Association between the Prime Diet Quality Score and depressive symptoms in a Mediterranean population with metabolic syndrome. Cross-sectional and 2-year follow-up assessment from PREDIMED-PLUS study

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Running Title: Prime Diet Quality Score and Depressive symptoms. Findings from PREDIMED-Plus study

Abstract:

The burden of depression is increasing worldwide, specifically in older adults. Unhealthy dietary patterns may partly explain this phenomenon. In the Spanish PREDIMED-Plus study we explored (1) the cross-sectional association between the adherence to the Prime Diet Quality Score- (PDQS), an a priori-defined high-quality food pattern and the prevalence of depressive symptoms at baseline (cross-sectional analysis), and (2) the prospective association of baseline PDQS with changes in depressive symptomatology after 2 years of follow-up. After exclusions, we assessed 6612 participants in the cross-sectional analysis and 5523 participants in the prospective analysis. An energy-adjusted high-quality dietary score (PDQS) was assessed using a validated food-frequency questionnaire (FFQ). The cross-sectional association between PDQS and the prevalence of depression, presence of depressive symptoms and prospectively assessed changes in depressive symptoms was evaluated through multivariable regression models (logistic and linear models and mixed linear-effects models). PDQS was inversely associated with depressive status in the cross-sectional analysis. Participants in the highest quintile of PDQS (Q5) showed a significantly reduced odds of depression prevalence as compared to participants in the lowest quartile of PDQS (Q1) [OR (95%) CI= 0.82 (0.68, 0.98))]. The baseline prevalence of depression decreased across PDQS quintiles (p for trend=0.015). A statistically significant association between PDQS and changes in depressive symptoms after 2-y follow-up was found (β (95%) CI = -0.67 z-score (-1.17, -0.18). A higher PDQS was cross-sectionally related to a lower depressive status. Nevertheless, the null finding in our prospective analysis, raises the possibility of reverse causality. Further prospective investigation is required to ascertain the association between PDQS and changes in depressive symptoms along time.

Keywords: prime diet quality score; depressive symptomatology; metabolic syndrome; PREDIMED-Plus study.

INTRODUCTION

Unipolar depression is a mental disorder that has experienced an unusual growing over the past 20 years. Based on data of the World Health Organization (WHO) in 2018, nearly of 322 million people of all ages suffered from depression [(1)]. According to age strata, these figures were significantly higher in older adults. In Spain, it is estimated that more than 1.1 million of community-dwelling people were affected by this disorder in 2010 [(2)].

Depression is considered as one of the main leading cause of disability, increasing personal and community costs [(3)]. In particular, late-life depression negatively affects health outcomes specifically on cardiovascular disease (CVD) in adults with Metabolic Syndrome (MetS) [(4)]. Traditional treatments based on antidepressant drugs are not enough to counteract its burden, besides to enhancing a great cost to the health care system [(5)].

Several risk factors for depressive symptoms in later life have been identified [(6)]. Among them, lifestyle factors, specifically diet are highlighted. Dietary intake has long been suggested as a contributing factor to this condition. Currently, a growing body of evidence has reported the association between dietary intake patterns and depression status [(7)]. In this sense, healthy dietary patterns like Mediterranean Dietary pattern (MedDiet) [(8; 9)] or anti-inflammatory dietary patterns [(10; 11)] have been considered in a protective, while the adherence to non-healthy dietary patterns such as a westernized dietary pattern seems to exert detrimental effect [(12; 13)].

Although dietary patterns reflect the complexity of dietary intake in relation to diseases [(14)], their use could be complex in nutritional epidemiology and does not provide an accurate assessment of dietary intake. On the one hand, the adherence to these patterns is based on the intake level of the population, and they also need complex software to compute the nutrient composition of the diet. On the other hand, they are not simple to administer and are difficult to apply across different countries [(15)].

The Prime Diet Quality Score (PDQS) is a simple food-based diet quality score developed by Fung et al.[(15)]. This score was devised as a simple tool to evaluate its association with the risk of CVD. Mainly, the PDQS distinguishes itself by the ability to differentiate healthy foods from unhealthy ones. Despite the use of this score in association with chronic diseases such as diabetes, hypertension and dyslipidemia [(16; 17)],

to our knowledge no study has assessed the association between PDQS and depression in older adults.

