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ORIGINAL CONTRIBUTION

# Prospective association between adherence to the Mediterranean diet and risk of depressive symptoms in the French SU.VI.MAX cohort

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**Abstract**
*Purpose* This study examines whether adherence to the Mediterranean Diet (MD) measured by several dietary indexes was associated with incident depressive symptoms in a large French cohort.
*Methods* The study sample consisted of 3523 participants from the Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) cohort who had at least three dietary records at baseline during the first 2 years of follow-up (1994–1996), free of depression at the beginning of the study (1996–1997) and available Center for Epidemiologic Studies Depression Scale (CES-D) data at the end of follow-up (2007–2009). The rMED was computed. Incident depressive symptoms were defined by a CES-D score ≥17 for men and ≥23 for women in 2007–2009. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using multivariable logistic regression models. Several sensitivity analyses were performed.
*Results* In the present study, 172 incident cases of depressive symptoms were identified during the follow-up (mean = 12.6 years). After adjustment for a wide range of potential confounders, adherence to the rMED score (continuous variable) was significantly associated with incident depressive symptoms in men (OR 0.91; 95% CI 0.83–0.99; $p = 0.03$), but not in women. Use of the Literature-Based Adherence Score to the Mediterranean Diet (LAMD) and the classic MD score (MDS) provide similar findings.
*Conclusions* In the current study, higher adherence to the Mediterranean Diet at midlife was associated with a lower risk of incident depressive symptoms, particularly in men, increasing scientific evidence for a beneficial role of Mediterranean Diet on health. Further investigations in particular among women are needed.

**Keywords** Mental health · Depressive symptoms · Mediterranean diet · Prospective study

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## Introduction

Depression is one of the most prevalent mental health disorders and a leading cause of disability worldwide. According to the World Health Organization (WHO), the depression-related disease burden represents approximately 11% of years lived with disability globally [1]. Thus, depression is an important public health issue for which there is an urgent need to identify modifiable factors, including diet.

Several studies have investigated the relationship of a posteriori-derived dietary pattern with risk of depression or depressive symptoms [2–7]. Overall, meta-analyses suggest a beneficial role of a healthy dietary pattern and

a detrimental role of Western dietary patterns concerning depression risk [2, 3]. However, the studies included in these meta-analyses were mostly cross-sectional. Among the few prospective studies carried out more recently, some have reported an association with a healthy diet in general [6, 7], others with an unhealthy diet [5], and still others have found non-significant associations between dietary patterns and depression or depressive symptoms [4].

Besides, few studies have employed a priori methods aiming to measure adherence to specific dietary patterns, in particular the Mediterranean diet (MD). The MD, characterized by high consumption of olive oil, whole grains and plant foods, low intake of saturated fat and sugar, and moderate consumption of fish, dairy products and red wine [8], is considered one of the best models for healthy eating owing to its beneficial role concerning cardiovascular disease [9], several cancers [10], diabetes [11], metabolic syndrome [12], inflammation and oxidative stress [13], and overall mortality [14]. In particular, recent evidence suggests that inflammation and oxidative stress may constitute possible underlying pathways of the potential link between diet and depression [15, 16]. This is supported by several studies which have reported a significant association between the inflammatory potential of diet and depression or depressive symptoms [17–20].

A meta-analysis including seven cross-sectional and only one cohort study concluded that high and moderate adherence to the MD was associated with a reduced risk for depression [21]. Following this review, one cross-sectional study [22] and three prospective studies have investigated the relationship between adherence to the MD and risk of depression [23–25]. Among these more recent studies, some were restricted to women [24] or older people [23]. In addition, one randomized trial comparing intervention groups (MD supplemented with nuts or extra virgin olive oil) to a control group (low-fat diet) with a median follow-up of 5.4 years showed non-significant effect of intervention on the incidence of depression [26]. However, when the analysis was restricted to participants with diabetes mellitus type 2, the intervention group following an MD supplemented with nuts had lower risk of depression compared with the control group. Besides, a prospective study using factor analysis to identify dietary patterns also reported an inverse association between the 'Mediterranean-style' diet (correlated with high consumption of vegetables, grains and red wine) and the incidence of depressive symptoms [27]. Thus, further prospective studies are needed to clarify and strengthen the evidence regarding the association of the MD with depression or depressive symptoms.

The aim of this study was to assess the long-term association of adherence to a Mediterranean diet using several dietary scores with the risk of depressive symptoms in a large sample of French adults, using detailed dietary data.

## Subjects and methods

### Study population

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study (1994–2002) was initially a randomized, double-blinded placebo-controlled trial which included a total of 13,017 participants. It aimed to evaluate the effect of a daily supplementation with antioxidant vitamins (vitamin C, vitamin E and beta-carotene) and minerals (selenium and zinc) at nutritional doses on the incidence of cancer, ischemic heart disease and overall mortality [28, 29]. At the end of the trial (2002), a total of 6850 subjects who had agreed to participate in a post-supplementation observational follow-up were included in the SU.VI.MAX 2 study (2007–2009).

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted in accordance with the Declaration of Helsinki, and were approved by the ethics committee for studies with human subjects of the Paris-Cochin Hospital (Comités de Consultation pour la Protection des Personnes se Prêtant à la Recherche Biomédicale (CCPPRB) no. 706 and no. 2364, respectively) and the "Commission National de l'Information et des Libertés" (CNIL no. 334641 and no. 907094, respectively). All participants provided written informed consent. The SU.VI.MAX trial was registered at http://www.clinicaltrials.gov/ct2/show/NCT00272428.

For this analysis, we selected participants who had available data from the Center for Epidemiologic Studies-Depression Scale (CES-D) at two time points (1996–1997 and 2007–2009) ($n=5464$), and who had completed at least 3 dietary records during the first 2 years of follow-up ($n=4267$). We excluded, participants with prevalent depressive symptoms at the 1st assessment (defined by CES-D $\geq$17 for men and $\geq$23 for women, $n=697$) [30] and participants who reported treatment for depression at baseline ($n=47$). In total 3523 participants were included in this prospective study (Fig. 1).

### Depressive symptoms

Depressive symptoms were measured using the French version of CES-D scale [30, 31]. The CES-D scale consists of 20 descriptive statements referring to the frequency of depressive symptoms during the previous week with four modalities (0 = 'less than 1 day'; 1 = '1–2 days'; 2 = '3–4 days'; and 3 = '5–7 days'). Total scores range from 0 to 60, with higher scores denoting more depressive symptoms. The French version of CES-D scale provides a sensitivity of 0.76 and a specificity of 0.71. To achieve this specificity and sensitivity level, the cut-off value of 17 for men and 23 for women was suggested by Führer and Rouillon [30]. To define the presence of depressive symptoms, we used in our

