ORIGINAL ARTICLE

Association of the Mediterranean Dietary Pattern With the Incidence of Depression

The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) Cohort

Almudena Sánchez-Villegas, BPharm, PhD; Miguel Delgado-Rodríguez, MD, PhD, MPH; Alvaro Alonso, MD, PhD; Javier Schlatter, MD, PhD; Francisca Lahortiga, BA, PhD; Lluis Serra Majem, MD, PhD; Miguel Angel Martínez-González, MD, PhD, MPH

Context: Adherence to the Mediterranean dietary pattern (MDP) is thought to reduce inflammatory, vascular, and metabolic processes that may be involved in the risk of clinical depression.

Objective: To assess the association between adherence to the MDP and the incidence of clinical depression.

Design: Prospective study that uses a validated 136-item food frequency questionnaire to assess adherence to the MDP. The MDP score positively weighted the consumption of vegetables, fruit and nuts, cereal, legumes, and fish; the monounsaturated- to saturated-fatty-acids ratio; and moderate alcohol consumption, whereas meat or meat products and whole-fat dairy were negatively weighted.

Setting: A dynamic cohort of university graduates (Seguimiento Universidad de Navarra/University of Navarra Follow-up [SUN] Project).

Participants: A total of 10 094 initially healthy Spanish participants from the SUN Project participated in the study. Recruitment began on December 21, 1999, and is ongoing.

Main Outcome Measure: Participants were classified as having incident depression if they were free of depression and antidepressant medication at baseline and reported a physician-made diagnosis of clinical depression and/or antidepressant medication use during follow-up.

Results: After a median follow-up of 4.4 years, 480 new cases of depression were identified. The multiple adjusted hazard ratios (95% confidence intervals) of depression for the 4 upper successive categories of adherence to the MDP (taking the category of lowest adherence as reference) were 0.74 (0.57-0.98), 0.66 (0.50-0.86), 0.49 (0.36-0.67), and 0.58 (0.44-0.77) (P for trend $<.001$). Inverse dose-response relationships were found for fruit and nuts, the monounsaturated- to saturated-fatty-acids ratio, and legumes.

Conclusions: Our results suggest a potential protective role of the MDP with regard to the prevention of depressive disorders; additional longitudinal studies and trials are needed to confirm these findings.

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UNIPOLAR MAJOR DEPRESsion is the leading cause of disability-adjusted years lost worldwide and the third leading cause of disability-adjusted years lost within developed countries.[1] Therefore, preventive strategies are needed to reduce its population impact and costs. Although the promotion of physical activity has been reported as an effective preventive measure,[2] scarce information exists with regard to other preventive strategies and specifically with regard to the role of diet in the prevention of this disorder.

In comparative studies,[3] the lifetime prevalence of mental disorders has been found to be lower in Mediterranean countries than in Northern European countries. Age-standardized suicide rates, which may indirectly reflect the prevalence of severe depression, tend also to be lowest in Mediterranean countries.[4] Therefore, without the exclusion of alternative explanations, it is plausible that the Mediterranean dietary pattern (MDP) may be protective against depression. A hallmark of the MDP is the abundant use of olive oil, which is rich in monounsaturated fatty acids (MUFAs). A beneficial effect of MUFA intake from olive oil with regard to depression has been hypothesized because such intake may improve the binding of serotonin to its receptors.[5] In fact, an inverse association between olive oil consumption and a 15-point geri-

Author Affiliations are listed at the end of this article.

atric depression scale score was recently reported.[6] This inverse association was mainly present at the higher end of the range, which signifies that high olive oil consumption was associated with lower risk of more-severe depression. This observation is consistent with that of a European study[4] that compared 15 countries and found the lowest suicide rates in Greece and also with another European international study[7] that found the lowest prevalence of depression in the Spanish sample among 9 compared samples. The consumption and availability of olive oil are higher in Greece and Spain than anywhere else in Europe.[6,8]

Evidence that supports the protective role of several nutrients present in the MDP has been reported in several studies. The ω-3 polyunsaturated fatty acids (PUFAs) are implicated in the dynamic structure of the central nervous system neuronal membranes and increase their fluidity and serotonin transport.[9] Folate and vitamins B_{12} and B_6, through methionine conversion, are involved in 1-carbon metabolism that acts in several methylation reactions, such as those that involve serotonin and other monoamine neurotransmitters.[10]

Although there is not complete consistency, some epidemiologic studies[6,11-20] that have analyzed the association between some nutrients and depression have suggested that important components of the MDP are likely to be associated with lower risk of clinical depression. Moreover, recent results of a small trial with obese children[21] and a cross-sectional study in a large Spanish sample[22] suggested a reduced risk of depression and better mental health associated with better adherence to the MDP. However, no previous prospective cohort study has assessed the role of an overall healthy dietary pattern on the incidence of depression.

We evaluated the relationship between adherence to a traditional MDP and risk of development of clinical depression. A secondary aim was to assess the role of each component of the MDP with regard to clinical depression incidence.