Thus, this study aims to explore (1) the cross-sectional association between the adherence to the Prime Diet Quality Score- (PDQS) and the prevalence of depressive symptoms at baseline (cross-sectional analysis), and (2) the prospective association of baseline PDQS with changes in depressive symptomatology after 2 years of follow-up in a Spanish cohort from PREDIMED-Plus trial.

METHODS

Design of the Study

The PREDIMED-Plus study is an ongoing 6-year multicentre, randomized, parallel-group and primary prevention trial conducted in Spain. The aim of the trial is to assess the effect of an intensive weight loss intervention program based on an energy-restricted traditional Mediterranean diet, physical activity promotion and behavioural support, on hard cardiovascular events, in comparison to usual care and dietary counselling intervention only with energy unrestricted Mediterranean Diet (control group). More detailed information concerning the study protocol can be found elsewhere [18].

Ethics Approval

The protocol of the study was written in accordance with the principles of the Declaration of Helsinki. The respective Institutional Review Board (IRB) of all study centres approved the study protocol. The trial was registered at the International Standard Randomized Controlled Trial (ISRCT) in 2014 with number 89898870. All participants provided written informed consent.

Participants and data collection procedures

Eligible participants were community-dwelling adults (men: aged 55-75 years, and women: aged 60-75 years) with overweight or obesity (body mass index (BMI) ≥27 and <40 kg/m^2) who were free of CVD at study recruitment, who met at least three components of the MetS according to the updated harmonized criteria of the International Diabetes Federation and the American Heart Association and National Heart, Lung, and Blood Institute [19].

From the 6874 participants enrolled in the PREDIMED-Plus study, we selected for the present analysis those participants who completed a semiquantitative Food Frequency Questionnaire (FFQ) and a depressive symptoms questionnaire (Beck Depression Inventory-II) at baseline. Those who failed to complete the Beck Depression Inventory-II questionnaire at baseline (n=21) were excluded from this sub-study. Among the available participants, we also excluded those individuals without information about dietary intake or with values for total energy intake in FFQ beyond predefined limits at baseline (<800 kcal/day or >4000 kcal/day for men); (<500 kcal/day or >3500 kcal)/day for women) [20] (n=241). The final sample for the **cross-sectional analysis** was 6612 participants. For the **longitudinal analysis**, we excluded those who failed to complete the Beck Depression Inventory-II questionnaire after 2 y of follow-up (n=1089). Finally, 5523 participants were included for the longitudinal analysis ***(Figure 1).*** Furthermore, out of the eligible individuals, we performed a sensitivity analysis excluding those participants who reported a clinical diagnosis of depression at baseline and/or those who had a Beck Depression Inventory-II score ≥18 points at baseline (n=1444).

Dietary Assessment

Data on dietary intake were collected at baseline by trained dieticians. This information was appraised by a validated 143-item semi-quantitative FFQ [21]. The questionnaire provides a list of foods commonly used by the Spanish population and includes 9 frequency options for a specified serving size, ranging from never or almost never to ≥ 6 times/day. In face-to-face interview, participants were asked about the frequency of consumption of each food item during the past year, specifying usual portion sizes.

Prime Diet Quality Score Construction

Using the baseline 143-item validated FFQ mentioned above, we calculated an energy-adjusted prime diet quality score (PDQS) using the residual method. This PDQS is based on the Prime Screen Questionnaire, a short diet assessment tool developed for clinical use to quickly assess diet quality [22] and widely used by other authors [15]. This score classifies foods as healthy and unhealthy based on 2 major considerations: 1) data from the literature on the direction of association with the risk of non-communicable diseases; and 2) nutrient contribution in the worldwide setting. According to this fact, the food groups included that were considered healthy were: vegetables (dark leafy

green vegetables, cruciferous vegetables, carrots and other vegetables), fruits (whole citrus fruits and other whole fruits), legumes, nuts, poultry, fish, eggs, whole grains and liquid vegetable oils. Meanwhile the non-healthy food groups included in the score were: red meat, potatoes, processed meat, whole milk dairy, refined grains and baked goods, sugar sweetened beverages, fried foods obtained away from home, and desserts and ice creams. The points of adherence in each food component were assigned according to the following criteria as follows: 0-1 serving/week (0 point) compared with 2-3 servings/week (1 point) compared with ≥4 servings/week (2 points) for the healthy food groups. Scoring was reversed and points deducted for the unhealthy food groups. Points for each food group were then summed to give an overall score. The PDQS has 21 food groups and ranges from 0 to 42 total points. Finally, PDQS was categorized in quintiles (Q) and the cutoff points were: Q1: <19.7, Q2: ≥19.7-<21.9, Q3: ≥21.9-<23.8, Q4: ≥23.8-<26.0, Q5: ≥26.0.

