Mediterranean dietary patterns and prospective weight change in participants of the EPIC-PANACEA project


ABSTRACT

Background: There is an association between a greater adherence to a Mediterranean diet and a reduced risk of developing chronic diseases. However, it is not clear whether this dietary pattern may be protective also against the development of obesity.

Objective: We assessed the association between the adherence to the Mediterranean dietary pattern (MDP), prospective weight change, and the incidence of overweight or obesity.

Design: We conducted a prospective cohort study [the European Prospective Investigation into Cancer and Nutrition–Physical Activity, Nutrition, Alcohol Consumption, Cessation of Smoking, Eating Out of Home, and Obesity (EPIC-PANACEA) project] in 373,803 individuals (103,455 men and 270,348 women; age range: 25–70 y) from 10 European countries. Anthropometric measurements were obtained at recruitment and after a median follow-up time of 5 y. The relative Mediterranean Diet Score (rMED; score range: 0–18) was used to assess adherence to the MDP according to the consumption of 9 dietary components that are characteristic of the Mediterranean diet. The association between the rMED and 5-y weight change was modeled through multiadjusted mixed-effects linear regression.

Results: Individuals with a high adherence to the MDP according to the rMED (11–18 points) showed a 5-y weight change of \(-0.16\, \text{kg}\) (95% CI: \(-0.24, -0.07\, \text{kg}\)) and were 10% (95% CI: 4%, 18%) less likely to develop overweight or obesity than were individuals with a low adherence to the MDP (0–6 points). The low meat content of the Mediterranean diet seemed to account for most of its positive effect against weight gain.

Conclusion: This study shows that promoting the MDP as a model of healthy eating may help to prevent weight gain and the development of obesity. Am J Clin Nutr 2010;92:912–21.

INTRODUCTION

Almost all countries are experiencing an obesity epidemic, which is accompanied by the increase of other comorbid conditions such as type 2 diabetes, hypertension, metabolic syndrome, cardiovascular diseases, and cancer as well as an increase in mortality rates (1). To stop or revert this trend, there is need for a much better understanding of the causation of obesity (2). The rapid rise in the prevalence of obesity worldwide suggests that environmental changes (mainly changes in diet and physical activity) associated with urbanization, globalization, and economic development are the major determinants in the development of obesity; however, the evidence from epidemiologic studies that links diet and physical activity to obesity is inconsistent, probably because of methodologic difficulties in accurately assessing habitual diets and physical activity, residual confounding, and/or reverse causality (1, 3–5).

The Mediterranean diet is the dietary pattern observed in the olive-growing areas of the Mediterranean region during the early 1960s, and it is characterized by the following: a high consumption of olive oil, legumes, unrefined cereals, fruit, and vegetables; a moderate consumption of dairy products, mostly as
cheese and yogurt; moderate wine consumption; a moderate-to-
high consumption of fish; and a low consumption of meat and
meat products (6, 7). The Mediterranean dietary pattern (MDP)
was proposed as a healthy dietary pattern on the basis of evidence
that emanated from the Seven Countries study (8). Many studies
since then have evaluated the adherence of subjects to the MDP
and have linked it to a reduction in overall mortality (6, 7, 9, 10),
the incidence or mortality from cardiovascular diseases (11–13),
the incidence or mortality from cancer (14, 15), the incidence
of type 2 diabetes (16), hypertension (17), and metabolic syndrome
(18, 19). Despite the fact that most of these chronic conditions are
also associated with obesity, the link between the MDP and
obesity is not clear. Several physiologic mechanisms have been
proposed to try to explain how key components of the MDP might
protect against weight gain (20, 21). However, others authors
have speculated the contrary (ie, that the Mediterranean diet may
promote excess energy intake and weight gain because of its high
fat content [from olive oil]). This hypothesis is supported by the
high prevalence of overweight and obesity observed in Medi-
terranean countries (22). A recent systematic review concluded
that the epidemiologic evidence regarding the relation between
the MDP and overweight/obesity was inconsistent, and given the
limitations in previous studies and the difficulties when assessing
the relation between diet and obesity, both intervention and
cohort studies were deemed necessary (23).

The objective of the current study was to assess the association
between the MDP and 1) prospective weight change and 2) the
likelihood of becoming overweight or obese in normal-weight
individuals in a large cohort of adult European individuals
participating in the European Prospective Investigation into
Cancer and Nutrition–Physical Activity, Nutrition, Alcohol
Consumption, Cessation of Smoking, Eating Out of Home, and
Obesity (EPIC-PANACEA) project.