METHODS

STUDY POPULATION

The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) Project is a multipurpose Spanish cohort composed of former students of the University of Navarra, registered professionals from some Spanish provinces, and other university graduates.[23] Information with regard to exposure and outcome is gathered by mailed questionnaires collected every 2 years. The recruitment of participants started on December 21, 1999, and is permanently ongoing because it is a dynamic cohort with recruitment continuously open. The overall follow-up rate approaches 90%. Before May 1, 2005, 15 441 participants had completed their baseline questionnaire. From them, we excluded participants lost to follow-up (1852), those who reported extremely low or high values for total energy intake (<800 kcal/d [men] and <500 kcal/d [women] or >4000 kcal/d [men] and >3500 kcal/d [women]),[24] patients with cancer or cardiovascular disease at baseline, users of antidepressant medication, or patients who reported physician-diagnosed depression at baseline. Some individuals met more than 1 of these exclusion criteria. Finally, 10 094 participants who had answered at least 1 follow-up questionnaire were included in analyses (median follow-up, 4.4 years) (**Figure**). The study was approved by the Human Research Ethical Committee at the University of Navarra. Voluntary completion of the first questionnaire was considered to imply informed consent.

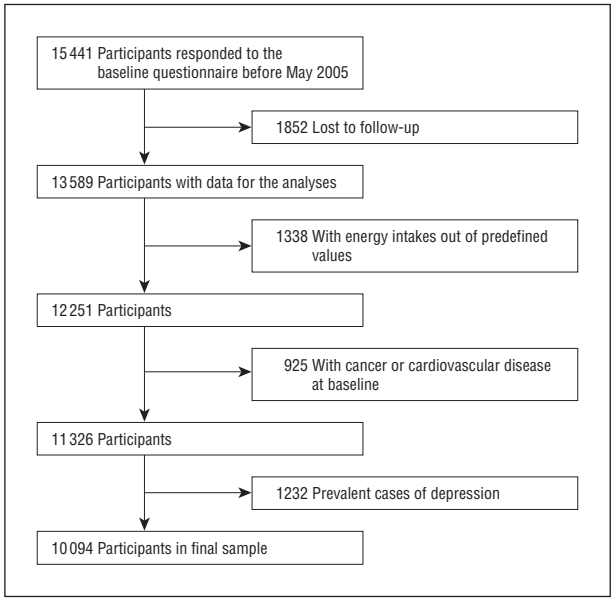

Figure. Flowchart for the Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) cohort study. Prevalent cases of hypertension were not considered as prevalent cases of cardiovascular disease. Therefore, participants with hypertension at baseline were included in all analyses.

EXPOSURE ASSESSMENT

Dietary intake was assessed during baseline by means of a semiquantitative food frequency questionnaire (136 food items) previously validated in Spain.[25] A trained dietitian updated the nutrient databank by means of the latest available information included in food composition tables for Spain.

Adherence of participants to the MDP was appraised in accordance with a score previously used by Trichopoulou et al.[26] This score is the most extensively used index to assess adherence to the MDP. Originally, this index included only 8 components to define the MDP: (1) high ratio of MUFAs to saturated fatty acids (SFAs), (2) moderate alcohol intake, (3) high intake of legumes, (4) high intake of cereal (such as bread), (5) high intake of fruit and nuts, (6) high intake of vegetables, (7) low intake of meat and meat products, and (8) moderate intake of milk and dairy products. Later, the same authors added another component: (9) high fish intake. We built the MDP index by the assignment of a score of 0 or 1 in accordance with the daily intake of each of the 9 components. With the exception of alcohol, the sex-specific medians of the sample were used as cutoff points. For each of the 6 protective components (MUFA/SFA ratio, legumes, cereal, fruit and nuts, vegetables, or fish), a participant received 1 point if his or her intake was over the sample median. The participant received 1 point if the intake was below the median for the 2 nonprotective components (dairy products or meat). For alcohol, 1 point was scored if consumption was 10 to 50 g/d for men or 5 to 25 g/d for women. This score, which ranges from 0 (minimal adherence) to 9 (maximal adherence), was categorized into 5 groups (0-2, 3, 4, 5, and 6-9 points).

To assess in separate analyses the relationship between each individual component of the MDP and the risk of depression, we adjusted the consumption of each for total energy intake

by means of the residual method and built quintiles. To better appraise the role of alcohol and type of alcoholic beverage, the consumption of wine, beer, and spirits was categorized into 3 groups: no consumption, any consumption of 25 g/d or less, and consumption of more than 25 g/d.