Outcome Assessment

Depressive symptoms were collected at baseline and yearly by trained PREDIMED-Plus staff through the Beck Depression Inventory-II (Beck-II) previously validated in Spanish population. The Beck Depression Inventory-II includes 21 questions with four possible answers sorted according to symptoms severity and score ranges from 0 to 63 points [(23)]. Prevalent depression was defined as the presence of depressive symptoms at baseline (Beck≥18 points) or the reporting of a lifetime prevalence of depression. Lifetime prevalence of depression was collected at baseline and defined as a self-reported life-time medical diagnosis of depression.. In the baseline analysis, in order to analyze depressive symptoms across categories of PDQS we considered the Beck-II score as a continuous outcome. Finally, to assess changes in depressive symptomatology after 2 years of follow-up, we have calculated the difference in Beck punctuation (2-year follow-up Beck-II questionnaire score minus baseline Beck-II´questionnaire score).

Covariate Assessment

At baseline and once yearly, trained staff collected information about socioeconomic and lifestyle factors. The variables included were sex, age, education level (primary level, secondary level and tertiary level which includes University studies), civil status (married or not, which includes: widowed, divorced/singled or others) and whether they

lived alone or not. Other lifestyle variables such as smoking habits (former smoker, never smoker and current smoker), sleep duration (hours per day), physical activity status (active, moderately active and less active) were recorded. Regarding sleep, participants reported their average daily sleeping time for both weekdays and weekends, using the non-validated open question "How many hours do you sleep on average per day on weekdays and weekends?" Leisure-time physical activity was assessed using the short form of the Minnesota Leisure Time Physical Activity Questionnaire validated in Spain [24; 25] (including questions to collect information about types of physical activity, their frequency (number of days), and duration (min/day)). Leisure-time activities were computed by assigning a metabolic equivalent score to each activity, multiplied by the time spent for each activity and summing up all activities. The intensity was assigned based on the compendium of physical activity [26]. Furthermore, at each visit, anthropometric variables were also measured by trained personnel: weight (using high-quality electronic calibrated scales, in kg) and height (using a wall-mounted stadiometer, in m^2). Body mass index (BMI) was calculated dividing weight by height squared. BMI measure was expressed (in kg/m^2).

Finally, personal history of chronic diseases (hypertension, dyslipidemia and type 2 diabetes) was collected from the patients 'medical records.

Statistical Analysis

The association between PDQS (in quintiles) and depressive symptoms at baseline was assessed using multivariable linear regression models. Logistic regression models were fitted to assess the relationship between PDQS and the prevalence of depression at baseline. Odds ratios (ORs) and their 95% CI were calculated considering the lowest quintile (PDQS= Q1) as the reference category. Linear mixed-effects models were used to explore the associations between concurrent changes in self-reported depressive symptomatology (Beck-II score) and quintiles of PDQS at 2 years of follow-up. Changes in repeated measured variables were calculated as the difference between the results from each follow-up assessment (changes from 0 to 2 years follow-up). To control for potential confounding factors, the results were adjusted for the sociodemographic and lifestyle variables mentioned previously. We analyzed the possible interaction between sex-age and depression. As well as, the possible modifier effect of allocation group in the outcome measured. In order to evaluate the effect that the recruitment center exerts on the dietary intervention and assuming in any case that

the results could be heterogeneous, we adjusted the models also for this variable. Finally, allocation group (intensive intervention group or usual care (control) group) were also taken into account in the longitudinal adjusted models.

We have used a significance level of 0.05 for all analyses. Data were analyzed using Stata (15.0, StataCorp LP, College Station, TX, USA).

RESULTS

Characteristics of the study subjects at baseline according to DDS quartiles

The current study included a total of 6612 participants (3414 men). The baseline characteristics of participants according to PDQS quintiles are presented in **Table 1**. Among those who showed better dietary quality intake (higher PDQS quintile, Q5), there were more women, older and tended to have lower BMI. Participants in the lowest quintile of PDQS (Q=1) were mainly smokers, participants with a higher educational level, less physically active and they did not live alone. No difference in disease prevalence and depressive status were found among PDQS quintiles.