SUBJECTS AND METHODS
Study population

The EPIC is a multicenter, prospective cohort study inves-
tigating the role of metabolic, dietary, lifestyle, and envi-
ronmental factors in the development of cancer and other chronic
diseases. Between 1992 and 2000, 521,448 apparently healthy
volunteers aged between 25 and 70 y were recruited in 23 centers
from 10 European countries (Denmark, France, Germany,
Greece, Italy, Netherlands, Norway, Spain, Sweden, and United
Kingdom). In France, Norway, Utrecht (Netherlands), and Naples
(Italy), only women were included. The selection of the study
population in each center was largely influenced by practical
considerations, and therefore, the sample is not intended to be
representative of each region. Approval for this study was
obtained from the ethical review boards of the International
Agency for Research on Cancer and from all local institutions
where participants had been recruited for the EPIC study. Details
of the recruitment and study design have been published else-
where (24–26). Updated information on lifestyle and anthropo-
metric data has been obtained from EPIC participants through
follow-up questionnaires (see supplemental material under
“Supplemental data” in the online issue for more information on
follow-up data collection in the EPIC study).

After excluding individuals with missing information on di-
etary or lifestyle variables, unavailable information on weight or
height, extreme values on anthropometric data, pregnancy and
individuals with an extreme ratio between energy intake and
energy requirement, 497,735 individuals were available for the
PANACEA analyses at baseline. For 121,866 subjects, follow-up
information on weight was not obtained for different reasons (see
supplemental material under “Supplemental data” in the online
issue), and hence, they were excluded from this study. In addi-
tion, participants with unrealistic weight changes were excluded.
Thus, 373,803 subjects (103,455 men and 270,348 women) were
Anthropometric assessment

Body weights and heights of subjects were measured at baseline in most centers with participants wearing no shoes. Body weight was corrected to reduce heterogeneity because of protocol differences in clothing worn during measurement by subtracting 1.5 kg in those individuals who were normally dressed and 1 kg in those participants who wore light clothing (27). For participants from France and Norway, only self-reported anthropometric values were obtained. For a health-conscious group based in Oxford, United Kingdom (a heterogeneous group of ovo-lacto vegetarians, pure vegans, fish but not meat eaters, and meat eaters), sex- and age-specific anthropometric values were predicted by using linear regression models from participants with both measured and self-reported body measures (referred to as Oxford correction equations in the remainder of the article) (28). Body mass index (BMI) at baseline was calculated as weight in kilograms divided by square height in meters, and individuals were classified as underweight [BMI (in kg/m²) < 18.5], normal weight (BMI of 18.5 to < 25), overweight (BMI of 25 to < 30), or obese (BMI ≥ 30). Because of the low number of underweight people (n = 5327; 1.4% of the sample), the categories of underweight and normal weight were combined into a single category. Anthropometric values at follow-up were self-reported by the participants in the follow-up questionnaire in all centers, except for participants in the centers of Cambridge (United Kingdom), and Doetinchem (Netherlands), in whom anthropometric measurements were taken by using the same protocol as baseline examinations.

Because the follow-up times were different according to centers [from 2 y in Heidelberg (Germany) to 11 y in Varese (Italy); median follow-up time: 5 y], and there was evidence of a linear association between weight gain and follow-up times in this population, the main outcome of the current study was the 5-y weight change (in kg), which is the difference between weight at follow-up and weight at baseline divided by time of follow-up (in years) and multiplied by 5.

We also applied the Oxford correction equations (28) to all people with self-reported weight (both at baseline and follow-up) to predict their likely measured weight and to calculate the corrected weight change in 5 y.

Dietary assessment and Mediterranean Diet Score

Usual food intakes were measured with country-specific validated dietary questionnaires (24, 26, 29, 30). Individual nutrient intakes (including energy, alcohol, and 25 nutrients) were derived from foods included in the dietary questionnaires through the standardized EPIC nutrient database (31). To correct for any systematic under- or overestimation of dietary intake between the study centers, a dietary calibration study was conducted. A random sample of 36,308 men and women (7.4% of the sample) completed a detailed computerized 24-h dietary recall, and nutrient intake was calculated by using the standardized EPIC nutrient database (30). Dietary exposures across centers were scaled by using an additive calibration (29). Briefly, the differences between the sex- and center-specific means of the values from the food-frequency questionnaire and the means of the 24-h recall values were calculated and added to the questionnaire values.

Adherence to the MDP was assessed by using the relative Mediterranean Diet Score (rMED) (32), which is a variation of the original Mediterranean Diet Score (6, 7). This score included 9 nutritional components that are characteristic of the MDP and included some presumably beneficial components (vegetables, legumes, fruit and nuts, cereals, fish and seafood, olive oil, and moderate alcohol consumption) and other presumably detrimental components (meat and meat products and dairy products). Each rMED component (apart from alcohol) was measured in grams per 1000 kcal (to express intake as energy density) (33). All components of the score (except for olive oil and alcohol) were divided into tertiles of dietary intake. A value of 0, 1, and 2 was assigned to the first, second, and third tertiles, respectively, of the intake of vegetables, legumes, fruit and nuts, cereals, and fish and seafood and positively scoring higher intakes for the beneficial components. The scoring was reversed for the 2 presumably detrimental components (meat and meat products and dairy products) by positively scoring lower intakes. The scoring for olive oil was modified because of the relatively large number of nonconsumers. Therefore, 0 was assigned to nonconsumers; 1 was assigned to subjects with an intake below the median olive oil consumption (calculated only within olive oil consumers), and 2 was assigned to subjects whose intake was equal to or above this median. For alcohol, a value of 2 was assigned to men with moderate alcohol consumption (intakes from 10 to < 50 g/d), and a value of 0 was assigned otherwise, whereas for women, the corresponding cutoffs were 5 and 25 g/d. Therefore, the rMED ranged from 0 (which indicated the lowest adherence to the MDP) to 18 (which indicated the highest adherence to the MDP). Finally, the rMED was further classified into categories to reflect low (0–6 points), medium (7–10 points), or high (11–18 points) adherence to the MDP.