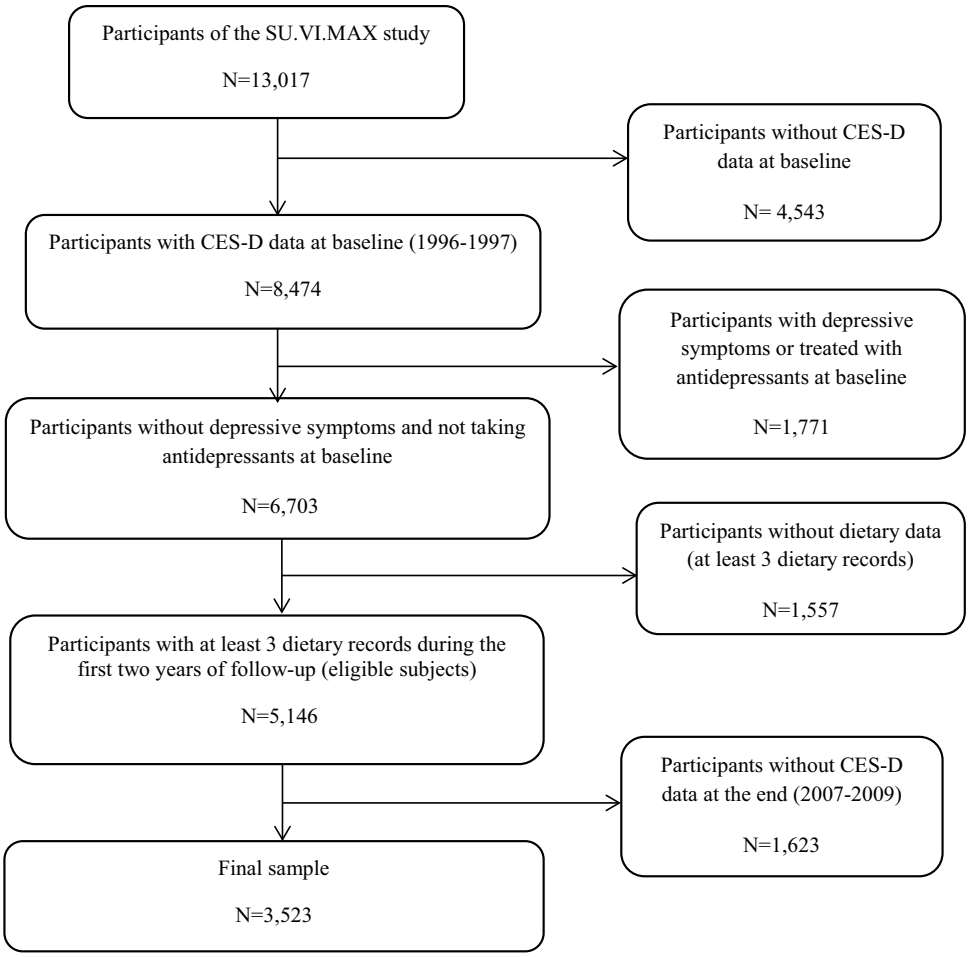


**Fig. 1** Flow chart of participant selection. *CES-D* Center for Epidemiologic Studies-Depression Scale; *SU.VI.MAX* Supplémentation en Vitamines et Minéraux Antioxydants

main analyses, these sex-specific cut-off validated for the French population. Incident cases of depressive symptoms were defined as participants who were free of depressive symptoms at the beginning of the study, who did not use antidepressants at baseline and who had depressive symptoms at the end of the follow-up.

### Dietary data and Mediterranean diet score

Baseline dietary intake information was obtained using repeated 24-h dietary records over a 2 year period (1994–1996). Information was collected every 2 months (6 records per year) so that each day of week and all seasons were covered, thus accounting for intra-individual variation in intake. Participants were assisted by an instruction manual that included validated photographs of foods represented in 3 main portion sizes, 2 intermediate and 2 extreme portion sizes [32]. We used a validated French food-composition table to estimate nutrient intake [33]. Daily food intake refers to the average consumption from all 24-h dietary records completed during the first 2 years of follow-up. The mean (SD) number of dietary records was 10.2 (3.0).

We estimated adherence to the MD using the relative Mediterranean diet score (rMED) described by Buckland et al. [34], and based on 9 "desirable" or "undesirable" dietary components was used. Health-wise, the "desirable" components include grains, vegetables (excluding potatoes), legumes, fruits and nuts, fresh fish, olive oil, and moderate alcohol consumption. In turn, the undesirable components include meat and dairy products. Each component (except for alcohol) was presented as grams per day per 1000 kcal, and divided into sex-specific tertiles. A value between 0 and 2 was assigned to each tertile for the "desirable" components. The scoring was reversed for the "undesirable" components. For alcohol consumption, 2 points were assigned if ethanol consumption was in the range 5–25 g/day for women and 10–50 g/day for men; otherwise, 0 point was attributed. The rMED was the sum of all 9 components, and the total score ranged from 0 point (no adherence) to 18 points (complete adherence).

### Covariates

Information about age (years), sex, educational level (primary, secondary or university level), marital status (living alone, married/living with a partner or separated/divorced/widowed), socio-professional status (unemployed, manual worker, employee/support staff or white-collar worker), and smoking status (never, former or current smoker) was self-reported by participants in the baseline questionnaire. Physical activity was assessed in 1998 using a French self-administered version of the Modifiable Activity Questionnaire (MAQ) [35]. Type, frequency, and duration of all activities performed at least 10 times for 10 min per session during leisure time over the past 12 months were reported. Thus, we assigned Metabolic Equivalent of Tasks (METs) to each leisure-time activity reported, using published compendiums, and calculated average MET hours per week [36, 37]. Anthropometric measurements were collected at the first clinical examination (1995–1996) and body mass index (BMI) was calculated as the ratio of weight to squared height (kg/m$^2$). BMI was split into four categories: underweight (≤18.5); normal weight (between 18.5 and 25); overweight (between 25 and 30) and obesity (≥30). During the follow-up, the incidence of cancer and cardiovascular diseases was recorded and validated by an external committee [29]. Some covariates (educational level, socio-professional status, marital status, BMI, physical activity, tobacco use and delay between both CES-D assessments) have missing values, however, the proportion of missing values was <5% for all variables. Thus, we performed imputations, using multivariable regression methods.

### Statistical analysis

Participants with dietary data during the first 2 years of follow-up, with CES-D data at baseline, without depressive symptoms and not taking antidepressants at baseline ($n = 5146$) were eligible for the present study. Participants included in the study were compared with excluded participants (i.e. without CES-D assessment at follow-up) using Chi square tests or $t$ tests. Baseline and nutritional characteristics were expressed as means ± standard deviation (SD) or numbers (percentages), and compared across tertiles of rMED using linear contrast or Cochran–Mantel–Haenszel tests. For descriptive purposes, nutrient intakes were energy-adjusted using the residual method [38].

Logistic regression models were used to evaluate the association between adherence to the MD (rMED score modeled as tertiles and as a continuous variable) and incidence of depressive symptoms. Linear trend across tertiles was estimated by modelling tertiles of rMED as an ordinal variable. All analyses were conducted in the full sample and by sex because that men and women respond in a different manner to depressive symptom and have different dietary behaviors [39]. Model 1 was unadjusted. Model 2 was adjusted for sex, age, supplementation group, educational level, marital status, socio-professional status, energy intake without alcohol (Kcal/day), number of 24 h-dietary records, interval between the two CES-D measurements, tobacco use status and physical activity. Further adjustments were tested. Model 3 was additionally adjusted for BMI and model 4 for first CES-D measurement. A supplementary model was performed to additionally account for incident cancer or major cardiovascular events during follow-up.