Cross-sectional association between PDQS and depressive symptomatology

We fitted a multivariable linear regression model to analyze depressive symptoms across categories of PDQS (**Table 2**) taking into account the Beck-II score as a continuous outcome. Depressive symptomatology was inversely associated with PDQS in both models (model 1 and 2). That is, the punctuation of depressive symptoms decreases across PDQS quintiles, in model 2 [multivariable β-coefficients (95% CI) = -0.73 (-1.29, -0.18) and -0.62 (-1.17, -0.06)] and for Q3 and Q4, respectively. Nevertheless, for the higher score of PDQS (Q5) we only found significant differences in model 1 (adjusted only for sex and age).

Cross-sectional associations between PDQS and prevalence of depression

Our results showed that PDQS was inversely associated with depressive status (≥18p at Beck II inventory at baseline and/or lifetime prevalence of depression) in logistic analysis (**Table 3**). Participants in the highest quintile of PDQS (Q5) showed a significant decrease in the odds of depression´s prevalence as compared to those participants in the lowest quintile (Q1) [OR (95% CI)= 0.82 (0.68, 0.98) for model 2, [OR (95% CI)= 0.77 (0.64,

0.92) for model 1]. This significant association was consistent across PDQS quintiles (*p for trend*=0.015).

Longitudinal associations between PDQS and changes in depressive symptomatology after 2 y-of follow-up

Table 4 shows main association between concurrent changes in self-reported depressive symptoms and PDQS after controlling for potential confounders. In multivariable-adjusted model 1, comparison of the highest versus the lowest quintile of PDQS revealed decreases in depressive symptomatology during the follow-up, Q5 vs. Q1 in model 1 (β -0.67 z-score, 95% CI -1.17, -0.18). Model 2, additionally adjusted as shown in table 4, did not found any significant difference.

In ancillary analysis (sensitivity analysis), we excluded those subjects with a Beck-II score higher than 18 points at baseline or with life-time prevalence of depression. In this sub-sample the results were no longer significant although the magnitude of effect was quite similar to that observed in the overall sample. A higher baseline PDQS (Q5 vs Q1) was associated with a decrease in depressive symptomatology [β-coefficient (95%) CI= -0.58 (-1.06, -0.11)] in model 1. Nevertheless, when we adjusted for potentially confounding factors, we did not find any significant association between PDQS and changes in depressive symptomatology after 2 y-of follow-up **(Supplementary Table 1).**

Understanding the possible impact of sex and age in the changes of depressive symptomatology (p for interaction <0.05), we performed a supplementary analysis stratified by sex and age (55-65 men/60-75 women, 65-75 both sex groups). A supplementary analysis stratifying by these covariates is shown in **Supplementary tables 2, 3 and 4.** In the cross-sectional analysis we found a significative association between PDQS and depressive symptomatology, (being the effect higher in older women (>65 years old) for depressive symptomatology (Supplementary table 2), but higher in older men for the prevalence of depression (Supplementary table 3)). In the prospective analysis the findings show a protective effect in younger population (women and men) but without a dose-response pattern (Supplementary table 4).

In order to assess a possible interaction between allocation group and PDQS in depression symptomatology, interaction terms were included in the longitudinal analyses. *We did not find any significant interaction between PDQS and primary trial*

intervention in association with Beck-II score at the baseline during the follow-up (data not shown, p for interaction >0.05).

DISCUSSION

In this substudy of the PREDIMED-Plus trial analyzed as an observational longitudinal cohort, we aimed to examine the association between PDQS and depression symptomatology in a community-dwelling adult population with overweight/obesity and MetS. Our findings suggest that participants with intermediate-high diet quality (Q3-Q4 vs. Q1 of PDQS) had lower depressive symptoms and a lower odds of depression´s prevalence than those with poorer diet quality at baseline. These associations were robust to adjustments for a range of health parameters and behavioural factors in cross-sectional analysis. However, we have to remark that when the association between PDQS and changes in depressive symptomatology after 2y of follow-up was assessed, the relationship was no longer significant.

