Romaguera, D; Guevara, M; Norat, T; Langenberg, C; Forouhi, NG; Sharp, S; Slimani, N; Schulze, MB; Buijsse, B; Buckland, G; Molina-Montes, E; Sanchez, MJ; Moreno-Iribas, MC; Bendinelli, B; Groni, S; van der Schouw, YT; Arriola, L; Beulens, JW; Boeing, H; Clavel-Chapelon, F; Cottet, V; Crowe, FL; de Lauzon-Guillan, B; Franks, PW; Gonzalez, C; Hallmans, G; Kaaks, R; Key, TJ; Khaw, K; Nilsson, P; Overvad, K; Palla, L; Palli, D; Panico, S; Quiros, JR; Rolandsson, O; Romieu, I; Sacerdote, C; Spijkerman, AMW; Teucher, B; Tjonneland, A; Tormo, MJ; Tumino, R; van der, ADL; Feskens, EJM; Riboli, E; Wareham, NJ; Interact, C (2011) Mediterranean diet and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study: the InterAct project. Diabetes care, 34 (9). pp. 1913-8. ISSN 0149-5992 DOI: https://doi.org/10.2337/dc11-0891

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Mediterranean Diet and Type 2 Diabetes Risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC) Study

The InterAct project

**OBJECTIVE**—To study the association between adherence to the Mediterranean dietary pattern (MDP) and risk of developing type 2 diabetes, across European countries.

**RESEARCH DESIGN AND METHODS**—We established a case-cohort study including 11,994 incident type 2 diabetic case subjects and a stratified subcohort of 15,798 participants selected from a total cohort of 340,234 participants with 3.99 million person-years of follow-up, from eight European cohorts participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The relative Mediterranean diet score (rMED) (score range 0–18) was used to assess adherence to MDP on the basis of reported consumption of nine dietary components characteristic of the Mediterranean diet. Cox proportional hazards regression, modified for the case-cohort design, was used to estimate the association between rMED and risk of type 2 diabetes, adjusting for confounders.

**RESULTS**—The multiple adjusted hazard ratios of type 2 diabetes among individuals with medium (rMED 7–10 points) and high adherence to MDP (rMED 11–18 points) were 0.93 (95% CI 0.86–1.01) and 0.88 (0.79–0.97), respectively, compared with individuals with low adherence to MDP (0–6 points) (P for trend 0.013). The association between rMED and type 2 diabetes was attenuated in people <50 years of age, in obese participants, and when the alcohol, meat, and olive oil components were excluded from the score.

**CONCLUSIONS**—In this large prospective study, adherence to the MDP, as defined by rMED, was associated with a small reduction in the risk of developing type 2 diabetes in this European population.

*Diabetes Care* 34:1913–1918, 2011

The Mediterranean dietary pattern (MDP) is characterized by a high consumption of unrefined cereals, fruits, vegetables, olive oil, and legumes; a moderate consumption of dairy products (mostly cheese and yogurt); moderate wine consumption; a moderate-to-high consumption of fish; and a low consumption of meat and meat products (1,2). Numerous epidemiological studies have assessed adherence to the MDP through a priori defined scores or indexes and have linked it to reduced chronic disease morbidity and mortality (3). The MDP has also been postulated as an effective diet for the prevention and treatment of type 2 diabetes (4,5). However, epidemiological evidence for an association between MDP and type 2 diabetes is limited. Two previous observational prospective studies (6,7) and one intervention study (8) found that higher adherence to the MDP was associated with a lower risk of developing type 2 diabetes. However, previous studies included small samples mostly consisting of at-risk individuals from Mediterranean populations, limiting generalizability to the general population.

The objective of our study was to assess the association between adherence to the MDP, using an a priori defined score, and incidence of type 2 diabetes among a large European population including Mediterranean and non-Mediterranean countries, with diversity of dietary patterns. We tried to overcome the methodological limitations of previous studies by ascertaining a large number of incident-verified diabetic case subjects in a cohort of apparently healthy participants at baseline, removing the problem of recall bias. The size of the study provides sufficient power to study the effect of multiple potential confounders, effect modifiers, and plausible mediators of the association between diet and type 2 diabetes, as well as to investigate the relative importance of the individual components of the MDP on type 2 diabetes risk.