OTHER COVARIATES ASSESSMENT

The baseline assessment gathered information with regard to sociodemographic characteristics (eg, sex, age, marital status, and employment status), anthropometric variables (eg, weight and height), lifestyle and health-related habits (eg, smoking status), and medical history (eg, chronic diseases and medication use). It also included a physical activity questionnaire that collects information about 17 activities and has demonstrated fair validity against a triaxial accelerometer.[27] An activity metabolic equivalent (MET) index was computed by the assignment of a multiple of resting metabolic rate (MET score) to each leisure-time activity, and a value of overall weekly MET hours was obtained. Self-perception of competitiveness, anxiety, and psychological dependence levels among the participants were ascertained by means of Likert scales. The estimates of reliability (test-retest intraclass correlation coefficients) in a subsample of our cohort for these scales were 0.58 (95% confidence interval [CI], 0.50-0.65), 0.61 (95% CI, 0.54-0.68), and 0.32 (95% CI, 0.22-0.42) for competitiveness, anxiety, and psychological dependence, respectively.

OUTCOME ASSESSMENT

We defined participants as having incident depression when they were free of depression and antidepressant treatment at baseline and positively responded to the question, "Have you ever been diagnosed as having depression by a medical doctor?" or who reported the habitual use of antidepressant drugs in any of the follow-up questionnaires. A self-reported physician-made diagnosis of depression has demonstrated acceptable validity in the validation study conducted in a subsample of our cohort by means of the Structured Clinical Interview for *DSM-IV* as the criterion standard applied by experienced psychiatrists masked to the answers to the questionnaires.[28] The percentage of confirmed cases of depression was 74.2% (95% CI, 63.3%-85.1%). The percentage of confirmed cases of nondepression was 81.1% (95% CI, 69.1%-92.9%). The estimated sensitivity and specificity for our population were 0.37 and 0.96, respectively.[28]

STATISTICAL ANALYSES

Cox (proportional hazards) regression models were fit to assess the relationship between the baseline adherence to the MDP and the incidence of depression. We also assessed the specific association of each component of the MDP score and the risk of depression. Hazard ratios (HRs) and their 95% CIs were calculated with the lowest category of adherence (or consumption) designated as the reference category. Tests of linear trend across increasing categories were conducted by assigning the medians to each category; this variable was treated as continuous.

In Cox models, age was the underlying time variable. Participants contributed to the follow-up period up to the date of return of their last questionnaire, diagnosis of depression, or death, whichever came first. In addition, the Cox model was stratified by birth cohort to control for calendar period and birth cohort effects.[29]

Other potential confounders included as covariates in the multiple Cox models were sex, marital status (married, other), number of children (continuous), employment status (employed, unemployed), number of work hours per week (none, <35, 35-45, >45), baseline body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and a quadratic term for baseline BMI (continuous), total energy intake (kilocalories per day), physical activity during leisure time (MET hours per week, continuous), smoking (never, past, and current smokers), and some correlates of health consciousness or proxies of an overall healthier lifestyle, such as days per week of consumption of alcoholic beverages (never, 1-2, 3-5, >5), driving after alcohol intake (no or yes), use of seat belt (no or yes), use of sunscreen (no or yes), periodic dental checkups (no or yes), and periodic medical checkups (no or yes). Among women, the analyses were also adjusted for menopausal status, previous mammography screening, and use of the Papanicolaou test. We also performed ancillary analyses after adjustment for scales that assessed the baseline self-perception of competitiveness, anxiety, and dependence levels of the participants and also after adjustment for incident events of cardiovascular disease. To address reverse causation, because being depressed at baseline may determine changes in baseline adherence to the MDP, multiple linear regressions were run by means of a cross-sectional approach. The β coefficients and their 95% CIs were calculated, with prevalence of depression at or before inception designated as the exposure and baseline adherence to the MDP as the outcome.

All P values presented are 2-tailed; $P < .05$ was considered statistically significant. The SPSS software package for Windows version 14.0 (SPSS Inc, Chicago, Illinois) was used for statistical analyses.

RESULTS

The main characteristics of the participants in accordance with categories of adherence to the MDP are presented in **Table 1**. Adherence to this pattern was higher among men, ex-smokers, and married and older individuals. Participants with higher adherence tended to be physically more active and showed a higher total energy intake.

We identified 480 new cases of depression during the follow-up period (156 in men and 324 in women). The association between adherence to the MDP and the risk of depression is given in **Table 2**. Inverse relationships were found for the upper categories of adherence to the MDP with reductions in depression risk higher than 30% in the multiple-adjusted models.

Further adjustment for marital status, number of children, use of seat belts, and other proxies of an overall healthier lifestyle did not change the reported associations (data not shown). Similarly, when the analyses were restricted to the women subsample (n = 5898) and the results were adjusted for all the possible confounders, such as menopausal status and use of screening tests (mammography and Papanicolaou test), the HRs and 95% CIs for the successive categories of MDP adherence were as follows: 1 (reference), 0.88 (0.61-1.28), 0.55 (0.37-0.84), 0.48 (0.30-0.76), and 0.74 (0.50-1.08).

To assess whether the psychological characteristics of the participants could confound the association, the model was also adjusted for self-perception of competitiveness, anxiety, and dependence levels of the participants in an ancillary analysis. The results did not change (data not shown).