Two other scoring systems to assess adherence to the MDP were also created: the modified Mediterranean Diet Score (mMDS), as described elsewhere (10, 12, 34), and a modified version of the rMED. The only difference from the rMED and its modified version was that the olive-oil component was replaced by vegetable oil intake (including olive, soya, sunflower, peanut, corn, grape, rapeseed, safflower, walnut, and other oils). The intake of vegetable oils was also adjusted for energy (g/1000 kcal) and divided into tertiles (a score of 0, 1, and 2 was assigned to the first, second, and third tertiles of intake, respectively). However, given the good consistency between the 3 MDP scores (Cronbach’s α reliability coefficient: 0.95), and the similarity in their associations with weight change, only the results of the rMED are shown in the current study.

Assessment of other covariates

Standard questionnaires were used to collect information on the participants’ sociodemographic characteristics and lifestyle variables (24). These variables were controlled for in the current study because they may be related both to dietary habits and weight gain. Information about the smoking status (never smoker, former smoker, and current smoker), educational level (according to the maximum achieved school level, whether primary school, technical school, secondary school, or university degree), physical
activity according to a validated physical activity index (classified into 4 categories: inactive, moderately inactive, moderately active, and active) derived from the cross-tabulation of physical activity at work (categorized as no or sedentary job, standing job, manual job, or heavy manual job) and the nonworking activities of cycling and sport (categorized as no leisure physical activity and \( \leq 0.5, >0.5 \text{ to} \leq 1, \text{or} >1 \text{ h/d} \)) (35), and menopausal status in women (premenopausal, perimenopausal, and postmenopausal) was used in the current study. There were participants with missing values for physical activity (\( n = 43,275; 11.6\% \) of the sample) and educational level (\( n = 4942; 1.3\% \) of the sample). We treated participants with missing data as a separate category for these 2 variables.

### Statistical analyses

The mean (±SD) 5-y weight change, both uncorrected and corrected by using the Oxford correction equations (28), and mean (±SD) rMED by selected covariates were presented as descriptive statistics. Differences in means among groups were compared by using one-factor analysis of variance. The association between adherence to the MDP and weight change was modeled by using multilevel mixed-effect linear regression with random effects on both intercept and slope (rMED), taking into account the clustering of the data within countries (level 3) and within centers (level 2; individuals are the first level in the analyses). The outcome variables were both the corrected (by using the Oxford correction equations) and uncorrected 5-y weight change (in kg). However, given that results were very similar, only the results obtained with the uncorrected weight change are presented. The explanatory variable in the current study was the rMED expressed both continuously (per 2-point increase) and per category increase (low, medium, and high adherence to the MDP). A calibrated version of the rMED was also constructed by using calibrated values of 8 dietary components of the MDP (except for alcohol), and the associations between the calibrated score and 5-y weight change were also assessed. We fitted multivariate-adjusted models that were controlled for the following potential confounders (as fixed effects): sex, age (in y, continuous), baseline BMI (continuous), follow-up time (in y, continuous), educational level (categorical), physical activity level (categorical), smoking status (categorical), menopausal status in women (categorical), total energy intake (in kcal, continuous), and misreporting of energy intake. Misreporting of energy intake was estimated by using the ratio of reported energy intake to the predicted basal metabolic rate (EI: BMR). Subjects were classified as underreporters (EI:BMR <1.14), plausible reporters (EI:BMR = 1.14–2.1), or overreporters (EI:BMR >2.1) of energy intake by using cutoff points proposed by Goldberg (36).

Sensitivity analyses were performed by excluding participants with any chronic disease (ie, heart disease, stroke, diabetes mellitus, and/or cancer) at baseline and excluding misreporters of energy (under- or overreporters of energy intake according to the Goldberg classification) (36). Also, plausible effect modifications by sex, age group (<40, 40 to <60, and \( \geq 60 \) y of age), European region (southern Europe, central Europe, and northern Europe), and baseline BMI category (BMI <25, 25 to <30, and \( \geq 30 \)) were explored by modeling interaction terms between these variables and the rMED and conducting stratified analyses.