The development of depressive illness is influenced by several factors, including genetic, hormonal and immunological factors. Diet can modulates each of these factors, and as a result, has impact on the development and course of this condition [(27)]. Traditionally, research on the association between diet and depression has focused primarily on nutrients such as fatty acids [(28)], and the group B vitamins involved in the synthesis of some neurotransmitters [(29)]. Nevertheless, the protective effect of diet on chronic diseases as depression comes from the cumulative and synergic effect of nutrients from different sources of foods, rather than from specific nutrients [(30)]. Currently, nutritional epidemiology has focused on associations between the effects of dietary patterns on health instead of isolated nutrients. Our results suggest a protective effect of a baseline adherence to an overall “healthy dietary pattern” rich in fruits, vegetables and legumes and low in processed meat and sweetened foods. In line with our findings, prospective large studies based on dietary patterns characterized by similar foods to those included in the PDQS as the Mediterranean diet or other healthy diets have reported an inverse relationship with depression outcomes in adults [(31; 32; 33)]. There are several plausible mechanisms underlying the association observed. One of them is that brain inflammation increase the risk of depression, thus foods as fruits and vegetables have been shown to have strong antioxidant/anti-inflammatory capacity, decreasing depression risk [(34)].

However, we cannot elucidate if the relationship between diet and depression could be bidirectional, causing a possible reverse causality bias. That is, personal dietary choices are related with depressive symptomatology, as diminished appetite [35] and/or an increased desire for unhealthy foods [36; 37], at the same time that unhealthy dietary habits increased the risk of developing depressive symptoms [38; 39]. In an attempt to avoid this possible bias in the relationship between PDQS and depressive symptomatology, we evaluated the association between PDQS and depressive symptomatology after 2 y of follow-up. In this case the results suggest a direct association between PDQS and changes in depressive symptoms although the findings were not significant. Contrary to our findings, a meta-analysis of 24 prospective studies reported that a high-quality diet, regardless of dietary pattern, was associated with a lower risk of depressive symptoms during the follow-up [32]. A possible explanation to the lack of statistical significance of our results could be exerted by the short follow-up period. This meta-analysis included studies with more than 2 years-of-follow up. A longer follow-up with more adequate induction period could be useful to definitively assess the role of dietary quality in depression. The meta-analysis performed by Molendijk et al. reported that those studies that control for this variable observed significant association [32]. Nevertheless, we found no association between dietary score and changes in depressive symptoms either with or without adjustment for baseline Beck II score in sensitivity analysis. In Japan, Nanri et al., examined the association between the dietary score based on the Japanese Food Guide Spinning Top and risk of depressive symptoms. Similarly to our results, these authors found a statistically significant association only in the cross-sectional design but not in the prospective analysis [40]. As in the previous study, the null finding in our prospective analysis, including sensitivity, raises the possibility of reverse causality mentioned above. Further prospective investigation is required to analyze the association between PDQS and depressive symptoms.

Strengths and Limitations

The current study has some limitations that need to be addressed. First, the community-dwelling population with overweight/obesity and MetS included in the study is not representative of the general population; however, our population represent an important proportion of current Western societies. Second, although the FFQ has been validated in nutritional studies [21] self-reporting questionnaires, in combination with

memory loss of older participants, might lead a no differential misclassification bias. However, this bias would tend the estimations towards the null; so, the association could be higher than that observed. Moreover, we excluded participants with energy intakes outside of predefined limits [20] and we used residual method in order to adjust for energy intake. Third, loss of participants after 2 y of follow-up could be a selection bias (only the more healthy participants were available for the longitudinal study) attenuating our associations. Another limitation to highlight in this substudy of the PREDIMED-Plus trial was the not adjustment by anti-inflammatory/immunomodulatory medications and drugs with potential psychotropic effects and personal/family history of depression that can modulate the results obtained. Despite of this, we have controlled our models by the main sociodemographic and lifestyles variables related to depressive status. Finally, the follow-up time (2 years) is probably quite short to evaluate changes in the outcome.

Notwithstanding the above limitations, our study includes several strengths that reinforce the results obtained. We used a repeated measurements of outcome (depressive symptomatology assessed by Beck II depression questionnaire inventory) over 2 years. Another strength is not only the use of a DDS that provides a more intuitive view of the whole dietary pattern, but also the study of each of the food groups we have identified some of them as important components linked with depression status. Finally, the large sample size and the considerable amount of baseline information collected in a large ongoing primary prevention trial, using a standardized protocol that reduces information bias regarding reported food intakes, sociodemographic characteristics and lifestyles are other strengths that should be considered.