**RESEARCH DESIGN AND METHODS**

Study population

Between 1992 and 2000, 521,448 apparently healthy volunteers aged between 25 and 70 years were recruited in 23 centers from 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the U.K.) participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. 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. Written informed consent was obtained from all participants before joining the EPIC study. Details of the recruitment and study design have been published elsewhere (9–11).
Mediterranean diet and type 2 diabetes risk

The InterAct Consortium was initiated to investigate how genetic and lifestyle factors interact in their influence on the risk of developing type 2 diabetes (12). InterAct partners ascertained and verified incident type 2 diabetic case subjects occurring in the EPIC cohort. With the exception of Norway and Greece, all EPIC countries participated in the InterAct project (n = 455,680). Individuals without stored blood (n = 109,625) or with prevalent diabetes status at baseline (n = 5,821) were not eligible for InterAct.

Type 2 diabetes case ascertainment and verification

We designed a pragmatic high-sensitivity approach for case ascertainment aimed at identifying potential incident diabetic case subjects and excluding individuals with known prevalent diabetes, using at least two multiple sources of evidence including self-report, linkage to primary or secondary care registers, drug registers, hospital admissions, and mortality data. Cases in Denmark and Sweden were not ascertained by self-report but were identified via local and national diabetes and pharmaceutical registers. Follow-up was censored on 31 December 2007 or the date of death, whichever occurred earlier. In total, 12,403 verified incident type 2 diabetic case subjects were identified.

The date of diagnosis for incident case subjects was set as either the date of diagnosis reported by the doctor, the earliest date that diabetes was recorded in medical records, the date of inclusion into the diabetes registry, the date reported by the participant, or the date of the questionnaire in which diabetes was first reported. If the date of diagnosis could not be ascertained from any of the sources listed above, the midpoint between recruitment and censoring was used (12).

Case-cohort construction

The case-cohort study included a random subcohort of 16,835 individuals selected from those with available stored blood samples, stratified by center. We oversampled for the proportion of prevalent type 2 diabetic case subjects in each center with the aim that, by center, the number of individuals in the subcohort (after later exclusion of individuals with prevalent diabetes) should be approximately similar to the number of incident case subjects. After exclusion of 548 individuals with prevalent diabetes and 133 with unknown diabetes status, 16,154 subcohort individuals were included in the analysis, of whom 778 had developed incident type 2 diabetes during follow-up. An overlap between the case set and the subcohort is a design feature of a case-cohort study.

Dietary assessment and Mediterranean diet score

Usual food intake was estimated using country-specific validated dietary questionnaires (13). Estimated individual nutrient intakes were derived from foods included in the dietary questionnaires through the standardized EPIC Nutrient Database (ENDB) (14). Participants within the lowest and highest 1% of the cohort distribution of the ratio of reported total energy intake:energy requirement were excluded from the current study (n = 736).

Adherence to MDP was assessed using the relative Mediterranean diet score (rMED) (15), a variation of the original Mediterranean diet score (1,2). This score included nine nutritional components characteristic of the MDP: some potentially beneficial components (vegetables, legumes, fruits and nuts, cereals, fish and seafood, olive oil, and moderate alcohol consumption) and other potentially detrimental components (meat and meat products and dairy products). Each rMED component (apart from alcohol) was measured as grams per 1,000 kcal (16). All components of the score (except for olive oil and alcohol, as described below) were divided into tertiles of dietary intake, according to the distribution observed in the overall subcohort. A value of 0, 1, and 2 was assigned to the first, second, and third tertiles, respectively, of the intakes of the beneficial components. The scoring was reversed for the two presumably detrimental components. The scoring for olive oil was modified because of the relatively large number of nonconsumers. Therefore, 0 was assigned to nonconsumers, 1 for participants with an intake below the median olive oil consumption (calculated only within olive oil consumers), and 2 for people whose intake was equal or above this median. For alcohol, a value of 2 was given to those with moderate alcohol consumption (ethanol intakes from 10 to <50 g/day in men and 5 and 25 g/day in women) and a value of 0 otherwise. Therefore, the rMED ranged from 0 (indicating the lowest adherence to the MDP) to 18 (the highest adherence to the MDP). The rMED was further classified in categories to reflect low (0–6 points), medium (7–10 points), or high (11–18 points) adherence to the MDP on the basis of previously published cutoff points (15).