We also evaluated the relative importance of each of the components of the rMED on weight change by subtracting alternately one component at a time from the original score. This meant that the score range was reduced to 0–16. To preserve comparability, we included these scores as continuous variables in the model and calculated the effect on weight change associated with a 1.8-point increase in the rMED (37).

To assess whether there was heterogeneity among countries in the association between the rMED and 5-y weight change, country-specific estimates were calculated (by using general linear models in countries with one center only or multilevel mixed-effect linear regression models in countries with more than

### TABLE 1

<table>
<thead>
<tr>
<th>Uncorrected 5-y weight change</th>
<th>Corrected 5-y weight change</th>
<th>rMED (0–18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>kg</td>
<td>kg</td>
<td>kg</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.35 ± 5.09</td>
<td>2.27 ± 5.03</td>
</tr>
<tr>
<td>Women</td>
<td>1.10 ± 4.99</td>
<td>2.08 ± 4.93</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 y</td>
<td>1.66 ± 5.15</td>
<td>3.01 ± 5.10</td>
</tr>
<tr>
<td>40 to &lt;60 y</td>
<td>1.01 ± 5.02</td>
<td>2.20 ± 4.94</td>
</tr>
<tr>
<td>( \geq 60 ) y</td>
<td>0.11 ± 4.91</td>
<td>1.47 ± 4.87</td>
</tr>
<tr>
<td>BMI category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m²</td>
<td>1.60 ± 4.16</td>
<td>2.55 ± 4.21</td>
</tr>
<tr>
<td>25 to &lt;30 kg/m²</td>
<td>0.55 ± 5.24</td>
<td>2.04 ± 5.16</td>
</tr>
<tr>
<td>( \geq 30 ) kg/m²</td>
<td>-1.10 ± 6.78</td>
<td>0.68 ± 6.66</td>
</tr>
<tr>
<td>European region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern Europe</td>
<td>-0.03 ± 5.10</td>
<td>1.65 ± 5.06</td>
</tr>
<tr>
<td>Central Europe</td>
<td>1.33 ± 5.32</td>
<td>2.42 ± 5.25</td>
</tr>
<tr>
<td>Northern Europe</td>
<td>0.87 ± 4.30</td>
<td>2.01 ± 4.25</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0.48 ± 5.15</td>
<td>1.94 ± 5.07</td>
</tr>
<tr>
<td>Primary school</td>
<td>0.80 ± 4.97</td>
<td>2.20 ± 4.89</td>
</tr>
<tr>
<td>Technical school</td>
<td>1.65 ± 4.76</td>
<td>2.35 ± 4.77</td>
</tr>
<tr>
<td>Secondary school</td>
<td>1.02 ± 4.82</td>
<td>2.21 ± 4.76</td>
</tr>
<tr>
<td>University degree</td>
<td>0.82 ± 4.79</td>
<td>2.11 ± 4.79</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td>0.44 ± 5.46</td>
<td>1.76 ± 5.39</td>
</tr>
<tr>
<td>Moderately inactive</td>
<td>0.78 ± 5.08</td>
<td>2.08 ± 5.01</td>
</tr>
<tr>
<td>Moderately active</td>
<td>0.95 ± 5.02</td>
<td>2.25 ± 4.95</td>
</tr>
<tr>
<td>Active</td>
<td>0.69 ± 5.02</td>
<td>2.27 ± 4.94</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>0.69 ± 4.87</td>
<td>2.03 ± 4.78</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.03 ± 5.08</td>
<td>2.05 ± 5.01</td>
</tr>
<tr>
<td>Former</td>
<td>1.99 ± 5.33</td>
<td>2.46 ± 5.23</td>
</tr>
</tbody>
</table>

1 All values are means ± SDs. Differences in means among groups were significant, \( P < 0.0001 \) (one-factor ANOVA).
2 Self-reported weight at either baseline or follow-up (for individuals with no measured weight available) was used to calculate weight change.
3 Oxford correction equations (28) were applied to individuals with self-reported weight at either baseline or follow-up to predict their likely measured weight and to calculate weight change.
4 Countries by region are as follows: southern Europe (Greece, Italy, and Spain), central Europe (France, United Kingdom, Germany, and Netherlands), and northern Europe (Denmark, Sweden, and Norway).
and random-effect meta-analyses ($I^2$) was used to pool these estimates. Because of differences in assessment of follow-up weight and/or different follow-up times, the centers in Germany (Heidelberg and Potsdam), United Kingdom (Cambridge, Oxford general population, and Oxford health conscious population), Netherlands (Utrecht, Doetinchem, and Amsterdam/Maastricht), and Sweden (Malmo and Umea) were treated as separate cohorts.