What our results suggest is that recommending diets with high diversity of vegetables, grains and protein food groups (fish/seafood, white meat, nuts and legumes) may represent an effective approach to improve depression outcomes in community-dwelling population. That is, in people with depressive symptoms, fostering healthy dietary patterns would presumably result in a far greater impact over prevalence and symptomatology on depression. Nevertheless, these associations were only found in cross-sectional analysis. It is necessary the entire cohort was followed-up for a longer period in order to establish significant associations between PDQS and depression status.

CONCLUSIONS

In summary, we observed that higher PDQS was related to a lower prevalence of depression and a lower depression symptomatology in Spanish community-dwelling with overweight/obesity and MetS at baseline. Nevertheless, the null finding in our prospective analysis, raises the possibility of reverse causality. Further prospective investigation is required to analyze the association between PDQS and depressive symptoms.

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Conflict of Interest

None.

Authorship

N.C.-I., L.S.-M, M.A.M.-G., J.S.-S., D.C., J.A.M., J.W., J.V., D.R., J.L.-M., R.E., A.B.-C, J.A.T., V.M., X.P., M.D.-R., P.M., J.V., L.D., E.R., A.S.-V. collected all the data from the PREDIMED-Plus trial. N.C.-I., A.S.-V. and A.B.-C. designed the study; performed the analysis; and wrote the first draft of the manuscript. All authors contributed to the editing of the manuscript. All authors have read and approved the final version of the manuscript.

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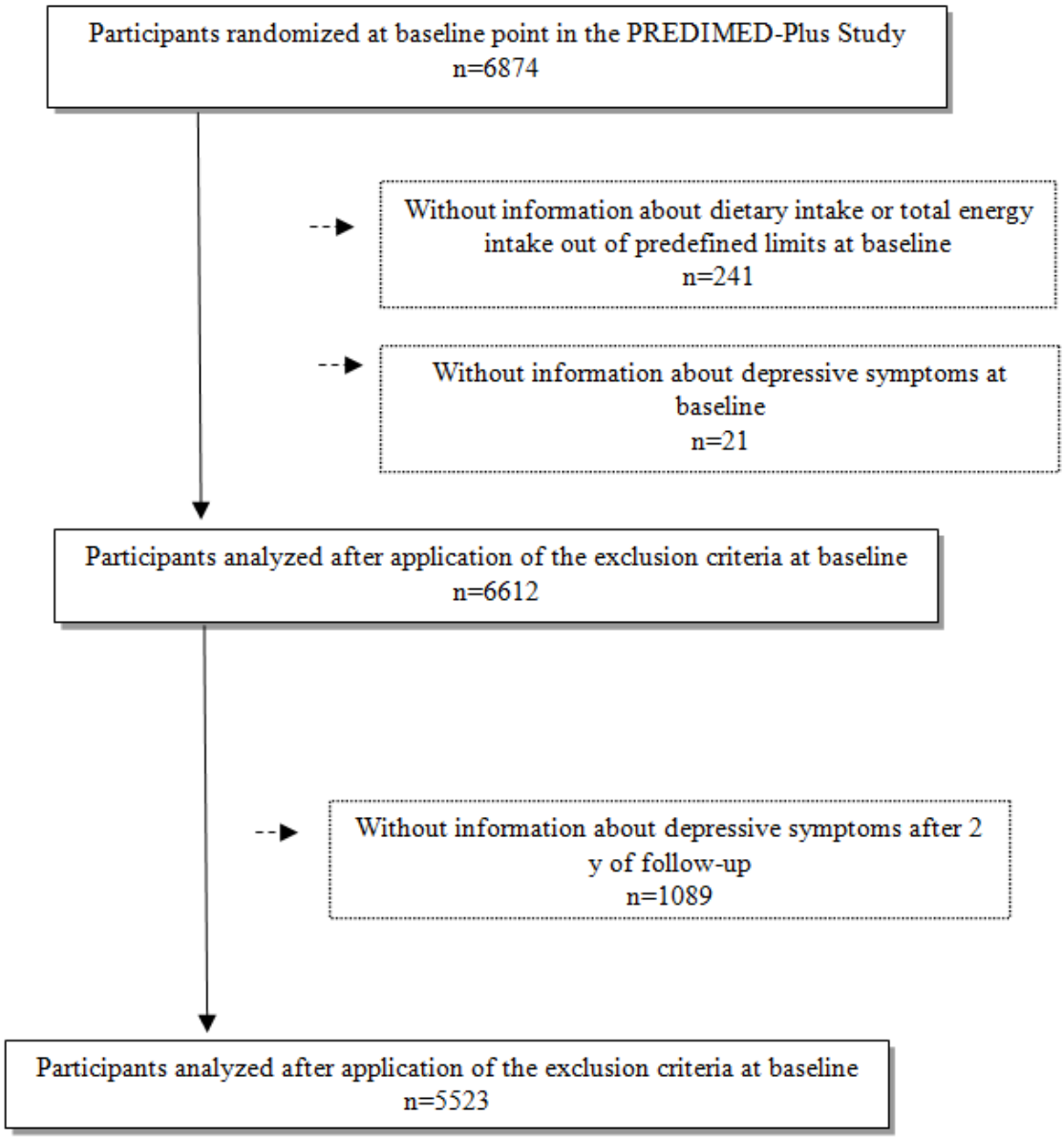