Assessment of other covariates

Standard questionnaires were used to collect information on the participants’ sociodemographic characteristics and lifestyle variables (9). For the current study, we used information about smoking status (never-smoker, former smoker, and current smoker) and number of cigarettes smoked per day (1–10, 11–20, and >20 cigarettes/day); educational level (no formal education, primary school, technical school, secondary school, and university degree); and an ordered four-category index of physical activity (17).

Weight, height, waist circumference (WC), and hip circumference were obtained at baseline using standardized protocols (18). BMI was calculated as weight in kilograms divided by squared height in meters (kg/m²).

In most participating centers, information on the presence of chronic conditions at baseline was collected, i.e., hypertension, hyperlipidemia, and previous cardiovascular disease (angina, stroke, and myocardial infarction). Information on family history of type 2 diabetes in a first-degree relative was collected for all participants except for individuals in Italy, Spain, Germany, and Oxford.

Statistical analysis

Cox proportional hazards regression, modified for the case-cohort design according to the Prentice method (19), was used to estimate the association between rMED and risk of type 2 diabetes. Age was used as the underlying time scale, with entry time defined as the participant’s age at recruitment and exit time as age at diagnosis of diabetes, censoring, or death (whichever came first). All analyses were stratified by center to control for center effects such as follow-up procedures and questionnaire design.

We evaluated the shape of the association of rMED with type 2 diabetes risk by using restricted cubic splines with five knots placed at the 5th, 25th, 50th, 75th, and 95th percentile of rMED distribution, which showed no evidence of departure from linearity. The rMED score was then assessed as a continuous variable (two-point increment) and as a categorical variable (low, medium, and high adherence to the MDP). The rMED categorical variable was scored from 1 to 3, and trend tests were calculated on these scores. Different models were used, with different
Table 1—Baseline characteristics of the InterAct subcohort according to level of adherence to the MDP (rMED categories)

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>rMED categories*</td>
<td>rMED categories*</td>
<td>Total</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>Total</td>
<td>Low</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,968</td>
<td>2,029</td>
<td>2,452</td>
<td>1,487</td>
<td>9,830</td>
<td>2,334</td>
<td>4,567</td>
<td>2,929</td>
</tr>
</tbody>
</table>

Sociodemographic characteristics

<table>
<thead>
<tr>
<th>Age at enrollment [mean years (SD)]</th>
<th>52.9 (9.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational level (%):</td>
<td></td>
</tr>
<tr>
<td>No formal education</td>
<td>5.5</td>
</tr>
<tr>
<td>Primary school</td>
<td>33.6</td>
</tr>
<tr>
<td>Technical or professional training</td>
<td>22.4</td>
</tr>
<tr>
<td>Secondary school</td>
<td>13.0</td>
</tr>
<tr>
<td>University degree</td>
<td>24.1</td>
</tr>
<tr>
<td>Not specified</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Anthropometry

<table>
<thead>
<tr>
<th>BMI [mean kg/m² (SD)]</th>
<th>26.6 (3.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference [mean (SD)]</td>
<td>95.1 (10.0)</td>
</tr>
<tr>
<td>Waist-to-hip ratio [mean (SD)]</td>
<td>0.94 (0.06)</td>
</tr>
</tbody>
</table>

Lifestyle (%)

<table>
<thead>
<tr>
<th>Physical activity</th>
<th>Inactive</th>
<th>Moderately inactive</th>
<th>Moderately active</th>
<th>Active</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18.0</td>
<td>30.4</td>
<td>25.5</td>
<td>24.5</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>19.3</td>
<td>27.4</td>
<td>24.6</td>
<td>26.2</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>17.5</td>
<td>31.3</td>
<td>25.8</td>
<td>23.7</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>17.0</td>
<td>33.0</td>
<td>26.0</td>
<td>23.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Smoking status (%)