To test the robustness of our findings, the following sensitivity analyses were performed: (1) use of inverse probability weighting (IPW) to account for a possible selection bias [40, 41]; (2) use of the "classic" MD Score (MDS) defined by Trichopoulou et al. [42], and the Literature-Based Adherence Score to the Mediterranean Diet (LAMD) which is not dependent of the sample as fixed cut-offs are used [14]; (3) use of a cut-off value of 16 to define presence of depressive symptoms in both men and women [31]. Specifically, to apply IPW, the probability of inclusion in the present study was calculated for each individual from the eligible population, using multivariable logistic regression. The inverse of that probability was multiplied by the sampling proportion ($n_{\text{include}}/n_{\text{eligible}}$) and was used as a weight in the logistic regression models. Concerning our analyses replacing the rMED by the MDS or LAMD, it should be noted that these three scores are similar in terms of included food groups, except that the MDS and the LAMD fish component also includes canned fish and that the MDS uses the ratio of monounsaturated to saturated fatty acids in place of the olive oil component. For the scoring, the MDS attributes 1 point if consumption of "desirable" components was at or above the sex-specific median value or consumption of "undesirable" components was below the sex-specific median value. For alcohol consumption, 1 point was assigned if ethanol consumption was in the range 5–25 g/day for women and 10–50 g/day for men; otherwise, 0 point was attributed. The MDS ranged between 0 and 9 points [42]. The LAMD scoring was presented in Supplemental table S1. Briefly, a value between 0 and 2 was assigned to food group by using fixed cut-off points (Portion sizes multiplied by the number of portions per day) determined from an extensive, published review of the literature [14]. As for the MDS, a maximum of points is attributed for high consumption of "desirable" components. Thus, the maximum value of the LAMD was 18 points [14]. All statistical tests were 2-sided, with a type I error set at <0.05. All analyses were performed using SAS software (Release 9.4, SAS institute Inc., Cary, NC, USA).

## Results

### Sample characteristics

A total of 3,523 participants (2031 women and 1492 men) were included in this analysis. Compared with excluded participants ($n=1623$), included participants were older, more often men, never-smokers, and allocated to the active supplementation group during the trial phase (Supplemental table S2). The mean (SD) age of participants was 49.5 years (6.2) at baseline. We identified 172 (4.9%) incident cases of depressive symptoms through the end of the follow-up.

Baseline characteristics of the participants across sex-specific tertiles of the rMED scores are presented in Table 1. In both sexes, participants with higher rMED scores (3rd tertile) compared to participants with lower MD adherence (1st tertile) were more often older, better educated and non-smokers. In addition, those women were more often allocated to the active supplementation group during the trial phase and those men were more likely to have a BMI value in the normal weight range. A higher rMED score was also associated in both sexes with higher energy intake from carbohydrates, higher intake of food groups contributing to "desirable" components as expected, total polyunsaturated fatty acids, fiber, most vitamins and minerals, but lower energy intake from lipids and protein, and lower intake of added sugars and saturated fatty acids (Table 2).

**Table 1** Baseline characteristics of the study sample across sex-specific tertiles of relative Mediterranean diet score

| Characteristics | Women ($n=2031$) | | | | Men ($n=1492$) | | | |
|---|---|---|---|---|---|---|---|---|
| | Tertile 1 | Tertile 2 | Tertile 3 | $P_{trend}$[a] | Tertile 1 | Tertile 2 | Tertile 3 | $P_{trend}$[a] |
| rMED range | 0–7 | 8–9 | 10–16 | | 1–7 | 8–10 | 11–17 | |
| *N* | 652 | 573 | 806 | | 422 | 589 | 481 | |
| Age (years) | 46.4 ± 6.3 | 47.8 ± 6.5 | 48.3 ± 6.4 | **<0.0001** | 51.9 ± 4.6 | 51.9 ± 4.8 | 52.6 ± 4.7 | **0.03** |
| Intervention group, *n* (%) | 316 (48.5) | 317 (55.3) | 446 (55.3) | **0.01** | 215 (50.9) | 317 (46.2) | 258 (46.4) | 0.43 |
| Marital status, *n* (%) | | | | 0.99 | | | | 0.75 |
| Living alone | 53 (8.1) | 47 (8.2) | 63 (7.8) | | 10 (2.4) | 17 (2.9) | 9 (1.9) | |
| Married or living with a partner | 538 (82.5) | 474 (82.7) | 670 (83.1) | | 387 (91.7) | 544 (92.4) | 449 (93.3) | |
| Separated, divorced or widowed | 61 (9.4) | 52 (9.1) | 73 (9.1) | | 25 (5.9) | 28 (4.7) | 23 (4.8) | |
| Educational level, *n* (%) | | | | **0.01** | | | | **0.01** |
| Primary | 124 (19.0) | 108 (18.9) | 109 (13.5) | | 99 (23.5) | 130 (22.1) | 89 (18.5) | |
| Secondary | 265 (40.6) | 234 (40.8) | 337 (41.8) | | 170 (40.3) | 206 (35.0) | 174 (36.2) | |
| University level | 263 (40.3) | 231 (40.3) | 360 (44.7) | | 153 (36.3) | 253 (42.9) | 218 (45.3) | |
| Socio-professional status, *n* (%) | | | | 0.38 | | | | 0.27 |
| Unemployed | 93 (14.3) | 80 (14.0) | 108 (13.4) | | 1 (0.2) | 3 (0.5) | 3 (0.6) | |
| Manual worker | 19 (2.9) | 15 (2.6) | 20 (2.5) | | 37 (8.8) | 37 (6.3) | 25 (5.2) | |
| Employee/support staff | 437 (67.0) | 364 (63.5) | 535 (66.4) | | 208 (49.3) | 285 (48.4) | 243 (50.5) | |
| White-collar worker | 103 (15.8) | 114 (19.9) | 143 (17.7) | | 176 (41.7) | 264 (44.8) | 210 (43.7) | |
| Smoking status, *n* (%) | | | | **0.03** | | | | **0.005** |
| Never-smoker | 388 (59.5) | 359 (62.6) | 503 (62.4) | | 138 (32.7) | 208 (35.3) | 187 (38.9) | |
| Former smoker | 173 (26.5) | 148 (25.8) | 231 (28.7) | | 220 (52.1) | 314 (53.3) | 250 (52.0) | |
| Current smoker | 91 (14.0) | 66 (11.5) | 72 (8.9) | | 64 (15.2) | 67 (11.4) | 44 (9.1) | |
| Physical activity (MET-hours/week) | 16.3 ± 18.9 | 17.0 ± 19.2 | 17.5 ± 18.2 | 0.23 | 23.1 ± 26.8 | 22.6 ± 22.4 | 24.9 ± 22.1 | 0.27 |
| Body mass index (kg/m²) | 23.0 ± 3.6 | 23.1 ± 3.3 | 22.8 ± 3.3 | 0.31 | 25.6 ± 2.7 | 25.1 ± 3.0 | 24.7 ± 3.0 | **<0.0001** |
| Body mass index, *n* (%) | | | | 0.51 | | | | **<0.0001** |
| Underweight | 30 (4.6) | 16 (2.8) | 19 (2.4) | | 0 | 3 (0.5) | 5 (1.0) | |
| Normal weight | 486 (74.5) | 436 (76.1) | 646 (80.1) | | 182 (43.1) | 299 (50.8) | 271 (56.3) | |
| Overweight | 105 (16.1) | 96 (16.7) | 108 (13.4) | | 207 (49.0) | 259 (44.0) | 173 (36.0) | |
| Obesity | 31 (4.8) | 25 (4.4) | 33 (4.1) | | 33 (7.8) | 28 (4.7) | 32 (6.6) | |
| Cancer, *n* (%) | 52 (8.0) | 41 (7.2) | 50 (6.2) | 0.19 | 32 (7.6) | 35 (5.9) | 40 (8.3) | 0.63 |
| Cardiovascular diseases, *n* (%) | 11 (1.7) | 6 (1.0) | 7 (0.9) | 0.16 | 35 (8.3) | 30 (5.1) | 36 (7.5) | 0.68 |

