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

The InterAct project

THE INTERACT CONSORTIUM*

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 MPD 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).

Corresponding author: Dora Romaguera, d.romaguera-bosch@imperial.ac.uk.
Received 13 May 2011 and accepted 10 June 2011.
DOI: 10.2337/dc11-0891
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0891/-/DC1.
*A complete list of the InterAct Consortium can be found in the Supplementary Data.
© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See http://creativecommons.org/licenses/by-nc-nd/3.0/ for details.

Downloaded from http://diabetesjournals.org/care/article-pdf/34/9/1913/609163/1913.pdf by guest on 11 November 2024

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/m^2).

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

Downloaded from http://diabetesjournals.org/care/article-pdf/34/9/1913/609163/1913.pdf by guest on 11 November 2024

Downloaded from http://diabetesjournals.org/care/article-pdf/34/9/1913/609163/1913.pdf by guest on 11 November 2024

Table 1—*Baseline characteristics of the InterAct subcohort according to level of adherence to the MDP (rMED categories)*

		Men				Women		
		rMED categories*				rMED categories*		
	Total	Low	Medium	High	Total	Low	Medium	High
n	5,968	2,029	2,452	1,487	9,830	2,334	4,567	2,929
Sociodemographic characteristics								
Age at enrollment [mean years (SD)]	52.9 (8.9)	52.9 (9.9)	53.6 (8.5)	51.7 (7.9)	52.1 (9.3)	52.7 (10.0)	52.7 (9.2)	50.8 (8.6)
Educational level (%)								
No formal education	5.5	0.7	4.8	13.0	8.8	1.6	7.7	16.2
Primary school	33.6	36.7	30.4	34.6	32.1	32.4	30.1	34.9
Technical or professional training	22.4	27.1	22.9	15.3	23.0	31.9	24.6	13.5
Secondary school	13.0	14.1	11.5	14.0	16.3	16.5	16.3	16.0
University degree	24.1	20.8	28.3	21.6	18.1	16.4	19.3	17.6
Not specified	1.4	0.6	2.1	1.5	1.8	1.1	2.0	1.9
Anthropometry								
BMI [mean kg/m^2 (SD)]	26.6 (3.6)	26.2 (3.7)	26.6 (3.4)	27.1 (3.5)	25.7 (4.5)	25.4 (4.5)	25.5 (4.4)	26.1 (4.6)
Waist circumference [mean (SD)]†	95.1 (10.0)	94.7 (10.4)	94.9 (9.9)	95.7 (9.7)	81.2 (11.2)	81.4 (11.6)	80.5 (10.9)	82.1 (11.3)
Waist-to-hip ratio [mean (SD)]†	0.94 (0.06)	0.95 (0.07)	0.94 (0.06)	0.94 (0.06)	0.80 (0.07)	0.80 (0.07)	0.79 (0.06)	0.80 (0.06)
Lifestyle (%)								
Physical activity								
Inactive	18.0	19.3	17.5	17.0	26.4	18.9	24.3	35.7
Moderately inactive	30.4	27.4	31.3	33.0	34.8	34.9	34.4	35.2
Moderately active	25.5	24.6	25.8	26.0	20.8	23.9	21.7	17.0
Active	24.5	26.2	23.7	23.5	16.8	20.1	18.4	11.7
Missing	1.7	2.6	1.7	0.5	1.2	2.2	1.2	0.4
Smoking status (%)								
Never	31.5	32.6	30.5	31.6	55.5	46.9	56.2	61.4
Former	36.4	32.7	39.4	36.6	21.3	21.6	21.7	20.4
Current (1–10 cigarettes/day)	8.8	9.2	7.9	9.8	10.1	12.5	9.9	8.5
Current (11–20 cigarettes/day)	11.0	13.5	9.6	10.0	9.4	14.6	8.5	6.7
Current (>20 cigarettes/day)	5.4	5.9	5.5	4.7	2.3	3.1	2.0	2.0
Current (NS number of cigarettes)	5.8	5.2	6.0	6.3	0.5	0.7	0.6	0.2
Missing	1.0	0.9	1.1	0.9	0.9	0.5	1.1	0.9
Medical/health indicators (%)								
History of cardiovascular disease‡	4.7	4.2	5.7	3.8	2.0	2.3	1.9	1.8
Missing	1.9	2.9	1.9	0.6	1.2	2.0	1.3	0.3
Hypertension	18.7	16.5	20.1	19.5	18.2	19.7	18.0	17.2
Missing	5.0	8.2	4.9	0.8	2.3	3.9	2.5	0.8
Hyperlipidemia§	21.7	16.2	22.6	24.9	14.0	10.5	13.8	16.2
Missing	10.7	21.7	10.3	2.2	6.8	11.4	7.9	3.0
History of diabetes in a first-degree relative‖	12.4	13.4	11.6	7.3	17.6	18.8	17.2	15.9
Missing	16.1	16.5	15.6	15.8	11.4	12.9	10.4	10.4