TABLE 2
Association between adherence to the Mediterranean diet according to the relative Mediterranean Diet Score (rMED) and (uncorrected) 5-y weight change (in kg) in EPIC-PANACEA (European Prospective Investigation into Cancer and Nutrition–Physical Activity, Nutrition, Alcohol Consumption, Cessation of Smoking, Eating Out of Home, and Obesity) participants ($n = 373,803$)

<table>
<thead>
<tr>
<th>rMED (0–18)</th>
<th>Observed dietary data</th>
<th>Calibrated dietary data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ (95% CI)$^1$</td>
<td>$P$</td>
</tr>
<tr>
<td>Per 2-point increase$^2$</td>
<td>$-0.05 (-0.07, -0.03)$</td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>Per category increase$^3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (0–6)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Medium (7–10)</td>
<td>$-0.04 (-0.10, 0.02)$</td>
<td>0.158</td>
</tr>
<tr>
<td>High (11–18)</td>
<td>$-0.16 (-0.24, -0.07)$</td>
<td>$&lt;0.0001$</td>
</tr>
</tbody>
</table>

$^1$ Obtained from multilevel mixed-effects linear regression models adjusted for sex, age, baseline BMI, follow-up time, educational level, physical activity level, smoking status, menopausal status in women, total energy intake, and misreporting of energy intake.

$^2$ rMED included as a continuous variable in the model.

$^3$ rMED included in categories in the model.

$^4$ Countries by region are as follows: southern Europe (Greece, Italy, and Spain), central Europe (France, United Kingdom, Germany, and Netherlands), and northern Europe (Denmark, Sweden, and Norway).

TABLE 3
Association between adherence to the Mediterranean diet according to the relative Mediterranean Diet Score (rMED) and (uncorrected) 5-y weight change (in kg) in specific population subgroups

<table>
<thead>
<tr>
<th>rMED (0–18)$^2$</th>
<th>$\beta$ (95% CI)$^2$</th>
<th>$P$</th>
<th>$P$ for heterogeneity$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.823</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>$-0.06 (-0.09, -0.02)$</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>$-0.05 (-0.08, -0.02)$</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>Baseline age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 y</td>
<td>$-0.08 (-0.13, -0.02)$</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>40 to &lt;60 y</td>
<td>$-0.05 (-0.08, -0.03)$</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>$\geq 60$ y</td>
<td>$-0.04 (-0.07, -0.01)$</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Baseline BMI category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m$^2$</td>
<td>$-0.05 (-0.07, -0.02)$</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>25 to &lt;30 kg/m$^2$</td>
<td>$-0.05 (-0.09, -0.02)$</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>$\geq 30$ kg/m$^2$</td>
<td>$-0.03 (-0.10, 0.04)$</td>
<td>0.450</td>
<td></td>
</tr>
<tr>
<td>European region$^4$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern Europe</td>
<td>$-0.11 (-0.14, -0.07)$</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>Central Europe</td>
<td>$-0.04 (-0.07, 0.00)$</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Northern Europe</td>
<td>$-0.03 (-0.06, 0.01)$</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>European region and baseline BMI category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Southern Europe</td>
<td></td>
<td></td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>&lt;25 kg/m$^2$</td>
<td>$-0.04 (-0.10, 0.01)$</td>
<td>0.118</td>
<td></td>
</tr>
<tr>
<td>25 to &lt;30 kg/m$^2$</td>
<td>$-0.10 (-0.15, -0.06)$</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>$\geq 30$ kg/m$^2$</td>
<td>$-0.16 (-0.24, -0.09)$</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>Central Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m$^2$</td>
<td>$-0.05 (-0.10, -0.01)$</td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>25 to &lt;30 kg/m$^2$</td>
<td>$-0.06 (-0.12, 0.01)$</td>
<td>0.090</td>
<td></td>
</tr>
<tr>
<td>$\geq 30$ kg/m$^2$</td>
<td>$0.05 (-0.08, 0.18)$</td>
<td>0.438</td>
<td></td>
</tr>
<tr>
<td>Northern Europe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25 kg/m$^2$</td>
<td>$-0.04 (-0.07, -0.01)$</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>25 to &lt;30 kg/m$^2$</td>
<td>$-0.03 (-0.07, 0.02)$</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>$\geq 30$ kg/m$^2$</td>
<td>$0.05 (-0.06, 0.17)$</td>
<td>0.366</td>
<td></td>
</tr>
</tbody>
</table>

$^1$ Included in the model as a continuous variable (2-point increase).

$^2$ Obtained from multilevel mixed-effects linear regression models adjusted for sex (except when analyses were stratified by sex), age, baseline BMI, follow-up time, educational level, physical activity level, smoking status, menopausal status in women, total energy intake, and misreporting of energy intake.

$^3$ Tested by adding an interaction term in the model between the variables and rMED.