Values are means ± standard deviation or numbers (percentages), $n=3523$

Bold $P_{trend}$ values are those that are statistically significant

[a] $P_{trend}$ values are based on linear contrast or Cochran–Mantel–Haenszel tests

**Table 2** Nutritional factors data across sex-specific tertiles of relative Mediterranean diet score

| Characteristics | Women ($n=2031$) | | | | Men ($n=1492$) | | | |
|---|---|---|---|---|---|---|---|---|
| | Tertile 1 | Tertile 2 | Tertile 3 | $P_{trend}$[a] | Tertile 1 | Tertile 2 | Tertile 3 | $P_{trend}$[a] |
| rMED range | 0–7 | 8–9 | 10–16 | | 1–7 | 8–10 | 11–17 | |
| *N* | 652 | 573 | 806 | | 422 | 589 | 481 | |
| Energy intake (Kcal/d) | 1845.2 ± 474.5 | 1883.4 ± 456.9 | 1857.4 ± 428.0 | 0.61 | 2600.3 ± 540.6 | 2478.0 ± 547.5 | 2486.9 ± 554.3 | **0.002** |
| Alcohol intake (g/d) | 11.6 ± 16.7 | 11.7 ± 13.6 | 10.2 ± 9.0 | **0.05** | 38.3 ± 30.6 | 26.4 ± 20.8 | 23.9 ± 15.1 | **<0.0001** |
| Energy intake without alcohol (Kcal/d) | 1764.2 ± 454.6 | 1801.3 ± 441.8 | 1786.1 ± 415.9 | 0.34 | 2331.8 ± 482.0 | 2293.1 ± 514.2 | 2319.7 ± 532.6 | 0.72 |
| Fruits and vegetables (g/d) | 318.5 ± 133.3 | 392.7 ± 159.1 | 458.0 ± 159.3 | **<0.0001** | 347.1 ± 149.3 | 430.0 ± 166.9 | 544.7 ± 186.5 | **<0.0001** |
| Legumes (g/d) | 5.3 ± 12.4 | 8.7 ± 14.0 | 11.7 ± 15.4 | **<0.0001** | 8.7 ± 18.0 | 13.0 ± 18.9 | 17.3 ± 21.4 | **<0.0001** |
| Olive oil (g/d) | 3.9 ± 2.5 | 5.5 ± 3.8 | 6.6 ± 3.7 | **<0.0001** | 4.9 ± 3.3 | 6.4 ± 3.9 | 8.5 ± 4.2 | **<0.0001** |
| Fish (g/d) | 26.4 ± 22.9 | 39.6 ± 32.1 | 49.2 ± 30.8 | **<0.0001** | 33.3 ± 28.8 | 50.2 ± 36.7 | 62.5 ± 37.4 | **<0.0001** |
| Added sugars (g/d) | 40.0 ± 21.2 | 38.1 ± 20.7 | 35.0 ± 17.6 | **<0.0001** | 49.8 ± 24.9 | 46.1 ± 23.0 | 42.7 ± 21.1 | **<0.0001** |
| Refined carbohydrate (g/d) | 156.5 ± 70.0 | 165.3 ± 73.0 | 167.1 ± 70.4 | **0.005** | 229.4 ± 85.6 | 230.8 ± 99.6 | 241.9 ± 99.6 | **0.05** |
| Fast food (g/d) | 8.6 ± 17.4 | 8.4 ± 16.7 | 6.9 ± 15.0 | **0.04** | 9.34 ± 18.9 | 6.61 ± 17.1 | 6.48 ± 14.2 | **0.01** |
| Carbohydrates (%)[b] | 40.9 ± 6.1 | 41.6 ± 6.2 | 42.8 ± 5.4 | **<0.0001** | 41.1 ± 6.0 | 41.8 ± 5.9 | 43.7 ± 6.1 | **<0.0001** |
| Protein (%)[b] | 18.0 ± 2.9 | 17.8 ± 2.9 | 17.4 ± 2.5 | **<0.0001** | 18.1 ± 2.6 | 18.1 ± 2.5 | 17.2 ± 2.3 | **<0.0001** |
| Lipids (%)[b] | 41.1 ± 5.1 | 40.6 ± 5.3 | 39.8 ± 5.0 | **<0.0001** | 40.8 ± 5.1 | 40.0 ± 4.9 | 39.1 ± 5.1 | **<0.0001** |
| Saturated fatty acids (g/d)[c] | 35.1 ± 4.9 | 33.5 ± 4.9 | 31.8 ± 5.1 | **<0.0001** | 44.4 ± 7.0 | 42.4 ± 6.2 | 39.5 ± 6.9 | **<0.0001** |
| Monounsaturated fatty acids (g/d)[c] | 30.2 ± 4.3 | 30.2 ± 4.9 | 30.0 ± 4.4 | 0.24 | 39.6 ± 5.9 | 38.8 ± 6.2 | 38.4 ± 6.0 | **0.005** |
| Polyunsaturated fatty acids (g/d)[c] | 11.5 ± 2.7 | 12.1 ± 3.0 | 12.5 ± 2.9 | **<0.0001** | 14.8 ± 3.6 | 15.2 ± 3.7 | 16.1 ± 3.9 | **<0.0001** |
| N-3 fatty acids (g/d)[c] | 0.7 ± 0.2 | 0.8 ± 0.2 | 0.8 ± 0.2 | **0.0002** | 0.9 ± 0.2 | 1.0 ± 0.2 | 1.0 ± 0.3 | **<0.0001** |
| Beta-carotene (μg/d)[c] | 3309.9 ± 1865.6 | 3941.2 ± 2401.0 | 4319.9 ± 2338.8 | **<0.0001** | 3487.5 ± 2078.8 | 4187.5 ± 2227.7 | 5169.9 ± 2454.4 | **<0.0001** |
| Vitamin C (mg/d)[c] | 83.7 ± 38.8 | 91.9 ± 37.8 | 104.0 ± 39.0 | **<0.0001** | 87.8 ± 40.3 | 99.3 ± 41.3 | 113.3 ± 43.3 | **<0.0001** |
| Vitamin D (μg/d)[c] | 2.2 ± 1.5 | 2.6 ± 1.6 | 2.7 ± 1.7 | **<0.0001** | 2.7 ± 1.5 | 3.2 ± 2.1 | 3.5 ± 2.2 | **<0.0001** |
| Vitamin E (mg/d)[c] | 10.8 ± 3.1 | 11.6 ± 3.2 | 12.5 ± 3.4 | **<0.0001** | 12.8 ± 3.7 | 13.9 ± 4.0 | 15.4 ± 4.3 | **<0.0001** |
| Vitamin B9 (μg/d)[c] | 269.2 ± 64.6 | 292.4 ± 68.8 | 314.3 ± 73.9 | **<0.0001** | 322.6 ± 61.1 | 348.5 ± 69.3 | 380.6 ± 74.4 | **<0.0001** |
| Vitamin B12 (μg/d)[c] | 6.4 ± 4.3 | 6.3 ± 3.7 | 6.4 ± 3.4 | 0.85 | 8.5 ± 4.8 | 8.6 ± 4.4 | 8.3 ± 4.5 | 0.45 |
| Magnesium (mg/d)[c] | 258.0 ± 45.2 | 265.5 ± 45.1 | 272.7 ± 46.4 | **<0.0001** | 341.7 ± 57.3 | 344.36 ± 54.3 | 351.8 ± 54.1 | **0.01** |
| Fiber (g/d)[c] | 15.6 ± 3.6 | 17.6 ± 4.0 | 19.7 ± 4.4 | **<0.0001** | 18.7 ± 3.8 | 21.9 ± 4.7 | 25.2 ± 5.3 | **<0.0001** |