Table 1. Characteristics of the Participants in Accordance With Categories of Adherence to the Mediterranean Dietary Pattern

Characteristic	Adherence to the Mediterranean Dietary Pattern Score					*P* Value[a]
	0-2 (n=1949)	3 (n=1860)	4 (n=2082)	5 (n=1881)	6-9 (n=2322)	
Age, mean (SD), y	33.3 (9.8)	35.7 (10.7)	36.8 (11.3)	38.0 (11.6)	41.3 (12.1)	<.001
BMI, mean (SD), kg/m^2	23.0 (3.4)	23.3 (3.3)	23.4 (3.4)	23.7 (3.5)	23.7 (3.3)	<.001
Physical activity during leisure time, mean (SD), MET h/wk	20.8 (20.0)	22.9 (19.5)	24.2 (20.7)	25.1 (23.3)	28.1 (24.7)	<.001
Alcohol intake, mean (SD), g/d	3.9 (8.1)	5.7 (10.8)	6.5 (9.5)	7.8 (11.2)	8.8 (10.3)	<.001
MUFA/SFA ratio, mean (SD)	1.09 (0.17)	1.20 (0.29)	1.27 (0.31)	1.35 (0.32)	1.51 (0.37)	<.001
Legume consumption, mean (SD), g/d	18 (14)	21 (19)	22 (16)	25 (19)	27 (17)	<.001
Cereal consumption, mean (SD), g/d	77 (61)	89 (69)	104 (76)	109 (71)	129 (79)	<.001
Fruit and nut consumption, mean (SD), g/d	187 (151)	264 (229)	320 (260)	389 (283)	494 (340)	<.001
Vegetable consumption, mean (SD), g/d	321 (193)	414 (289)	495 (271)	564 (309)	694 (356)	<.001
Meat and meat products consumption, mean (SD), g/d	196 (79)	184 (77)	182 (76)	175 (77)	153 (72)	<.001
Milk and dairy products consumption, mean (SD), g/d	317 (231)	248 (210)	224 (207)	185 (187)	123 (141)	<.001
Fish consumption, mean (SD), g/d	64 (36)	80 (47)	94 (59)	108 (66)	128 (59)	<.001
Total energy intake, mean (SD), kcal/d	2218 (597)	2277 (633)	2386 (620)	2447 (607)	2510 (582)	<.001
No. of children, mean (SD)	1.0 (1.4)	1.0 (1.5)	1.1 (1.5)	1.1 (1.5)	1.2 (1.5)	.004
Men, %	40.1	38.6	42.0	42.6	44.0	.01[b]
Smoking status, %						<.001[b]
Never smoker	54.9	51.1	47.5	47.0	44.0	
Past smoker	21.6	24.2	27.5	29.7	35.4	
Current smoker	23.5	24.7	25.0	23.3	20.6	
Married, %	40.9	49.2	51.0	52.3	59.9	<.001[b]
Unemployed, %	4.8	5.5	4.8	4.7	3.7	.10[b]
Driving after alcohol intake, %[c]	50.1	52.3	53.4	53.3	52.8	.27[b]
Use of seat belts, %[c]	85.9	85.7	85.8	86.6	87.6	.33[b]
Use of sunscreen, %[c]	86.2	86.8	85.0	85.4	87.3	.24[b]
Use of screening tests, %						
Medical checkup	70.6	71.2	69.5	70.6	70.5	.81[b]
Dental checkup	91.0	91.1	90.4	90.3	90.4	.87[b]
Mammography[d]	18.9	21.6	21.7	21.8	23.2	.13[b]
Papanicolaou test[d]	40.1	41.4	41.6	39.8	41.7	.82[b]
Menopausal status, %[d]						
Postmenopausal	52.8	53.9	55.4	55.9	53.3	.49[b]
Hours worked per week, %						.08[b]
None	15.1	14.1	13.1	13.6	13.6	
<35	17.2	17.2	16.6	16.6	16.6	
35-45	38.0	40.1	38.5	38.3	38.3	
>45	29.6	28.6	31.8	31.4	31.4	
Personality scores (range, 0-10), mean (SD)						
Competitiveness	6.9 (1.8)	6.9 (1.8)	7.0 (1.8)	7.0 (1.8)	7.0 (1.8)	.99[e]
Anxiety	6.0 (2.3)	6.0 (2.2)	6.0 (2.2)	6.1 (2.2)	6.0 (2.2)	.87[e]
Psychological dependence	3.8 (2.8)	3.8 (2.9)	3.7 (2.9)	3.7 (2.9)	3.5 (2.9)	<.001[e]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

[a] *P* values are shown for analysis of variance test.

[b] *P* values are shown for χ^2 test.

[c] Includes only participants who drive or sunbathe (self-reported).