<table>
<thead>
<tr>
<th>Never</th>
<th>Current (0–10 cigarettes/day)</th>
<th>Current (11–20 cigarettes/day)</th>
<th>Current (&gt;20 cigarettes/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31.5</td>
<td>8.8</td>
<td>11.0</td>
<td>5.4</td>
</tr>
<tr>
<td>32.6</td>
<td>9.2</td>
<td>13.5</td>
<td>7.9</td>
</tr>
<tr>
<td>30.5</td>
<td>7.9</td>
<td>9.6</td>
<td>4.7</td>
</tr>
<tr>
<td>31.6</td>
<td>8.5</td>
<td>14.6</td>
<td>7.6</td>
</tr>
<tr>
<td>55.5</td>
<td>10.1</td>
<td>12.5</td>
<td>6.6</td>
</tr>
<tr>
<td>46.9</td>
<td>12.5</td>
<td>16.0</td>
<td>9.0</td>
</tr>
<tr>
<td>56.2</td>
<td>12.4</td>
<td>16.0</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Medical/health indicators (%)

| History of cardiovascular disease | 4.7   | 4.2   | 5.7   | 3.8   | 2.0   | 2.3   | 1.9   | 1.8   |
| Hypertension                     | 18.7  | 16.5  | 20.1  | 19.5  | 18.2  | 19.7  | 18.0  | 17.2  |
| Hyperlipidemia                   | 21.7  | 16.2  | 22.6  | 24.9  | 14.0  | 10.5  | 13.8  | 16.2  |

<table>
<thead>
<tr>
<th>History of diabetes in a first-degree relative</th>
<th>12.4</th>
<th>13.4</th>
<th>11.6</th>
<th>7.3</th>
<th>17.6</th>
<th>18.8</th>
<th>17.2</th>
<th>15.9</th>
</tr>
</thead>
</table>

*rMED categories: low adherence to the MDP (rMED 0–6); medium adherence to the MDP (rMED 7–10); high adherence to the MDP (rMED 11–18).†Excludes London, where waist circumference was not recorded.

‡History of cardiovascular disease at baseline: myocardial infarction, angina, or stroke.

§Excludes Malmo and Umea, where it was not asked.

¶Excludes Italy, Spain, Germany, and Oxford, where family history of diabetes was not asked.
levels of adjustment: first, a crude model was run; then the model was further adjusted for sex and BMI; and finally we ran a multiple adjusted model that also included educational level, smoking status, physical activity, and total energy intake. There were some participants with missing values for physical activity (n = 382, 1.41% of the sample), educational level (n = 235, 0.87%), and smoking status (n = 247, 0.91%). We treated participants with missing data as a separate category for these three variables.

We evaluated the relative importance of each of the components of rMED on type 2 diabetes risk by subtracting one component at a time from the original score, as previously reported (20).

Effect modifications by sex, age-group (<30, 30–59, and ≥60 years), baseline BMI category (BMI <25, 25 to <30, and ≥30 kg/m²), smoking status (former smokers, current smokers, and never-smokers), and history of diabetes in a first-degree relative were assessed by modeling interaction terms between these variables and rMED and conducting stratified analyses.

To ascertain whether the association between MDP and diabetes risk was mediated through specific risk factors, models were additionally adjusted for WC (after excluding participants in Umeå, Sweden, where WC was not measured; n = 1,796), hyperlipidemia (after excluding participants in Umeå and Malmö, Sweden, where hyperlipidemia was not reported; n = 5,272), and hypertension (individually and simultaneously). Sensitivity analyses were performed excluding participants with cardiovascular disease at baseline (myocardial infarction, stroke, and angina), self-reported hypertension, self-reported hyperlipidemia, and obesity (BMI ≥30 kg/m²); excluding the first 2 years of follow-up; and excluding mis-reporters of energy (both under-reporters [individuals with a ratio of energy intake:basal metabolic rate, or EI:BMR, <1.14] and over-reporters [EL:BMR >2.1], based on the cutoff points proposed by Goldberg et al. [21]). A calibrated version of the rMED correcting for any systematic under- or overestimation of dietary intake among countries was constructed on the basis of a calibration study in a random subsample of EPIC using a detailed computerized 24-h dietary recall (14). Dietary exposures across countries were scaled using an additive calibration (13). Finally, heterogeneity among countries in the association between rMED and type 2 diabetes risk was assessed by calculating country-specific estimates and using random-effect meta-analyses (12).

All statistical analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC) and STATA 10.0 (StataCorp, College Station, TX).