*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 Umea, 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 (<50, 50–59, and ≥60 years), baseline BMI category (BMI <25, 25 to <30, and ≥30 kg/m^2), 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 Umea, Sweden, where WC was not measured; n = 1,796), hyperlipidemia (after excluding participants in Umea and Malmo, 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/m^2); 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 [EI: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 (I^2).

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 identified 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 the 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)*

Number of case subjects/number of subcohort*	Categories of rMED†									
	Low (3,879/3,902)		Medium (5,103/6,767)		High (4,380/7,392)			Two-point increment in rMED‡ (11,994/15,049)		
	HR§	95% CI	HR§	95% CI	HR§	95% CI	P (trend)	HR§	95% CI	P
Crude model	1.00	Referent	0.74	0.70–0.79	0.65	0.60–0.71	<0.001	0.88	0.86–0.90	<0.001
Sex- and BMI-adjusted model	1.00	Referent	0.87	0.81–0.94	0.80	0.72–0.89	<0.001	0.94	0.91–0.96	<0.001
Multiple adjusted model	1.00	Referent	0.93	0.86–1.01	0.88	0.79–0.97	0.013	0.96	0.94–0.99	0.002

*Numbers in the subcohort exclude type 2 diabetic case subjects. †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). ‡rMED included as a continuous variable (range 0–18). §Modified Cox proportional hazards regression models stratified by center. Mutliple adjusted models were adjusted for sex, BMI (as 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).

Downloaded from http://diabetesjournals.org/care/article-pdf/34/9/1913/609163/1913.pdf by guest on 11 November 2024

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

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

*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.

rMED and diabetes risk was similar after excluding the first 2 years of follow-up or participants with chronic disease at baseline (myocardial infarction, stroke, angina, hypertension, hyperlipidemia, or obesity). The association was slightly strengthened when both sets of exclusion were applied simultaneously. The association between rMED and diabetes risk was unchanged when the components of the score were calibrated using additive calibration and when mis-reporters of energy were excluded (Supplementary Table A3).

Country-specific HRs and pooled HRs for type 2 diabetes associated with a two-point increment in rMED are shown in Supplementary Fig. A1. There was evidence of heterogeneity in the association between countries (I^2 59%, *P* for heterogeneity 0.012). The pooled HR estimate obtained using random-effect meta-analyses was 0.93 (95% CI 0.89–0.98; *P* = 0.001). In post hoc meta-regression analyses to examine possible explanations for the observed heterogeneity, mean age was the only variable related to the country-specific estimate of the association between MDP and incident diabetes (*P* = 0.019) (Supplementary Fig. A2).

CONCLUSIONS—In this large European case-cohort study, higher adherence to the MDP as defined by rMED was associated with a lower risk of developing type 2 diabetes. Individuals with a high rMED score range (11–18 points) were 12% (95% CI 3–21) less likely to develop diabetes than individuals with low rMED scores (0–6 points). The alcohol, meat, and olive oil components of the rMED 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 association between MDP and type 2 diabetes. Our limitations include the use of a clinical definition of incident type 2 diabetes not based on glucose measurement. It is possible that we did not identify individuals 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 Mediterranean diet. We excluded known cases of diabetes at baseline but did not screen the entire cohort to exclude people who had prevalent but clinically unrecognized disease. The focus on the exclusion of clinically recognized cases was to avoid the issues of recall bias of exposures, where reporting would have been affected by the diagnosis of diabetes. The presence of a small proportion of prevalent but unrecognized cases of diabetes among the control cohort would have a negligible effect on the measure of association. 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 calibrated version of the rMED and repeated the analyses after excluding plausible mis-reporters of energy intake, with no apparent change in results. Our findings might be explained by reverse causality if changes in diet occurred after being diagnosed with a chronic disease; indeed, the association between rMED and diabetes risk was slightly strengthened after excluding participants with chronic diseases at baseline and those developing diabetes within the first 2 years of follow-up.

Two previous observational prospective studies have evaluated the association between the MDP 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 incident 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 current study, which included a much larger sample size of apparently healthy participants from eight European countries. A recent randomized controlled trial

Downloaded from http://diabetesjournals.org/care/article-pdf/34/9/1913/609163/1913.pdf by guest on 11 November 2024

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.