[d] Includes only women. Samples sizes for each category were as follows: 0 to 2, n=616; 3, n=616; 4, n=669; 5, n=604; and 6 to 9, n=693.

[e] *P* values are shown for regression models.

In another ancillary analysis, the results were also adjusted for the incidence of new cardiovascular disease during follow-up but previous to the development of depression. The HRs (95% CIs) for the successive categories of adherence in this analysis were as follows: 1 (referent), 0.74 (0.57-0.98), 0.66 (0.50-0.87), 0.49 (0.36-0.67), and 0.58 (0.44-0.77) (*P* for trend <.001). When we restricted the analysis to incident cases that corresponded exclusively to participants who reported a physician-made diagnosis of depression (with the exclusion of those who only reported the use of antidepressant medication but not a physician-made diagnosis, n=143), the results did not materially change (Table 2, model 3).

To avoid a possible reverse causation bias (that is, participants who were subclinically depressed at baseline and could change their diet as a consequence of preexisting depression), we repeated the analysis with the exclusion of those cases of depression reported in the first 2 years of follow-up (n=243). The HRs (95% CIs) for the fourth and fifth categories of MDP adherence were not attenuated, but they even exhibited a stronger inverse association: 0.42 (0.27-0.66) and 0.50 (0.33-0.74), respectively.

Table 2. Association Between Adherence to the Mediterranean Dietary Pattern and Risk of Depression

Variable	Adherence to the Mediterranean Dietary Pattern Score (Median Score)					*P* Value for Trend
	0-2 (2)	3 (3)	4 (4)	5 (5)	6-9 (6)	
No. of cases per person-years	126/8866	91/8253	97/9240	67/8131	99/9715	
Crude rates per 10^3 (95% CI)[a]	14.2 (11.8-16.9)	11.0 (8.9-13.5)	10.5 (8.5-12.8)	8.2 (6.4-10.5)	10.2 (8.3-12.4)	
Model 1						
HR (95% CI)[b]	1 [Reference]	0.74 (0.57-0.98)	0.66 (0.50-0.86)	0.49 (0.36-0.67)	0.58 (0.44-0.77)	<.001
Model 2						
No. of cases per person-years	67/8748	48/8167	46/9138	32/8061	44/9605	<.001
HR (95% CI)[b]	1 [Reference]	0.73 (0.50-1.06)	0.56 (0.38-0.83)	0.42 (0.27-0.66)	0.50 (0.33-0.74)	
Model 3						
No. of cases per person-years	86/8726	65/8155	61/9116	50/8075	75/9631	.007
HR (95% CI)[b]	1 [Reference]	0.79 (0.57-1.09)	0.67 (0.48-0.93)	0.56 (0.39-0.80)	0.69 (0.50-0.96)	

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] The CIs for rates were calculated with Stata by means of an exact method.
[b] By definition, if the 95% CI of the HR does not include the unity (HR=1.00), the results are statistically significant (2-tailed $P<.05$). For model 1, the HRs were estimated with Cox regression and adjusted for sex, age (years), smoking status (never, current, past smoker), body mass index (calculated as weight in kilograms divided by height in meters squared) and its quadratic term, physical activity during leisure time (metabolic equivalent hours per week), energy intake (kilocalories per day), and employment status (no or yes). Model 2 was the same as model 1 but excludes participants with early depression (those observed only during the first 2 years of follow-up; n=243). Model 3 was the same as model 1 but excludes participants who reported the use of antidepressant medication during follow-up but not a physician-made diagnosis of depression (n=143).

Table 3. Association Between the Consumption of Each Component of the Score Built to Assess the Adherence to the Mediterranean Dietary Pattern and Risk of Depression

Component of the Score[a]	Sex-Specific Median, g/d[b]		HR (95% CI) for Depression in the 4 Upper Quintiles of Each Item Compared With the Lowest Quintile				*P* Value for Trend
	Men	Women	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Vegetables	398	485	0.88 (0.67-1.17)	0.87 (0.66-1.16)	0.94 (0.71-1.25)	0.93 (0.69-1.24)	.81
Fruit and nuts	236	290	0.69 (0.53-0.91)	0.67 (0.51-0.88)	0.69 (0.52-0.91)	0.61 (0.45-0.82)	.007
Legumes	21	21	0.76 (0.58-1.00)	0.73 (0.55-0.96)	0.65 (0.49-0.86)	0.76 (0.57-1.00)	.03
Cereal	86	79	0.95 (0.72-1.26)	0.85 (0.64-1.13)	0.86 (0.64-1.15)	0.81 (0.60-1.07)	.16
Fish and seafood	85	84	0.83 (0.64-1.09)	0.63 (0.47-0.85)	0.77 (0.58-1.02)	0.85 (0.64-1.13)	.31
Meat and meat products	177	167	0.92 (0.67-1.26)	0.98 (0.72-1.32)	1.14 (0.84-1.53)	1.35 (1.01-1.80)	.008
Whole-fat dairy	181	136	0.73 (0.53-1.02)	1.00 (0.74-1.35)	1.18 (0.89-1.56)	1.11 (0.83-1.48)	.03
MUFA/SFA ratio	1.19	1.24	0.94 (0.71-1.23)	0.81 (0.61-1.07)	0.73 (0.54-0.98)	0.76 (0.56-1.02)	.04
Alcohol[c]			0.85 (0.64-1.13)	1.07 (0.82-1.40)	0.79 (0.58-1.06)	0.84 (0.62-1.14)	.35