Values are means ± standard deviation, $n=3523$

[a] $P_{trend}$ values are based on linear contrast or Cochran–Mantel–Haenszel tests

[b] Values are percentages of total daily energy intake (without alcohol)

[c] Values were adjusted for energy intake using the residual method

### Association between adherence to the Mediterranean diet and depressive symptoms

An inverse association, that however was non-significant was found between the rMED score (continuous variable) and incidence of depressive symptoms in the full sample (Table 3). In sex-specific models, an inverse relationship was observed between the rMED score and depressive symptoms among men. In model 2, a 1-point increase in the rMED score was associated with a 9% reduction of the risk of depressive symptoms (OR 0.91, 95% confidence interval 0.83–0.99). The associations were non-significant among women. Additional adjustment for BMI did not substantially modify the associations (model 3). An inverse relationship was also observed across rMED tertiles, but the associations were non-significant.

### Sensitivity analyses

The use of IPW to account for potential selection bias did not substantially modify the observed associations (Table 4). Next, use of the MDS provided similar results in terms of trends but the linearity of the association across MDS tertiles was less clear (Supplemental table S3). In the models using the LAMD score, a significantly lower risk of depressive symptoms was observed in the full sample (OR 0.91, 95% confidence interval 0.84–0.98) and in men (OR 0.86, 95% confidence interval 0.76–0.98) (Supplemental table S4). Applying a cut-off value of 16 to define depressive symptoms leads to non-significant findings, but the associations were also similar in terms of trends (Supplemental table S5).

**Table 3** Prospective association between adherence to the Mediterranean diet (rMED score in tertiles and as a continuous variable) and incident depressive symptoms, SU.VI.MAX study

| Model | Tertile 1 | Tertile 2 | Tertile 3 | $P_{trend}$ | Continuous | $P^e$ |
|---|---|---|---|---|---|---|
| All participants ($n=3523$) | | | | | | |
| rMED range | 0–7 | 8–10 | 11–17 | | | |
| *n* | 1074 | 1444 | 1005 | | | |
| Model 1[a] | 1(ref) | 1.05 (0.74–1.48) | 0.64 (0.42–0.99) | 0.06 | 0.94 (0.89–0.99) | 0.03 |
| Model 2[b] | 1(ref) | 1.09 (0.76–1.55) | 0.70 (0.45–1.08) | 0.14 | 0.95 (0.90–1.01) | 0.08 |
| Model 3[c] | 1(ref) | 1.10 (0.77–1.56) | 0.71 (0.46–1.10) | 0.16 | 0.95 (0.90–1.01) | 0.10 |
| Model 4[d] | 1(ref) | 1.16 (0.81–1.66) | 0.78 (0.50–1.21) | 0.34 | 0.96 (0.91–1.02) | 0.23 |
| Women ($n=2031$) | | | | | | |
| rMED range | 0–7 | 8–9 | 10–16 | | | |
| *n* | 652 | 573 | 806 | | | |
| Model 1[a] | 1(ref) | 1.42 (0.87–2.32) | 0.88 (0.54–1.45) | 0.56 | 0.98 (0.91–1.05) | 0.52 |
| Model 2[b] | 1(ref) | 1.49 (0.91–2.45) | 0.95 (0.57–1.59) | 0.80 | 0.99 (0.91–1.06) | 0.70 |
| Model 3[c] | 1(ref) | 1.49 (0.91–2.45) | 0.95 (0.57–1.59) | 0.80 | 0.99 (0.91–1.06) | 0.70 |
| Model 4[d] | 1(ref) | 1.65 (1.00–2.72) | 1.05 (0.62–1.75) | 0.91 | 1.00 (0.93–1.08) | 0.96 |
| Men ($n=1492$) | | | | | | |
| rMED range | 1–7 | 8–10 | 11–17 | | | |
| *n* | 422 | 589 | 481 | | | |
| Model 1[a] | 1(ref) | 0.76 (0.44–1.32) | 0.49 (0.26–0.94) | 0.03 | 0.89 (0.82–0.97) | 0.01 |
| Model 2[b] | 1(ref) | 0.80 (0.46–1.40) | 0.57 (0.29–1.10) | 0.09 | 0.91 (0.83–0.99) | 0.03 |
| Model 3[c] | 1(ref) | 0.84 (0.48–1.48) | 0.58 (0.29–1.13) | 0.11 | 0.91 (0.83–0.99) | 0.04 |
| Model 4[d] | 1(ref) | 0.86 (0.48–1.53) | 0.63 (0.32–1.25) | 0.19 | 0.91 (0.83–1.00) | 0.05 |

*CES-D* Center for Epidemiologic Studies-Depression Scale; *rMED* relative Mediterranean diet; *SU.VI.MAX* Supplémentation en Vitamines et Minéraux Antioxydants

Values are odds ratios (95% confidence intervals)

[a]Not adjusted

[b]Adjusted for age, sex, supplementation group during the trial phase, educational level, marital status, socio-professional status, energy intake without alcohol, number of 24h-dietary records, interval between the two CES-D measurements, tobacco use status, and physical activity

[c]Adjusted for all variables in model 2 and Body mass index

[d]Adjusted for all variables in model 3 and first CES-D measurement

[e]*P* for linear relation (rMED score as a continuous variable)

