted OR = 0.67 [95% CI: 0.53-0.85], P<0.001). This highly significant inverse association persisted in all analyses either when we included all the sample, or analysed men and women separately. In every analysis, the estimates for the ORs were monotonically decreasing across successive categories of adherence to MeDiet (figure 1).

Tests for linear trend across successive quintiles of adherence to the MeDiet were significant only for diabetes and obesity, but inverse associations were especially intense when the simultaneous clustering of the four risk factors was used as the outcome. There was no significant association when we assessed the global risk of
coronary mortality estimated with the SCORE equation across categories of adherence to the MeDiet [14]. The sex- and age-adjusted mean risk (%) was 7.4%, 7.1%, 7.5%, 7.5% and 7.3% (p=0.92) respectively for participants with <8, 8, 9, 10 or ≥11 points in the adherence to the MeDiet.
DISCUSSION

Our results, showing an inverse association between adherence to MeDiet and cardiovascular risk, are consistent with previous findings designed with different goals as compared to our study [15-17]. Some observational studies have found inverse associations between adherence to a MeDiet and a lower risk of obesity [18-21], diabetes [22, 23], or hypertension [24, 25]. Nevertheless, there is no complete consistency, because some studies have reported no association between adherence to MeDiet and BMI [26] or hypertension [27]. On the other hand, in a subsample of the PREDIMED trial (n = 772) we reported that the overall profile of cardiovascular risk factors was improved after three months of intervention in participants assigned to a MeDiet [10]. Now, consistently with our previous report, we have observed an inverse cross-sectional association in a larger sample which supports the hypothesis that promoting adherence to a traditional MeDiet may be able to reduce the clustering of metabolic risk factors. However, we did not observe any statistically significant association between adherence to the MeDiet and the coronary mortality risk estimated with the SCORE equation. This could be explained because SCORE risk estimates are based on current absolute levels of risk factors (total cholesterol, blood pressure and current smoking), and these risk factors were under medical treatment in our participants or might have changed because of previous behavioural counselling to quit smoking.

Some potential limitations of our study are related to the cross-sectional design and its inherent limitations. The major drawback of this design is the possibility of reverse causation bias. However, the potential impact of this bias would lead to expect a positive association between adherence to a MeDiet and the prevalence of metabolic
disorders because high-risk patients with metabolic disorders maybe more likely to change their food habits as a consequence of the diagnosis of these conditions. This would be very likely because in our setting the prevailing dietary change promoted by physicians within the standard of care for individuals with several risk factors is to recommend a Mediterranean-type diet. Therefore, the negative association we have found would not be expected as a consequence of this bias. In any case, a potential reverse causation bias would tend to conceal a true protective effect of the MeDiet. It could be also argued that among individuals who are at high risk of CVD the prevalence of metabolic disorders is higher than in general population. In this context, the main problem would be a lower between-subjects variability than what would be expected in a general population sample. However, the fact that we have been able to demonstrate an inverse association in this high-risk population, further supports the existence of a true association between a higher adherence to MeDiet and a lower prevalence of metabolic conditions. On the other hand, more attention should be given to subjects prone to develop cardiovascular events in order to reduce their cardiovascular risk burden. In this sense, nutritional strategies to promote the MeDiet should be specially applied to high-risk subjects who exhibit a clustering of risk factors as a first step to reduce unacceptable high absolute rates of cardiovascular morbidity and mortality both in Western and developing countries.

A very interesting finding of our study was that the inverse association between MeDiet and metabolic disorders became stronger when we assessed the coexistence of some of them. This result may suggest that a higher adherence to a MeDiet may hinder the development of detrimental common mechanisms involved in the genesis of these disorders. In summary, our findings, assessed in a large sample of high-risk subjects,
suggest that a MeDiet may be an excellent model for the prevention of the CVD and related metabolic disorders. However, further prospective studies and trials are needed to confirm our findings.
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   Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation,
   and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

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APPENDIX


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Table 1. Characteristics of participants according to baseline adherence to the Mediterranean-diet 14-point score