Abbreviations: CI, confidence interval; HR, hazard ratio; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.
[a] Energy-adjusted components consumption.
[b] Median of consumption used to build the Mediterranean dietary pattern. These medians, as used to define the components of the Mediterranean dietary pattern score, were not adjusted for energy intake. The HR was adjusted for sex, age (years), smoking status (never, current, past smoker), body mass index (calculated as weight in kilograms divided by height in meters squared) and its quadratic term, physical activity during leisure time (metabolic equivalent hours per week), energy intake (kilocalories per day), and employment status (no or yes). The HRs (95% CIs) are presented for the 4 upper quintiles (second through fifth) by use of the first quintile as reference.
[c] Alcohol consumption was not adjusted for energy intake. For alcohol, as a component of the Mediterranean dietary pattern score, 1 point was scored if the consumption was moderate (10-50 g/d for men and 5-25 g/d for women). Therefore, alcohol medians were not used.

Table 3 gives the association between energy-adjusted baseline consumption of the different MDP components (quintiles) and the risk of self-reported depression. Participants with the lowest consumption (first quintile) were considered to comprise the reference category. The multiple adjusted HRs (95% CIs) of depression for successive quintiles of consumption of fruit and nuts were 1 (referent), 0.69 (0.53-0.91), 0.67 (0.51-0.88), 0.69 (0.52-0.91), and 0.61 (0.45-0.82). The linear trend across categories of fruit and nut consumption was statistically significant (*P* for trend=.007). Similar estimates were obtained for consumption of legumes and the MUFA/SFA ratio with statistically significant dose-response relationships. With regard to fish intake, a reduction in risk of more than 20% was observed for intermediate quintiles (third and fourth), although the linear trend was not significant. Conversely, significant adverse linear trend tests were observed for whole-fat dairy and meat consumption.

When we merged the 3 upper quintiles (third through fifth) and compared them to the lowest quintile, significant associations were found for some of the supposedly beneficial items of the score. The HRs (95% CIs) were 0.67 (0.54-0.84) for fruit and nuts, 0.71 (0.57-0.88) for legumes, 0.73 (0.59-0.91) for fish, and 0.79 (0.63-1.00) for the MUFA:SFA ratio.

Moderate alcohol consumption yielded an HR of 0.81 (95% CI, 0.62-1.06), whereas for higher intake the HR was 0.94 (95% CI, 0.74-1.18). We also assessed the association with different types of beverages (wine, beer,

or spirits), but no clear association was found for any of them (HR [95% CI] for the highest consumption vs no consumption: wine = 0.92 [0.73-1.16], beer = 0.84 [0.67-1.05], and spirits = 1.07 [0.54-2.10]).

Finally, to ensure the direction of the association between the adherence to the MDP and the risk of depression, a cross-sectional analysis was performed to assess the association between being depressed at or before baseline and the 9-point score of adherence to the MDP. No difference in adherence was found between depressed (n = 1232) and nondepressed participants (10 094) at baseline (sex and age adjusted $\beta = -.005$, $P = .93$; multiple-adjusted $\beta = .014$, $P = .79$).

COMMENT

An inverse association between adherence to the MDP and the risk of self-reported clinical depression has been found in this longitudinal analysis of the SUN cohort. The specific mechanisms by which a better adherence to the MDP could help to prevent the occurrence of depression are not well known.

Alterations in endothelial cell signaling cascades, proinflammatory cytokines, insulin and glucose homeostasis, and elevations in plasma homocysteine levels have been reported to be present in patients with depression.[30-37] On the other hand, the MDP has been proposed as a healthy dietary pattern because it is related to reductions in these vascular, inflammatory, and metabolic processes through improvements in endothelial function, decreases in proinflammatory cytokines production, and favorable changes in the mechanisms responsible for the metabolic syndrome.[38-49] So, it makes sense to hypothesize a potential protective role of an overall healthy food pattern, such as the MDP, with regard to depression risk.

Endothelial cells synthesize and secrete brain-derived neurotrophic factor (BDNF),[50] a peptide that is critical for axonal growth, neuronal survival, and synaptic plasticity.[30] An emerging concept in neuroscience is that perturbations in the health of cerebral endothelium (such as some loss of the neuroprotection afforded by BDNF) may mediate progressive neuronal dysfunction.[50] Moreover, BDNF levels have been reported to be reduced in patients with depression, and antidepressants seem to upregulate BDNF and other neurotrophic and growth factors.[51] Therefore, one of the potential mechanisms that could relate adherence to the MDP with lower depression risk might be hypothesized through improving BDNF production because of favorable effects of the MDP on endothelial function.