**Table 4** Prospective association between adherence to the Mediterranean diet (rMED score) and incident depressive symptoms, estimated using inverse probability weighting, SU.VI.MAX study

| Model | Tertile 1 | Tertile 2 | Tertile 3 | $P_{trend}$ | Continuous | $P^e$ |
|---|---|---|---|---|---|---|
| All participants ($n=3523$) | | | | | | |
| rMED range | 0–7 | 8–10 | 11–17 | | | |
| *n* | 1074 | 1444 | 1005 | | | |
| Model 1[a] | 1 (ref) | 1.05 (0.75–1.48) | 0.65 (0.42–0.99) | 0.06 | 0.94 (0.89–0.99) | 0.03 |
| Model 2[b] | 1 (ref) | 1.11 (0.78–1.56) | 0.71 (0.46–1.10) | 0.17 | 0.95 (0.90–1.01) | 0.10 |
| Model 3[c] | 1 (ref) | 1.11 (0.79–1.57) | 0.72 (0.47–1.11) | 0.19 | 0.96 (0.90–1.01) | 0.12 |
| Model 4[d] | 1 (ref) | 1.16 (0.82–1.65) | 0.79 (0.51–1.22) | 0.38 | 0.97 (0.91–1.02) | 0.27 |
| Women ($n=2031$) | | | | | | |
| rMED range | 0–7 | 8–9 | 10–16 | | | |
| *n* | 652 | 573 | 806 | | | |
| Model 1[a] | 1 (ref) | 1.43 (0.90–2.30) | 0.88 (0.54–1.43) | 0.58 | 0.98 (0.92–1.05) | 0.62 |
| Model 2[b] | 1 (ref) | 1.53 (0.95–2.47) | 0.99 (0.60–1.63) | 0.96 | 1.00 (0.93–1.07) | 0.93 |
| Model 3[c] | 1 (ref) | 1.53 (0.95–2.48) | 0.99 (0.60–1.64) | 0.96 | 1.00 (0.93–1.07) | 0.93 |
| Model 4[d] | 1 (ref) | 1.67 (1.03–2.71) | 1.08 (0.65–1.78) | 0.77 | 1.01 (0.94–1.09) | 0.75 |
| Men ($n=1492$) | | | | | | |
| rMED range | 1–7 | 8–10 | 11–17 | | | |
| *n* | 422 | 589 | 481 | | | |
| Model 1[a] | 1 (ref) | 0.75 (0.44–1.29) | 0.48 (0.25–0.91) | 0.02 | 0.89 (0.81–0.97) | 0.01 |
| Model 2[b] | 1 (ref) | 0.80 (0.46–1.39) | 0.55 (0.28–1.08) | 0.08 | 0.90 (0.82–0.98) | 0.02 |
| Model 3[c] | 1 (ref) | 0.84 (0.48–1.47) | 0.57 (0.29–1.11) | 0.10 | 0.91 (0.83–0.99) | 0.03 |
| Model 4[d] | 1 (ref) | 0.86 (0.48–1.52) | 0.61 (0.31–1.22) | 0.17 | 0.91 (0.82–0.99) | 0.04 |

*CES-D* Center for Epidemiologic Studies-Depression Scale; *rMED* relative Mediterranean diet; *SU.VI.MAX* Supplémentation en Vitamines et Minéraux Antioxydants

Values are odds ratios (95% confidence intervals)

[a]Not adjusted

[b]Adjusted for age, sex, supplementation group during the trial phase, educational level, marital status, socio-professional status, energy intake without alcohol, number of 24-hdietary records, interval between the two CES-D measurements, tobacco use status, and physical activity

[c]Adjusted for all variables in model 2 and Body mass index

[d]Adjusted for all variables in model 3 and first CES-D measurement

[e]*P* for linear relation (rMED score as a continuous variable)

## Discussion

In this large prospective study, we investigated the association between adherence to the MD and incident depressive symptoms over a 13 years follow-up period. The use of rMED to measure adherence to the MD shows an inverse association, which however was non-significant in the overall study sample. However, in sex-specific analyses, we observed a 9% reduction in the risk of depressive symptoms for each 1-point rMED increase among men, while non-significant association was observed among women. Sensitivity analyses using the MDS, a cut-off value of 16 to define depressive symptoms, and IPW to correct for potential selection bias lead to similar findings, also the associations were non-significant by applying the cut-off value of 16 to define depressive symptoms. Finally, an inverse association between LAMD score and depressive symptoms was observed in the full sample and among men.

### Comparison with other studies

The prospective studies that examined relationship between the MD and depression or depressive symptoms reported a beneficial role of a high level of adherence to the MD on the risk of depressive symptoms [23–25, 43], consistently with our findings observed in men. Of note, the above-mentioned studies exhibit differences as regards design and methodology including characteristics of the samples, assessment methods and follow-up. For instance, one of these studies was conducted among women and used CES-D score as a continuous variable [24], while another was conducted among people aged 65 years and over [23]. Interestingly, in the study conducted by Sánchez-Villegas et al., accounting for variation of the diet over time leads to attenuated findings [25]. In addition, using time-varying covariates in the Australian Longitudinal Study on Women's Health leads to the loss of the significant association found between diet quality and depression [24]. However, our results cannot be

directly compared to the results in the study conducted by Rienks et al., because the 'Mediterranean-style' diet was identified by factor analysis and included only vegetables, grains and red wine consumption [27].

Our findings may also be interpreted in light of results observed with the healthy dietary pattern extracted using a posteriori methods. Indeed, the available studies argue for a protective effect of a healthy pattern on the risk of depression [2, 3]. In the meta-analysis of Lai et al., including 13 observational studies (of which 4 prospective studies), the authors reported a 16% reduction in risk of depression associated with high adherence to a healthy dietary pattern characterized by high consumption of fruit, vegetables, fish, and whole grains, which are the core components of the MD [3].

In our study, we did not detect any significant relationships among women. In line with this result, the Nurses' Health Study reported non-significant association between Western and Prudent pattern scores (Prudent pattern characterized by high intake of fruits, vegetables, fish, whole-grain products and low-fat dairy) and depression risk [44]. Possible explanations of our finding could include limited statistical power (0.68 in our study), or classification bias related to depressive symptoms among women. Indeed, women generally report more depressive symptoms than do men [45]. Although we used a higher CES-D cut-off for women, we cannot rule out the possibility of false positive cases in the women sub-group. This may also explain the non-significant associations found applying a cut-off value of 16 to define depressive symptoms.

## Mechanisms

A number of plausible pathways have been suggested to explain the association between diet and depression, including inflammation, oxidative stress as well as a modulation of the synthesis of neurotransmitters [15, 16, 46]. Indeed, epidemiological studies have reported an inverse association between adherence to a MD and the levels of inflammatory [47–49] and oxidative stress markers [50]. Specifically, inflammation occurs as a result of an imbalance between pro-inflammatory and anti-inflammatory mediators. In the brain, pro-inflammatory cytokines such as IL-6 and TNF-α, influence nearly all pathways involved in the pathophysiology of depression such as alterations in the expression of neurotransmitters, neuroendocrine function and synaptic plasticity [51].