Figure 1. Flow chart of the study participants

Table 1. Baseline characteristics of PREDIMED-Plus participants according to quintiles of PDQS

	Q1 (n=1323)	**Q2 (n=1322)**	**Q3 (n=1323)**	**Q4 (n=1322)**	**Q5 (n=1322)**	**P value**
Age (y), Mean ±SD	63.8 ± 5.1	64.9 ± 4.9	65.1 ± 4.8	65.3 ± 4.8	65.9 ± 4.6	<0.001
Sex, n (%)						
Male	861 (65.1)	739 (55.9)	687 (51.9)	602 (45.5)	525 (39.7)	<0.001
Smoking habits, n (%)						
Current Smoker	235 (17.7)	170 (12.9)	146 (10.9)	158 (12.0)	110 (8.4)	<0.001
Former Smoker	584 (44.1)	613 (46.3)	572 (43.3)	559 (42.3)	535 (40.4)	
Never Smoker	499 (37.7)	530 (40.1)	598 (45.2)	600 (45.4)	675 (51.1)	
Without information	5 (0.4)	9 (0.7)	7 (0.5)	5 (0.4)	2 (0.2)	
Physical Activity, n (%)						
Less active	891 (67.6)	850 (64.5)	777 (58.8)	737 (56.0)	689 (52.3)	<0.001
Moderately active	199 (15.1)	221 (16.8)	272 (20.6)	265 (20.1)	292 (22.2)	
Active	228 (17.3)	247 (18.7)	272 (20.6)	315 (23.9)	337 (25.6)	
Educational level, n (%)						
Tertiary	321 (24.4)	276 (20.8)	282 (21.4)	265 (20.0)	306 (23.2)	<0.001
Secondary	428 (32.3)	376 (28.5)	370 (27.9)	407 (30.9)	325 (24.7)	
Primary	574 (43.3)	670 (50.7)	670 (50.7)	651 (49.1)	691 (52.2)	
Civil status, n (%)						
Married	1011 (76.3)	1033 (78.1)	1034 (78.2)	1011 (76.5)	966 (73.1)	0.013
Living alone (yes), n (%)	137 (10.4)	139 (10.5)	150 (11.4)	163 (12.3)	223 (16.9)	<0.001
BMI (kg/m^2), Mean ±SD	32.8 ± 3.5	32.6 ± 3.5	32.5 ± 3.4	32.4 ± 3.4	32.3 ± 3.5	0.002
Presence of diseases, n (%)						
Hypercholesterolemia	900 (67.9)	918 (69.4)	916 (69.2)	912 (69.0)	934 (70.7)	0.575
Type 2 diabetes	381 (28.8)	375 (28.4)	366 (27.7)	362 (27.4)	335 (25.3)	0.445
Hypertension	1112 (84.1)	1121 (84.8)	1100 (83.1)	1098 (83.1)	1084 (82.0)	0.782
Depressive symptoms (≥18p) and/or physician diagnosis of depression, n (%)	369 (27.9)	332 (25.1)	331 (25.0)	351 (26.5)	381 (28.8)	0.119

Abbreviations: (BMI): Body Mass Index, (Q): quintile, (SD): Standard Deviation. Values are presented as means ± SD for continuous variables and n (%) for categorical variables. Pearson's chi-square test was performed for categorical variables and ANOVA test for continuous variables.

Table 2. Multivariable linear regression models for the association between PDQS and symptomatology of depression in the PREDIMED-Plus study participants. Regression coefficients (95% Confidence intervals). Cross-sectional analysis.