<table>
<thead>
<tr>
<th></th>
<th>Adherence to Mediterranean Diet</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Low adherence &amp; High adherence</td>
<td>≤8</td>
<td>≥9</td>
</tr>
<tr>
<td>Score (range 0 to 14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>1349</td>
<td>1855</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>67.0 (6.1)</td>
<td>67.3 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>57.8</td>
<td>56.7</td>
<td></td>
</tr>
<tr>
<td>Low physical activity (%)</td>
<td>35.2</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>15.7</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>Married (%)</td>
<td>75.2</td>
<td>77.6</td>
<td></td>
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<tr>
<td>Lower educational level (%)</td>
<td>71.8</td>
<td>71.3</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.0 (4.2)</td>
<td>29.7 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Total energy intake (KJ)</td>
<td>9634 (2844)</td>
<td>10148 (2825)</td>
<td></td>
</tr>
<tr>
<td>Carbohydrate (%E)*</td>
<td>42.2 (7.1)</td>
<td>40.8 (7.0)</td>
<td></td>
</tr>
<tr>
<td>Protein (%E)*</td>
<td>16.7 (3.0)</td>
<td>16.5 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Fat (%E)*</td>
<td>38.7 (6.7)</td>
<td>39.8 (6.7)</td>
<td></td>
</tr>
<tr>
<td>SFA (%E)*</td>
<td>10.4 (2.2)</td>
<td>9.8 (2.2)</td>
<td></td>
</tr>
<tr>
<td>MUFA (%E)*</td>
<td>18.9 (4.4)</td>
<td>20.0 (4.4)</td>
<td></td>
</tr>
<tr>
<td>PUFA (%E)*</td>
<td>6.0 (2.1)</td>
<td>6.4 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Fibre intake (g/d)</td>
<td>23.9 (8.2)</td>
<td>27.2 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (g/d)</td>
<td>7.7 (14.1)</td>
<td>10.2 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Olive oil (g/d)</td>
<td>35.4 (17.7)</td>
<td>44.7 (18.7)</td>
<td></td>
</tr>
<tr>
<td>Nuts (g/d)</td>
<td>7.7 (11.5)</td>
<td>12.9 (15.9)</td>
<td></td>
</tr>
</tbody>
</table>

*% of total energy intake

1BMI, body mass index

2SFA, saturated fatty acids

3MUFA, monounsaturated fatty acids

4PUFA, polyunsaturated fatty acids
Table 2. Association between a higher adherence to the Mediterranean diet (higher adherence = score greater than the median, ≥9) and cardiovascular risk factors (or their combinations). Odds Ratios (95% CIs)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Both (n = 3204)</th>
<th>Men* (n = 1372)</th>
<th>Women* (n = 1832)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.81 (0.68-0.98)</td>
<td>0.91 (0.71-1.17)</td>
<td>0.72 (0.55-0.94)</td>
</tr>
<tr>
<td>Multivariate-adjusted*</td>
<td>0.82 (0.68-0.98)</td>
<td>0.91 (0.71-1.17)</td>
<td>0.74 (0.56-0.96)</td>
</tr>
<tr>
<td>P value for linear trend***</td>
<td>0.36</td>
<td>0.83</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.86 (0.74-0.99)</td>
<td>0.89 (0.71-1.10)</td>
<td>0.84 (0.69-1.01)</td>
</tr>
<tr>
<td>Multivariate-adjusted*</td>
<td>0.85 (0.74-0.98)</td>
<td>0.88 (0.70-1.10)</td>
<td>0.84 (0.69-1.01)</td>
</tr>
<tr>
<td>P value for linear trend***</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.81 (0.71-0.94)</td>
<td>0.90 (0.72-1.12)</td>
<td>0.76 (0.63-0.91)</td>
</tr>
<tr>
<td>Multivariate-adjusted**</td>
<td>0.84 (0.73-0.97)</td>
<td>0.94 (0.75-1.18)</td>
<td>0.79 (0.65-0.96)</td>
</tr>
<tr>
<td>P value for linear trend***</td>
<td>0.008</td>
<td>0.92</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>All four risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.66 (0.52-0.83)</td>
<td>0.61 (0.41-0.90)</td>
<td>0.70 (0.52-0.93)</td>
</tr>
<tr>
<td>Multivariate-adjusted**</td>
<td>0.67 (0.53-0.85)</td>
<td>0.62 (0.41-0.93)</td>
<td>0.73 (0.55-0.97)</td>
</tr>
<tr>
<td>P value for linear trend***</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*No significant interaction was found between adherence to MedDiet & sex (P>0.30 for all models)

*Additionally adjusted for leisure-time physical activity (tertiles), smoking (5 categories), marital status (4 categories), educational level (4 categories), and BMI (3 categories).

**Adjusted for all the mentioned variables except for BMI.

*** The median for each quintile of adherence to the Mediterranean diet was modelled as a continuous variable in the fully adjusted model.
Figure 1. Association between adherence to the Mediterranean diet and the prevalence of all four disorders (diabetes, hypertension, obesity and hypercholesterolemia). Odds Ratios (95% CIs), adjusted for sex, age, leisure-time physical activity (tertiles), smoking (5 categories), marital status (4 categories), and educational level (4 categories).