Long-chain omega-3 fatty acids (derived from fish), and mainly docosahexaenoic acid, which is most abundant in the brain, inhibit the release of pro-inflammatory cytokines and increase the levels of brain-derived neurotrophic factors, leading to an improvement in neurotransmission and synaptic plasticity [52, 53]. In turn, antioxidants (derived from olive oil, legumes, fruit and nuts) reduce oxidative stress resulting from an excess of Reactive Oxygen Species (ROS). When present in excess, ROS inflict damages, affecting cellular constituents with the formation of pro-inflammatory molecules [54]. As for B vitamins (supplied by whole grain, vegetables, legumes, fruit and nuts), they play an important role in the synthesis of neurotransmitters that affect mood [55]. Recently, microbiota-based mechanisms have been proposed based on the links between gut inflammation and the brain through the vagus nerve. Indeed, short-chain fatty acids, which are produced during fermentation of dietary fiber by intestinal microbiota, could have a positive impact on immune functioning [56, 57].

Overall, the beneficial effect of healthy diet, particularly of the MD on depression may thus partly be attributed to its core components, which ensure an adequate intake of omega-3 fatty acids, monounsaturated fatty acids, antioxidant nutrients and B vitamins [58].

## Strengths and limitations

Some limitations of the present study should be noted. First, caution is needed when generalizing our findings as the participants are motivated volunteers in a long-term nutrition-focused study. Despite the prospective design of our study, reverse causality could not be entirely excluded due to the observational design. Finally, despite the wide range of confounders accounted for in the models, others unmeasured factors such as family history of depressive disorders, stressful life events, sleep disorders, the number of subjects living at home and personality traits might have led to potential residual confounding. In addition, no information was available during follow-up on antidepressants and the diagnosis of depression. However, adjustment for cancer and cardiovascular disease during follow-up did not substantially modify our findings (data not shown). Finally, as aforementioned, our study may be underpowered leading to non-significant association.

The present study also exhibits a number of important strengths including its prospective design, the large sample, and the quality of the dietary data based on repeated 24h dietary records to improve the assessment of intra-individual variation in consumption. Another strength is the availability of CES-D at baseline, hence the ability to screen and exclude individuals with depressive symptoms at baseline. In addition, we performed several sensitivity analyses to estimate the robustness of our findings.

In conclusion, this large prospective study provides evidence that adherence to the MD, may help in reducing depressive symptom incidence, in particular among men. It suggests the promotion of a healthy diet, characterized by a high consumption of fruit and vegetables, fish, whole grain products and olive oil, may be an effective strategy for the primary prevention of depressive symptoms. Further

prospective studies are needed to better identify and subsequently target high-risk subgroups.

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**Compliance with ethical standards**

**Conflict of interest** Cédric Lemogne has received honoraria for board membership from Lundbeck and for speaking at invited symposia from Astra Zeneca, Daiichi-Sankyo, Lundbeck and Servier. None of the other authors declare any conflict of interest.

## References

1. World Health Organization (2013) Mental health action plan 2013–2020. World Health Organization, Geneva
2. Rahe C, Unrath M, Berger K (2014) Dietary patterns and the risk of depression in adults: a systematic review of observational studies. Eur J Nutr 53:997–1013
3. Lai JS, Hiles S, Bisquera A, Hure AJ, McEvoy M, Attia J (2014) A systematic review and meta-analysis of dietary patterns and depression in community-dwelling adults. Am J Clin Nutr 99:181–197
4. Gougeon L, Payette H, Morais J, Gaudreau P, Shatenstein B, Gray-Donald K (2015) Dietary patterns and incidence of depression in a cohort of community-dwelling older Canadians. J Nutr Health Aging 19:431–436
5. Tsai HJ (2015) Dietary patterns and depressive symptoms in a Taiwanese population aged 53 years and over: results from the Taiwan Longitudinal Study of Aging. Geriatr Gerontol Int10
6. Dipnall JF, Pasco JA, Meyer D, Berk M, Williams LJ, Dodd S, and Jacka FN (2015) The association between dietary patterns, diabetes and depression. J Affect Disord 174:215–224
7. Ruusunen A, Lehto SM, Mursu J, Tolmunen T, Tuomainen TP, Kauhanen J, and Voutilainen S (2014) Dietary patterns are associated with the prevalence of elevated depressive symptoms and the risk of getting a hospital discharge diagnosis of depression in middle-aged or older Finnish men. J Affect Disord 159:1–6
8. Trichopoulou A, Martinez-Gonzalez MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, Mozaffarian D, de LM (2014) Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med 12:112
9. Martinez-Gonzalez MA, Bes-Rastrollo M (2014) Dietary patterns, Mediterranean diet, and cardiovascular disease. Curr Opin Lipidol 25:20–26
10. Ostan R, Lanzarini C, Pini E, Scurti M, Vianello D, Bertarelli C, Fabbri C, Izzi M, Palmas G, Biondi F, Martucci M, Bellavista E, Salvioli S, Capri M, Franceschi C, Santoro A (2015) Inflammaging and cancer: a challenge for the Mediterranean diet. Nutrients 7:2589–2621
11. Koloverou E, Esposito K, Giugliano D, Panagiotakos D (2014) The effect of Mediterranean diet on the development of type 2 diabetes mellitus: a meta-analysis of 10 prospective studies and 136,846 participants. Metabolism 63:903–911
12. Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D (2013) Mediterranean diet and metabolic syndrome: an updated systematic review. Rev Endocr Metab Disord 14:255–263
13. Martinez-Gonzalez MA, Salas-Salvado J, Estruch R, Corella D, Fito M, Ros E (2015) Benefits of the Mediterranean Diet: insights From the PREDIMED Study. Prog Cardiovasc Dis 58:50–60
14. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A (2014) Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr 17:2769–2782
15. Patel A (2013) Review: the role of inflammation in depression. Psychiatr Danub 25(Suppl 2):S216–S223
16. Lopresti AL, Hood SD, Drummond PD (2013) A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise. J Affect Disord 148:12–27
17. Shivappa N, Schoenaker DA, Hebert JR, Mishra GD (2016) Association between inflammatory potential of diet and risk of depression in middle-aged women: the Australian Longitudinal Study on Women's Health. Br J Nutr 116:1077–1086
18. Akbaraly T, Kerlau C, Wyart M, Chevallier N, Ndiaye L, Shivappa N,Hebert JR, Kivimaki M (2016) Dietary inflammatory index and recurrence of depressive symptoms: results from the Whitehall II Study. Clin Psychol Sci 4:1125–1134
19. Sanchez-Villegas A, Ruiz-Canela M, Fuente-Arrillaga C, Gea A, Shivappa N, Hebert JR, Martinez-Gonzalez MA (2015) Dietary inflammatory index, cardiometabolic conditions and depression in the Seguimiento Universidad de Navarra cohort study. Br J Nutr 114:1471–1479
20. Lucas M, Chocano-Bedoya P, Schulze MB, Mirzaei F, O'Reilly EJ, Okereke OI, Hu FB, Willett WC, Ascherio A (2014) Inflammatory dietary pattern and risk of depression among women. Brain Behav Immun 36:46–53
21. Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN, Kosti R, Scarmeas N (2013) Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol 74:580–591
22. Veronese N, Stubbs B, Noale M, Solmi M, Luchini C, Maggi S (2016) Adherence to the Mediterranean diet is associated with better quality of life: data from the Osteoarthritis Initiative. Am J Clin Nutr 104:1403–1409
23. Skarupski KA, Tangney CC, Li H, Evans DA, Morris MC (2013) Mediterranean diet and depressive symptoms among older adults over time. J Nutr Health Aging 17:441–445
24. Lai JS, Oldmeadow C, Hure AJ, McEvoy M, Byles J, Attia J (2016) Longitudinal diet quality is not associated with depressive symptoms in a cohort of middle-aged Australian women. Br J Nutr 115:842–850
25. Sanchez-Villegas A, Henriquez-Sanchez P, Ruiz-Canela M, Lahortiga F, Molero P, Toledo E, and Martinez-Gonzalez MA (2015) A longitudinal analysis of diet quality scores and the risk of incident depression in the SUN Project. BMC Med 13:197
26. Sanchez-Villegas A, Martinez-Gonzalez MA, Estruch R, Salas-Salvado J, Corella D, Covas MI, Aros F, Romaguera D, Gomez-Gracia E, Lapetra J, Pinto X, Martinez JA, Lamuela-Raventos RM, Ros E, Gea A, Warnberg J, and Serra-Majem L (2013) Mediterranean dietary pattern and depression: the PREDIMED randomized trial. BMC Med 11:208–211