	Q1 (n=1323)	**Q2 (n=1322)**	**Q3 (n=1323)**	**Q4 (n=1322)**	**Q5 (n=1322)**
PDQS					
Model 1	0 (Ref.)	-0.23 (-0.78,0.33)	**-0.93 (-1.48,-0.37)**	**-0.85 (-1.41, -0.29)**	**-0.73 (-1.29, -0.17)**
Mean ±SE	9.00±0.20	8.78±0.20	8.01±0.20	8.16±0.20	8.30±0.20
Model 2	0 (Ref.)	-0.15 (-0.70, 0.40)	**-0.73 (-1.29, -0.18)**	**-0.62 (-1.17, -0.06)**	-0.36 (-0.92, 0.20)
Mean ±SE	8.90±0.20	8.70±0.20	8.12±0.20	8.27±0.20	8.48±0.20

Values are presented as adjusted means±SE, together with β-coefficients and 95%CI for symptomatology of depression (Beck Depression Inventory II) as continuous variable according to PDQS. Model 1: Adjusted for sex and age. Model 2: Additionally adjusted for smoking habits, physical activity, educational level, BMI, living alone, civil status, sleep duration and presence of chronic diseases. The interaction between sex-age and depression symptomatology was not significant (p=0.414). Values presented in bald showed a statistically significant association ($p<0.05$). Abbreviations: (BMI), Body mass index; (PDQDS), Prime diet quality score; (Q), quintile.

Table 3. Multivariable logistic regression models for the association between PDQS and prevalence of depression in the PREDIMED-Plus study participants. Odds ratios (95% Confidence intervals). Cross-sectional analysis.

	Q1 (n=1323)	**Q2 (n=1322)**	**Q3 (n=1323)**	**Q4 (n=1322)**	**Q5 (n=1322)**	**P for trend**
PDQS						
Model 1	1 (Ref.)	**0.76 (0.64,0.91)**	**0.72 (0.60,0.86)**	**0.73 (0.61, 0.87)**	**0.77 (0.64, 0.92)**	**0.001**
Mean ±SE	0.31±0.02	0.26±0.01	0.25±0.01	0.25±0.01	0.26±0.01	
Model 2	1 (Ref.)	**0.77 (0.64, 0.93)**	**0.75 (0.62, 0.90)**	**0.77 (0.64, 0.92)**	**0.82 (0.68, 0.98)**	**0.015**
Mean ±SE	0.30±0.01	0.26±0.01	0.25±0.01	0.26±0.01	0.27±0.01	

Values are presented as adjusted means±SE, together with OR and 95%CI for prevalence of depression (≥18p at Beck Depression Inventory II and/or lifetime prevalence of depression) as categorical variable according to PDQS. Model 1: Adjusted for sex and age. Model 2: Additionally adjusted for smoking habits, physical activity, educational level, BMI, living alone, civil status, sleep duration and presence of chronic diseases. The interaction between sex-age and depression symptomatology was not significant (p=0.430).Values presented in bald showed a statistically significant association (p<0.05). Abbreviations: (BMI), Body mass index; (PDQS), prime dietary quality score; (Q), quintile.

Table 4. Association of concurrent changes in self-reported depressive symptoms and PDQS after 2 year of follow-up in the PREDIMED-Plus trial (n=5523). Prospective analysis.

	Q1 (n=1069)	**Q2 (n=1083)**	**Q3 (n=1108)**	**Q4 (n=1130)**	**Q5 (n=1133)**
PDQS					
Model 1	0 (Ref.)	**-0.52 (-1.01,-0.03)**	-0.28 (-0.77,0.21)	-0.33 (-0.82, 0.16)	**-0.67 (-1.17, -0.18)**
Model 2	0 (Ref.)	-0.38 (-0.87,0.12)	-0.08 (-0.58,0.42)	-0.19 (-0.68, 0.31)	-0.33 (-0.84, 0.17)

The values shows the β coefficients (95% CIs) for changes in depressive symptomatology after 2-y of follow-up as continuous variable according to PDQS. Mixed-effects linear models were performed. Model 1: Adjusted for sex and age. Model 2: Additionally adjusted for depressive symptomatology at baseline, smoking habits, physical activity, educational level, BMI, living alone, civil status, sleep duration, presence of chronic diseases, allocation group and recruitment centre. The interaction between sex-age and depression symptomatology was not significant (p=1.00).Values presented in bald showed a statistically significant association (p<0.05). Abbreviations: (BMI), body mass index, (PDQS), prime dietary quality score; (Q), quintile.