$^4$ Countries by region are as follows: southern Europe (Greece, Italy, and Spain), central Europe (France, United Kingdom, Germany, and Netherlands), and northern Europe (Denmark, Sweden, and Norway).
Random-effect meta-analyses were used to obtain a summary of follow-up weight measures, as previously explained, and country (or center, for centers with differences in assessments) were run in each

Multivariate-adjusted logistic regression models (by using the

Table 1

Association between adherence to the Mediterranean diet according to the relative Mediterranean Diet Score (rMED) and (uncorrected) 5-y weight change (in kg) after subtracting one dietary component at a time from the score

| rMED minus & | \( \beta \) (95% CI) \( P \) |
|----------------|----------------|-----------------|
| fruit and nuts | \(-0.05 \ (-0.08, -0.03) \) | \(<0.0001\) |
| vegetables     | \(-0.06 (-0.09, -0.04)\)   | \(<0.0001\) |
| legumes        | \(-0.05 (-0.07, -0.03)\)   | \(<0.0001\) |
| cereals        | \(-0.04 (-0.06, -0.02)\)   | \(<0.0001\) |
| fish and sea fish | \(-0.06 (-0.09, -0.04)\)   | \(<0.0001\) |
| meat and meat products | \(-0.01 (-0.03, 0.02)\)   | 0.509 |
| dairy products | \(-0.04 (-0.07, -0.02)\)   | 0.001 |
| olive oil      | \(-0.05 (-0.06, -0.03)\)   | \(<0.0001\) |
| alcoholic      | \(-0.04 (-0.07, -0.02)\)   | \(<0.0001\) |

\(^{1}\) Range of rMED score was 0–16 after subtracting each component at a time. The scores were included as continuous variables in the model, and the effect on weight change was calculated per 1.8-point increase in scores.

\(^{2}\) Obtained from multilevel mixed-effects linear regression models adjusted for sex, age, baseline BMI, follow-up time, educational level, physical activity level, smoking status, menopausal status in women, total energy intake, and misreporting of energy intake.

Secondary analyses were carried out to study the association between adherence to the MDP and the likelihood of becoming overweight or obese (BMI ≥25) after 5 y of follow-up. For this association, only individuals that had a BMI <25 at baseline were considered (n = 197,522; 52.8% of the sample). Their BMI after 5 y was calculated taking into account the 5-y weight change and their baseline height. A total of 15.8% of those who had a BMI <25 at baseline were overweight or obese after 5 y. Multivariate-adjusted logistic regression models (by using the same set of covariates as previously described) were run in each country (or center, for centers with differences in assessments of follow-up weight measures, as previously explained), and random-effect meta-analyses were used to obtain a summary estimate [pooled odds ratio (OR)].

\( P <0.05 \) was regarded as statistically significant. All statistical analyses were performed with the STATA statistical package 10.0 (STATA, College Station, TX).

RESULTS

The uncorrected mean (±SD) 5-y weight gain was 0.89 ± 5.03 kg in the current population. When self-reported weight was corrected by using the Oxford correction equations, it was observed that, on average, individuals gained 2.13 ± 4.96 kg in 5 y. On average, younger people (aged <40 y), individuals with baseline BMI <25, participants from central European countries, individuals with a technical school educational level, moderately physically active and physically active people, and former smokers tended to gain more weight than did other population subgroups. Adherence to the MDP according to the rMED was greater in younger individuals, individuals from southern European countries, people with BMI ≥30, participants with a university degree, individuals with an inactive lifestyle, and never smokers (Table 1).

The multiaadjusted 5-y weight changes (uncorrected) associated with the increase in the rMED constructed by using uncalibrated (observed) and calibrated dietary data are shown in

Table 2. A greater adherence to the MDP was significantly associated with a lower prospective weight gain. Hence, a 2-point increase in the rMED predicted −0.05 kg (95% CI: −0.07, −0.02 kg) less weight gain in 5 y. When categories of the rMED were compared, it was observed that those with a high adherence to the MDP (rMED of 11–18 points) showed −0.16 kg (95% CI: −0.24, −0.07 kg) less weight gain in 5 y than did people with a low adherence to MDP (rMED of 0–6 points). When calibrated data were used to construct the rMED, the association between the rMED and 5-y weight change remained significant, but it was slightly attenuated.

A similar association between adherence to the MDP and prospective weight change was observed in men and women (P for interaction = 0.823). The protective effect of MDP against weight gain was stronger in younger people (<40 y of age), and in nonobese (BMI <30) individuals at baseline (P for interactions <0.0001). Despite no evidence for heterogeneity in European regions (P for interaction = 0.203), a 2-point increase in the rMED predicted a lower weight gain in participants from southern European countries, compared with central and northern countries. It should be noted that a significant interaction between BMI categories, European region, and rMED was observed (3-way interaction term; \( P \) for interaction <0.0001). Hence, in individuals with a normal weight at baseline, the effect of the rMED on weight change was very similar independent of their European region of origin. However, divergent effects of rMED on weight change were observed in obese individuals from different European regions; although the effect of rMED on weight change seemed to be stronger in obese individuals in southern Europe, in central and northern Europe, rMED was unrelated to weight changes in the obese (Table 3).