**RESULTS**—After exclusions, 11,994 incident type 2 diabetic case subjects were included and a subcohort of 15,798 was selected (including an overall of 749 diabetic case subjects). Information on the distribution of case subjects and characteristics of the sample by country are in Supplementary Table A1. Table 1 shows the sociodemographic, anthropometric, lifestyle, and health characteristics of the subcohort by category of the rMED.

The crude hazard ratios (HRs) for type 2 diabetes in the medium and high category of the score were 0.74 (95% CI 0.70–0.79) and 0.65 (0.60–0.71), respectively, compared with the lowest category (P for trend < 0.0001). These risk estimates were attenuated after adjustment for confounders; adjusted HRs for diabetes were 0.93 (0.86–1.01) in the medium category and 0.88 (0.79–0.97) in the high category of rMED (P for trend 0.013). Overall, in the multiple adjusted model, a two-point increment in rMED was associated with a 4% (1–6) reduction in the risk of type 2 diabetes (Table 2).

The contribution of each component of rMED on diabetes risk was assessed by sequential subtraction of components from the score (Supplementary Table A2). The association of rMED with diabetes risk was attenuated after excluding the alcohol (HR 0.98, 95% CI 0.95–1.01), meat (0.98, 0.95–1.00), and olive oil (0.97, 0.95–1.00) components.

Results of stratified analyses by sex, age-group, baseline BMI category, smoking status, and history of diabetes are shown in Table 3. There was evidence of effect modification by age-group (P for interaction 0.019). No association between rMED and diabetes was observed among the youngest participants (<50 years of age). Although the interaction was not statistically significant, the association between rMED and diabetes risk was stronger among normal-weight participants, never-smokers, and individuals without a family history of type 2 diabetes.

The effect estimate of rMED on diabetes risk did not change after further adjustment for hyperlipidemia, hypertension, and WC (both individually and simultaneously). The association between

### Table 2—HRs of type 2 diabetes according to level of adherence to the MDP (rMED score)

<table>
<thead>
<tr>
<th>Categories of rMED</th>
<th>HR§ 95% CI</th>
<th>P trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.99 (1.00, 0.99)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Medium</td>
<td>0.97 (0.95, 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>High</td>
<td>0.94 (0.91, 0.97)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

†Numbers in the subcohort exclude type 2 diabetic case subjects. §Modifications were 0.001. **Multiple adjusted models were adjusted for sex, BMI (as a continuous variable), and total calorie intake (as a continuous variable)."
BMI (kg/m²) 0.088
Age (years) 0.019
Smoking status 0.393

The occurrence of heterogeneity in the association
in Supplementary Fig. A1. There was evi-
tance of heterogeneity in the association
for type 2 diabetes associated with a
between MDP and type 2 diabetes. However, the association between
for type 2 diabetes. Individuals with a high
MED score (11–18 points) were
less likely to develop
diabetes than individuals with low
MED scores (0–6 points). The alcohol, meat,
and olive oil components of the
accounted for most of the observed
Strengths of this study include the
large sample size of healthy individuals at
baseline, from which we ascertained a
large number of verified incident cases of
type 2 diabetes during 4 million person-
years of follow-up. We also included both
Mediterranean and non-Mediterranean
countries and were able to control for a
large number of plausible confounders,
effect modifiers, and factors that may lie
in the etiological pathway of the associa-
tion between MDP and type 2 diabetes.
Our limitations include the use of a clin-
ical definition of incident type 2 diabetes
not based on glucose measurement. It is
possible that we did not identify individ-
uals who became biochemically diabetic
during follow-up but who did not come
to clinical recognition. However, this
would only be an issue for the estimation
of association with a baseline factor if that
factor was itself linked to the likelihood of
being tested for diabetes during follow-
up. This would not be the case of the
MED diet. We excluded known
cases of diabetes at baseline but did not
screen the entire cohort to exclude people
who had prevalent but clinically unre-
ognized disease. The focus on the exclu-
sion of clinically recognized cases was to
avoid the issues of recall bias of expo-
sures, where reporting would have been
affected by the diagnosis of diabetes.
The presence of a small proportion of prev-
alent but unrecognized cases of diabetes
among the control cohort would have a
negligible effect on the measure of asso-
ciation. Diet and other lifestyle variables
were assessed once at baseline. Therefore,
changes in lifestyle could not be taken
into account in these analyses. Validated
country-specific dietary questionnaires
were used to assess usual dietary intake.
To try to limit measurement error and
reporting bias, we constructed a calibra-
tion version of the MED and repeated the
analyses after excluding plausible mis-
reporters of energy intake, with no ap-
parent change in results. Our findings
might be explained by reverse causality
if changes in diet occurred after being
diagnosed with a chronic disease; in-
deed, the association between MED and
diabetes risk was slightly strengthened
after excluding participants with chronic
diseases at baseline and those develop-
ing diabetes within the first 2 years of
follow-up.