A high consumption of red wine and olive oil, important components of the MDP, can improve the postprandial endothelial function in healthy individuals.[38] More importantly, improvements in endothelial function have been attributed to a better adherence to the overall MDP.[39-41] Reductions in low-grade systemic inflammation status are also attributed to the MDP and may partially explain the inverse association between the MDP and clinical depression. Depressive disorders are associated with increased production of proinflammatory cytokines, such as interleukins 1 and 6 and C-reactive protein.[31-35] These cytokines, whose levels are in part determined by dietary intake, may inhibit BDNF expression, interfere with neurotransmitter metabolism, and alter neurotransmitter messenger RNA. The MDP has been shown to reduce the levels of these cytokines and inflammatory modulators.[39,40,42-44]

Finally, it is well known that coronary heart disease (CHD) and some of its major risk factors, such as hypertension,[52] obesity,[53] diabetes mellitus,[54] metabolic syndrome,[55,56] or low high-density lipoprotein cholesterol levels,[55] could be more prevalent among depressed patients. These major cardiovascular risk factors improve substantially with better adherence to the MDP. The MDP is associated with better glucose metabolism,[40,45] reductions in blood pressure,[40,46] and protection against abdominal obesity,[40,47] the metabolic syndrome,[48,49] and higher high-density lipoprotein cholesterol levels.[40,50] In any case, the effect of the MDP with regard to depression did not seem to be mediated through CHD in our cohort because when our analyses were adjusted for the occurrence of CHD during follow-up, the results did not change. The most likely explanation, therefore, is that the beneficial effects of a better adherence to the MDP with regard to CHD and depression are mediated by the accrual of several diverging or largely independent mechanisms.

Consistent with our findings, a small trial[21] with obese children recently found that the promotion of the MDP together with weight loss led to reduced depression scores. Also, a cross-sectional study[22] supports the beneficial effect of the MDP with regard to mental health. Nevertheless, to our knowledge, this is the first time that the association between adherence to the MDP and the incidence of depression has been assessed in a large prospective cohort study.

The main components of the MDP ensure an adequate intake of ω-3 PUFAs (from fish), MUFAs (from olive oil), and natural folate and other B vitamins (from legumes, fruit and nuts, and vegetables). Some previous epidemiologic studies[11-16,57] have mainly suggested a beneficial role of ω-3 fatty acids with regard to depression, although there are inconsistencies. Fish consumption has also been inversely associated with depression risk in several epidemiologic studies,[14,16] although the consistency for these results is also not complete. The SUN cohort, in another analysis,[14] found that moderate to high levels of fish consumption (third through fourth quintiles) exhibited a relative risk reduction of mental disorders greater than 30%. We have replicated those results specifically for depression in this analysis with a longer follow-up and a higher number of participants. Our results are consistent with the possibility that very low fish consumption is associated with an increased risk of depression, but once a threshold of intake is reached, no further reduction in risk is obtained.

High olive oil consumption is a good source of MUFAs (oleic acid) and represents a salient characteristic of the MDP. The beneficial effect of the MDP with regard to depression can be partly attributed to olive oil.[5,58] Besides its antioxidant properties, olive oil increases the δ-9 desaturase enzyme activity and maintains, in this manner, the physiochemical properties of neuronal mem-

branes.[58] However, epidemiologic evidence with regard to the association between olive oil consumption and depression is scarce.[6,59,60] Recently, a Greek follow-up study[6] reported that olive oil was inversely associated with geriatric depression risk scores. The significant inverse linear trend that we have found for the MUFA/SFA ratio is largely consistent with those results. In addition, a beneficial effect of olive oil consumption with regard to depression symptoms has been proposed as a possible explanation for the lack of effect of ω-3 PUFA relating to depression found in several randomized trials where olive oil was used in the control group as placebo.[57,61,62]

Adherence to the MDP also ensures sufficient intake of folate and B vitamins. Methionine is a precursor of *S*-adenosylmethionine, which acts in several methylation reactions, such as those that involve serotonin and other monoamine neurotransmitters with antidepressant properties. Folate is required for the synthesis of methionine from homocysteine, and vitamins B_{12} and B_6 also serve as cofactors for enzymes involved in homocysteine metabolism.[10,13] Few cross-sectional[13,15,19,20] and follow-up studies[18,19] have analyzed the role of B-vitamin intake with regard to depression; those studies obtained conflicting results.

However, the role of the overall dietary pattern may be more important than the effect of single components. It is plausible that the synergistic combination of a sufficient provision of ω-3 fatty acids together with other natural unsaturated fatty acids and antioxidants from olive oil and nuts, flavonoids, and other phytochemicals from fruit and other plant foods and large amounts of natural folates and other B vitamins in the overall MDP may exert a fair degree of protection against depression.