The association between the rMED and weight gain did not change after excluding individuals with chronic diseases at baseline (ie, heart disease, stroke, diabetes mellitus, and cancer) (\( \beta = -0.06; 95\% \text{ CI} = -0.08, -0.04 \)) and misreporters of energy intake (both under- and overreporters of energy according to the Goldberg method) (\( \beta = -0.04; 95\% \text{ CI} = -0.06, -0.02 \)) from the total sample (results not shown in tables). The contribution of each component of the rMED on weight change was assessed by subtracting one component at a time from the score (Table 4). Overall, the effect of the rMED on 5-y weight changes was similar after excluding each of its components with the exception of meat and meat products; when the meat and meat-product component was not taken into account in the construction of the score, the association between rMED and weight change was no longer significant.

Heterogeneity in the association between the rMED and weight change in countries was explored by using the meta-analyses approach (\( I^2 \)) (Figure 1). A significant degree of heterogeneity across countries was observed (\( I^2 = 74.3\% \); \( P \) for heterogeneity <0.0001). In most countries, there was an inverse association between the adherence to the MDP and weight change; however, in Cambridge (United Kingdom), Doetinchem (Netherlands), and Umea (Sweden) positive, albeit not significant, associations between MDP and weight change were observed.

Finally, the research question of whether adherence to the MDP could be protective against the development of overweight or obesity in people that were normal weight at baseline was explored. A 2-point increase in the rMED was associated with a 3% (95% CI: 1%, 5%) lower odds of becoming overweight or
obese in 5 y (Figure 2). When adherence to the MDP was assessed in categories, it was observed that, compared with individuals with a low adherence to the MDP (rMED of 0–6 points), the OR of becoming overweight or obese for individuals with a medium adherence to the MDP (rMED of 7–10 points) was 0.94 (95% CI: 0.89, 0.99); the corresponding OR for individuals with a high adherence to the MDP (rMED of 11–18) was 0.90 (95% CI: 0.82, 0.96) (data not shown).

DISCUSSION

Results of this prospective study indicated that a high adherence to the MDP may reduce the likelihood of gaining weight and becoming overweight or obese after 5 y of follow-up. The effect of the MDP on weight change was rather weak; however, this could be attributed, in part, to the overall low average weight gain observed in this population. In fact, the 0.16 kg 5-y weight-gain difference observed between individuals with a low and high adherence to the MDP according to the rMED represented 18% of the mean 5-y weight change observed in the current population. Also, a change from the lowest to the highest category of the rMED reduced the likelihood of becoming overweight or obese in 5 y by 10%.

Results of this study should be interpreted with caution because of the difficulties caused when the relation between diet and obesity in epidemiologic studies are assessed. One of the limitations of this study is the use of self-reported weight at follow-ups in most of the study centers. There is evidence that self-reported weight tends to be underestimated (38). This may explain the overall low average weight gain observed in this population. When self-reported weight was corrected by using the Oxford correction equations, the average weight gain was similar to that observed in the 2 centers [Cambridge (United Kingdom) and Doetinchem (Netherlands)] with measured data at baseline and follow-up as well as in other European studies with measured anthropometrical data (<400 g/y) (39). Also, the use of self-reported data at follow-up may have introduced a bias because of the systematic underreporting of weight in specific population subgroups, such as the overweight or obese subgroups (28, 40, 41). The use of a corrected weight gain (by using the Oxford correction equations) as the exposure variable of interest in our models did not change the estimate (data not shown). Other limitations of the current study are the likely presence of measurement errors because of the use of dietary questionnaires, residual confounding, or selection bias.

Strengths of this study include its prospective design, the large sample of participants from Mediterranean and non-Mediterranean European countries, the use of validated questionnaires, the standardization of dietary measurements across centers using additive calibration, and the possibility of taking into account the plausible misreporting of energy intake in our models.
Results of this study are in agreement with those of a previous prospective study conducted within the Spanish cohort of the EPIC (42); however, 2 other prospective studies did not find a significant association between the MDP and the incidence of overweight or obesity (43, 44). Differences in results across studies could be attributed to the use of different scores, the use of different confounding factors in statistical models, or the handling of underreporting. In addition, compared with previous studies, the sample size of the current study was larger, and the dietary pattern of study participants was more heterogeneous, which may have increased the power of the study to detect an association.

We applied different scores to assess the adherence of individuals to the MDP. The 3 scores were significantly associated with weight change. We decided to present the association between rMED and weight change, given that this scoring system presented some advantages over other scoring criteria, such as the use of energy-adjusted dietary components as a way of correcting for the measurement error associated with dietary questionnaires (45), the use of tertiles to categorize components of the score (which may increase the power to predict changes in weight), and the use of olive oil and/or vegetable oils as a component of the score (46). The score that included olive oil and the score that included vegetable oils yielded similar results; nevertheless, results for the scores constructed by using olive oil were shown in this study because olive oil is a key component of the MDP and an important contributor to the healthy aspects attributed to this diet (47, 48).