Two previous observational prospec-
tive studies have evaluated the association
between the MED and new-onset of type 2
diabetes, one of which included highly
educated individuals from Spain with
only 33 incident diabetic case subjects
(6). The other included Italian recent
myocardial infarction patients (998 inci-
dent diabetic case subjects) (7). In both of
these studies, a higher Mediterranean diet
score predicted a lower risk of subsequent
development of type 2 diabetes. The small
sample size of the Spanish study and the
selected nature of the Italian population
limit the conclusions that can be drawn
from these data. However, the results are
generally consistent with those of the cur-
rent study, which included a much larger
sample size of apparently healthy par-
ticipants from eight European countries.
A recent randomized controlled trial

**Table 3**—Multiple adjusted HRs of type 2 diabetes associated with a two-point
increment in the rMED in population subgroups

<table>
<thead>
<tr>
<th></th>
<th>Number of cases/ number of subcohort</th>
<th>HR†</th>
<th>95% CI</th>
<th>P for interaction‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5,946/5,597</td>
<td>0.96</td>
<td>0.93–1.00</td>
<td>0.144</td>
</tr>
<tr>
<td>Female</td>
<td>5,670/9,452</td>
<td>0.95</td>
<td>0.91–0.98</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>2,637/5,681</td>
<td>1.00</td>
<td>0.94–1.06</td>
<td>0.019</td>
</tr>
<tr>
<td>50–59</td>
<td>5,604/6,119</td>
<td>0.95</td>
<td>0.91–0.98</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>3,753/2,249</td>
<td>0.96</td>
<td>0.92–1.00</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>1,666/6,936</td>
<td>0.92</td>
<td>0.88–0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>25–29</td>
<td>5,266/5,987</td>
<td>0.95</td>
<td>0.92–0.98</td>
<td>0.73</td>
</tr>
<tr>
<td>≥30</td>
<td>5,062/2,126</td>
<td>0.99</td>
<td>0.95–1.03</td>
<td>0.057</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>4,882/7,038</td>
<td>0.95</td>
<td>0.92–0.99</td>
<td>0.393</td>
</tr>
<tr>
<td>Former</td>
<td>3,716/4,038</td>
<td>0.97</td>
<td>0.92–1.01</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>3,295/3,827</td>
<td>0.96</td>
<td>0.92–1.01</td>
<td></td>
</tr>
<tr>
<td><strong>History of diabetes in a first-degree relative§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3,441/5,474</td>
<td>0.92</td>
<td>0.88–0.96</td>
<td>0.527</td>
</tr>
<tr>
<td>Yes</td>
<td>1,935/1,138</td>
<td>0.96</td>
<td>0.90–1.04</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in the subcohort exclude type 2 diabetic case subjects. †Modified Cox proportional hazards regression models stratified by center and adjusted for sex, BMI (as a continuous variable), educational level (no formal education, primary school, technical/professional school, secondary school, and longer education including university degree), physical activity (inactive, moderately inactive, moderately active, and active), smoking status (never, former, and three categories of current smoker: 1–10 cigarettes day⁻¹, 11–20 cigarettes day⁻¹, and >20 cigarettes day⁻¹), and total calorie intake (as a continuous variable). ‡Heterogeneity among subgroups was tested by adding an interaction term in the model between these variables and rMED. §Family history of diabetes was not ascertained in the centers in Italy, Spain, Germany, and Oxford.