27. Rienks J, Dobson AJ, Mishra GD (2013) Mediterranean dietary pattern and prevalence and incidence of depressive symptoms in mid-aged women: results from a large community-based prospective study. Eur J Clin Nutr 67:75–82
28. Hercberg S, Preziosi P, Briancon S, Galan P, Triol I, Malvy D, Roussel AM, Favier A (1998) A primary prevention trial using nutritional doses of antioxidant vitamins and minerals in cardiovascular diseases and cancers in a general population: the SU.VI.MAX study–design, methods, and participant characteristics. SUpplementation en VItamines et Mineraux AntioXydants. Control Clin Trials 19:336–351
29. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briancon S (2004) The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med 164:2335–2342
30. Führer R and Rouillon F. (1989) The French version of the Center for Epidemiologic Studies-Depression Scale. Psychiatrie et Psychologie 4:163–166
31. Radloff LS (1977) The CES-D Scale, a self-report depression scale for research in the general population. Appl Psychol Meas 1:385–401
32. Le Moullec N, Deheeger M., Preziosi P, et al (1996) Validation du manuel photos utilisé pour l'enquête alimentaire de l'étude SU.VI.MAX. Cahier de Nutrition et de Diététique 31:158–164
33. Hercberg,Sc (2005) Table de composition SU.VI.MAX des aliments.
34. Buckland G, Agudo A, Lujan L, Jakszyn P, Bueno-de-Mesquita HB, Palli D, Boeing H, Carneiro F, Krogh V, Sacerdote C, Tumino R, Panico S, Nesi G, Manjer J, Regner S, Johansson I, Stenling R, Sanchez MJ, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Allen NE, Key TJ, Bingham S, Kaaks R, Overvad K, Jensen M, Olsen A, Tjonneland A, Peeters PH, Numans ME, Ocke MC, Clavel-Chapelon F, Morois S, Boutron-Ruault MC, Trichopoulou A, Lagiou P, Trichopoulos D, Lund E, Couto E, Boffeta P, Jenab M, Riboli E, Romaguera D, Mouw T, Gonzalez CA (2010) 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 91:381–390
35. Vuillemin A, Oppert JM, Guillemin F, Essermeant L, Fontvieille AM, Galan P, Kriska AM, Hercberg S (2000) Self-administered questionnaire compared with interview to assess past-year physical activity. Med Sci Sports Exerc 32:1119–1124
36. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr (1993) Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 25:71–80
37. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS (2000) Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 32:S498–S504
38. Willett W, Stampfer MJ (1986) Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 124:17–27
39. Castetbon K, Vernay M, Malon A, Salanave B, Deschamps V, Roudier C, Oleko A, Szego E, Hercberg S (2009) Dietary intake, physical activity and nutritional status in adults: the French nutrition and health survey (ENNS, 2006–2007). Br J Nutr 102:733–743
40. Seaman SR, White IR (2013) Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res 22:278–295
41. Shen C, Li X, Li L, Were MC (2011) Sensitivity analysis for causal inference using inverse probability weighting. Biom J 53:822–837
42. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D (2003) Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 348:2599–2608
43. Sanchez-Villegas A, Delgado-Rodriguez M, Alonso A, Schlatter J, Lahortiga F, Serra ML, Martinez-Gonzalez MA (2009) Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Arch Gen Psychiatry 66:1090–1098
44. Chocano-Bedoya PO, O'Reilly EJ, Lucas M, Mirzaei F, Okereke OI, Fung TT, Hu FB, Ascherio A (2013) Prospective study on long-term dietary patterns and incident depression in middle-aged and older women. Am J Clin Nutr 98:813–820
45. Kessler RC, Bromet EJ (2013) The epidemiology of depression across cultures. Annu Rev Public Health 34:119–138
46. Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M (2013) So depression is an inflammatory disease, but where does the inflammation come from? BMC Med 11:200. doi:10.1186/1741-7015-11-200.:200-211
47. Koloverou E, Panagiotakos DB, Pitsavos C, Chrysohoou C, Georgousopoulou EN, Grekas A, Christou A, Chatzigeorgiou M, Skoumas I, Tousoulis D, Stefanadis C (2016) Adherence to Mediterranean diet and 10-year incidence (2002–2012) of diabetes: correlations with inflammatory and oxidative stress biomarkers in the ATTICA cohort study. Diabetes Metab Res Rev 32:73–81
48. Casas R, Sacanella E, Urpi-Sarda M, Chiva-Blanch G, Ros E, Martinez-Gonzalez MA, Covas MI, Salas-Salvado J, Fiol M, Aros F, Estruch R (2014) The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. PLoS One 9:e100084
49. Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C (2004) Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: The ATTICA Study. J Am Coll Cardiol 44:152–158
50. Dai J, Jones DP, Goldberg J, Ziegler TR, Bostick RM, Wilson PW, Manatunga AK, Shallenberger L, Jones L, Vaccarino V (2008) Association between adherence to the Mediterranean diet and oxidative stress. Am J Clin Nutr 88:1364–1370
51. Miller AH, Maletic V, Raison CL (2009) Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 65:732–741
52. Tassoni D, Kaur G, Weisinger RS, Sinclair AJ (2008) The role of eicosanoids in the brain. Asia Pac J Clin Nutr 17(Suppl 1):220–228
53. Parker G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D (2006) Omega-3 fatty acids and mood disorders. Am J Psychiatry 163:969–978
54. Bakunina N, Pariante CM, Zunszain PA (2015) Immune mechanisms linked to depression via oxidative stress and neuroprogression. Immunology 144:365–373
55. White DJ, Cox KH, Peters R, Pipingas A, Scholey AB (2015) Effects of four-week supplementation with a multi-vitamin/mineral preparation on mood and blood biomarkers in young adults: a randomised, double-blind, placebo-controlled trial. Nutrients 7:9005–9017
56. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR (2009) Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature 461:1282–1286
57. Dash S, Clarke G, Berk M, Jacka FN (2015) The gut microbiome and diet in psychiatry: focus on depression. Curr Opin Psychiatry 28:1–6
58. Martinez-Gonzalez MA, Sanchez-Villegas A (2016) Food patterns and the prevention of depression. Proc Nutr Soc 75:139–146