Acknowledgments—The InterAct study received funding from the European Union (Integrated Project LSHM-CT-2006-037197 in the Framework Programme 6 of the European Community). In addition, InterAct investigators acknowledge funding from the following agencies: G.B.: Health Research Funds (Fundación de Investigación Sanitaria [FIS]) of the Spanish Ministry of Health (Exp. P10710130) and RTICC (R06/0020); Y.T.v.d.S. and J.W.B.: Verification of diabetes cases was additionally funded by NL Agency Grant IGE05012 and an incentive grant from the board of the University Medical Centre (UMC) Utrecht; F.C.-C.: Ligue contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, INSERM; F.L.C., T.J.K., and K.K.: Cancer Research UK; G.H.: The county of Västerbotten; R.K.: Deutsche Krebshilfe; K.K.: Medical Research Council UK; K.O. and A.T.: Danish Cancer Society; D.P.: Ministero della Salute-regione Toscana Progetto Integrato Oncologia-PIO; J.R.Q.: Asturias Regional Government; A.M.W. and D.L.v.d.A.: Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch Zorg Onderzoek Nederland (ZON), World Cancer Research Fund (WCRF), and Statistics Netherlands (the Netherlands); M.-J.T.: Health Research Fund (FIS) of the Spanish Ministry of Health, the CIBER en Epidemiología y Salud Pública (CIBERESP), Spain, and Murcia Regional Government (no. 6236); R.T.: Associazione Iblea per la Ricerca Epidemiologica (AIRE-ONLUS) Ragusa, AVIS-Ragusa, Sicilian Regional Government and AIRC-Italy. The funders had no role in study design, data collection, and analysis; decision to publish; or preparation of the manuscript.

No potential conflicts of interest relevant to this article were reported.

D.R. wrote the manuscript with close assistance from working team members.

The authors thank all EPIC participants and staff for their contribution to the study.

References

1. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. BMJ 1995;311:1457–1460
2. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348:2599–2608
3. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. Am J Clin Nutr 2010;92:1189–1196
4. Schröder H. Protective mechanisms of the Mediterranean diet in obesity and type 2 diabetes. J Nutr Biochem 2007;18:149–160
5. Esposito K, Maiorino MI, Ceriello A, Giugliano D. Prevention and control of type 2 diabetes by Mediterranean diet: a systematic review. Diabetes Res Clin Pract 2010;89:97–102
6. Martínez-González MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM, et al. Adherence to Mediterranean diet and risk of developing diabetes: prospective cohort study. BMJ 2008;336:1348–1351
7. Mozaffarian D, Marfisi R, Levantesi G, et al. Incidence of new-onset diabetes and impaired fasting glucose in patients with recent myocardial infarction and the effect of clinical and lifestyle risk factors. Lancet 2007;370:667–675
8. Salas-Salvadó J, Bulló M, Babio N, et al. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. Diabetes Care 2011;34:14–19
9. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr 2002;5:1113–1124
10. Riboli E, Kaaks R. The EPIC Project: rationale and study design: European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26(Suppl. 1):S6–S14
11. Bingham S, Riboli E. Diet and cancer: the European Prospective Investigation into Cancer and Nutrition. Nat Rev Cancer 2004;4:206–215
12. The InterAct Consortium. Design and cohort description of the InterAct Project: an examination of the interaction of genetic and lifestyle factors on the incidence of type 2 diabetes in the EPIC Study. Diabetologia. 30 June 2011 [Epub ahead of print]
13. Kaaks R, Riboli E. Validation and calibration of dietary intake measurements in the EPIC project: methodological considerations: European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol 1997;26(Suppl. 1):S15–S25
14. Slimani N, Deharveng G, Unwin I, et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. Eur J Clin Nutr 2007;61:1037–1056
15. Buckland G, Agudo A, Luján L, et al. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Am J Clin Nutr 2010;91:381–390
16. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27
17. Wareham NJ, Jakes RW, Rennie KL, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6:407–413
18. Haftenberger M, Lahmann PH, Panico S, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002;5:1147–1162
19. Barlow WE, Ichikawa L, Rosner D, Izumi S. Analysis of case-cohort designs. J Clin Epidemiol 1999;52:1165–1172
20. Trichopoulou A, Bamia C, Trichopoulos D. Anatomy of health effects of Mediterranean diet: Greek EPIC prospective cohort study. BMJ 2009;338:b2337
21. Goldberg GR, Black AE, Jebb SA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr 1991;45:569–581

Downloaded from http://diabetesjournals.org/care/article-pdf/34/9/1913/609163/1913.pdf by guest on 11 November 2024