CONCLUSIONS—In this large European case-cohort study, higher adherence to the MDP as defined by MED was associated with a lower risk of developing type 2 diabetes. Individuals with a high MED score range (11–18 points) were 12% (95% CI 3–21) less likely to develop diabetes than individuals with low MED scores (0–6 points). The alcohol, meat,
and olive oil components of the MED accounted for most of the observed association.

Strengths of this study include the
large sample size of healthy individuals at
baseline, from which we ascertained a
large number of verified incident cases of
type 2 diabetes during 4 million person-
years of follow-up. We also included both
Mediterranean and non-Mediterranean
countries and were able to control for a
large number of plausible confounders,
effect modifiers, and factors that may lie
in the etiological pathway of the associa-
tion between MDP and type 2 diabetes.
Our limitations include the use of a clin-
ical definition of incident type 2 diabetes
not based on glucose measurement. It is
possible that we did not identify individ-
uals who became biochemically diabetic
during follow-up but who did not come
to clinical recognition. However, this
would only be an issue for the estimation
of association with a baseline factor if that
factor was itself linked to the likelihood of
being tested for diabetes during follow-
up. This would not be the case of the
MED diet. We excluded known
cases of diabetes at baseline but did not
screen the entire cohort to exclude people
who had prevalent but clinically unre-
ognized disease. The focus on the exclu-
sion of clinically recognized cases was to
avoid the issues of recall bias of expo-
sures, where reporting would have been
affected by the diagnosis of diabetes.
The presence of a small proportion of prev-
alent but unrecognized cases of diabetes
among the control cohort would have a
negligible effect on the measure of asso-
ciation. Diet and other lifestyle variables
were assessed once at baseline. Therefore,
changes in lifestyle could not be taken
into account in these analyses. Validated
country-specific dietary questionnaires
were used to assess usual dietary intake.
To try to limit measurement error and
reporting bias, we constructed a calibra-
tion version of the MED and repeated the
analyses after excluding plausible mis-
reporters of energy intake, with no ap-
parent change in results. Our findings
might be explained by reverse causality
if changes in diet occurred after being
diagnosed with a chronic disease; in-
deed, the association between MED and
diabetes risk was slightly strengthened
after excluding participants with chronic
diseases at baseline and those develop-
ing diabetes within the first 2 years of
follow-up.

Two previous observational prospec-
tive studies have evaluated the association
between the MED and new-onset of type 2
diabetes, one of which included highly
educated individuals from Spain with
only 33 incident diabetic case subjects
(6). The other included Italian recent
myocardial infarction patients (998 inci-
dent diabetic case subjects) (7). In both of
these studies, a higher Mediterranean diet
score predicted a lower risk of subsequent
development of type 2 diabetes. The small
sample size of the Spanish study and the
selected nature of the Italian population
limit the conclusions that can be drawn
from these data. However, the results are
generally consistent with those of the cur-
rent study, which included a much larger
sample size of apparently healthy par-
ticipants from eight European countries.
A recent randomized controlled trial
Conducted among elderly people from Spain with cardiovascular risk factors showed that a non–energy-restricted traditional Mediterranean diet supplemented with either olive oil or nuts reduced the risk of developing type 2 diabetes, compared with a low-fat diet (8). However, this trial was limited by the supplementation of both Mediterranean diets with sources of unsaturated fatty acids. It is uncertain if the observed association was related to the Mediterranean diet per se, or to the supplementation with unsaturated fat.

We observed a similar HR for type 2 diabetes risk when a random-effect meta-analysis was used to pool country-specific estimates, but found evidence of country heterogeneity in the association between rMED and type 2 diabetes risk. In a meta-regression analysis, mean age was the only variable related to the country-specific estimates of the association between MDP and diabetes risk. Countries with average older ages in their cohorts (France, U.K. [general population], and Denmark) tended to show stronger associations between MDP and diabetes risk. This is consistent with our finding of effect modification by age-group. We found no other significant interactions, but there was a nonsignificant tendency for the association to be stronger among the older nonobese never-smokers and individuals without family history of type 2 diabetes.

In conclusion, the results of this large case-cohort study show that adherence to the MDP, as defined by rMED, is associated with a small reduction in the risk of developing type 2 diabetes in this European population. These results highlight the potential of eating a healthy dietary pattern in the prevention of type 2 diabetes.

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References