A possible alternative explanation of our reported results could be related to an environmental or genetic predisposition. In this way, some individuals more vulnerable to depression could also be predisposed to several unhealthy behaviors because of genetic or environmental factors (cultural trends, upbringing, peer pressure, and family or social networks). Thus, the relationship between the adherence to the MDP and clinical depression might not be causal. Individuals capable of the maintenance of a healthy lifestyle (exercising, quitting smoking, and following the MDP) could be highly motivated and conscious about their health status. Although all the analyses have been adjusted for several proxies of a healthy lifestyle, because of the observational nature of our study, we cannot rule out the possibility that some unknown or unmeasured confounders related to lifestyle might have biased our reported associations. Moreover, it is plausible that some of these participants may have personality traits associated with better mental health, such as high self-control and willpower. These features could protect them against the development of a psychiatric illness such as depression. However, when we adjusted our estimates in ancillary analyses for some psychological characteristics of our participants (competitiveness, anxiety, and psychological dependence levels), the reported associations did not change. The moderate test-retest reliability of these scales represents a weakness, and we used them only in ancillary analyses in an attempt to reduce the degree of potential confounding induced by personality characteristics. In any case, we acknowledge the possibility of residual confounding even after adjusting for those characteristics.

The possibility of reverse causality could be thought of as an alternative explanation for our results. Participants with subclinical depression at the beginning of the study might have changed their food habits because of their mood disorder, which would lead them to a decrease in the consumption of supposedly healthy food items. However, our data are not consistent with this explanation because the exclusion of depression cases diagnosed during the first 2 years of follow-up strengthened the magnitude of the association.

Another potential limitation of our study is related to the methods used for the case ascertainment of clinical depression, based on self-reports and/or the use of antidepressant drugs, that could be used for treating conditions other than depression. Nevertheless, when we conducted additional sensitivity analyses by exclusion of those individuals who reported only the use of antidepressant medication, the results did not change. The use of self-report to collect a physician-made diagnosis of clinical depression could have led to an overestimation or underestimation of incidence rates of depression. The underestimation of true cases, and consequently of low sensitivity but very high specificity, seems more probable, as the estimates of our validation study suggested.[28] In an independent study,[63] underdiagnosis of depression was found in 44.3% of patients who attended a primary care center. Theoretically, with perfect specificity, nondifferential sensitivity of disease misclassification will not bias the relative risk estimate.[64] In addition, the participants from our cohort are highly educated and highly motivated to participate in the study, so it is unlikely that they may have misreported the correct diagnosis. Similarly, although the validity and reliability of our food frequency questionnaire have been evaluated,[25] nondifferential misclassification might also exist in dietary exposures, and it is likely that this factor would bias the estimates toward the null.

On the other hand, some potential confounders, particularly those related to psychological characteristics such as family history of depressive disorders, use of illicit drugs, loneliness, or social networks of participants, have not been collected for the SUN cohort. The lack of control for these potential confounders demands caution in the interpretation of our findings. We also acknowledge the limitation of nondifferentiation between depression subtypes.

In summary, the results of our analysis suggest the possibility that the MDP is protectively associated with depression. We acknowledge that our findings must be confirmed by additional prospective studies with better control of other potential confounders and also by trials with a more objective and rigorous assessment of the outcome.

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Author Affiliations: Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Spain (Drs Sánchez-Villegas and Serra-Majem); Division of Preventive Medi-

cine and Public Health, University of Jaén, Spain (Dr Delgado-Rodríguez); Department of Preventive Medicine and Public Health, Clinic of the University of Navarra, Pamplona, Spain (Drs Sánchez-Villegas, Alonso, and Martínez-González); Department of Psychiatry and Medical Psychology, University of Navarra (Drs Schlatter and Lahortiga); and Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis (Dr Alonso).

Correspondence: Miguel Angel Martínez-González, MD, PhD, MPH, Department of Preventive Medicine and Public Health, University of Navarra—Clinic of the University of Navarra, Pamplona, Spain (mamartinez@unav.es).

Author Contributions: *Study concept and design:* Sánchez-Villegas and Martínez-González. *Acquisition of data:* Sánchez-Villegas, Schlatter, Lahortiga, and Martínez-González. *Analysis and interpretation of data:* Sánchez-Villegas, Delgado-Rodríguez, Alonso, and Martínez-González. *Drafting of the manuscript:* Martínez-González. *Critical revision of the manuscript for important intellectual content:* Sánchez-Villegas, Delgado-Rodríguez, Alonso, Schlatter, Lahortiga, Serra Majem, and Martínez-González. *Statistical analysis:* Sánchez-Villegas and Martínez-González. *Obtained funding:* Sánchez-Villegas, Delgado-Rodríguez, and Martínez-González. *Administrative, technical, and material support:* Sánchez-Villegas and Martínez-González. *Study supervision:* Sánchez-Villegas and Martínez-González.

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