Potential mechanisms by which the MDP may protect against weight gain and obesity development have been proposed, such as the low-energy density, the high-fiber content, and the low glycemic index of this dietary pattern (20, 23, 34). In this study, we showed that the low meat and meat-product content of the MDP may also be a central element that explains its association with lower weight gain. The high saturated fat content and high energy density of meat may explain its detrimental effects on weight gain.

The protective effect of the MDP against weight gain seemed to be stronger in younger individuals than in older people. This could be explained by the fact that weight gain and its determinants in older populations (>60 y) may differ from those in younger populations (49). In the overall sample, normal-weight and overweight people also showed higher effect estimates than did obese individuals. The greater average weight gain in normal-weight and overweight people and the likely underreporting of weight at follow-up in the obese may explain these results. The exception was for obese individuals from southern European countries, who displayed a strong inverse association between the MDP and weight gain. The reason for such a strong inverse association is difficult to elucidate; however, it seems that misreporting of diet and weight changes in the obese in this population may be an important factor. Indeed, when we

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**FIGURE 2.** Likelihood of becoming overweight or obese in 5 y associated with a 2-point increase in the relative Mediterranean Diet Score (rMED). Country- or center-specific odds ratios (ORs) were calculated by using logistic regression adjusted for sex, age, baseline BMI, follow-up time, educational level, physical activity level, smoking status, menopausal status in women, total energy intake, and misreporting of energy intake. The overall estimate was calculated by using random-effects meta-analyses. UK, United Kingdom; NL, Netherlands; SE, Sweden.
repeated the analyses in obese people from southern European countries, excluding misreporters of energy intake, and used the corrected weight (according to the Oxford correction equations), the association between the rMED and weight change was attenuated and became not significant ($\beta = -0.09; 95\% CI: -0.18, 0.01$).

There was evidence of heterogeneity among study centers in the association between MDP scores and weight gain. In Cambridge (United Kingdom) and Doetinchem (Netherlands), which were the 2 centers with measured weight at follow-up, and Umeå (Sweden), positive, albeit not significant, associations between the MDP and weight change were observed. In 2 previous studies carried out within 6 study centers of the EPIC, a similar degree of heterogeneity was observed (50, 51). We tested in post hoc metaregression analyses whether any of the country-specific covariates entered in our models (ie, the percentage of women, physically active individuals, people with a university degree, nonsmokers, mean baseline BMI, mean baseline age, mean follow-up time, and mean rMED) could explain the observed heterogeneity among centers. The mean rMED was the only variable that was partly related to the center-specific estimate of the association between MDP and weight change ($P = 0.073$). Hence, centers with a lower adherence to the MDP (such as the Umeå, Doetinchem, and Cambridge centers) tended to show a less-strong association between MDP and weight change. In other words, the effect of the rMED on weight gain may only be observed when the level of adherence to MDP is high. Taking into account the overall low adherence to the MDP in non-Mediterranean countries, this would explain the weaker association in these countries.

In conclusion, this observational prospective study shows that eating a Mediterranean-like diet may help to prevent weight gain and the development of overweight and obesity. Long-term intervention studies that promote the consumption of the MDP are necessary to confirm the protective effect of this diet against the development of obesity.

The authors’ responsibilities were as follows—PHMP: principal investigator of the EPIC-PANACEA project and guarantor of the article; ER: overall coordinator of the EPIC study, which was conceptualized, designed, and implemented in collaboration with the main investigators in the collaborating countries as follows: Denmark (A Tjønneland), France (PC-C and M-CB-R), Germany (HB), Greece (A Trichopoulou), Italy (DP, RT, and PV), Netherlands (HBB-d-M and PHMP), Norway (EL), Spain (LR, MJS, PA, and AB), Sweden (JM), and United Kingdom (NW and TK) (these authors contributed to the study design, subject recruitment, and data collection and acquisition and are responsible for the ongoing follow-up and management of the EPIC cohort); DR and TN: conceived the current study; DR: responsible for the design of the study, analyses of data, interpretation of results, and drafting of the manuscript, with close assistance from TN, A-CV, TM, AMM, AA, GB, and PHMP and taking into account the comments and suggestions of the coauthors; contributors from the collaborating centers (NS, S Rinaldi, EC, VC, S Rohrmann, BT, MB, JH, MUIJ, CCD, NT, JMH, JL, EAS, PO, AN, CA, AM, FLB, EW, IJ, VH, TB, DE, and AO): provided the original data, information on the respective populations, and advice on study design, analysis, and interpretation of the results; and all coauthors: had the opportunity to comment on the analysis and interpretation of the findings and approved the final version of the manuscript. None of the authors declared a conflict of interest.

REFERENCES


27. Haftenberger M, Lahmann PH, Panico S, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European...


